Improving Wellbeing in At-Risk Frontotemporal Dementia

A thesis submitted to University College London (UCL)

for the degree of Doctor of Philosophy

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Declaration

I, Caroline Victoria Greaves confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Frontotemporal dementia (FTD) is a highly heritable group of neurodegenerative disorders, with around 30% of patients having a strong family history. The majority of that heritability is accounted for by autosomal dominant mutations in the chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), and microtubule-associated protein tau (*MAPT*) genes. Many people live with genetic risk of FTD for much of their lives, which comes with numerous uncertainties (e.g., their mutation status, the age at symptom onset and the phenotype they might develop) which make it difficult to plan for the future. Caring for symptomatic loved ones, worry about children and for some, the need for assisted fertility, pose additional challenges and contribute to an emotionally overwhelming experience. Despite this, little research has been done into this experience, resulting in a lack of psychological support available. This thesis aims to further understand the lived experience of being at-risk of fFTD, to develop tailored psychological support for those at-risk, and outline recommendations for genetic testing in FTD. This thesis begins by describing the psychological problems associated with living at-risk, including depression, anxiety and need for psychosocial support. This is built upon using qualitative data to characterise the at-risk lived experience, experience of predictive testing and support needs. This data is then used in the application of the MRC complex intervention development framework, to design an ACT-based psychological intervention using a person-centred approach. Qualitative data surrounding predictive testing experience and a Delphi methodology are used to develop expert and patient perspective recommendations for genetic testing in FTD. Finally, a novel exploratory study investigates the presence of broad autism traits and schizotypy in presymptomatic FTD, and their association with severity. This work provides evidence of increased depression and anxiety in fFTD, and an elevated need for psychosocial support, as well as characterisation of the lived at-risk experience. The development of a tailored psychological intervention and FTD specific genetic testing protocol provides the basis for improved support and predictive testing experience for those at-risk. This will become increasingly relevant as disease modifying therapy trials progress.

Impact statement

The impact of familial frontotemporal dementia is devastating to all those affected. The onset of behavioural, language, motor and neuropsychiatric symptoms around midlife is not only distressing for the individual living with the diagnosis and caregiver, but the hereditary nature means that there are implications for siblings and children. The knowledge that one may develop similar symptoms in future understandably has a huge emotional impact and serious implications for an individual's future. Despite this, little is currently known regarding the lived experience of being at-risk of FTD, meaning that the population remains underserved in terms of specialist psychological support. In addition, predictive testing and counselling protocols are extrapolated from those designed for use in Huntington's disease, therefore some key issues associated with genetic risk of fFTD may not be addressed. This may lead to a sub-standard experience of predictive testing for such individuals, making an already distressing situation more difficult.

This thesis investigates the lived experience of fFTD, including mood symptoms, autistic and schizotypal traits, need for psychosocial referral, and qualitative evaluation of the feelings and experiences and support needs associated with living at-risk. Further to this, I outline the development of a tailored acceptance and commitment therapy-based psychological intervention designed for use in this group, as well as expert and patient recommendations for genetic testing in FTD.

The findings outlined in this thesis are relevant across academia and clinical practice. The qualitative and quantitative evaluation of the psychological impact, and support needs while living at-risk furthers understanding of the at-risk experience within the field. This has important implications for understanding mood symptoms in asymptomatic mutation carriers and potentially into prodromal disease stages. Considering the limited literature on this topic, the work reported in chapter 5 provides an empirical and theoretical basis for future interventions to be built upon. Findings regarding the at-risk experience and the intervention developed may also be extrapolated for use in other hereditary neurodegenerative disorders. Finally, the international collaboration used in Chapter 3 and 6 provides a cross-culturally applicable genetic testing protocol, as well as allowing extrapolation of findings regarding the psychological impact of living at-risk.

The findings of this thesis also have clinical implications, providing access to specialist information and psychological support to improve wellbeing and quality of life in at-risk individuals. There also may be educational benefits for clinicians who lack experience in fFTD, providing genetic counsellors, psychologists and mental health professionals with the necessary context and tools to aid their interactions with these individuals in clinic. Finally, as FTD research moves towards clinical trials, improved understanding of the at-risk experience and the availability of a psychological intervention designed for this purpose will likely become increasingly important, especially considering treatments have not yet been successful.

The findings of this thesis have been disseminated at various national and international conferences, including the Alzheimer's Association International Conference (2019 and 2021), and the International Conference for Frontotemporal Dementia (2022). Dissemination of findings at academic conferences, as well as public engagement events is also important in furthering public understanding of FTD and genetic risk, in turn improving peer support available to this group.

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The journey to submitting this thesis has been a rollercoaster. My first couple of years were made more challenging by my diagnosis of anxiety, we then spent two years in a global pandemic, following which I received a diagnosis of chronic fatigue syndrome. The past two years have been the hardest in my life, and at the times when my illness was at its worst, I had no idea how I would possibly be able to finish my PhD work. I feel so incredibly lucky to have been able to lean on the support of so many friends, family and colleagues throughout this time, without which I would not have got to this point.

I have had the greatest privilege to work with the GENFI team for the past 6 years. From starting as a research assistant fresh from my undergraduate degree at 21, to becoming a PhD student. This has given me the most amazing opportunities and beginning to my career, for which I am so grateful. The chance to work with such eminent researchers across the world, and travel to attend and present at international conferences is unique and I am so appreciative for all I have learnt. The most lasting impact of this work, for me, has been getting to know the families involved in GENFI. Over the years people's stories have touched my heart and so many have referred to the GENFI team as an extension of their family, which I think is the greatest complement to the work that we do. Our work to understand FTD would be nothing without the selfless contributions of all those who participate, and I hope in the not too distant future that this will lead to a cure.

This work was funded by the FTD studentship in memory of David Blechner. I would like to thank Judith Blechner from the bottom of my heart for her continued support over the years as well as the opportunity to carry out this work in her late husband David's memory. I am incredibly grateful, and I hope that this work is a fitting tribute.

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Division of labour

The work in this thesis was carried out by CVG in collaboration with researchers and colleagues at the Dementia Research Centre (DRC), UCL Queen Square Institute of Neurology, the UCL division of Psychology and Language Science, GENFI consortium sites based at Cambridge University, Università degli Studi di Milano Statale, Sorbonne Université, Paris Brain, Hôpital Pitié-Salpêtrière, University of Barcelona and Built by Knights – a web developer. See below for an outline of contributions.

CVG – Caroline V Greaves

JDR – Jonathan D Rohrer

JCS – Joshua C Stott

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SG – Sophie Goldsmith

NL – Nayana Lahiri

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ILB – Isabelle Le Ber

DR - Daisy Rinaldi

JJ – Jordi Junca

CT – Carolin Timberlake

GF – Giorgio Fumagalli

LCR – Lucy Chisman-Russell

NK – Nick Knight - Built by Knights

Contributions	
Chapter 1: Introduction	
Adapted from a first author review published in the Journal of Neurology (2019), see UCL research paper declaration form. Written by CVG and revised by CVG and JDR.	
Chapter 3: Using quantitative methods to understand the at-risk experience	
Questionnaire design	CVG in collaboration with JDR and JCS
Data collection	CVG in collaboration with local GENFI site PIs and co-ordinators DR, ILB, JJ, CT and GF
Data analysis	CVG with statistical support from LCR
Writing	CVG
Chapter 4: Using qualitative interview to understand the at-risk experience and support needs in familial FTD	
Interview schedule	CVG in collaboration with JDR and JCS
Participant recruitment	CVG
Data collection and transcription	CVG
Coding	CVG, reviewed by CF
Theme generation	CVG
Review and refinement of themes	CVG and JCS
Writing	CVG
Chapter 5: Determining the feasibility of a tailored psychological intervention for those at-risk of familial frontotemporal dementia	
Review of the literature	CVG
Qualitative data collection	CVG
Data analysis	CVG
Intervention framework development	CVG in collaboration with JDR and JCS
Intervention material design and creation	CVG
Review of materials and design	CVG, EH, JCS and JDR
Web-design	CVG and NK
Check-in session design	CVG, EH and JCS
Writing	CVG
Chapter 6: Developing a tailored diagnostic testing protocol for use in frontotemporal	

dementia	
Delphi consensus questionnaire design	CVG in collaboration with JDR, JCS and NL
Delphi consensus questionnaire re-iteration	CVG in collaboration with JDR
Delphi consensus data collection	CVG
Data analysis	CVG
Creation and adaptation of recommendations	CVG
Writing	CVG
Chapter 7: Developing a tailored predictive testing protocol for use in frontotemporal dementia	
Delphi consensus questionnaire design	CVG in collaboration with JDR, JCS and NL
Delphi consensus questionnaire re-iteration	CVG in collaboration with JDR
Qualitative data collection	CVG
Delphi consensus data collection	CVG
Data analysis	CVG
Creation and adaptation of recommendations	CVG
Writing	CVG
Chapter 8: Investigating autistic traits and schizotypy in the presymptomatic phase of FTD	
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Data analysis	CVG
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Publications

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Conference presentations/abstracts

AAIC 2019

Posters:

Depression and anxiety in the 'at-risk' phase of frontotemporal dementia

ARUK 2021

Poster:

Exploring the experiences of living at risk of familial frontotemporal dementia

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Posters:

Developing a consensus protocol for genetic testing in frontotemporal dementia

Exploring the experiences of living at risk of familial frontotemporal dementia

AAIC 2022

Oral presentation:

Using semi-structured interview to develop a tailored psychological intervention for individuals at risk for familial Frontotemporal dementia

ICFTD 2022

Poster:

Autistic traits and schizotypy in presymptomatic familial frontotemporal dementia

UCL Research Paper Declaration Form
referencing the doctoral candidate's own published work(s)

1. **For a research manuscript that has already been published** (if not yet published, please skip to section 2)

   a) **What is the title of the manuscript?**

   An update on genetic frontotemporal dementia

   b) **Please include a link to or doi for the work**

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   c) **Where was the work published?**

   Journal of Neurology

   d) **Who published the work?** (e.g. OUP)

   Springer Nature

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   2019

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   The review of the literature was carried out and written up by Caroline Greaves. The paper was revised for publication by Caroline Greaves and Prof. Jonathan Rohrer

4. **In which chapter(s) of your thesis can this material be found?**

   Chapter 1 - Introduction

5. **e-Signatures confirming that the information above is accurate** (this form should be co-signed by the supervisor/ senior author unless this is not appropriate, e.g. if the paper was a single-author work)

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Chapter 1. Introduction

1.1. An overview of Frontotemporal dementia

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder presenting with distinct changes in behaviour, language and motor function. Despite often being considered a rare disease, FTD is probably the most common form of dementia experienced in people under the age of 60 (Hogan et al., 2016), with an estimated lifetime risk of one in 742 (Coyle-Gilchrist et al., 2016). It is characterised by progressive changes in behaviour, personality, language production and comprehension and motor function (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). The behavioural variant (bvFTD) is characterised by changes in personality while the language variant (known as primary progressive aphasia, PPA), is typically associated with progressive speech production or comprehension difficulties (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). People with FTD can also develop motor deficits, either amyotrophic lateral sclerosis (FTD-ALS) or parkinsonism, in the latter case often with specific features of a corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) (Armstrong et al., 2013; Höglinger et al., 2017; Strong et al., 2017). Approximately a third of FTD is familial (fFTD, Rohrer et al., 2009), with an autosomal dominant inheritance pattern from three main genes; the chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) (Mahoney et al., 2012; Snowden et al., 2015).

1.2. Heritability, genes and phenotype

Phenotype

As it is a heterogeneous disorder, there are several clinical phenotypes that can be observed under the 'FTD umbrella'. Diagnostic criteria categorises FTD syndromes into behavioural variant (bvFTD, Rascovsky et al., 2011) and language variants (also known as primary progressive aphasia, or PPA, Gorno-Tempini et al., 2011), however there are a number of presentations that fall outside these categories and many that overlap. As described above, bvFTD is characterised by profound changes in behaviour and personality, while the language variant can be further subdivided into non-fluent variant primary progressive aphasia (nfvPPA), semantic variant primary

progressive aphasia (svPPA) and logopenic aphasia (lvPPA) (Gorno-Tempini et al., 2011; Harris et al., 2013). There is also an additional language syndrome, often called primary progressive aphasia not otherwise specified (PPA-NOS), mixed or unclassified PPA, used for a minority of cases who do not neatly fit criteria for the three main PPA syndromes.

Notably, there are also a number of motor syndromes associated with FTD that may occur alone, or in conjunction with another FTD presentation, including motor neurone disease (MND) and amyotrophic lateral sclerosis (ALS), overlapping most commonly with bvFTD to form FTD-ALS or FTD-MND (Strong et al., 2017). There are also a number of atypical Parkinsonian syndromes, so called as they resemble Parkinson's disease, these include progressive supranuclear palsy (PSP, Snowden, 2023) and corticobasal syndrome (CBS, Armstrong et al., 2013). Furthermore, a subset of individuals with FTD will display prominent neuropsychiatric symptoms, most commonly including hallucinations and delusions, occasionally misdiagnosed as adult-onset primary psychiatric disorders.

Primary diagnoses are defined based on the first and most predominant symptom(s) observed, however there are a number of 'overlap syndromes' describing those for which a number of symptoms occur equally predominantly.

While this thesis will focus on asymptomatic individuals, it is important to understand the complexity, heterogeneity and unpredictable nature of symptomatic FTD in order to appreciate the uncertainty associated with disease onset and future symptoms when living at-risk.

Behavioural variant FTD

Behavioural variant FTD is the most common phenotype reported in both sporadic and familial FTD (Hogan et al., 2016) and is associated with progressive changes in behaviour and personality. In order to meet criteria for 'probable bvFTD' at least three of the following five features must be observed, as well as one cognitive feature (usually impaired executive functioning with relative preservation of episodic and visuospatial functioning); disinhibition, apathy, loss of sympathy or empathy, perseverative, compulsive and ritualistic behaviours, hyperorality or dietary changes (Rascovsky et al., 2011).

Disinhibition commonly refers to impulsive behaviour, for example risky financial decisions like gambling or poor investment, and social inappropriateness such as inappropriate jokes or laughter, or sexually inappropriate behaviour (Piguet et al., 2011). Apathy describes symptoms of 'emotional blunting' or lack of positive affect, with patients often displaying lethargy and a disinterest in activities or hobbies that previously engaged them (Convery et al., 2019; Piguet et al., 2011). A lack of sympathy and/or empathy often relates to a lack of understanding for other's physical or emotional state, for example they may demonstrate a lack of concern or inappropriate response like laughing when a child is crying (Convery et al., 2019; Piguet et al., 2011). Stereotypic, compulsive or ritualistic behaviours can include repetitive movements such as rubbing or tapping, as well as more ritualistic acts like hoarding (Convery et al., 2019; Piguet et al., 2011). Hyperorality often refers to binge eating or drinking, and dietary preferences can alter to include a preference for sweet food (Convery et al., 2019; Piguet et al., 2011). A lack of insight into one's own behaviour is also characteristic of bvFTD, making diagnostic processes difficult, lengthy and often reliant on the observations of family members (Convery et al., 2019). As such, prior to diagnosis, individuals with bvFTD commonly experience misdiagnosis with other conditions such as depression, and marital issues or 'mid-life crises' are often cited as explanations for early behavioural changes (Ducharme et al., 2015; Zapata-Restrepo et al., 2021).

Primary progressive aphasias

Non-fluent variant PPA

NfvPPA, otherwise known as progressive non-fluent aphasia (PNFA), is characterised by 'effortful' speech production which is often agrammatic and involves impaired motor speech production (apraxia); however single word comprehension and object naming remain intact (Convery et al., 2019; Gorno-Tempini et al., 2011). As a result of agrammatism, patients with nfvPPA tend to find sentence construction challenging, instead using short phrases without the use of connecting words (Convery et al., 2019; Mesulam, 2003; Rohrer et al., 2007). Binary reversals may also be observed in nfvPPA whereby when asked a 'yes/no' question or one with binary response options, the intended response is reversed i.e. saying 'yes' instead of 'no', or a 'stock' phrase is used (Convery et al., 2019; Warren et al., 2016). As the disease progresses speech

production deteriorates, sometimes to mutism (Convery et al., 2019; Gorno-Tempini et al., 2004). Language comprehension is also affected, beginning with grammatically complex sentences, and progressing over time to a lack of comprehension of simple conversational speech (Convery et al., 2019; Grossman, 2005; Mesulam, 2003).

Semantic variant PPA

The hallmark feature of svPPA is reduced semantic knowledge leading to naming difficulties (anomia) and word comprehension (Rohrer et al., 2008). Semantic naming impairment commonly begins with higher level, more specific and less frequent words and objects e.g. ostrich, progressing over time to include more commonly used words and objects, as well as broader concepts e.g. bird (Convery et al., 2019; Hoffman et al., 2014). Speech is typically fluent, however can be difficult to interpret.

Logopenic variant PPA

Patients with lvPPA present with slow, hesitant speech with lengthy pauses as they search for the correct word. Speech is non-fluent as a result of pauses, as well as continuous rewording of phrases (Gorno-Tempini et al., 2004, 2008, 2011). Single word repetition and semantic knowledge is preserved, however ability to repeat phrases or sentences is impaired (Convery et al., 2019). Patients may exhibit phonological errors, e.g. changing a single sound in a word e.g. ‘octogus’ instead of ‘octopus’, or omission of part of a word e.g. ‘slee’ instead of ‘sleep’ (Croot et al., 2012; Gorno-Tempini et al., 2008). Orofacial praxis remains well preserved and grammar is often simple but correct (Gorno-Tempini et al., 2008). Although lvPPA falls within the category of PPA, there is often underlying Alzheimer’s disease (AD) pathology, therefore it is considered an atypical form of AD, rather than part of the FTD spectrum (Ahmed et al., 2012; Rohrer et al., 2012).

Motor syndromes

Motor Neurone Disease and Frontotemporal Dementia–Motor Neurone Disease

FTD can also present initially with ALS, the most common form of MND, presenting with progressive muscle weakness, atrophy and muscle fasciculations affecting the

limbs or the bulbar muscles usually. If it affects the latter it may also cause dysarthria and dysphagia (Abramzon et al., 2020; Hobson et al., 2016). ALS may occur alone but about 15% of people will develop FTD symptoms (FTD-ALS), most commonly bvFTD (Strong et al., 2017). Studies estimate that up to 50% of individuals with ALS develop behavioural or cognitive impairment without meeting criteria for FTD (ALS-bi or ALS-ci for behavioural and cognitive impairment) and up to 30% of individuals with FTD develop motor dysfunction not meeting criteria for ALS (Burrell et al., 2011; Strong et al., 2017).

Atypical parkinsonism

FTD can also present as, or overlap with atypical parkinsonian disorders, such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). PSP (Richardson's syndrome) commonly presents with frequent falls, axial rigidity and postural instability with a supranuclear gaze palsy (Baizabal-Carvallo & Jankovic, 2016; Steele et al., 1964). CBS typically causes asymmetric rigidity and limb apraxia, focal dystonia, cortical sensory loss and myoclonus, as well as the alien limb phenomena (Baizabal-Carvallo & Jankovic, 2016; Chahine et al., 2014). Atypical parkinsonian syndromes co-occur most commonly with bvFTD (Siuda et al., 2014), however less commonly they may also co-occur with PPA, usually overlapping with nfvPPA (Peterson et al., 2021; Rohrer et al., 2010).

Neuropsychiatric presentations

FTD symptomatic presentations may also overlap with several primary psychiatric disorders (Ducharme et al., 2015) posing a diagnostic challenge. Psychotic symptoms can also be prominent presenting factors, including delusions, often delusions of persecution, and hallucinations (Snowden, 2023), and negative psychotic symptoms such as social and emotional withdrawal, blunted affect and formal thought disorders (Gossink et al., 2017). Neuropsychiatric symptoms have been identified in up to 46% FTD mutation carriers, and at all disease stages, across all disease groups, as well as in pathologically confirmed post-mortem cases (Landqvist Waldö et al., 2015; Samra et al., 2023).

Heritability

FTD is a highly heritable disorder but, almost uniquely within the neurodegenerative disease spectrum, it is neither purely genetic (like Huntington's disease, HD) nor a mainly sporadic condition, i.e. occurring unpredictably, without a discernible genetic cause (like Alzheimer's disease) (Figure 1). Most case series suggest that around one-third of people will have FTD due to a pathogenic mutation with the remaining two-thirds considered to have sporadic disease (Goldman et al., 2005; Rohrer et al., 2009).The extent of heritability of FTD has been the subject of a number of studies, with many of the initial investigations relying on the dichotomy between a 'present' or 'absent' family history. However, more nuanced family history scoring systems have been developed for FTD (Beck et al., 2008a; Rohrer et al., 2009; Wood et al., 2013) revealing a complex picture of heritability. Using the modified Goldman score (Beck et al., 2008b; Rohrer et al., 2009) a strong family history [scores of one to three] was found in 31% (Rohrer et al., 2009), whilst using the Penn score an equivalent strong family history [high or medium categories] was found in 26% (Wood et al., 2013). All of these studies show variability in heritability across the clinical phenotypes e.g. a strong family history has been found in 48% of people with bvFTD but only 12% of people with PPA (Wood et al., 2013). Heritability of the motor phenotypes is less clear (mainly due to small numbers in most studies) e.g. a strong family history has varied from 10 to >40% in FTD-ALS (Goldman et al., 2005; Po et al., 2014; Rohrer et al., 2009).

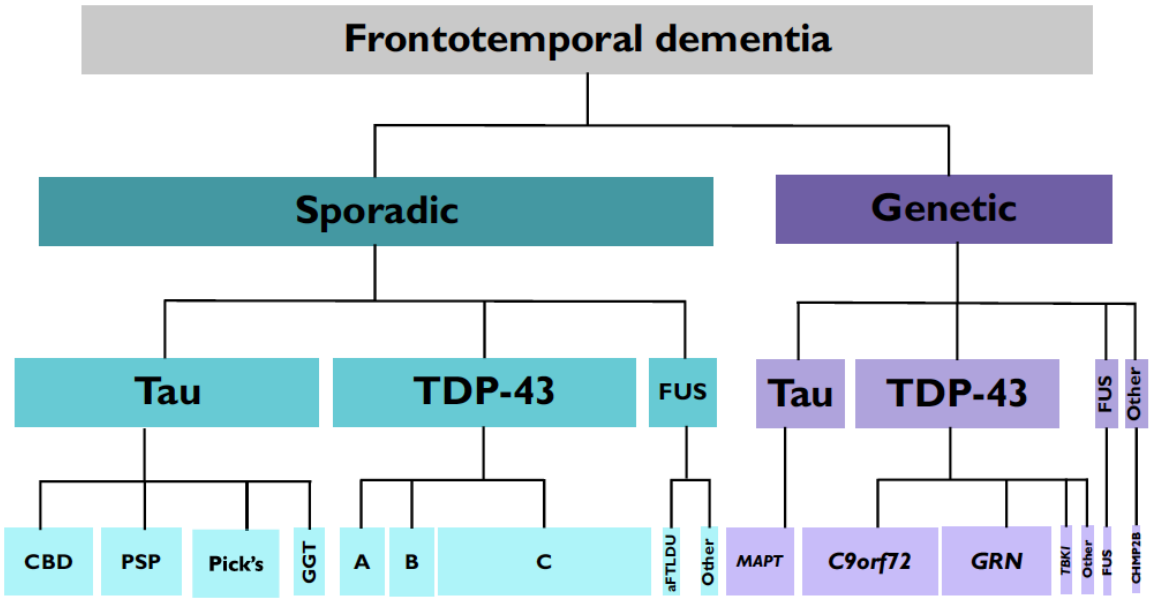


Figure 1 - The landscape of the frontotemporal dementia spectrum disorders. About

70% is sporadic with approximately equal numbers of TDP-43 proteinopathies and tauopathies (including corticobasal degeneration, CBD progressive supranuclear palsy, PSP Pick's disease, GGT globular glial tauopathy), and a smaller number of FUSopathies (including atypical frontotemporal lobar degeneration *with ubiquitin inclusions, aFTLDU). About 30% is genetic with TDP- 43 proteinopathies being the commonest cause (mutations in C9orf72 (usually TDP-43 types A or B), GRN (type A), TBK1 (types A or B), VCP (type D), SQSTM1, and TARDBP) then tauopathies (mutations in MAPT), FUSopathies (mutations in FUS) and other proteinopathies (mutations in CHMP2B)*

Variability of heritability by clinical phenotype

BvFTD is the most heritable of the FTD syndromes. Around 34–58% of those with a diagnosis of bvFTD are considered to have a 'strong family history' (modified Goldman score of one to three or 3.5) (Po et al., 2014; Rohrer et al., 2009). The heritability of FTD-ALS is poorly studied, with wide variation in different case series, all of which have been very small. Goldman et al., (2005) found that FTD-ALS displayed a higher percentage of autosomal dominant inheritance than other phenotypes (37%) and a strong family history (modified Goldman score of one to three) in 59% of cases. Rohrer et al., (2009) found only 10% of FTD-MND to be considered familial, while Po et al., (2014) found 22% of those with FTD-ALS to have a strong family history. PPA is much less heritable than bvFTD or FTD-ALS. The most heritable form of PPA is nfvPPA [6.9% autosomal dominant inheritance (Goldman et al., 2005) and 30-34.5% with a strong family history (Goldman et al., 2005; Rohrer et al., 2009)]. The incidence of genetic mutations in svPPA is very low [1.9% autosomal dominant (Goldman et al., 2005) although 17-22% have a strong family history (Goldman et al., 2005; Rohrer et al., 2009)]. LvPPA is most commonly due to AD, and if biomarker positive for AD, an FTD-causing mutation would not be expected. The fourth group of PPA-NOS is poorly understood, although in some reports, *GRN* mutations are associated with this mixed PPA phenotype. Similarly to PPA, CBS and PSP are less heritable than the other phenotypes, however CBS still has a considerable percentage of autosomal dominant inheritance [6-9% (Goldman et al., 2005; Rohrer et al., 2009) and between 37% and 53% heritability in those with a strong family history (Goldman et al., 2005; Rohrer et al., 2009)]. PSP is less heritable than CBS, [5.6% autosomal dominant (Goldman et al., 2005) and 33% with a strong family history (Goldman et al., 2005; Rohrer et al.,

2009)].

There are a number of combined phenotypes where heritability is even less clear. Rohrer et al., (2009) found autosomal dominant inheritance in 13% of those with a combined PNFA-CBS phenotype and 38% with a strong family history. Tan et al., (2019) report an underacknowledged heritability of PPA-ALS. 12% of the cohort of individuals with PPA were found to also fulfil diagnostic criteria of ALS. A strong family history was identified in 57% of this subset, compared to 10% of those without ALS. This was largely driven by the overlap of nfvPPA-ALS rather than svPPA-ALS and of the nfvPPA sample, 60% were found to have the *C9orf72* expansion. However, these results are based on small sample sizes.

Due to the wide-ranging clinical presentations seen within the FTD spectrum, individuals can present to a variety of clinical services, most commonly, cognitive neurology, movement disorders and psychiatric services. As such, FTD can often be misdiagnosed as other disorders depending on an individual's clinical phenotype. Therefore, there is likely a large under-ascertainment of cases. In addition to this, due to age related penetrance in FTD, there may also be an underestimation of risk, meaning many more families may be at-risk of fFTD than previously thought.

Genes

The majority of the heritability of FTD is accounted for by autosomal dominant mutations in three genes: progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*) (Mahoney et al., 2012; Snowden et al., 2012). Each genetic group causes between ~5-10% of all FTD, with geographical variability in different case series (e.g. a predominance in Northern Italy and the Basque country of *GRN* mutations (Barandiaran et al., 2012; Borroni et al., 2011). Overall, *C9orf72* seems to be the most common worldwide cause of genetic FTD, followed by *GRN* and then *MAPT*: a recent international study found 41.3% of FTD mutations were in the *C9orf72* group, 34.8% in the *GRN* group, and 23.9% in the *MAPT* group (Moore et al., 2020). A list of pathogenic and other variants in these genes has been collated online: 184 *GRN* and 78 *MAPT* pathogenic variants are currently described (FTDtalk, n.d). This number excludes the majority of missense variants in *GRN*, many of which may be risk factors for Alzheimer's disease rather

than a Mendelian cause of FTD, although identifying pathogenicity is not always easy (Redaelli et al., 2018).

In recent years, mutations in an increasing number of genes have been associated with autosomal dominant FTD: *VCP* (2004), *CHMP2B* (2005), *TARDBP* (2008), *FUS* (2009), *SQSTM1* (2012), *CHCHD10* (2014), *TBK1* (2015), *OPTN* (2015), *CCNF* (2016), *TIA1* (2017). Cumulatively they account for less than 5% of all FTD, with most only found in a small number of families across the world. Recent studies have identified *TANK-binding kinase 1 (TBK1)* as the third most common cause of familial FTD-TDP pathology and likely the fourth overall most common cause of genetic FTD (Freischmidt et al., 2017; Pottier et al., 2015), accounting for between 1-2% of all cases (although the pathogenic nature of many of the reported missense variants remains unclear . *TBK1* is a loss of function mutation, resulting in a 50% depletion of the TBK1 protein.

The missing heritability of FTD

Case series show that testing for all known FTD-causing genes does not find a genetic cause for all people with an autosomal dominant genetic FTD phenotype (de Majo et al., 2018; Po et al., 2014). Some patients with a behavioural presentation of dementia have mutations in one of the familial Alzheimer's disease genes (often *Presenilin 1*) (Mendez & McMurtray, 2006). There are also people who have mutations in the *CSF1R* gene and other leukodystrophies who present with dementia with prominent behavioural symptoms (Sundal et al., 2012), but usually the presence of extensive white matter disease on brain imaging leads away from an FTD diagnosis (Ahmed et al., 2013; Zhuang et al., 2020). Nonetheless, there remain some families with an autosomal dominant FTD syndrome without a known genetic cause.

Age at onset and disease duration

Age at symptom onset is variable in each of the genetic forms of FTD, with intrafamilial variability (even within the same generation) of at least a decade in some families (particularly *GRN*). The question of how age at onset and disease duration varies in genetic FTD has been investigated for the main FTD-causing genes *C9orf72, GRN* and *MAPT* in a recent large international study (Moore et al., 2020). Mean age at onset of symptoms was youngest in the *MAPT* group (49.5 years) followed by *GRN* (61.3)

and *C9orf72* (65.3) and individual age at onset correlated with parental age at onset and mean family age at onset, with the strongest correlation in the *MAPT* group (r=0.45 [parental age at onset] and r=0.63 [mean familial age at onset]) followed by *C9orf72* (r=0.32, r=0.36) and *GRN* (r=0.22, r=0.18). Mean disease duration was shortest in the *C9orf72* group (6.4 years), followed by the *GRN* group (7.1 years) and then the *MAPT* group (9.3 years). Correlations were not strong enough to predict age at symptom onset in presymptomatic individuals for *C9orf72* expansions and *GRN* mutations, however mean familial age at onset may be used as guidance to predict age at onset in asymptomatic *MAPT* carriers. Therefore, within the most common genetic causes of FTD, age at symptom onset can be wide ranging and parental and mean family age at onset are unpredictable predictors of individual age at onset in asymptomatic mutation carriers.

Age related penetrance and modifying factors

Whilst *MAPT* mutations are fully penetrant in most cases, both *GRN* (Gass et al., 2006a) and *C9orf72 (Murphy et al., 2017a)* mutations exhibit age-related penetrance with a small number of carriers in their 80s (and 90s) yet to develop symptoms. In both *GRN* and *C9orf72* mutation carriers, *TMEM106B* has been identified as a genetic modifier, the association being stronger with *GRN* than with *C9orf72* (Nicholson & Rademakers, 2016): a lower age at onset in *GRN* may well be related to carrying the risk allele, with homozygous carriers of the protective allele rarely found in symptomatic *GRN* carriers, suggesting this may be a factor in age-related penetrance (Pottier et al., 2018). Another recently identified modifier of disease risk in *GRN* carriers, *GFRA2*, did not seem to affect age at onset (Pottier et al., 2018). However, a study of *C9orf72* carriers identified a locus on chromosome six containing two overlapping genes (*LOC101929163* and *C6orf10*) in which a polymorphism at rs9357140 was associated with age of onset: median age of onset in GG carriers was six years earlier than AA carriers (Zhang et al., 2018). The significance of the *C9orf72* repeat expansion length remains unclear, with no definitive evidence of an association with age of onset (Fournier et al., 2019). Little is known about factors that modify of age at onset in the *MAPT* group although a recent study suggested that ApoE ε4 carriers had a lower age at onset in tauopathies including *MAPT* mutations (Koriath et al., 2019).

Phenotypic heterogeneity within mutation groups

The most common clinical presentation of all genetic forms is bvFTD, but all phenotypes within the FTD spectrum are observed and differences in clinical presentation exist between the different genetic groups. Phenotypic heterogeneity can also be observed not only within each mutation but also within families.

MAPT

MAPT mutation carriers may have prominent semantic impairment alongside behavioural impairment, but that is rarely a presenting feature, nor are other forms of PPA; however, CBS (1.8%, Moore et al., 2020) and, in rare cases, PSP (4.2%, Moore et al., 2020) may both occur, although never FTD-ALS.

GRN

In contrast, *GRN* mutations can present as a PPA syndrome in 13.6% cases, either a nonfluent variant of PPA (9.1% cases) or a mixed phenotype (PPA-NOS) not clearly fitting in to one of the three described subtypes (3.1% cases). CBS can be observed with *GRN* mutations in around 4% of cases while PSP is rare (0%) (Beck et al., 2008b; Moore et al., 2020; Yu et al., 2010). CBS may occur either alone or in conjunction with PPA, but PSP and FTD-ALS are almost never seen.

C9orf72

C9orf72 expansion carriers may have an atypical neuropsychiatric presentation of bvFTD with associated hallucinations or delusions, in some cases leading to an initial primary psychiatric diagnosis (Devenney et al., 2018; Ducharme et al., 2017), and significantly, family members of *C9orf72* carriers have a greater risk of developmental and psychiatric disorders including autistic spectrum disorders, psychotic illnesses including schizophrenia, mood disorders and suicide (Devenney et al., 2018). Unlike the other two major genetic groups *C9orf72* expansions can cause FTD-ALS or ALS alone (DeJesus-Hernandez et al., 2011). PPA is a rare phenotype but is usually a nonfluent variant when present, and similarly parkinsonian disorders can occur but are infrequent as a presenting syndrome. Atypical parkinsonian disorders are rare with CBS being seen infrequently and even less so, PSP (Lesage et al., 2013; Moore et

al., 2020; Schottlaender et al., 2015; Wilke et al., 2016). Also unlike the other genetic groups, hyperkinetic movement disorders may occur, and *C9orf72* is said to be associated with a Huntington's disease-like phenotype on some occasions (Bourinaris & Houlden, 2018; Dewan et al., 2021; UK Huntington's Disease Prediction Consortium et al., 2016). 1.95% of HD phenocopy cases in a UK cohort were found to carry the mutation, making it the most common cause of an HD phenocopy syndrome (Hensman Moss et al., 2014) .

The phenotypic picture in the other, less common, genetic groups is less clear. *TBK1* mutations can cause bvFTD, PPA, CBS, FTD-ALS and ALS alone – this unique combination within a single family can be particularly suggestive of a *TBK1* mutation (Gijselinck et al., 2015; Swift et al., 2021; Van Mossevelde et al., 2016). In those with a diagnosis of FTD, disinhibition is commonly a prominent feature and early memory loss also observed (Van Mossevelde et al., 2016). *TBK1* and *TARDBP* mutations can both be associated with focal temporal lobe atrophy and semantic variant PPA (Caroppo et al., 2015; Floris et al., 2015; Koriath et al., 2017), an unusual genetic FTD phenotype as this variant of PPA is almost always sporadic. As with the more common genetic causes of FTD, bvFTD is a common *VCP* associated phenotype, however symptoms such as dysnomia, dyscalculia, paraphasic errors and later alexia and agraphia can also be observed . Again, in *SQSTM1* mutation carriers, the most common FTD phenotype observed was bvFTD, with concomitant FTD-ALS also observed . *CHMP2B* is largely associated with bvFTD (Skibinski et al., 2005), ALS has also been reported with *CHMP2B* (Cox et al., 2010; Parkinson et al., 2006). The *FUS* gene is most commonly associated with ALS, however there are infrequent cases of FTD-ALS linked to *FUS* mutations (Broustal et al., 2010). A small number of studies have also discovered *FUS* mutations in patients diagnosed with bvFTD and CBS (Huey et al., 2012; Van Langenhove et al., 2010).

1.3. Natural history studies and biomarkers

Until recently, clinical studies of genetic FTD have been small and single centre. However, the Genetic FTD Initiative (GENFI) started recruiting in 2012 and now encompasses 44 centres across Europe and Canada. This is a natural history study with detailed phenotyping of both presymptomatic and symptomatic mutation carriers (Rohrer et al., 2015). In the US, a similar study (ARTFL/LEFFTDS) has been running

for the last few years. Collaboration across natural history studies of genetic FTD across the world has started through the creation of the FTD Prevention Initiative, aiming to share information and inform future clinical trial design. Much of the work being performed in these studies (and in other single centre investigations) over the last few years has aimed to develop validated biomarkers that robustly measure disease onset, staging and progression (Figure 2). The following sections highlight recent work in this field.

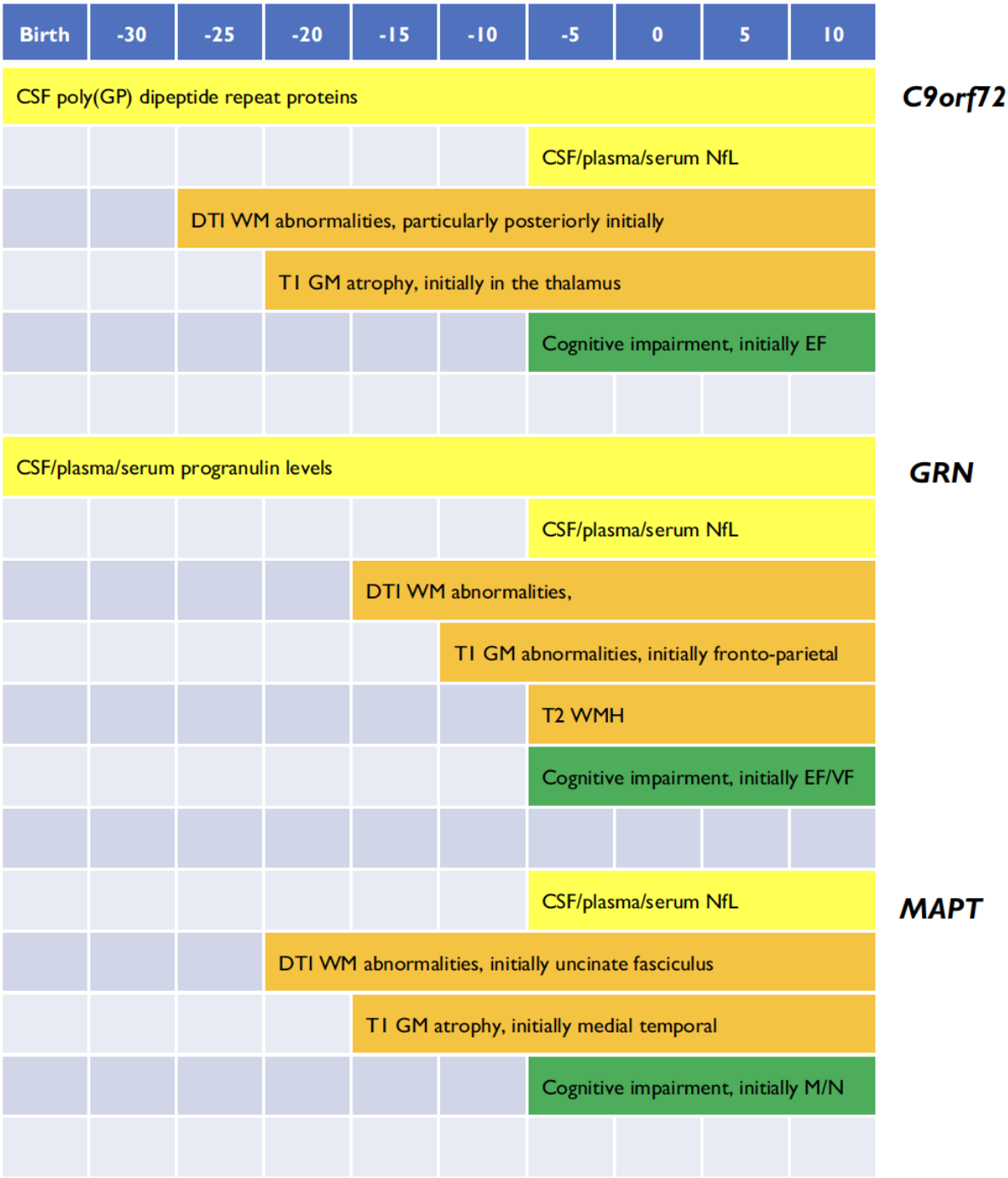


Figure 2 - Schematic of fluid, imaging and cognitive biomarker profiles across the lifespan of *C9orf72*, *MAPT* and *GRN* mutation carriers. NfL neurofilament light chain, DTI diffusion tensor imaging, WM white matter, WMH white matter hyperintensities, GM grey matter, EF executive function, VF verbal fluency, M memory; N naming

Cognition

Neuropsychometric measures are abnormal in presymptomatic carriers around five years prior to expected symptom onset (Rohrer et al., 2015). Whilst executive function deficits seem common across the different genetic groups, specific patterns of cognitive decline have been identified at a presymptomatic stage in *MAPT*, *GRN* and *C9orf72* mutation carriers (Rohrer et al., 2015). A number of studies have now shown that *MAPT* mutation carriers have both naming and episodic memory difficulties presymptomatically (Cheran et al., 2019; Jiskoot et al., 2018; Rohrer et al., 2015), consistent with early medial temporal lobe atrophy (Rohrer et al., 2015). As mentioned above, whilst most people develop bvFTD, some develop PPA, and one study has shown that longitudinal preclinical decline on phonology and letter fluency tasks was predictive of conversion to a nonfluent variant PPA phenotype in *GRN* carriers (Jiskoot et al., 2018).

Neuropsychiatric and functional measures

Validated measures of psychiatric symptoms or functional decline are limited in genetic FTD. The Neuropsychiatric Inventory (NPI) has been the most studied, although was not designed with FTD in mind, and does not include all relevant psychiatric symptoms that are seen in FTD (Premi et al., 2016). The Cambridge Behavioural Inventory (CBI) has been used in the GENFI study and has shown changes in proximity to symptom onset (Rohrer et al., 2015), although as with many behavioural questionnaires there can be variability over time in FTD. More specific measures of particular symptoms such as loss of empathy (e.g., the Interpersonal Reactivity Index) or impaired self-monitoring (e.g., the Revised Self-Monitoring Scale) have not yet been well studied in genetic FTD. In terms of measuring disease severity and decline in function over time, an adaptation of the Clinical Dementia Rating scale for FTD (commonly called the CDR plus NACC FTLD) shows promise in genetic FTD (Premi et al., 2016), as does the FTD Rating Scale (FRS) (Mioshi et al., 2010), but more detailed studies of these and other novel measures are required.

Imaging

Grey matter atrophy and hypometabolism both appear to occur at least 10 years before symptom onset in genetic FTD, whilst white matter tract abnormalities are seen earlier (Meeter et al., 2017). However, there is variability both in timing and location between the different genetic groups.

Grey matter atrophy (T1-weighted MRI)

In presymptomatic *MAPT* mutation carriers atrophy is present about fifteen years prior to symptom onset in the anterior and medial temporal lobes, orbitofrontal lobe and insula (Cash et al., 2018; Rohrer et al., 2015), whilst in *GRN* mutation carriers, presymptomatic atrophy can be observed in frontal, parietal, and insular cortex as well as the striatum around ten years prior to symptom onset (Cash et al., 2018; Rohrer et al., 2015). Symptomatic *GRN* mutation carriers commonly have a very asymmetrical pattern of brain atrophy, and this asymmetry can be observed around five years prior to onset (Rohrer et al., 2015). *C9orf72* mutation carriers appear to have earlier grey matter volume loss than the other two groups, before the age of 40 (Bertrand et al., 2018), and potentially more than 25 years prior to symptom onset (Rohrer et al., 2015). This appears to be particularly focused on the posterior thalamus and its cortical connections (Bertrand et al., 2018; Cash et al., 2018; Rohrer et al., 2015).

Volumetric MRI studies of genetic FTD have particularly highlighted the importance of subcortical structures in the pathogenesis of FTD, and more recent work using novel postprocessing techniques has aimed to study the subregions within these structures e.g. there are differential patterns of atrophy within hippocampal subregions in the different genetic groups: *MAPT* mutation carriers had involvement of CA1-4, *C9orf72* expansion carriers CA4, CA1 and the dentate gyrus, and *GRN* mutation carriers the presubiculum and subiculum (Bocchetta et al., 2018).

There has been less focus on longitudinal investigation of grey matter atrophy, however, rates of atrophy vary between genetic groups with faster rates in *GRN* mutation carriers during the symptomatic period (allowing measurement over short time periods: (Sha et al., 2017) compared with the other groups. Around the time of symptom onset, there seems to be a more gradual progression of atrophy in *MAPT* mutation carriers but a rapid change in volume loss in *GRN* mutation carriers (Jiskoot

et al., 2019).

Few studies have investigated disease staging of genetic FTD. One novel machine-learning methodology combining subtyping and staging identified genetic FTD subtypes and their stages over time from structural T1-weighted imaging alone (Young et al., 2018). Interestingly, whilst *GRN* and *MAPT* mutation carriers appeared to fall mainly into a single group, there were two distinct patterns of disease progression for *C9orf72* expansion carriers – it remains unclear pathophysiologically what differs between these two groups.

White matter hyperintensities (T2-weighted MRI)

A number of studies have now shown that white matter hyperintensities (which are generally an unusual finding in FTD) are characteristic of *GRN* mutations (Caroppo et al., 2014; Sudre et al., 2019). This is mainly in symptomatic mutation carriers (although for unclear reasons only a subset of patients), but there is also an association in presymptomatic mutation carriers with time from expected symptom onset (Sudre et al., 2019). Pathological studies of these white matter hyperintensities suggest they are not vascular but are associated with prominent white matter microglial activation and microglial dystrophy (Woollacott et al., 2018).

Hypometabolism (FDG-PET)

Patterns of hypometabolism commonly mirror the pattern of grey matter atrophy in genetic FTD (Caroppo et al., 2015; Cistaro et al., 2014; Deters et al., 2014; Diehl-Schmid et al., 2019; Jacova et al., 2013), with presymptomatic deficits also shown around ten years prior to symptom onset.

Structural connectivity (DTI)

Changes in white matter integrity are commonly measured with diffusion tensor imaging (DTI), although newer techniques such as neurite orientation dispersion and density imaging (NODDI) have recently been developed. Studies in genetic FTD suggest that changes can be observed as far back as 30 years prior to symptom onset (Jiskoot et al., 2018). As with grey matter atrophy there appear to be distinct patterns of early white matter involvement in the different groups: presymptomatic *MAPT*

mutation carriers have alterations in the uncinate fasciculus and parahippocampal cingulum while *GRN* mutation carriers show involvement of the anterior and posterior internal capsule (Jiskoot et al., 2018). Presymptomatic *C9orf72* expansion carriers have earlier white matter tract pathology, which occurs in posterior tracts such as the posterior thalamic radiation, the posterior corona radiata and the splenium of the corpus callosum (Jiskoot et al., 2018; Lee et al., 2017). A single study of NODDI suggests it may be more sensitive than DTI for detecting early white matter change in *C9orf72* expansion carriers (Wen et al., 2019).

Functional connectivity (resting state fMRI)

There have been fewer investigations of functional connectivity but small studies implicate particularly the salience network and a medial pulvinar thalamus-seeded network in presymptomatic *C9orf72* expansion carriers (Lee et al., 2017), the default mode network in *MAPT* mutation carriers (Whitwell et al., 2011) and a frontoparietal network in *GRN* mutation carriers (Dopper, 2014; Pievani et al., 2014; Premi et al., 2014).

Tau PET

Studies of novel radioligands developed to bind tau protein have so far not proven to be particularly helpful in FTD, binding much more strongly to paired helical filament (PHF)-tau found mainly in Alzheimer's disease than to other forms of tau found in the primary tauopathies. However, two particular *MAPT* mutations (V337M and R406W) are associated with PHF-tau and have shown strong binding with the AV1451 tracer (Jones et al., 2018; Smith et al., 2016; Spina et al., 2017). Unfortunately, there is also off-target binding of this tracer, with binding seen in non-tau diseases such as in *C9orf72* expansions, where the major pathology is TDP-43 (Bevan-Jones et al., 2018).

Blood and CSF biomarkers

The fluid biomarker field in genetic FTD has yet to identify many robust measures, e.g., neither CSF nor blood assays of tau or TDP-43 are yet to yield FTD-specific markers. However, recent work has identified three markers which will play an important role in forthcoming trials: neurofilament light chain (NfL), progranulin and poly(GP) dipeptide repeat proteins (DPRs).

Increased NfL levels (both in CSF and blood) reflect axonal damage and appear to be a measure of disease intensity and predict progression and survival in genetic FTD . Levels are highest in *C9orf72*-associated ALS and lowest in *MAPT* mutation carriers (Meeter et al., 2016). Longitudinal analysis of samples seems to suggest that levels change not long prior to symptom onset in genetic FTD, increasing by three- to four-fold during conversion (Meeter et al., 2016). Whilst an increase in NfL is not specific for FTD, and levels are increased in multiple neurological diseases, evidence from other diseases suggests a decrease in levels could be a measure of successful disease modification in trials (Winter et al., 2019).

Low serum, plasma or CSF progranulin levels have almost perfect sensitivity and specificity for detecting pathogenic *GRN* mutations (Galimberti et al., 2018; Meeter et al., 2016). Levels are low from the earliest time period of presymptomatic genetic FTD that they have been measured [during adulthood] and are relatively stable over time (Meeter et al., 2016). CSF and plasma levels are relatively poorly correlated (r=0.54: Meeter et al., 2016), and little work has been done to investigate measures that affect the variability of progranulin levels. This future research is important as increasing progranulin levels back towards normal levels (and therefore theoretically restoring normal progranulin function) will be a key biomarker for disease modifying trials in *GRN* carriers.

Increased poly(GP) levels have been identified in the CSF of *C9orf72* expansion carriers both presymptomatically and symptomatically (Gendron et al., 2017; Lehmer et al., 2017; Meeter et al., 2018). One study found slightly lower levels in presymptomatic expansion carriers compared with symptomatic carriers (Meeter et al., 2018) but that has not been seen consistently. More work needs to be performed to understand variability further, but like NfL, decreasing levels of CSF poly(GP) post-treatment may be suggestive of disease modification in future trials.

A particular focus of biomarker research in genetic FTD is the development of markers of neuroinflammation. CHIT1 and YKL-40 are microglial markers that appear to be raised in symptomatic genetic FTD (Oeckl et al., 2019) with little evidence for a change during the presymptomatic period so far. In a small study, CSF sTREM2 levels were raised in *GRN* mutation carriers but not the other genetic groups (Woollacott et al., 2018).

1.4. The ‘at-risk’ and presymptomatic phases of FTD

Due to autosomal dominant inheritance patterns, the children and siblings of an individual with a diagnosis of FTD who has a confirmed pathogenic FTD mutation, live with 50% risk of carrying that mutation themselves. As discussed above, the main FTD mutations are almost fully penetrant, therefore those at-risk individuals who inherit the genetic mutation will expect to develop symptoms of FTD at some point during their lifetime (Woollacott & Rohrer, 2016). Those with 50% risk of an FTD mutation are broadly referred to as ‘at-risk’. This provides the opportunity to study the pre-symptomatic phase of the disease in those who are mutation carriers (also referred to as presymptomatic or asymptomatic), using their non-carrier siblings as a natural family control group. Extrapolating from research in HD, estimates suggest that around 20% of individuals at-risk undergo predictive testing in order to learn their mutation status (Craufurd et al., 1989; Quaid et al., 2008), therefore the majority of at-risk individuals live with this risk for much of their lives. Although individuals may have predictive testing to learn their mutation status, a number of key questions still remain; when will symptoms start, what phenotype will present, and what is the expected disease duration? See Figure 3 for a depiction of some important issues faced throughout the time course of familial FTD.

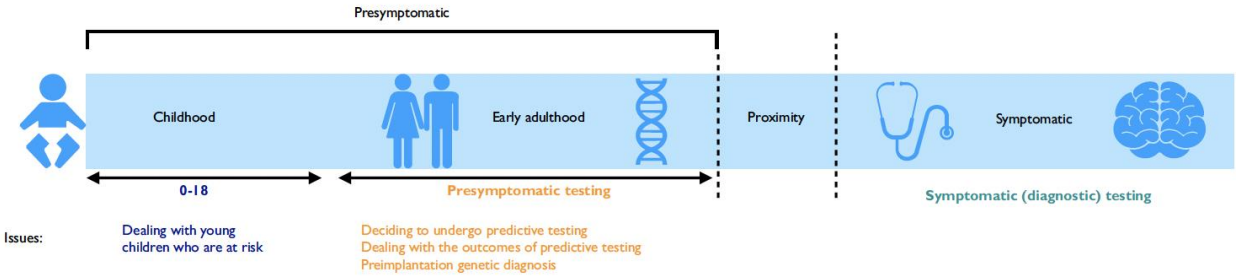


Figure 3 – A depiction of the time course and some important issues faced throughout the stages of genetic FTD. There is commonly a period in proximity to onset of FTD where subtle symptoms may be present but diagnostic testing has not been met – this requires careful assessment and discussion.

There is much to be learnt from studying the presymptomatic disease phase in order to further understanding of FTD as a whole. Despite *C9orf72* dipeptide repeats likely being present from birth, as well as 50% loss of function in progranulin, the disease does not onset until adulthood for reasons currently unknown. Similarly, as displayed

in Figure 2, white matter abnormalities and grey matter atrophy can be observed up to 25 years prior to FTD symptom onset in *C9orf72* mutation carriers and 15-20 years prior in *GRN* and *MAPT*. Changes in cognitive functioning begin to be observed, initially in executive functioning, verbal fluency, memory and naming up to five years prior to symptom onset. Raised neurofilament light-chain (NfL) can also be used as a predictor of disease onset within a period of five years (Rojas et al., 2021).

The at-risk phase of FTD poses some unique challenges for those individuals within it, regardless of mutation status. The lack of certainty regarding mutation status (for those who do not want predictive testing), disease onset, duration, and presenting phenotype can lead to anxiety regarding the future and an inability to plan. In addition, many learn of their risk in early adulthood, and as such having children is an important consideration. Some choose to have children 'traditionally', while others abstain or undergo fertility treatments like preimplantation genetic diagnosis (PGD). However, those who have children prior to learning of their risk may find their children's risk an added concern. For at-risk individuals, their own risk is often not their priority, as commonly they will be involved in the care of a symptomatic parent or relative, which poses many challenges of its own. Therefore, one can understand that this experience may be particularly challenging and overwhelming, with many important factors to consider and manage at once. However, due to the lack of understanding within both the public and many healthcare professionals regarding non-Alzheimer's dementias, support and understanding for the above challenges can be lacking. Recent research by Devenney et al., (2018) also suggests that family members of *C9orf72* mutation carriers may have an increased risk of various psychiatric and developmental disorders such as autistic spectrum disorder (ASD), schizophrenia and psychosis. Thus, it may be expected that living at-risk is a psychologically challenging experience. However, there has been little research to investigate this within those at-risk of FTD.

1.5. Genetic testing in FTD

Diagnostic genetic testing, otherwise known as symptomatic genetic testing, is available for symptomatic individuals with a diagnosis of FTD, and predictive genetic testing for individuals with a 50% risk of fFTD (i.e., a symptomatic first degree relative). There are many complex implications of both diagnostic and predictive testing for not only the individual themselves, but also for their wider family and future generations.

These issues are introduced below and discussed throughout this thesis.

1.5.1. Diagnostic genetic testing

Testing in symptomatic patients with dementia has changed in recent years. Next generation sequencing (NGS) or whole genome sequencing (WGS) panels are now available to test multiple genes at the same time (Koriath et al., 2018). Issues that remain to be solved in clinical genetic testing include: how to decide the pathogenicity of certain variants (of which more are now found because of NGS and WGS); the exact length at which *C9orf72* expansions become pathogenic (as intermediate length expansions are not clearly causative of disease (Ng & Tan, 2017); and what to do when no mutation is found in a family with autosomal dominant FTD.

Diagnostic testing is an important element of clinical care for many families, as this is often the first step to confirming a mutation within a family. The decision to have diagnostic testing is not an easy one and issues often arise from complex family dynamics and differing opinions, therefore careful counselling from healthcare professionals can be vital. This process often holds the key to allow for predictive testing in other relatives, therefore, it is important to ensure a systematic approach in terms of to whom diagnostic testing should be offered, in order to prevent additional barriers to predictive testing in future. Another important implication of diagnostic testing for families has come with the advent of preimplantation genetic diagnosis (PGD), a process similar to invitro fertilisation (IVF), which allows for genetic screening of embryos of a confirmed mutation carrier and implants only mutation negative embryos – ensuring a mutation negative child. In order to qualify for PGD on the NHS in the UK a number of criteria must be satisfied and it can be a lengthy process to confirm a mutation via diagnostic testing, and then again using predictive testing in order to begin the PGD process. As such, timely information regarding a potential genetic diagnosis within a family, and information on PGD can provide families with increased hope and choice regarding their future. For the individual themselves, a confirmed genetic mutation does not affect clinical care at the current moment, however in recent years there has been significant progress in clinical trials of potential disease halting or modifying treatments. Therefore, genetic testing may open up the possibility for the individual to participate in clinical trials, or in future, receive a potential therapy.

1.5.2. Presymptomatic genetic testing

Once a causal mutation has been established in a symptomatic relative, the option of predictive genetic testing can be raised with at-risk family members. While potential treatments for FTD are still lacking, appropriate clinical care for presymptomatic populations is fundamental. The genetic counselling and support systems in place lag far behind those seen in other neurodegenerative disorders. Whilst in practice the HD predictive genetic testing protocol is currently used as the gold standard (MacLeod et al., 2013), there are a number of key distinctions between HD and FTD that mean that the HD protocol may not be appropriate for the FTD population (Molinuevo et al., 2005), including age-related penetrance, unpredictable age at onset of symptoms, and phenotypic heterogeneity. Similarly, access, experiences and attitudes towards predictive testing can vary depending on location (Crook et al., 2017), and development of an FTD-specific protocol may be more suitable.

The HD predictive guidelines stress the importance of psychological evaluation in presymptomatic carriers, with others suggesting that psychological assessment is a necessary process for identifying an individual's risk of experiencing an adverse psychological reaction to presymptomatic testing (Goldman, 2015). There remains a large proportion of individuals who live at-risk of FTD who decide against predictive testing – probably about 80% of this population (Rohrer et al., 2015). These individuals receive little or no support as many will not have even been through genetic counselling, and little work has been done to identify their psychological needs. Initial research does suggest that rates of depression and mood disorders are higher within FTD families compared to the general population, even in non-carriers (Cheran et al., 2018). One method of helping such individuals is the provision of specific support groups aimed at providing peer support and information about the at-risk period – the Rare Dementia Support (RDS) familial FTD support group in the UK is one such example (Rare Dementia Support, n.d.). Specific interventions at an appropriate time such as cognitive behaviour therapy have yet to be trialled.

1.6. Clinical trials and emerging therapies

There are currently no disease-modifying therapies for genetic FTD but trials are now underway or planned in each of the three main genetic FTD groups. Early therapeutic

intervention, ideally in the presymptomatic phase when cognitive functioning remains relatively preserved, will likely see the greatest effect, however clinical trials will explore administration within the symptomatic group before moving into presymptomatic use. Antisense oligonucleotide therapy shows promise for both *C9orf72* expansions (Jiang et al., 2016) and *MAPT* mutations (DeVos et al., 2017) whilst adenoassociated viral vector (AAV) gene therapy is a potential avenue for disease modification in *GRN* carriers . Small molecule therapies and tau monoclonal antibodies are also being developed for tauopathies (with a potential for use in *MAPT* mutations) (Jadhav et al., 2019), and other options for *GRN* mutations include modification of proteins such as sortilin and HDAC that lead to increased *GRN* levels (Lee et al., 2014; She et al., 2017). An anti-sortilin monoclonal antibody is currently in phase 3 of clinical trials, now recruiting mutation carriers within the presymptomatic phase (U.S. National Library of Medicine, 2023; Rhinn et al., 2022). Alternative therapeutic methods targeting *GRN* are also in active clinical trial phases, including using 'brain shuttle' technology (protein transfer vehicle) to move protein across the blood-brain barrier (Alzforum, 2023; U.S. National Library of Medicine, 2024c). Two gene replacement therapies using AAV carrying a functional copy of *GRN* are also being trialled using administration directly into the cisterna magna (U.S. National Library of Medicine, 2024a,b).

Despite taking huge steps forward in recent years, there are several problems that make developing clinical trials in FTD challenging. Although it is the second most common form of dementia under the age of 65, the relative distribution of symptomatic individuals in *MAPT* and *GRN* mutation groups remains within the hundreds world-wide (Moore et al., 2020), making trials of multiple therapeutic interventions challenging.

In summary, much has been learnt about genetic FTD in the last decade, with the majority of autosomal dominant FTD now accounted for. The development of collaborative international multicentre natural history studies in GENFI and ARTFL/LEFFTDS has brought together researchers and families, and has helped to set the background for clinical trials that are now getting started and being planned. An associated support network for those living at-risk of genetic FTD is important and there is work to be done in improving this, but with the advent of specific gene-targeted

therapeutics there is hope in the community. The development of clinical trials has also brought a new outlook on familial FTD to those families affected, bringing hope of potentially curative treatments for future generations. However, this change may bring new issues in terms of wellbeing, as although promising, success in clinical trials is not guaranteed. In particular, when thinking of and carrying out presymptomatic trials, many individuals may consider learning their mutation status in order to participate. However, if unsuccessful, this information cannot be removed and this, alongside an unsuccessful trial, may pose a significant challenge to the individual. Similarly, a recent clinical trial recruiting presymptomatic individuals defined raised NfL levels as eligibility criteria, therefore providing individuals who passed screening with the estimation that symptoms will develop within five years (U.S. National Library of Medicine, 2023 ; Rojas et al., 2021). Therefore, careful consideration is needed in terms of ensuring the wellbeing of individuals at-risk throughout this process and providing appropriate support to ensure the safety of those involved.

1.7. Thesis rationale

Living at-risk and undergoing predictive testing are undoubtedly psychologically challenging experiences and those who choose not to have predictive testing will live 'at-risk' for many years, often with minimal contact from healthcare professionals. Despite this, due to the relatively rare nature of FTD, there is limited peer and professional support available. This problem is echoed in the HD literature with 38% of young people reporting that they did not have support (Lewit-Mendes et al., 2018). Those supported were rarely supported by genetic or HD specialists and 91% felt that professional support regarding their risk would be helpful (Lewit-Mendes et al., 2018). There is also no provision within the NHS to provide specialist psychological support, meaning that at-risk individuals rely on standard NHS talking therapies pathways to access support, which, is unlikely to be relevant to their unique situation.

In the UK, mental health support is commonly accessed via the primary care pathway, or more recently through self-referral to NHS talking therapies. NHS talking therapies provide a range of evidence based talking therapies designed to support individuals experiencing low mood and anxiety. There are a number of delivery modalities, including self-help resources, group sessions, and one-to-one. NHS talking therapies also work with a range of therapeutic models, most commonly cognitive behavioural

therapy (CBT) but also including models such as interpersonal therapy (IT) and mindfulness-based cognitive therapy (MBCT). While this has been a successful approach to depression and anxiety in the general population, for some at-risk individuals whose mental health is significantly impacted by their risk this may not be appropriate for several reasons. Firstly, as the therapist or psychologist is unlikely to be familiar with FTD, the progress and ultimate success of therapy sessions may rely on the individual educating the therapist on FTD and the associated challenges. A process which at the least may be lengthy and frustrating due to the time-limited nature of such sessions, and at the worst, may require reliving traumatic events. Secondly, due to the therapists' lack of knowledge on the subject they are unlikely to be able to provide any necessary psychoeducation to help the individual manage their adjustment to their risk, or signpost to relevant resources, research or support services that may be able to provide more specialist knowledge. Finally, the approaches and models used within these services may not be appropriate for use in individuals living with genetic risk of fFTD. Although models such as CBT have a substantial evidence base for use in varied populations, there is no evidence regarding efficacy within individuals at-risk of hereditary neurodegenerative conditions (including FTD and Huntington's disease [HD]). Core CBT components like cognitive restructuring, behavioural activation and problem solving may not be suitable for use in this context, as worries experienced are often rational and cannot be modified by behaviour change or restructuring, and many problems reported associated with fFTD do not have solutions. Similarly, perception of CBT may be a barrier to those at-risk, an adept therapist may be able to identify issues in the application of the model and modify their approach to suit the individual. However, as CBT is an established therapeutic approach, there may be preconceived ideas, or misconceptions within the public's idea of CBT that prevent them from engaging with the approach.

Similarly, there may also be issues with genetic counselling and predictive testing for those at-risk of fFTD. The current genetic counselling guidelines are designed for use in HD and therefore counsellors and geneticists who are less familiar with FTD may find it difficult to cover complex topics and issues that are specific to FTD (such as intermediate repeat expansions in *C9orf72*), in appropriate depth. This in turn may lead to a less comprehensive counselling process for those at-risk of FTD compared to diseases such as HD. Additionally, due to the lack of a specific FTD testing protocol,

some important elements of the genetic counselling process, such as post-test support, may be missed.

The recent UK Government dementia strategy (UK Department of Health, 2022), emphasises the need for early diagnosis in dementia, as well as a focus on 'living well with dementia'. Those living at-risk of fFTD, although not experiencing symptoms, live within the 'world' of FTD on a daily basis, and therefore it is important to also recognise the importance of 'living well at-risk'. In order to do so, alongside the development of disease modifying treatment trials, a focus is needed on providing timely and appropriate specialist support for those at-risk. There are a number of ways in which support may provide a meaningful difference to the at-risk community. Firstly, improved understanding of FTD, and the challenges of living at-risk amongst healthcare professionals may provide increased validation regarding the difficulties of their lived experience. Secondly, tailored psychological support carried out by professionals specialising in FTD would provide an opportunity to learn more regarding the disease, as well as a therapeutic approach designed with the challenges of living at-risk in mind. However, in order to develop such support, further understanding of the at-risk lived experience is needed as there is extremely limited literature regarding the effect of living at-risk on one's mental health and wellbeing.

1.8. Aims and objectives

The overarching research questions of this thesis can be summarised into two questions; what is the lived experience of individuals at-risk of familial FTD? And how can we best support individuals through the 'at-risk' period? Specifically, this thesis aims to investigate the at-risk lived experience using quantitative and qualitative methods and to use data regarding this lived experience in the development of a tailored support intervention for use in at-risk FTD, as well as using expert consensus and patient perspectives to develop an FTD-specific genetic testing protocol. In investigating the lived experience of individuals at-risk, this will allow for the development of a psychological intervention based on this qualitative data, including participant perspectives of their own support needs, involving participants as stakeholders from the beginning of intervention development. Similarly, the development of an FTD-specific genetic testing protocol aims to minimise the problems observed by patients during their experiences of predictive testing, and

incorporate expert consensus to achieve a comprehensive and supportive genetic testing experience.

The research questions outlined above were generated in collaboration with GENetic Frontotemporal dementia Initiative (GENFI) research participants at the University College London Dementia Research. Throughout a number of years as a research assistant working with this population, and with Professor Rohrer, we observed many at-risk individuals struggling to adjust to living at-risk, following genetic testing, and attempting to seek additional support. However, we noted that no specialist services exist to provide this support, and some families reported dissatisfaction with the genetic testing and counselling process. Therefore, this project was initially developed to understand the specific difficulties that exist within this population, and support required, in order to inform the development of a bespoke psychological intervention. As this project was conceived shortly prior to the COVID-19 pandemic, in-person research was halted for a substantial period and research was adapted to take place online if possible. During this period, a qualitative study was developed in order to gather data on the at-risk lived experience and support needs in a remote manner. This design minimised the effect of the pandemic on the data on people's mental health, as was recognised as a confounding variable in questionnaire studies, such as that in Chapter 3. In addition, as the study outlined in Chapter 3 progressed, it was apparent that, whilst it demonstrated a need for psychosocial intervention, data was limited on what this intervention may involve in order to serve the specific needs of the population. As such, the rich data associated with qualitative research was deemed a valuable addition to the existing studies outlined in this thesis, towards the aim of developing a tailored psychological intervention for individuals at-risk of fFTD.

Whilst prior work within this population allowed for a deeper and well-rounded understanding of the at-risk experience, and existing rapport with the study population, this may also have given rise to some preconceived biases, particularly regarding the needs of the population. I acknowledged throughout this thesis that the population studied here are extremely engaged individuals, who may be motivated to participate in research due to having increased difficulty adjusting to their risk, therefore the findings presented in this thesis must be viewed through this lens. In addition, working with, and supporting these individuals may have generated preconceived ideas

regarding the experience reported, the support that would be suitable, and how genetic testing may be improved for this population. In turn this may have led to some bias in the qualitative interview schedule and themes chosen to report. In attempt to mitigate these effects, I reviewed the interview schedule and themes with both my secondary supervisor JS, who does not work directly with this group, as well as psychologists and researchers from outside the Dementia Research Centre as part of my thesis committee. Experts by experience were also engaged throughout to ensure the work remained grounded within the population it intended to serve.

1.9. Thesis outline and research hypotheses

Chapter 3 describes a quantitative approach to understanding the at-risk experience using the Genetic Psychosocial Risk Instrument *plus*, a questionnaire designed and adapted for this study. This questionnaire included a number of questions exploring the 'journey' of being at-risk, standardised measures of depression and anxiety, the GAD-7 and PHQ-9, as well as the Genetic Psychosocial Risk Instrument to measure need for psychosocial referral within those with genetic risk. Scores on standardised measures were compared by both known status (i.e., known mutation carriers, known non-carriers and those who had not undergone predictive testing), in order to investigate the effect of one's perception of their genetic status on depression and anxiety symptoms, and psychosocial risk, and biological status (i.e., whether someone is actually a mutation carrier or not). I hypothesise the following; there will be a significant effect of status knowledge on depression and anxiety, and there will be a significant effect of biological status on depression and anxiety for the C9orf72 group, and for depression in the MAPT group.

In Chapter 4, qualitative interviews were used to gather more rich and detailed data, exploring the individual's experience at-risk as well as the support they received and that which they felt they needed. Due to the inductive approach taken to thematic analysis, there are no explicit hypotheses regarding the findings of this analysis however thematic analysis was employed used to generate a number of themes regarding two main research questions; what are the feelings and experiences of living at-risk of fFTD? And what are the support needs while living at-risk of fFTD?

Chapter 5 builds upon the data reported in Chapter 4, using the MRC complex

intervention development framework and a person-centred approach to co-production to outline the use of qualitative data in the development of a tailored psychological intervention for use in at-risk FTD. A review of the literature was conducted and a summary of the intervention throughout each iterative stage is provided, with the final stage demonstrating a prototype of the intervention in preparation for feasibility testing. Within this chapter I hypothesise that the use of the MRC complex intervention development framework and a co-production model will create a robust intervention and will increase feasibility and acceptability of the resulting intervention.

Chapter 6 employs a Delphi consensus methodology to provide expert opinion on how best to provide diagnostic testing for people with an FTD syndrome.

Similarly, Chapter 7 uses qualitative data regarding patient experiences of predictive testing, in addition to expert recommendations in order to develop an FTD-specific predictive testing protocol, building upon the 'gold-standard' HD protocol already in use.

In Chapter 6 and 7 I hypothesise that experts will largely accept the existing genetic testing recommendations for HD, with minor amendments and additions to improve suitability for FTD. In particular, regarding diagnostic testing I hypothesise that experts will recommend more widespread offering of diagnostic testing for those phenotypes associated with increased hereditary. For predictive testing recommendations, I hypothesise that experts will recommend guidelines that provide the potential for at-risk individuals to pursue future genetic testing where possible, in balance with the uncertainty of variants of unknown significance, i.e. experts will not recommend 'blind' genetic testing.

Finally, Chapter 8 describes an exploratory study using the Broad Autism Phenotype Questionnaire (BAPQ) and short Oxford-Liverpool Inventory of Feelings and Experiences (sO-LIFE) to investigate the presence of broad autism traits and schizotypy within FTD asymptomatic mutation carriers. I hypothesise that C9orf72 mutation carriers will demonstrate significantly higher autistic and schizotypal traits compared with non-carriers, MAPT and GRN carriers.

Chapter 2. Methods I

2.1. Chapter overview

The main aim of this thesis is to identify the psychological and neuropsychiatric consequences associated with living at-risk of fFTD in order to provide tailored support throughout their life journey including the process of predictive counselling and testing. This chapter outlines the general methods used throughout this thesis and summarises the cohorts studied, as well as outlining ethical procedures, study protocols and analyses.

2.2. Participant cohort

The participants studied within this thesis (Chapter 3, Chapter 4, Chapter 5, Chapter 7 and Chapter 8) are asymptomatic individuals with autosomal dominant risk of developing FTD, as well as known non-carrier family controls. Participants were a subset of individuals recruited from the GENetic Frontotemporal Dementia Initiative (GENFI), a multicentre cohort study of individuals at-risk of, or affected by, familial FTD, run from University College London. Chapter 6 is comprised of an alternative sample of specialist clinicians associated with GENFI, rather than participants enrolled in the initiative.

2.2.1. GENFI

The GENetic FTD Initiative (GENFI) is an international observational study investigating familial FTD, centrally coordinated by researchers from the Dementia Research Centre (DRC) at University College London (UCL). There are 44 sites enrolled in the initiative across 15 countries over Europe and Canada, all of whom follow the standardised procedure outlined below.

GENFI has gathered longitudinal observational data since its conception in 2012 and has since transitioned through three phases of development, with the current phase 'GENFI–3' focusing on research to aid progression towards clinical trials. Participants are eligible to participate in GENFI if they; a) have a symptomatic diagnosis of one of the FTD syndromes and a confirmed genetic diagnosis of a known pathogenic mutation in; *MAPT, GRN, TBK1, VCP, TARDBP, FUS, SQSTM1* or *UBQLN2* genes,

or with a pathogenic expansion in the *C9ORF72* gene.; or b) are asymptomatic with a first degree relative with a confirmed genetic diagnosis of FTD. First degree relatives refer to relatives who share approximately 50% DNA, e.g., a parent, a full sibling or child. The affected family member does not need to be involved in the study in order for the asymptomatic individual to participate, however proof of the mutation present within the family is required, usually via a neurogenetics laboratory report. Individuals are largely recruited from neurogenetics clinics and cognitive disorders clinics, or through family members already involved in the study. Asymptomatic participants can be stratified into two groups; those who carry the genetic mutation ('mutation carriers') and mutation negative controls ('non-carriers'). Therefore, non-carriers can be considered a within-family control group, having grown up in the same environment, a family affected by familial FTD, as those who carry the mutation. However, participants do not need to know their own genetic status in order to take part in the study, therefore this group is commonly collectively referred to as presymptomatic or, as they will be referred to in this thesis; 'at-risk'.

GENFI subjects at UCL are recruited from a number of services; a specialist tertiary referral dementia service at the National Hospital for Neurology and Neurosurgery, and from families entered into our research programme at the Dementia Research Centre, UCL Queen Square Institute of Neurology and approved Participant Identification Centres.

Prior to the initiation of GENFI-3 in Summer 2022, all GENFI participants would attend an annual research visit. However, in order to maximise resources and prioritise those nearing phenoconversion, those under the age of 30 are now seen every two years, while those closer to symptom onset are seen annually.

All participants in GENFI undergo genotyping as part of the study. For those that have not undergone predictive testing within a genetics clinic, results of genotyping are known only to a 'Genetic Guardian' at the research site, with the clinical research team and the participant themselves blind to that information i.e., no information is disclosed on a research basis. This procedure aims to prevent bias from researchers during data collection and also avoids accidental disclosure of genetic information to those who do not otherwise know their status. Individuals who have undergone predictive testing may express their positive or negative genetic status to the research team but are not

under any obligation to do so. In order to analyse data within GENFI, the Genetic Guardian links the genetic testing result with a pseudonymised participant code. This allows for comprehensive analysis between mutation carriers and non-carriers without compromising the individual's right to choose whether to know their genetic information.

Chapters 3, 4, 5 and Chapter 8 of this thesis use quantitative and qualitative methods to investigate the at-risk experience in individuals at-risk of familial FTD, including those with unknown status, known mutation carriers and known non-carriers. The majority of participants were recruited from the UCL GENFI cohort, however a subset of data used in Chapter 3 was collected by researchers from the Paris, Milan and Barcelona GENFI sites.

2.3. Ethics

Ethical approval was obtained locally from the Research Ethics Committees associated with each individual GENFI site. Local ethical approval for GENFI at UCL was granted by the Queen Square Research Ethics Committee.

2.3.1. Information and consent

Participant and informant information sheets and consent forms were approved by the Research Ethics Committee, in accordance with the Declaration of Helsinki (2013). Information sheets were provided to participants prior to consent to ensure clarity on what participation in the study entails. Both participants and informants were given the opportunity to ask questions regarding participation and the information provided, prior to signing the consent form. Consent forms were signed either in person on arrival at the research centre, or online using Docusign software (DocuSign., n.d. www.docusign.com).

Data is kept anonymously and confidentially, in accordance with the Data Protection Act and General Data Protection Regulation (GDPR and DPA, 2018). All participants were assigned a pseudonymised, numerical code under which their information is recorded and stored. No more information is collected than necessary and participants were informed and reminded of their right to withdraw from the study at any point.

2.3.2. Managing risk of harm

Several procedures are in place during research visits in order to manage and reduce risk of harm to both participants and researchers. Participants are required to provide details of their emergency contact during the visit and symptomatic individuals should be accompanied by their informant or a study partner wherever possible. The principal investigator (PI) is contactable throughout the duration of the research visit in case of emergency.

During the research visit, particularly during cognitive examination or neuropsychology assessment, the researcher remains vigilant for signs of distress and periodically checks in with the participant to ensure that they are comfortable and happy to continue the assessment. A discussion is had with the participant regarding continuation of assessment, should they appear distressed. A break in testing may be a suitable measure to reduce distress, however if the participant exhibits continued signs of distress, the assessment should be discontinued.

Researchers are also mindful of signs of safeguarding issues such as intimate partner violence, coercive control, self-harm and suicidal ideation. If researchers observe indications of these issues they are discussed with the individual themselves, prior to informing the PI and initiating safeguarding procedures.

2.3.3. Data collection, handling and storage

All data gathered throughout a GENFI research visit is processed and uploaded to a secure online database; XNAT (www.xnat.org) using a pseudonymised code. Personal information is protected in accordance with UCL's Information Governance policy, the General Data Protection Regulation and the Data Protection Act 2018. Biological data is processed and analysed by a research technician prior to being uploaded to the XNAT database. MRI scans are reviewed by a neurologist to check for incidental or anomalous findings, following this, images are processed by the imaging specialist research assistant and uploaded to XNAT. Additional questionnaire data gathered in Chapters 3 and 8 were recorded in encrypted Microsoft Excel spreadsheets and stored on the DRC secure server. Similarly, qualitative interview recordings and anonymous transcriptions were stored on the DRC secure server.

Questionnaire data gathered in Chapter 6 and 7 was also recorded in encrypted Microsoft Excel spreadsheets and stored on the DRC secure server.

2.4. Study protocol

GENFI participants complete a standardised battery of assessments across all sites, including clinical, neuropsychiatric, cognitive, imaging and bio-sample assessments. Participants may opt out of certain components such as venepuncture, lumbar puncture and MRI scan but may still take part in other components of the study. Participants in the main study may also be invited to participate in optional sub-studies that may be available. Research visits are commonly scheduled across one or two days depending on symptom severity and availability of the participant and necessary facilities (see below for a typical research visit schedule).

Table 1 - An example GENFI research visit timetable

PROCEDURE	Day 1		Day 2	
	AM	PM	AM	PM
Taking of consent	✓			
Medical history and examination	✓			
Venepuncture and Urinalysis	✓			
MRI scan				✓
Lumbar puncture		✓		
Informant interview		✓		
Neuropsychology			✓	
Retinal imaging (if applicable)				✓
Actigraphy (if applicable)				✓

All individuals are asked to provide details of a willing informant who has insight into the participants symptoms (if applicable), behaviour and personality. Informants are ideally people with a close personal relationship to the participant, such as a spouse or partner, first-degree relative or close friend and are invited to attend the annual research visit. Informants complete a number of questionnaires to assess participants' behavioural and personality change, and care needs, as well as their own health, anxiety and caregiver burden. These are completed either during the research visit, online or by phone, within 12 weeks of the research visit.

Travel, accommodation and meal expenses are reimbursed to the participant and their informant, should they attend the visit. No payment is provided for participation in the

study, in accordance with ethical approval.

2.4.1. Clinical assessment

A clinical assessment is completed by a neurologist specialising in FTD. The assessment can take up to 60 minutes and is conducted as a discussion between the neurologist and participant, as well as their informant. A personal, medical and family history is taken, including current medications, height and weight. The clinician assesses whether the participant meets the relevant diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). This is followed by a comprehensive assessment of symptom severity using the standardised Clinical Dementia Rating scale (CDR®) and CDR plus National Alzheimer's Coordinating Centre FTLD (CDR® plus NACC FTLD) measures, encompassing behaviour, language, and cognitive components plus added motor and neuropsychiatric components. The presence or absence of phenomena is recorded and rated on a four-point scale where 0 corresponds to 'absent', 0.5 is questionable, 1 is 'mild', 2 is 'moderate' and 3 is 'severe impairment'. A 'sum of boxes' and global score can then be generated. The clinician will also carry out a standard neurological assessment, as well as a cognitive exam including the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). A blood sample is taken and some participants may also undergo a lumbar puncture.

2.4.2. Functional and neuropsychiatric assessment

Functional and neuropsychiatric assessments were conducted using informant report and self-report questionnaires. These were completed either via traditional pen and paper, or online using Limesurvey software (Limesurvey GmbH. LimeSurvey: An Open Source survey tool. LimeSurvey GmbH, Hamburg, Germany. URL http://www.limesurvey.org). Questionnaire hyperlinks were distributed to participants and informants in advance of the visit and could be completed prior, during or up to 12 weeks following the research visit date. Informant questionnaires include the Cambridge Behavioural Inventory Revised (CBI-R), the Frontotemporal dementia Rating Scale (FRS), the Modified Interpersonal Reactivity Index (mIRI), and the Revised Self-Monitoring Scale. Both participants and informants were invited to complete the Broad Autism Phenotype Questionnaire (BAPQ). Participant

questionnaires included the Short Oxford-Liverpool Inventory of Feelings and Experiences (sO-LIFE), General Anxiety Disorder-7 (GAD-7), and the Patient Health Questionnaire-9 (PHQ-9).

Table 2 - Table of standardised measures included in GENFI function and neuropsychiatric assessment

	Test name	Test acronym	Informant at all visits	Informant at first visit only	Participant at all visits	Participant at first visit only
A	Cambridge Behavioural Inventory – Revised	CBI-R	✓			
B	Frontotemporal dementia Rating Scale	FRS	✓			
C	Brief Dimensional Apathy Scale	b-DAS	✓			
D	Modified Interpersonal Reactivity Index	mIRI	✓			
E	Revised Self-Monitoring Scale	RSMS	✓			
F	Broad Autism Phenotype Questionnaire	BAPQ		✓		
G	HEXACO Personality Inventory-Revised	HEXACO-PI-R		✓		
H	Short Oxford-Liverpool Inventory of Feelings and Experiences	sO-LIFE				✓
I	Physical Activity Scale	PASE			✓	
J	Cognitive Activity Scale	CAS			✓	
K	General Anxiety Disorder-7	GAD-7			✓	
L	Patient Health Questionnaire-9	PHQ-9			✓	
M	Warwick-Edinburgh Mental Well-Being Scale	WEMWBS			✓	

2.4.3. Neuropsychology assessment

A standard neuropsychology battery is completed as part of every GENFI visit to assess cognition. This battery is designed to cover a range of cognitive domains including episodic memory, executive function, naming, verbal fluency and social cognition. Neuropsychology testing was conducted by research assistants trained in administering the assessment. The researcher is usually placed across a table from the participant, in a quiet room, with assessment materials presented on the table or displayed on an iPad. Participants are reassured throughout the assessment in order to reduce performance related anxiety and breaks are provided where necessary.

2.4.4. Magnetic resonance imaging

All participants undergo magnetic resonance imaging (MRI) if they are willing and able. The MRI protocol includes volumetric T1 and T2 imaging, diffusion tensor imaging for tractography, arterial spin labelling imaging and resting state functional MR imaging. Scans at UCL were conducted on a Siemens Prisma 3T scanner, and on a variety of 3T scanners across other GENFI sites. All scans were quality checked and those with significant artefact were removed. Should incidental findings occur, this is further reviewed with the PI and clinical follow up is arranged with the participant and relevant medical practitioner.

2.4.5. Biological samples

Blood, CSF and urine samples are collected, processed and analysed in accordance with the Human Tissue Act 2004. Blood samples are taken for plasma, serum, DNA and RNA analysis. Up to 60ml of blood may be donated at each visit, and up to 20ml CSF. All samples are processed without delay and stored at -80°C. Prior to freezing, samples are separated into aliquots to prevent multiple freeze-thaw cycles.

2.5. Statistical analyses

Statistical analyses were performed using Stata MP (version 16.1) for Mac (64-bit Intel). Distribution of data across the mean was assessed using histogram visualisation, and statistically confirmed using Shapiro Wilk tests. Non-normally distributed data required non-parametric analysis or appropriate transformation of data.

Demographic differences between participant groups, such as age and years in education were assessed using t-test, or Mann-Whitney U tests for non-normal distribution. Categorical variables, such as gender, were compared using chi-squared tests.

A number of correlational analyses were carried out in Chapter 3 to investigate the effect of years to estimated parental age at onset, on standardised measure scored (on GAD-7, PHQ-9 and GPRI questionnaires). Pearson correlations were used where data was normally distributed. Where data was not normally distributed, Spearman's

Rank correlations were used as a non-parametric alternative.

Chapter 3 and 8 also employ the use of linear regression models in order to investigate the relationship between standardised measure score (as a dependant variable) and one or more predictor variables. This was used to examine the relationship between standardised measure score, mutation status, with gender and years in education as co-variates. Where data was not normally distributed, bootstrapping was used with 2000 replications. Post-hoc pairwise comparisons were carried out to compare between each sub-group analysed. This was used to assess the interactions between each possible combination of variables, reporting a predicted difference score, *p*-value to indicate significance and confidence intervals. No corrections were made for multiple comparisons within these analyses due to the exploratory nature of the studies, therefore findings must be interpreted with caution, particularly those close to the significance level of 0.05.

For further detail on statistical methods, see Chapter 3.3.4 and 8.3.4.

2.6. Non-statistical analyses

This thesis is comprised of a number of methodologies, including qualitative and consensus methodologies. Qualitative data was transcribed using Trint transcription software (*Trint*, 2021, https://trint.com), coding and thematic analysis was done using NVivo 12 Pro software (*NVivo*, 2018). Demographic data was compiled using Microsoft Excel (*Microsoft Excel*, 2018) and Braun and Clarke's six-step approach to thematic analysis was used to generate themes from the data. Coding of two interviews were compared to coding carried out by independent rater, and coding similarities and differences reviewed by both raters. Themes were reviewed by JCS. For further detail on qualitative analysis and non-statistical methods, see Chapter 4.3.5.

Descriptive data reported from the Delphi consensus in Chapter 6 and 7 were analysed using Microsoft Excel (*Microsoft Excel*, 2018), for further detail on this analysis see Chapter 6.3.1.3.

2.7. COVID-19

I began this PhD in 2019, shortly before the beginning of the COVID-19 pandemic. Therefore, much of this work took place during COVID lockdown and studies required adjustment to be suitable for remote data collection. I was extremely conscious that I was researching mental health and wellbeing in a time when people's mental health and wellbeing were strained for reasons owing to the pandemic. Therefore, it felt appropriate to suspend much of this research for significant periods throughout the height of the pandemic, for both ethical reasons and to prevent bias due to COVID related health anxiety. I also contracted post-COVID19 chronic fatigue syndrome as a result of COVID infection in March 2020, leading to further delays and challenges in relation to completing this work. Research at the DRC was not able to fully restart until April 2021, with COVID protocols in place to minimise the spread of infection, however other GENFI sites were not able to continue collecting data for projects outlined in this thesis due to COVID related issues (e.g. limited data from Milan in Chapter 3). Therefore, there were significant delays in recruiting participants to the study, as well as adjusting data collection methods and carrying out projects remotely. The work presented in this thesis was conducted during or following the COVID-19 pandemic, with the unique challenges of this explored where appropriate.

Chapter 3. Using quantitative methods to understand the at-risk experience

3.1. Chapter overview

As the first data chapter within this thesis, this chapter describes the use of an adapted questionnaire to explore the experience of living at-risk of fFTD. This questionnaire comprised of a number of standardised measures to investigate depression, anxiety and need for psychosocial support, as well as a number of exploratory questions to assess aspects such as predictive testing, and more broadly, mental health and support. This study aimed to assess the presence of depression, anxiety and psychosocial risk in individuals at-risk of fFTD, as well as determining the association of such aspects with status knowledge (known mutation status based on predictive testing or lack thereof), and biological status (determined through blinded genotyping). The overarching goal of this was to determine the psychological impact of living at-risk in order to inform whether psychological intervention may be warranted in this population.

3.2. Introduction

As fFTD is an autosomal dominant disorder, those with an affected first degree relative live 'at-risk' and have a 50% chance of carrying the mutation. According to studies in Huntington's disease (HD), approximately 20% of those at-risk go on to have predictive genetic testing (Craufurd et al., 1989; Quaid et al., 2008). Reports of predictive testing uptake in FTD are similar, ranging from seven to 20% (McCrae et al., 2001; Paulsen et al., 2013; Riedijk et al., 2009; Rohrer et al., 2015; Steinbart, 2001). Throughout this thesis, this group of individuals will be referred to as at-risk, regardless of whether they know their genetic status. FTD is highly unpredictable and for those at-risk, there is added uncertainty regarding their genetic status, the age symptoms may onset and what these symptoms will be. Family members of *C9orf72* carriers also have a greater risk of psychiatric disorders and autistic spectrum disorder (ASD) (Devenney et al., 2018). Thus, it may be expected that living at-risk is a psychologically challenging experience. As there is little literature on this in FTD, literature from other autosomal dominant disorders such as hereditary cancers were reviewed. However, due to the existence of physical health treatments for these disorders, the lived experience of individuals at-risk of such cancers was not appropriate for extrapolation to FTD, therefore we must look to other hereditary neurological disorders such as HD.

Psychological wellbeing is considered the experience of positive affect, satisfaction and contentment, alongside the absence of negative emotion, or symptoms consistent with psychopathology such as depression and anxiety. It is important to maintain psychological wellbeing throughout life as there are numerous positive associations such as improved physical health and life-expectancy (Boehm, 2018). Challenging life-events, such as learning that you are at-risk of a familial neurodegenerative disease such as FTD, may challenge this psychological wellbeing. This may be observed as an increase in negative emotion or symptomatology, such as increased distress, depression or anxiety. There is evidence of increased depressive symptoms in familial neurodegenerative disease mutation carriers and those living with autosomal dominant 50% risk (Aschenbrenner et al., 2020; Cecchin et al., 2007; Poos et al., 2022; Ringman, 2004). Devenney et al., (2018) found that relatives of *C9orf72* kindreds had a higher probability of developing mood disorders such as depression or

anxiety than noncarriers, as well as a higher probability of suicidality. Furthermore, a recent study found anxiety and depression in 46% fFTD mutation carriers compared to 24.5% controls, with a significantly higher levels of depression and anxiety observed at the prodromal disease stage, compared to asymptomatic stage, indicating that mood disorder symptoms are associated with symptom onset in addition to genetic risk (Samra et al., 2023). Therefore, it is important to further understand mood symptoms associated with living at-risk to provide suitable psychological support and aid diagnostic processes for those with prodromal symptoms which may in future allow for early treatment or participation in clinical trials. However, the impact of living at-risk of fFTD on psychological wellbeing and mental health remains unclear.

There has been a relatively considerable amount of research into the predictive testing experience in HD compared to other hereditary neurodegenerative diseases, however the evidence regarding the psychological impact is equivocal (Crozier et al., 2015). Studies have revealed varied findings in terms of depression, anxiety and distress experienced throughout the predictive testing process and the trajectory of wellbeing post-test.

On one hand, some studies demonstrate little effect of predictive testing on mental health and wellbeing, or in some cases an improvement. On review of the literature, Paulsen et al. (2013) summarised that there was a lack of ‘catastrophic’ reactions following predictive testing, as well as few differences observed between those found to be mutation carriers and non-carriers, with any differences largely resolving with time (Molinuevo et al., 2005; Paulsen et al., 2013; Steinbart, 2001a). Over time, following predictive testing, improvements have been reported in depressive symptoms (Decruyenaere et al., 2003; Galluzzi et al., 2022) and anxiety (Decruyenaere et al., 2003) as well as general wellbeing (Wiggins et al., 1992) and distress (Almqvist et al., 2003). Participants reported relief from uncertainty and opportunity for planning as positive outcomes of predictive testing (Codori and Brandt, 1994; Galluzzi et al., 2022; Goh et al., 2013; Meiser & Dunn, 2000; Wiggins et al., 1992). A majority of participants have also been reported as feeling ‘great benefit’ from the knowledge of their genetic status, and rating their lives as ‘very good’ six months post-test (Goh et al., 2013; Tibben et al., 1997). Similarly, despite reports of psychological burden, anxiety and guilt in mutation carriers, many displayed adaptive

coping responses by focusing on what they gained from testing and their coping strategies (Codori and Brandt, 1994). This is also reflected within a smaller literature base for other hereditary neurodegenerative diseases such as familial ALS (fALS), FTD and familial AD (fAD). In fALS, participants reported positive changes to their lives following receipt of their genetic information which also allowed for future planning (Fanos et al., 2011). Similarly, findings in FTD suggest that the vast majority of those tested felt it to be beneficial, despite some evidence of depression, anxiety and avoidance (Molinuevo et al., 2005; Paulsen et al., 2013; Steinbart, 2001a).

However conversely, there is also a body of evidence to suggest there may be a deterioration in mental health following predictive testing, with Timman stating that the lack of harmful reactions and reports of the benefits of predictive testing, should be treated with caution (Timman et al., 2004). Timman et al. (2004) also found greater hopelessness in mutation carriers, one week post-test, with hopelessness rising above baseline levels again seven to 10 years following the test. Shortly following the test (one week), participants also experienced increased intrusion and avoidance, however this decreased following 1.5 years (Timman et al., 2004). Furthermore, they found that those who reported reduced hope, experienced increased intrusive thoughts, demonstrated more avoidant coping strategies, had worse pre-test wellbeing and mutation carriers were less likely to return for post-test follow up or counselling compared to distressed non-carriers (Timman et al., 2004). Similarly, another study indicated increased levels of suicidal thoughts or self-injurious behaviour for both carriers and non-carriers (Robins Wahlin et al., 2000).

In addition, there is evidence to suggest that, although psychological distress or burden may be observed immediately following predictive testing, as discussed above, this was not static over time suggesting that psychological wellbeing may fluctuate (Crozier et al., 2015; Hayden and Bombard, 2005). One recent study found a significant increase in depression and anxiety as participants' age increased (Sobregrau et al., 2022), this is in line with findings that mutation carriers demonstrated increased pessimism leading up to symptom onset (Timman et al., 2004). A number of studies report increased avoidant coping within mutation carriers compared to non-carriers (Decruyenaere et al., 2003; Tibben et al., 1997; Timman et al., 2004), however Tibben et al., (1997) found that this effect resolved within three years. Timman et al.,

(2004) found a temporal peak in psychological symptoms a few years post-test, with avoidance increasing again seven to 10 years post-test, suggesting avoidance may peak and trough over time, potentially increasing as mutation carriers approach disease onset. Meanwhile, Tibben found increased anxiety, depression and hopelessness in gene carriers or high risk mutation carriers returned to baseline within six months to one year (Etchegary, 2011; Tibben, 2007; Tibben et al., 1997) and HD related intrusive thoughts decreased in six months (Tibben et al., 1997). Similarly, anxiety and depression in non-carriers decreased within one year post-test and remained the same in mutation carriers (Decruyenaere et al., 2003).

It may be expected that the psychological reaction following predictive testing may differ depending on the individual's genetic status, with those receiving a 'favourable' result reacting more positively than those who did not. This was the case for some, with a number of studies finding an increase in denial and avoidant behaviour in mutation carriers and a decrease in non-carriers (Tibben et al., 1997; Timman et al., 2004), as well as significantly reduced levels of depression two years following predictive testing for non-carriers compared to mutation carriers (Crozier et al., 2015; Larsson et al., 2006; Lickleder et al., 2008; Robins Wahlin et al., 2000). Similarly, Almqvist et al. (2003) reported a higher frequency of clinically significant adverse events (e.g. depression) in mutation carriers vs non-carriers within two years post-test (Almqvist et al., 2003; Paulsen et al., 2013). However, reactions within non-carriers were not wholly positive. Despite feeling some relief, survivor guilt was found to manifest in non-carriers who were processing their own relief alongside simultaneous concern for family members (Codori and Brandt, 1994; Fanos et al., 2011). Similarly, although those with reduced risk of HD demonstrated reduced depressive symptoms, 10% required additional counselling (Bloch et al., 1992; Decruyenaere et al., 1996; Huggins et al., 1992). However contrastingly, Cohn-Hokke et al., (2018) found no significant differences in anxiety and depression between carriers, non-carriers and those at-risk with unknown status.

Despite inconclusive conclusions regarding the psychological impact of predictive testing, reasons for pursuing testing remain consistent. Reasons for undergoing testing commonly include decreasing uncertainty, worry and anxiety, allowing for greater control over life and decision making; specifically, future planning, financial

planning and family planning (Cohn-Hokke et al., 2018; Fanos et al., 2011; Goh et al., 2013; Paulsen et al., 2013; Steinbart, 2001a). Other reasons for testing included planning for retirement, the decision to have children, career plans, to allow for potential participation in clinical trials and the repercussions for family and the effect on personal relationships (Cohn-Hokke et al., 2018; Fanos et al., 2011; Goh et al., 2013; Paulsen et al., 2013; Steinbart, 2001a). Reasons against predictive testing included worry and symptom searching, maintaining hope, a fear of regret and guilt, as well as a personal belief of carriership (Fanos et al., 2011).

Therefore, the literature creates a confusing landscape to understand the at-risk experience. There are also factors that may mediate psychological distress in this group, including an inability to estimate age at onset for the disease, unpredictability of disease progression in terms of phenotype and disease duration, the lack of an available treatment and a lack of or delay in diagnosis or receiving genetic results (Crozier et al., 2015; McAllister et al., 2007), many of which are inherent to the FTD at-risk experience. Prior depressive episodes, history of depression in the family and participant's preconceived expectation of the test result may also mediate psychological distress (Decruyenaere et al., 1996; Gargiulo et al., 2009; Horowitz et al., 2001; Larsson et al., 2006; Lickleder et al., 2008; Witjes-Ane, 2002). Increased distress has also been reported in those lost to follow up and long-lasting distress in those who were motivated for testing by non-specific relief of uncertainty (Decruyenaere et al., 2003; Timman et al., 2004). One possible explanation for this fluctuation of psychological wellbeing over time could be due to a fluctuation in the relevancy and salience of genetic risk as an individual progresses through life. When making important life decisions such as a house purchase, or having children, risk may be highly relevant, and therefore wellbeing may decrease. However, in the meantime, individuals may be able to live alongside their risk, without a decrease in wellbeing. Predictive testing is a highly challenging life event, making an individual's risk highly relevant and salient at this time, and it follows that the receipt of this information may cause a decline in wellbeing. However, as the evidence above suggests, the process of adjustment is not always linear. This is supported by Samra et al., (2023), who found symptoms of depression and anxiety in asymptomatic, prodromal and symptomatic individuals fluctuated over time.

There are a number of limitations to this body of work. Firstly, as reviewed above, there is a lack of consistency in results and conclusions regarding the psychological impact of predictive testing in those at-risk of familial neurodegenerative diseases. This may be due to a high variability in measures and timescales used within study designs, however it may also be due to studies being too reductionist when looking at this experience. Such studies often do not account for other factors of the at-risk experience that may mediate an individual's psychological response to being at-risk or following predictive testing, such as significant life events like a parent's illness or death of a family member. Due to the nature of hereditary neurodegenerative diseases like fFTD these life events are often intrinsically linked to a person's view of their risk or genetic status, therefore it is important to take a more holistic view to understand the at-risk experience better, outside the predictive testing experience.

Secondly, study samples are often biased as individuals who are more psychologically vulnerable are less likely to request testing and pass psychological evaluation, therefore those who go through testing may be more mentally resourceful and prone to better adjustment (Codori et al., 1994). Studies are typically conducted with specialized and experienced genetic counsellors, therefore participants may receive a 'best-case scenario' (Roberts, 2019). Furthermore the timing of follow-up may be inappropriate (Roberts, 2019), typically occurring weeks or months following the test, which may lack sensitivity. There have also been few longitudinal studies, although one such study reported increased hopelessness as carriers neared their parental age at onset (Timman et al., 2004).

As detailed above, much of the current literature on the psychological impact of living at-risk focuses on the predictive testing process and experience, however this is a reductionist approach. Those who do not know their status account for up to 80% of those at-risk and yet little is known about this group. There is a small body of evidence assessing the pure at-risk experience. McAllister et al., (2007) found that at-risk participants reported struggling with anxiety about their risk and caring for relatives, anxiety and guilt relating to their children's risk and uncertainty about when or if they might develop symptoms. Similarly, a study of young people found 82% felt anxious about their risk, 65% saw it as a barrier in life and 64% wanted certainty about their genetic status (Lewit-Mendes et al., 2018). They also found higher mean depression

and anxiety scores in those at-risk compared to adults in the general population (Lewit-Mendes et al., 2018). Therefore, there is some evidence to suggest that purely living at-risk may be psychologically challenging for some. Further to this, despite the similarities between FTD and HD, there is no evidence to suggest that extrapolation of these lived experiences is appropriate. Although HD can encompass motor, cognitive and psychiatric deficits, this forms a more homogenous clinical presentation, removing some of the uncertainty observed regarding prediction of inherited phenotype in FTD. Similarly, HD penetrance is complete, in comparison to the age-related penetrance observed in some FTD mutations, and for some, HD repeat length can provide information regarding age at onset. Therefore, the experience of predictive testing for HD and FTD may be quite dissimilar, as more nuanced counselling may be required as a result of the increased uncertainty and unpredictability of FTD.

There has also been a small amount of research within FTD which demonstrates similar findings to the literature in HD. Depression and anxiety symptoms have been reported in prodromal bvFTD patients, however these were observed to be “shallow”, “short-lived” and did not reach a diagnostic threshold (Gregory, 1999). Anxiety was observed in 25% of participants at baseline but no longer evident at follow up (Surampalli et al., 2015). However, Cheran et al., (2018) found increased prevalence of anxiety and major depressive disorder (MDD) in *MAPT* non-carriers and increased ‘depressive disorder not otherwise specified’ (clinically significant symptoms that do not meet MDD criteria) in mutation carriers. They argue that, similarly to HD, early dysfunction of networks involved in emotion in FTD may manifest as mood changes that do not meet criteria for major depressive disorder.

Overall, the rationale behind this study was to better understand the at-risk experience in fFTD in order to develop and provide better tailored support to those living at-risk. In addition, with clinical trials ongoing and more on the horizon, there is likely to be increased relevancy and salience of genetic risk for many. This will bring its own psychological challenges and may increase predictive testing uptake, however there is no guarantee that a treatment will be uncovered soon therefore it is important that we understand the at-risk experience in order to better support individuals through this new phase. Furthermore Sobregrau et al. (2022) states that assessment and

understanding of factors such as anxiety, depression and coping mechanisms may help clinicians to deliver a better predictive testing experience and provide appropriate support to suit an individual's needs. In addition, as stated above mood disorder symptoms have recently been found to overlap with the prodromal phase of fFTD, therefore improved understanding of the at-risk experience may have direct implications for clinical care and aid the diagnostic process in individuals experiencing prodromal symptoms. Due to the phenotypic heterogeneity observed in FTD, and different presentations associated with certain genetic mutations for example., psychiatric symptoms in C9orf72 (Ducharme et al., 2017), and depression in MAPT (Cheran et al., 2018), it will also be important to investigate whether such nuances may be observed between genetic groups in the presymptomatic disease stage. Ascertaining whether this effect is driven biologically, or rather by knowledge of status through predictive testing, will also have important implications for the genetic counselling process. Therefore, this project aimed to investigate the psychological implications of living at-risk of fFTD, including symptoms of depression and anxiety, and need for psychosocial referral.

3.3. Methods

3.3.1. Participants

Participants were 151 adults recruited from five of the largest GENFI sites; UCL, UK (n=76), Cambridge, UK (n=10), Paris, France (n=44), Milan, Italy (n=3) and Barcelona, Spain (n=19). Participants were asymptomatic individuals with an autosomal dominant family history of fFTD and a first-degree relative with a pathogenic mutation in either *C9orf72*, *GRN*, *MAPT* or *TBK1*. One participant recruited from Cambridge, UK, was excluded due to a lack of a confirmed FTD mutation in their family. Those individuals who had undergone predictive testing were categorised as known mutation carriers and known non carriers, while the remaining participants who had not, were referred to as 'unknown status'. Biological status remained blinded for those with unknown status. See Table 3 for demographic information. All participants were enrolled in GENFI at their local site, except for a subset of participants from Paris who were recruited through a cognitive neurology clinic. Local ethical approval was granted for all sites involved in the study.

3.3.2. Questionnaire development and translation

The GPRI*plus* is a questionnaire developed by combining three existing standardised questionnaires; the Genetic Psychosocial Risk Instrument (GPRI), the Generalised Anxiety Disorder scale 7 (GAD-7) and the Patient Health Questionnaire nine-item depression module (PHQ-9), with a number of additional questions. The GAD-7 and PHQ-9 questionnaires were selected as they are commonly used scales to assess depression and anxiety symptom severity, as well as being short in length and available in a wide range of languages. Additional questions were regarding genetic history, mental and physical health and support received or wanted. Age at symptom onset for symptomatic family members was also gathered in order to calculate estimated years to symptom onset for at-risk individuals, based on their mean family age at onset. Although this is not an accurate predictor of symptom onset (Moore et al., 2020), at the time of beginning this project there were few other ways in which to estimate proximity to onset. Additionally, as this study was concerned with the effect of individual's perceptions of their own risk, mean family age at onset was felt to be in line with how at-risk individuals often estimate their own expected age at symptom

onset. Validated translations of the GAD-7 and PHQ-9 were used, and individual sites translated the remaining GPRI and additional items. For the full questionnaire see Appendix 1.

Genetic Psychosocial Risk Instrument (GPRI)

The GPRI (Esplen et al., 2013) is a 20-item questionnaire designed to screen psychosocial risk in those undergoing genetic testing for adult onset hereditary diseases. Demographic items are weighted so that presence of a diagnosis, caring for or losing family members due to the disease in question receive five points, while the absence of these characteristics is scored as one. Ten statements are provided referring to beliefs and worries regarding risk of inheriting the disease, for example, 'If I learn that I have a genetic mutation, I believe that I will have more problems in my life' and 'my worries about the disease affect my daily mood'. Participants score their agreement with these items on a scale from zero to five for the first statement, and one to five for the remaining statements. Items are rated on a six-point scale where 'strongly disagree' scores one, 'neither agree/disagree' scores three and 'strongly agree' scores five, for the first statement, the answer 'not applicable' scores zero, and three thereafter. Following this are two statements; 'I have generally felt sad in the past month' and 'I have generally felt nervous and anxious in the past month'. These statements are scored from one to five, with one corresponding to 'not at all' and five 'almost all the time'. The final questions relate to experience of emotional or mental health problems, including thoughts of suicide, as well as experience of therapy or counselling. The presence of emotional problems, mental health problems or thoughts of suicide receive scores of five, while absence is scored as one. Similarly past or present experience of counselling or therapy is scored as five, while lack of this scores one. A total score of 50 serves as a threshold for psychosocial referral. Validation of the GPRI reports sensitivity of 84% and specificity of 60% (Esplen et al., 2013).

GAD-7

The GAD-7 (Spitzer et al., 2006) is a seven-item screening and severity assessment tool for anxiety disorders. Participants rate each item on a four-point Likert scale categorising frequency of symptoms in the previous two weeks from 'not at all' (0) to 'nearly every day' (3). A total score from zero to 21 can be generated and categorised

as ‘mild’ (five to nine), ‘moderate’ (10-14) or ‘severe’ (15-21). A sensitivity of 89% and specificity of 82% has been reported for the GAD-7 in screening for Generalised Anxiety Disorder (GAD) using the threshold of ≥10 (Spitzer et al., 2006), and 83% and 84% respectively using the cut off of eight or more (Kroenke et al., 2007; Plummer et al., 2016). A systematic review of screening tools concluded that the GAD-7 was the best measure for identifying generalised anxiety disorder (Herr et al., 2014).

PHQ-9

Similarly to the GAD-7, the PHQ-9 (Spitzer et al., 1999) is a nine item tool for depressive disorders. The PHQ-9 uses the same scale as described above. A total score from zero to 27 can be generated, and severity categories are as described above with an added moderately severe (15-19). It is a well validated measure with a sensitivity of 88% and a specificity of 88% for a score of ≥10 for major depressive disorder (Kroenke et al., 2001).

3.3.3. Study design and procedures

Recruitment for this study began in 2019 and continued until March 2022. The initial recruitment phase began in person, recruiting consecutively during participant’s annual GENFI visit. In order to aid recruitment and prevent issues relating to missing data that were acknowledged when using pen and paper questionnaires, the questionnaire was uploaded to Qualtrics software (Qualtrics version 3 2021 copyright © 2021, Qualtrics, 2021, Provo, Utah, USA). Qualtrics logic was used to request that participants responded to all questions, to prevent missing data where possible, however a prefer not to say option was provided for more sensitive topics. Following this, participants were invited to complete the questionnaire either during their research visit or via email. Participants were provided with an explanation of the purpose of the study and an anonymous hyperlink to complete it using Qualtrics. Participants were also informed of safety procedures regarding the sensitivity of some of the topics covered within the questionnaire, in the study invitation email. My email address was provided at the end of the questionnaire in order to allow participants to contact me with any concerns regarding their data or the project. Data for those participants who used Qualtrics was stored on the Qualtrics server and regularly downloaded to the secure DRC server. An alert was programmed for any participant

who reported a risk to themselves or others in order that this was promptly followed up and safety procedures put in place.

Study recruitment at non-UCL sites was carried out by local GENFI study coordinators. Cambridge participants were provided with the same anonymous hyperlink used at UCL and an email study invitation template was provided to the study coordinator to explain the study prior to participation. International sites were provided with a translated questionnaire pdf and an encrypted data collection proforma on Microsoft Excel (Microsoft Excel, 2018). Pseudonymised GENFI codes and date of birth were gathered as participant identifiers in order to cross-reference with centrally stored GENFI demographic information.

Data was continuously reconciled throughout the study. Where questionnaire responses contained missing data, participants were contacted to request a complete response. Following this process, participants who did not provide full GAD-7, PHQ-9 and GPRI responses were removed from the dataset. For additional questionnaire items, the calculation of the descriptive statistics presented was adjusted to allow for any missing data, however this was minimal.

3.3.4. Materials

The questionnaire was administered using traditional pen and paper, as well as Qualtrics software version 3 2021 copyright © 2021 (Qualtrics, 2021, Provo, Utah, USA) and Microsoft Excel (Microsoft Excel, 2018).

3.3.5. Statistical analyses

Statistical analysis was performed using STATA 16 software (16.1, StataCorp LLC, College Station, TX).

1.1.1.1. Demographics

Statistical differences between each group were assessed for each demographic characteristic. Independent t-tests and Mann-Whitney U tests were used to assess differences between biological status groups and age at survey, years in education and years to parental age at onset. One-way ANOVAs and Kruskal-Wallis tests were

also carried out to investigate differences in age at survey, years in education and years to parental age at onset by reported status groups, biological status split by mutation type and reported status split by mutation type. Chi-squared tests were also used to investigate gender differences between the above groups.

1.1.1.2. Questionnaire items

Descriptive statistics were reported for binary and categorical questionnaire items. Number of participant responses and percentage of participant responses were reported for each response category, across demographic groups where appropriate. Median and interquartile ranges were computed for questionnaire responses using Likert-scales. Qualitative data was grouped by topic and number of responses within each topic displayed. Chi-square tests were conducted to analyse questionnaire items within section three with binary outcomes (e.g., yes/no) comparing by gender, reported (known) status, biological status and mutation groups. Chi-square tests were used for questions regarding experience of emotional problems in the past, mental health diagnoses, suicidal ideation, feelings of sadness, nervousness and anxiety within the past month and undergoing counselling in the past and/or present.

3.3.5.1. Standardised measure analyses

Normality was assessed for each standardised measure (GAD-7, PHQ-9 and GPRI) using visual analysis of histograms and statistically using Shapiro-Wilk tests.

Reported status and biological status

These analyses compared GAD-7, PHQ-9 and GPRI score between reported status groups, i.e., those who have had predictive testing and reported their subsequent mutation status (known non-carriers, known mutation carriers and unknown status), and biological status groups i.e. blinded biological status for those with unknown status. Therefore, linear regression models were conducted for each measure, with test score as the dependent variable and reported status or biological also included in the model. Demographic characteristics such as gender and years in education were included as co-variates within the model based on literature suggesting that these factors are associated with GAD-7 and PHQ-9 score (Kocalevent et al., 2013; Löwe et al., 2008), as well as more generally with mental health (Araya, 2003; Galluzzi et

al., 2022; Riecher-Rössler, 2017; Steele et al., 2007). For those measures where data was not normally distributed, bootstrapping was used with 2000 replications. Post-hoc pairwise comparisons were also computed to allow further insight into any significant associations between status groups.

Reported status and biological status by mutation type

Reported status and biological status groups were also stratified by mutation type; *C9orf72*, *GRN* and *MAPT,* due to their nuanced differences in clinical presentation, particularly in relation to psychological and psychiatric symptoms. The above linear regression models were also conducted to compare standardised measure score across reported and biological genetic status groups by mutation type. Post-hoc pairwise comparisons compared standardised measure scores between genetic and mutation groups.

Correlational analyses

Correlations were run to assess the relationship between scores on standardised measures (GAD-7, PHQ-9 and GPRI) and years to parental age at onset. Pearson correlations were used for normally distributed data, while Spearman correlations were run for non-normal distributions.

3.4. Results

3.4.1. Demographic characteristics

A total of 151 participants completed the GPRI*plus* questionnaire, across four countries and five GENFI sites; UCL, UK (n=76), Cambridge, UK (n=9), Paris, France (n=44), Milan, Italy (n=3) and Barcelona, Spain (n=19). Seven participants were removed due to missing data.

No significant differences were identified between reported status groups for age at survey (p=0.42), years to parental age at onset (p=0.72), years in education (p=0.35), and gender (p=0.23). There were no significant differences between biological status groups for years to parental age at onset (p=0.32), years in education (p=0.50) and gender (p=0.45). No significant differences were found for reported status groups by mutation type for age at survey (p=0.10), years in education (p=0.47) and gender (p=0.17). There were no significant differences identified for biological status groups by mutation type for age at survey (p=0.29), years to parental onset (p=0.06), years in education (p=0.48) and gender (p=0.10).

There was a significant difference in age at survey between biological status groups (p=0.03) and in years to parental onset by reported status and mutation type (p=0.02).

Females were slightly overrepresented, accounting for 56% (n=85) of the total sample, and males accounting for 42% (n=64). Participant's years in education ranged from three to 21 years, with the mean number of years in education being 17 (standard deviation [SD] = 4). The age range of respondents at the time of completion was 26 to 74 years, with a mean age of 44 (SD = 11). A parental age at symptom onset was available for 114 participants, ranging from 38 to 75, with a mean parental age at onset of 57 (SD = 8). Years to parental age at onset were calculated for all 114 participants with this data available, with a range of -15 to 32 years, with negative values corresponding to those individuals who had already surpassed the age at which their affected parent became symptomatic. The mean years to parental age at onset was 13 years (SD = 11).

Table 3 - Participant demographics

N	151
Gender (F : M)	85 : 64
UCL Cambridge Paris Milan Barcelona	76 9 44 3 19
Mean years in education Range	17 (4) 3-21
Mean age at survey (SD) Range	44 (11) 26-74
Mean parental AAO Range	57 (8) 38-75
Mean years to parental AAO Range	13 (11) -15-32

Eighty-seven individuals (58%) had undergone predictive testing to learn their genetic status, of which 66 (76%) were found to be carriers of an FTD-causing genetic mutation, and 21 (24%) were non-carriers. Sixty-two individuals (41% of the total sample) did not currently know their own genetic status. All (except two) participants had been genotyped, allowing me to look also at biological status; 60% of participants were found to be carriers of one of the four main FTD pathogenic mutations, and 38% were non-carriers. The missing 2% here corresponds to the two individuals for whom biological status was missing.

Table 4 - Percentage distribution of participants across reported status and biological status groups, by genetic group

		C9orf72	*GRN*	*MAPT*	*TBK1*	**Total**
Reported (known) status	Unknown	23%	13%	5%	1%	41%
	Mutation carrier	19%	17%	8%	0%	44%
	Non-carrier	8%	3%	3%	0%	14%
Biological status	Real carrier	28%	21%	11%		60%
	Real non-carrier	21%	12%	5%		38%
Total		**50%**	**33%**	**15%**	**1%**	

Section 1 – Living at-risk

1.1. At what age did you find out that you were at-risk of FTD or a related condition?

The mean age participants learnt that they were at-risk of fFTD was 34.9 years of age (SD = 11.7), however this was wide-ranging, from the age of three to 63. The mean age at which individuals learnt of their risk differed depending on the genetic mutation found within their family, with those from *MAPT* families learning of their risk earlier (M=30.1 years of age, [SD=13.6]) than *GRN* (M=37.2, [SD=10.1]) and *C9orf72* families (M=34.2, [SD=12.05]). While this was not statistically significant across all genetic groups, pairwise comparisons revealed that individuals at-risk of *MAPT* learnt of their risk significantly younger than those at-risk of *GRN* mutations (p=0.02).

Section 2 – Genetic counselling and presymptomatic genetic testing

2.1 Have you ever had genetic counselling?

Table 5 - Number and percentage of participants who had genetic counselling

	N	**%**
Yes	83	56%
No	65	44%
Total	148	

Eighty-three (56%) individuals answered that they had genetic counselling, the first step in the predictive testing process. The remaining 44% either chose not to have predictive testing or did not receive the genetic counselling element.

2.2 Have you had presymptomatic genetic testing?

As reported above, 87 (58%) individuals had predictive testing and 62 (42%) had not. The time since individuals had predictive testing ranged from one month to 20 years prior to completing the questionnaire, with a mean of 3.4 years (SD=3.1).

Fifteen individuals (10%) of those who had counselling did not go on to have testing, while 19 (13%) of those who had predictive testing, did not have genetic counselling.

2.3 How long did you consider having genetic testing for before you had the test?

Those who had predictive testing were asked how long they considered having testing prior to undergoing the test. Fifty-three percent considered this decision for less than six months, 19% for between six months and one year, 7% for one to two years, 7% for two to three years and 14% for more than three years.

Table 6 - Number and percentage of participants at each response level for time considered genetic testing

	N	**%**
<6 months	47	53%
6 months - 1 year	17	19%
1 year to 2 years	6	7%
2 years - 3 years	6	7%
More than 3 years	12	14%
Total	88	

2.4a Did presymptomatic genetic testing show that you were a carrier of the genetic mutation?

Those who had predictive testing reported their subsequent genetic status; 66 (76%) were found to carry a genetic mutation known to cause fFTD, and 21 (24%) were found

not to carry the mutation.

2.4b On a scale of 0-100% what do you think your risk is of carrying a mutation?

Those who did not have predictive testing were asked to estimate their perception of their risk on a scale of 0-100%. All participants who responded to this question were at 50% risk of carrying a mutation for fFTD. Responses ranged from 0% to 100%, with 68% believing their risk to be 50%. Participant's perception of their risk is displayed below.

Table 7 - Number and percentage of participant responses within each category of genetic risk percentage estimation

	N	%
0% - 24%	6	10%
25% - 49%	2	3%
50%	43	68%
51% - 75%	9	14%
100%	3	5%
Total	**63**	

2.5 To what extent were the following reasons important in your decision to have presymptomatic testing?

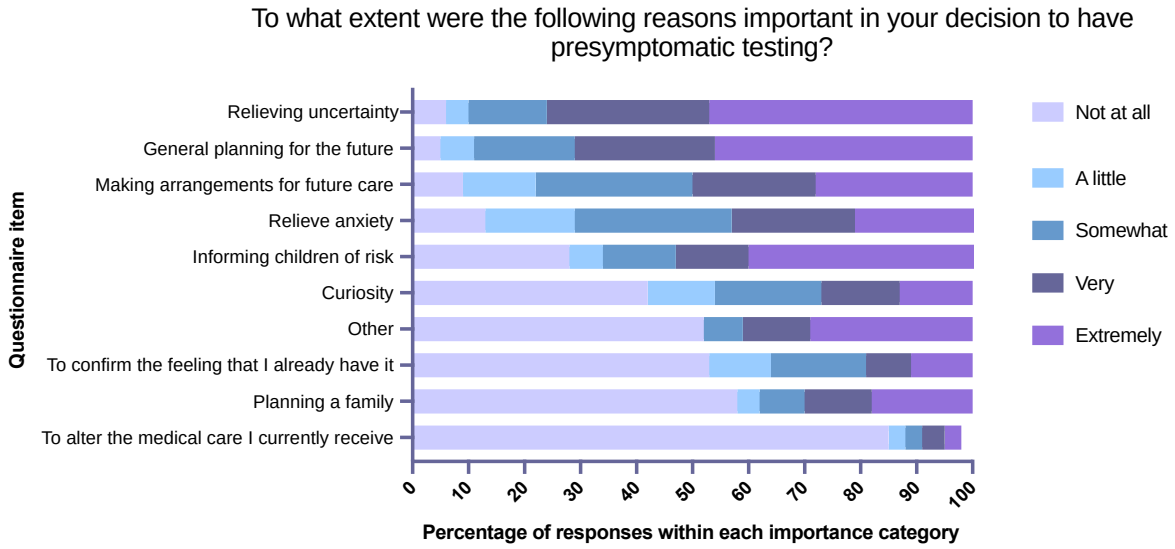


Figure 4 - Stacked bar chart showing percentage responses within each importance level for each questionnaire item

Participants were asked how important the following factors were in their decision making. Percentage responses for each item is shown in Figure 4. As responses were recorded using a Likert scale and as such, data was categorical, the median importance are reported for each item. Relieving uncertainty, general planning for the future, informing children of their risk and making arrangements for future care were considered the most important factors, with median ratings of 4, corresponding to 'very' important. This was followed by relieving anxiety, (median = 3 – 'somewhat' important), curiosity (median = 2 – 'a little' important). Altering current medical care, confirming the feeling you already have it and planning a family were rated as 'not at all' important (median = 1). Median response values and interquartile ranges are demonstrated for each item in Table 8. Participants were asked to state any other factors that they considered important in a free answer box. Qualitative responses were grouped into a number of topics, the number of responses for each topic is displayed in Table 9. Other factors included becoming involved with research, finding a cure, planning for the future, particularly financial planning, their experience with their symptomatic parent, for future children and to inform children of their risk and 'I wanted to know".

Table 8 - Median importance rating and IQR for each item regarding reasons for having predictive testing

	Relieving uncertainty	General planning for the future	Informing children of risk	Making arrange-ments for future care	Relieve anxiety	Curiosity	To alter the medical care I currently receive	To confirm the feeling that I already have it	Planning a family	Other
Median importance	**4**	**4**	**4**	**4**	**3**	**2**	**1**	**1**	**1**	**1**
IQR	1	2	4	2	2	0	2	3	3	4

Note: possible scores ranged from 1-5, where 1 was not at all and 5 was extremely

Table 9 - Qualitative response topics for 'other factors' option regarding reasons for having predictive testing

Topic	N
Get involved with research	6
- To find a cure	2
Planning	
- To plan for the future	2
- Financial planning	2
- Pension planning	1
Experience with symptomatic parent	2
For children	
- To inform children of their risk	2
- So that they can make informed choices (regarding PGD)	1
- Didn't want to pass gene to future children	1
"I wanted to know"	2
To relieve pressure and worry for partner	1
Availability	1
"Information is power"	1
To spot early signs and symptoms	1
Personal circumstances	1
For prevention	1
To confirm my interest in following the scientific development (knowledge and treatment)	1
Application for euthanasia (non-UK)	1
Take control of health	1
Live life as peacefully and be happy as possible	1

2.6 To what extent were the following reasons important in your decision to not have presymptomatic testing?

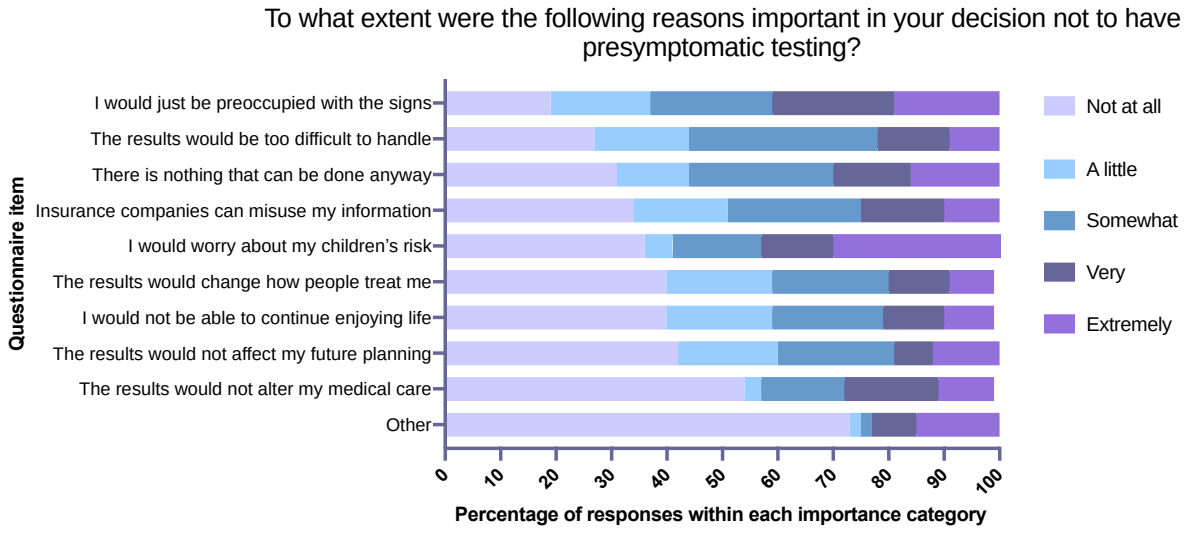


Figure 5 - Stacked bar chart showing percentage responses within each importance level for each questionnaire item

Participants were also asked how important certain factors were in their decision not to have predictive testing, this was reported on the same Likert scale as above, percentage responses at each importance level are shown for each item in Figure 5. The most important reasons rated by participants for not having predictive testing were; ‘the results would be too difficult to handle’, ‘there is nothing that can be done anyway’, worry about children’s risk and preoccupation with signs of symptom onset, all with median ratings of 3, corresponding to ‘somewhat’ important. ‘The results would not affect my future planning’, ‘I would not be able to continue enjoying life’, ‘the results would change how people treat me’ and insurance misuse were all rated as ‘a little’ important with median importance ratings of 2. The final two items were rated as ‘not at all’ important; ‘the results would not affect my medical care’ and other, both with median scores of 1. Median response values and interquartile ranges for each item are reported in Table 10.

As above, participants were asked to state other factors that they considered important in their decision not to have predictive testing. As above, qualitative data was categorised into topics and number of responses recorded in Table 11.

Table 10 - Median importance rating and IQR for each item regarding reasons against having predictive testing

	The results would be too difficult to handle	There is nothing that can be done anyway	I would worry about my children’s risk	I would just be preoccupied with the signs	The results would not affect my future planning	I would not be able to continue enjoying life	The results would change how people treat me	Insurance companies can misuse my information	The results would not alter my medical care	Other
Median importance	**3**	**3**	**3**	**3**	**2**	**2**	**2**	**2**	**1**	**1**
IQR	2	3	4	2	2	2	2	2	3	1

Note: possible scores ranged from 1-5, where 1 was not at all and 5 was extremely

Table 11 - Qualitative response topics for 'other factors' option regarding reasons against having predictive testing

Topic	N
Lack of treatment	2
Partner's views	1
They were too busy to consider it	1
They wouldn't trust decision making if they knew they carried the mutation	1
Focused on caring needs of relative	1
Friends were not supportive	1
They had no concerning feelings regarding mutation status	1
Lack of clarity on when in life onset may happen	1

Section 3 – Mental and physical health

3.1 a) Have you had emotional problems in the past?

Overall, 47% respondents had experienced emotional problems in the past. This was evenly distributed across participant demographics (genetic group, gender, real mutation status and reported mutation status), with no significant differences observed between groups.

b) Have you ever had any diagnosed mental health problems?

Twenty-seven percent of participants reported themselves as having had a mental health diagnosis, 16% had a previous diagnosis and 11% ongoing. Of all those with a mental health diagnosis, 51% were from families affected by *C9orf72*, 26% *MAPT* and 21% *GRN*. Percentage of participants with previous, ongoing or any prior and/or ongoing diagnoses are reported in Table 12 stratified by demographic characteristics. There was a significant difference in mental health diagnoses by gender ($\chi^2(2) = 15.3$, $p<0.01$). Of those with a mental health diagnosis, significantly more were female (85%), than male (15%). Similarly, there was a significant difference in mental health diagnosis when stratifying by biological status and genetic group ($\chi^2(6) = 12.8$, $p<0.05$), with fewer diagnoses observed in the *GRN* mutation carrier group.

Table 12 - Percentage of participants with a previous or ongoing mental health diagnosis, by genetic group, gender and biological status

		Previous	Ongoing	Any prior and/or ongoing diagnoses
Genetic group	*C9orf72*	43%	67%	51%
	GRN	30%	7%	21%
	MAPT	26%	27%	26%
Gender	Female	83%	88%	85%
	Male	17%	13%	15%
Biological status by gene group	Non-carriers	35%	40%	36%
	C9orf72 mutation carriers	31%	47%	36%
	GRN mutation carriers	9%	7%	8%
	MAPT mutation carriers	26%	7%	18%

c) If the answer to Question 1b is yes, what diagnosis was made?

The majority of diagnoses were of depression (n=27) followed by anxiety (n=23). Of those with depression and anxiety diagnoses, 12 had a combination of both diagnoses. Other 'diagnoses' stated by the participant included; stress, obsessive compulsive disorder (OCD), "neuroses", work related stress and personal issues.

d) Since finding out that you were at risk of FTD, have you had emotional problems that have led to you having thoughts about suicide?

Eleven percent of participants reported having experienced suicidal ideation since learning they were at-risk, with an additional 4% choosing not to answer this question and instead utilising the 'prefer not to say' option provided. Percentage of participants reporting suicidal ideation currently, more than six months ago and more than one year ago, are reported in Table 13. The majority of suicidal ideation occurred more than one year prior to survey completion. More females reported suicidal ideation compared to males, however this was not statistically significant. Significantly more known mutation carriers reported suicidal ideation compared to known non-carriers and those with unknown status ($\chi^2(6) = 12.6$, $p<0.05$).

Table 13 - Percentage of participants reporting suicidal ideation at different time points, by genetic group, gender and reported status

		Yes - total	Yes - currently	Yes – more than 6 months ago	Yes – more than 1 year ago
Genetic group	*C9orf72*	47%	-	-	47%
	GRN	27%	-	7%	20%
	MAPT	27%	7%	-	20%
Gender	Female	67%	7%	7%	53%
	Male	33%	-	-	33%
Reported (known) genetic status	Known mutation carriers	67%	7%	-	60%
	Known non-carriers	27%	-	-	27%
	Unknown	7%	-	7%	0%

e) In the past month have you:

- felt generally sad

- felt nervous and anxious

Regarding a feeling of sadness in the past month, the median score was 2 (IQR = 2), corresponding to 'hardly ever', however 47% of participants scored themselves between 'sometimes' and 'almost all of the time'. This was the same for nervousness and anxiety in the past month (median = 2, IQR = 1), with 49% scoring between 'sometimes' and 'almost all of the time'. Percentage of participants feeling sadness and nervousness and anxiety at each frequency level is reported in Table 14. There was a significant effect of gender on both sadness score ($\chi^2(4) = 12.6$, $p=0.01$) and nervousness and anxiety ($\chi^2(4) = 15.7$, $p<0.01$). There was a significant effect of gender on both sadness score ($\chi^2(4) = 12.6$, $p=0.01$) and nervousness and anxiety ($\chi^2(4) = 15.7$, $p<0.01$), with females experiencing both sadness, and nervousness and anxiety more frequently than males.

Table 14 - Percentage of participant responses at each frequency level for feelings of sadness and nervousness and anxiousness

	Sadness			Nervous & anxious		
	Total	Females	Males	Total	Females	Males
1 - Not at all	30%	23%	39%	25%	18%	34%
2 - Hardly ever	23%	17%	31%	27%	24%	33%
3 - Sometimes	36%	46%	23%	34%	38%	30%
4 - Often	10%	13%	7%	12%	20%	2%
5 - Almost all the time	1%	0%	0%	3%	0%	2%

3.2 Has being aware of your at-risk status changed your mental health?

Participants were asked to rate the change in their mental health since finding out about their risk on a 7-point Likert scale, where 1-3 signifies a change for the worse, 4 is no change and 5-7 signifies a change for the better. The median rating was 4 (IQR = 1), corresponding to no change. Fifty-two percent of respondents rated their mental health as not changing since learning of their risk, 37% rated that their mental health changed for the worse and 11% changed for the better (see Table 15). There were no significant differences based on participant demographics.

Table 15 - Number and percentage of participant responses for change in mental health following risk disclosure

		N	%
Changed for the worse	1	6	4%
	2	18	12%
	3	30	21%
No change	4	75	52%
Changed for the better	5	7	5%
	6	6	4%
	7	3	2%

3.3 If you have had presymptomatic genetic testing, has that changed your mental health?

Those who had predictive testing were also asked to rate the change in their mental health since having predictive testing on the 7-point scale as detailed in question 3.2. The median rating was 4 (IQR = 1), signifying no change. As above, 52% respondents rated their mental health as not changing since having predictive testing, 22% rated

that their mental health changed for the worse and 26% changed for the better (see Table 16). Again, as above there were no significant differences observed based on participant demographics.

Table 16 - Number and percentage of participant responses regarding change in mental health following predictive testing

		N	%
Changed for the worse	1	1	1%
	2	6	7%
	3	12	14%
No change	4	45	52%
Changed for the better	5	13	15%
	6	4	5%
	7	5	6%

3.4 To what extent do you currently agree with the following statements:

As part of the original GPRI questionnaire, participants were asked to rate 10 statements from 0 to 5 based on how strongly they agreed with the statement. For the first item 0 corresponded to not applicable, 1 was strongly disagree, 3 was neither agree nor disagree and 5 was strongly agree. For items two to 10 the scale was the same, however 'not applicable' was also scored as five due to the questionnaire weighting. For all items except item two, the median rating was 3, suggesting that participants didn't agree nor disagree. For item two – "I am concerned about my risk of getting the disease, however this concern interferes minimally with my everyday life", the median rating was 4, signifying agreement with the statement. Median response values, interquartile range (IQR) and percentage of participant responses are reported in Table 17.

Table 17 - Median rating, IQR and percentage responses for Genetic Psychosocial Risk Instrument (GPRI) item ' to what extent do you believe in the following statements'

	I will have more problems in my life	I am concerned about my risk of getting the disease, however this concern interferes minimally with my everyday life	I will change plans for my career or profession	I will have difficulties in my family relationships	The disease for which I am at risk is currently causing a significant disruption in my family life	I am worried that my test result will impact on my relationship with my significant other (or future partner)	I am worried about talking to my children (young or adult) about the heritable nature of the disease	My worries about the disease affect my daily mood	I often find myself worrying or preoccupied with my risk of getting the disease	I feel guilty that I might pass on the disease risk to my children
Median	**3**	**4**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
IQR	**2**	**1**	**2**	**3**	**3**	**3**	**1**	**2**	**2**	**1**
0	9%	-	-	-	-	-	-	-	-	-
1	13%	11%	21%	32%	32%	29%	17%	33%	22%	15%
2	13%	4%	15%	11%	15%	13%	7%	17%	13%	5%
3	19%	26%	30%	24%	26%	27%	47%	28%	33%	44%
4	33%	40%	21%	27%	18%	22%	16%	20%	24%	14%
5	14%	19%	13%	6%	8%	8%	13%	3%	9%	22%

Note: possible scores ranged from 0-5 for the first statement, where 0 is not applicable, 1 is strongly disagree and 5 is strongly agree, and from 1-5 thereafter

3.5 Have you had counselling with a counsellor and/or mental health professional in the past?

Seventy-two percent of participants reported that they had counselling in the past (see Table 18 for percentage responses by demographic groups). There was a significant gender difference observed ($\chi^2(1) = 7.4$, $p<0.01$), with significantly more females having had counselling than males. There was also a significant difference when stratified by gene group and biological status ($\chi^2(3) = 9.4$, $p=0.03$).

Table 18 - Percentage of participants reporting having had counselling in the past, by genetic group, gender and biological status

		Yes	**No**
Genetic group	*C9orf72*	71%	29%
	GRN	64%	36%
	MAPT	91%	9%
Gender	Female	81%	19%
	Male	61%	39%
Biological status by gene group	Non-carriers	72%	28%
	C9orf72 mutation carriers	74%	26%
	GRN mutation carriers	58%	42%
	MAPT mutation carriers	100%	
Total		72%	28%

3.6 Are you currently seeing a counsellor and/or mental health professional about any emotional concerns?

Sixty-two percent of participants reported that they were currently seeing a counsellor or mental health professional about an emotional concern (see Table 19 for percentages of participants undergoing counselling across demographic groups). There was a significant difference when stratified by gene group and biological status ($\chi^2(3) = 12.6$, $p<0.01$)

Table 19 - Percentage of participants reporting currently undergoing counselling, by genetic group, gender and biological status

		Yes	No
Genetic group	*C9orf72*	61%	39%
	GRN	50%	50%
	MAPT	87%	13%
Gender	Female	68%	32%
	Male	56%	44%
Biological status by gene group	Non-carriers	61%	39%
	C9orf72 mutation carriers	67%	33%
	GRN mutation carriers	42%	58%
	MAPT mutation carriers	94%	6%
Total		62%	38%

Section 4 – Support during the at-risk period

4.1 Have you had any support during the at-risk period?

Thirty-nine percent of respondents had accessed support during the at-risk period, leaving 61% without having experienced support.

4.2 If you have accessed support (or attempted to), how easy was it to get?

Those individuals who had received support while at-risk were also asked how easy it was to access this support on a 7-point scale where 1 was extremely easy and 7 extremely difficult. The median response was 3 (IQR = 3). Percentage responses at each level are reported in Table 20.

Table 20 - Number and percentage of participant responses for each difficulty level regarding ease of accessing support

	N	%
1 – Extremely easy	18	26%
2	12	17%
3	9	13%
4	17	25%
5	6	9%
6	3	4%
7 – Extremely difficult	4	6%
Total	69	

4.3 If you have accessed support, how much have you benefited from it?

Those who accessed support were also asked how much they benefitted from the support they received on a 7-point scale where 1 was hugely beneficial and 7 was not at all beneficial. The median rating was 3.5 (IQR = 3). Percentage responses at each level are reported in Table 21.

Table 21 - Number and percentage of participant responses for each level regarding benefit of support received

	N	%
1 - Hugely	17	25%
2	9	13%
3	8	12%
4	13	19%
5	9	13%
6	4	6%
7 – Not at all	8	12%
Total	68	

3.4.2. GAD-7

The mean raw GAD-7 score across all groups was 4 (SD=4.35). GAD-7 scores can also be stratified by symptom severity, where scores of one to five signify mild anxiety symptoms, six to 10 are moderate and scores of 11 or above signify severe anxiety symptoms. When stratified by severity categories, 66% participants displayed no symptoms, 24% mild symptoms and 11% moderate or severe (see Table 22). Fifteen percent met the reported caseness threshold of eight or more, and 10% met the threshold of ≥10. GAD-7 mean scores and standard deviations are displayed below in Table 23 stratified by demographic groups.

Table 22 - Number and percentage of participants scoring within each GAD-7 severity category

Severity category	N	%
None	93	66%
Mild	34	24%
Moderate	9	6%
Severe	6	4%

Table 23 - GAD-7 mean scores and standard deviations by demographic characteristics

		N	GAD-7 score	
			Mean	SD
Reported status				
	Unknown	55	3.13	3.32
	Known non-carrier	18	5.06	6.16
	Known mutation carrier	63	4.17	4.42
Biological status				
	Non-carrier	53	4.00	4.57
	Carrier	82	3.87	4.32
Gender				
	Female	77	4.86	4.92
	Male	59	2.66	3.21
Genetic group				
*Those at-risk of *TBK1* were excluded from this analysis as there were too few to make meaningful conclusions	*C9orf72*	71	2.44	2.84
	GRN	44	4.89	5.00
	MAPT	22	6.95	5.33

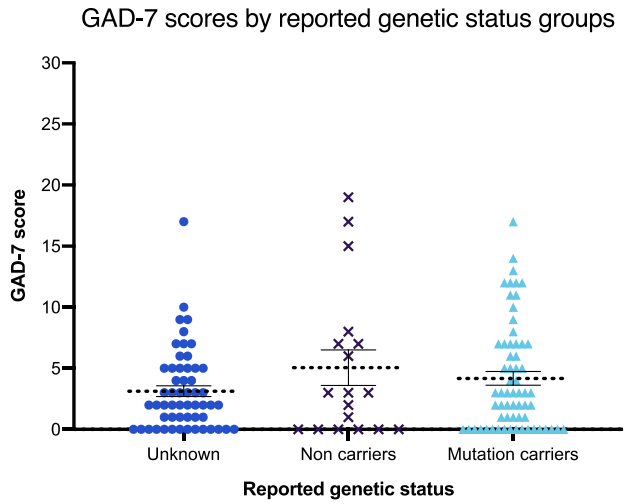
3.4.2.1. Does knowing status affect GAD-7 score?

There was no significant difference in GAD-7 score between reported status groups (unknown status, known non-carriers and known mutation carriers). A significant difference in GAD-7 score was observed between genders (p<0.01). Pairwise comparisons revealed that GAD-7 scores were significantly lower in males compared with females (mean difference = -1.98, p<0.01). No other significant differences were observed.

However, when reported status was stratified by genetic group, there was a significant difference observed in GAD-7 score between gene and reported status groups for *C9orf72* mutation carriers (p=0.02) and *MAPT* mutation carriers (p=0.02). Pairwise comparisons revealed significantly lower GAD-7 scores in *C9orf72* mutation carriers compared to non-carrier controls (mean difference = -2.06, p=0.02), *GRN* mutation carriers (mean difference = -3.39, p<0.01), and *MAPT* mutation carriers (mean difference = -5.36, p<0.001). GAD-7 scores were significantly higher in *MAPT* mutation carriers compared to non-carriers (mean difference = 3.30, p=0.02), *C9orf72* with unknown status (mean difference = 4.64, p<0.01) and *MAPT* with unknown status (mean difference = 4.68, p<0.01). The *C9orf72* group with unknown status and *MAPT* with unknown status both scored significantly lower compared to *GRN* mutation carriers (mean difference = -2.66, p=0.02 and mean difference = -2.70, p=0.03 respectively). As above, there was also a significant effect of gender (p<0.01), with males scoring significantly lower than females (mean difference = -2.22, p<0.01).

Figure 6a-b show the distribution of GAD-7 scores across reported status groups.

a)



b)

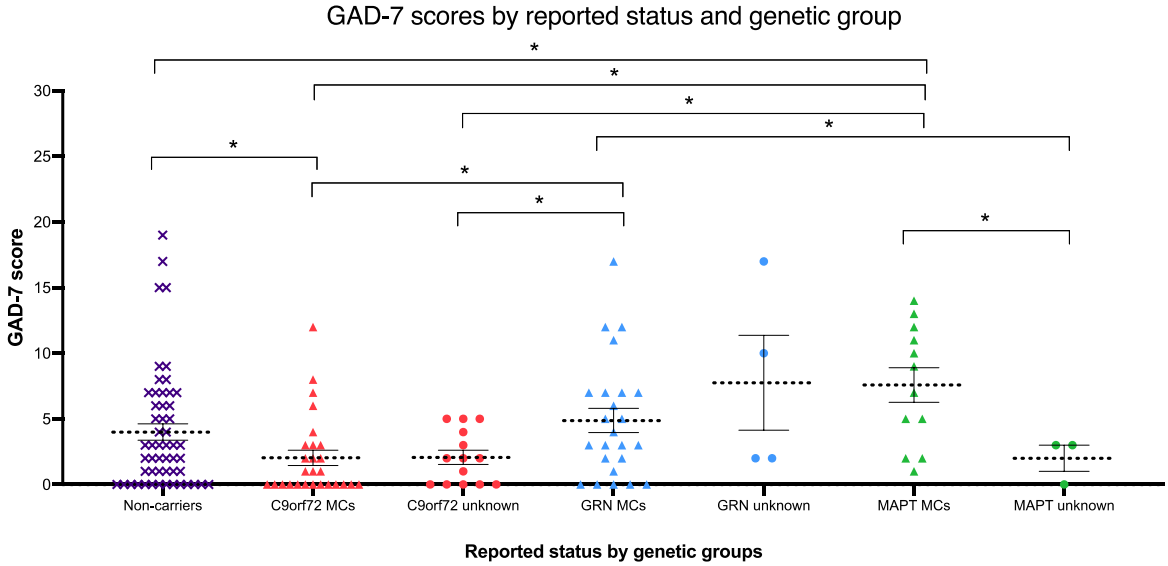


Figure 6 a-b - Scatter plots demonstrating the distribution of GAD-7 scores across reported status groups. Horizontal dotted lines show the mean GAD-7 score for each group and asterixis indicate significant comparisons. Asterisks denote p<0.05.

3.4.3. Does biological status affect GAD-7 score?

There was also no significant difference in GAD-7 score between biological status groups (mutation carriers vs non-carriers). Again, a significant difference in GAD-7 score was observed between genders (p<0.01). Pairwise comparisons revealed significantly lower GAD-7 scores in males compared with females (mean difference = -2.21, p<0.01). No other significant differences were observed.

When biological status was stratified by genetic group, however, there was a significant difference in GAD-7 score. Pairwise comparisons revealed *C9orf72* mutation carriers scored significantly lower compared to non-carriers (mean difference = -1.84, p=0.16), *GRN* mutation carriers (mean difference = -3.48, p<0.01) and *MAPT* mutation carriers (mean difference = -4.22, p<0.001). There was also a trend towards significance in *MAPT* mutation carriers compared to non-carrier controls (p=0.60). A significant effect of gender was observed (p<0.01), with pairwise comparisons revealing, consistent with the findings reported above, that males scored significantly lower on GAD-7 compared to females (mean difference = -2.29, p<0.01).

Figure 7a-b show the distribution of GAD-7 scores across biological status groups.

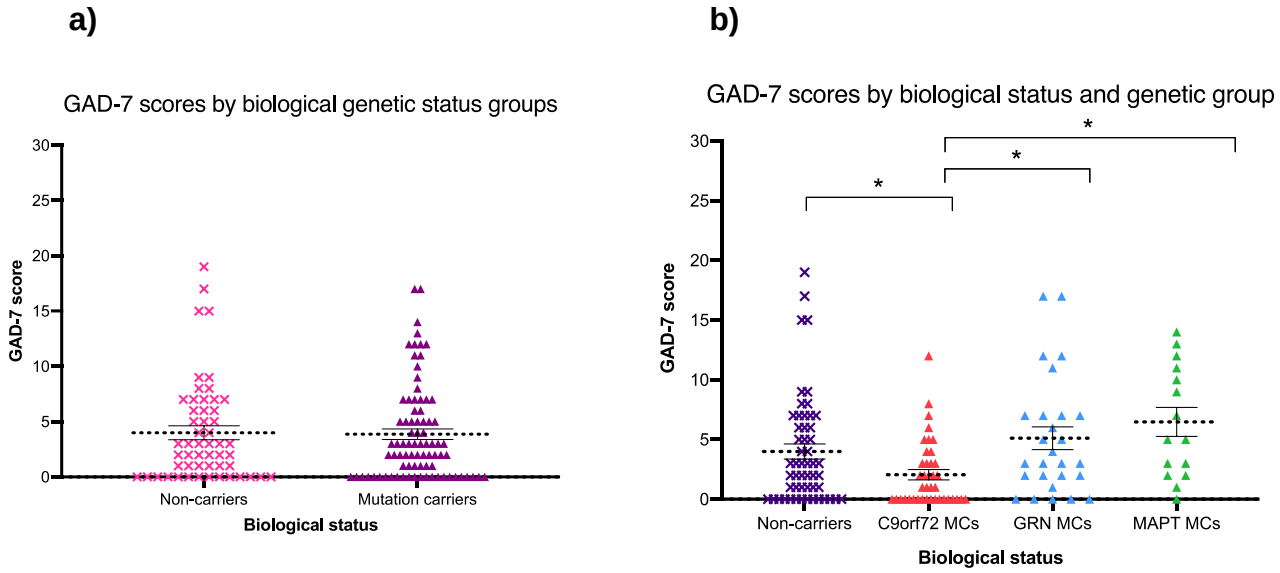


Figure 7 a-b - Scatter plots demonstrating the distribution of GAD-7 scores across biological status groups. Horizontal dotted lines show the mean GAD-7 score for each group and asterixis indicate significant comparisons. Asterisks denote p<0.05.

3.4.3.1. Do years to parental onset correlate with GAD-7 score?

A Spearman correlation revealed no correlation between years to parental age at onset and GAD-7 score.

Table 24 – GAD-7 mean differences between groups, p-values and confidence intervals for each comparison within linear regression models

Model	Comparisons	Mean difference	*p*-value	95% confidence interval	
				Lower	Upper
Reported status					
	Non-carrier vs unknown	1.91	0.21	-1.10	4.91
	Mutation carrier vs unknown	1.02	0.13	-0.32	2.35
	Mutation carrier vs non-carrier	-0.87	0.58	-3.99	2.22
	Male vs female	-1.98	<0.01*	-3.32	-0.64
	Years in education	0.08	0.38	-0.10	0.26
Biological status					
	Mutation carriers vs non-carriers	0.44	0.96	-1.49	1.57
	Male vs female	-2.21	<0.01*	-3.61	-0.80
	Years in education	0.02	0.83	-0.17	0.21
Gene group and reported status					
	C9orf72 mutation carriers vs non-carriers	-2.06	0.02*	-3.79	-0.33
	GRN mutation carriers vs non-carriers	1.32	0.25	-0.95	3.60
	MAPT mutation carriers vs non-carriers	3.30	0.02*	0.52	6.08
	C9orf72 unknown vs non-carriers	-1.34	0.13	-3.08	0.40
	GRN unknown vs non-carrier	3.64	0.38	-4.41	11.70
	MAPT unknown vs non-carriers	-1.38	0.19	-3.42	0.67
	GRN mutation carriers vs C9orf72 mutation carriers	3.39	0.01*	1.05	5.72
	MAPT mutation carriers vs C9orf72 mutation carriers	5.36	<0.001*	2.65	8.07
	C9orf72 unknown vs C9orf72 mutation carriers	0.72	0.40	-0.97	2.42
	GRN unknown vs C9orf72 mutation carriers	5.70	0.17	-2.36	13.76

	MAPT unknown vs C9orf72 mutation carriers	0.68	0.55	-1.57	2.94
	MAPT mutation carriers vs GRN mutation carriers	1.98	0.23	-1.24	5.19
	C9orf72 unknown vs GRN mutation carriers	-2.66	0.02*	-4.89	-0.44
	GRN unknown vs GRN mutation carriers	2.32	0.58	-5.86	10.50
	MAPT unknown vs GRN mutation carriers	-2.70	0.03*	-5.12	-0.28
	C9orf72 unknown vs MAPT mutation carriers	-4.64	<0.01*	-7.47	-1.81
	GRN unknown vs MAPT mutation carriers	0.34	0.94	-8.16	8.84
	MAPT unknown vs MAPT mutation carriers	-4.68	<0.01*	-7.78	-1.81
	GRN unknown vs C9orf72 unknown	4.98	0.23	-3.09	13.05
	MAPT unknown vs C9orf72 unknown	-0.04	0.97	-2.25	2.18
	MAPT unknown vs GRN unknown	-5.02	0.23	-13.21	3.18
	Male vs female	-2.22	<0.01*	-3.64	-0.81
	Years in education	0.00	0.96	-0.18	0.19
Gene group and biological status	*C9orf72 mutation carriers vs non-carriers*	-1.84	0.02*	-3.34	-0.35
	GRN mutation carriers vs non-carriers	1.64	0.15	-0.57	3.85
	MAPT mutation carriers vs non-carriers	2.38	0.06	-0.10	4.87
	GRN mutation carriers vs C9orf72 mutation carriers	3.48	<0.01*	1.40	5.57
	MAPT mutation carriers vs C9orf72 mutation carriers	4.22	<0.001*	1.87	6.58
	MAPT mutation carriers vs GRN mutation carriers	0.74	0.62	-2.16	3.64
	Male vs female	-2.29	<0.01*	-3.68	-0.89
	Years in education	-0.05	0.78	-0.20	0.15

3.4.4. PHQ-9

The mean PHQ-9 score across all groups was 4 (SD = 4.40). As detailed above with the GAD-7, PHQ-9 scores can be similarly stratified by symptom severity. Scores of five to nine indicate mild symptoms, 10 to 14 are moderate, 11 to 19 moderately severe symptoms and 20 to 27 are severe depressive symptoms. Sixty-seven percent of participants displayed no symptoms on the PHQ-9 measure, 21% had mild depressive symptoms and 13% scored from moderate to moderately severe (see Table 25). No participants scored within the severe depressive symptoms category. Thirteen percent of participants received PHQ-9 scores above the threshold of ≥10 described in the literature.

PHQ-9 mean scores and standard deviations are displayed below in Table 26 stratified by demographic groups.

Table 25 - Number and percentage of participants scoring within each PHQ-9 severity category

Severity category	N	%
None	94	67%
Mild	30	21%
Moderate	12	9%
Moderately severe	5	4%
Severe	0	0%

Table 26 - PHQ-9 mean scores and standard deviations by demographic characteristics

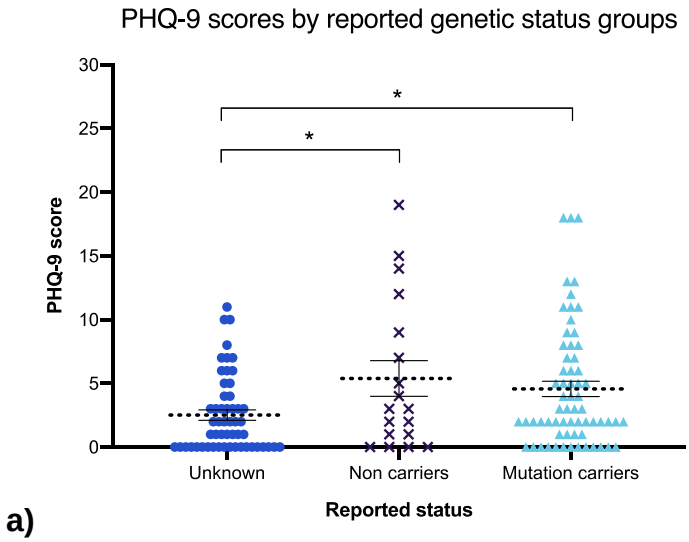
		N	PHQ-9 score	
			Mean	SD
Reported status				
	Unknown	53	2.45	2.98
	Known non-carrier	18	5.39	5.95
	Known mutation carrier	64	4.56	4.74
Biological status				
	Non-carrier	52	3.71	4.34
	Carrier	82	3.92	4.53
Gender				
	Female	76	4.43	4.84
	Male	59	3.02	3.73
Genetic group				
*Those at-risk of *TBK1* were excluded from this analysis as there were too few to make meaningful conclusions	*C9orf72*	70	2.57	3.02
	GRN	44	4.66	5.12
	MAPT	22	6.36	5.46

3.4.4.1. Does knowing status affect PHQ-9 score?

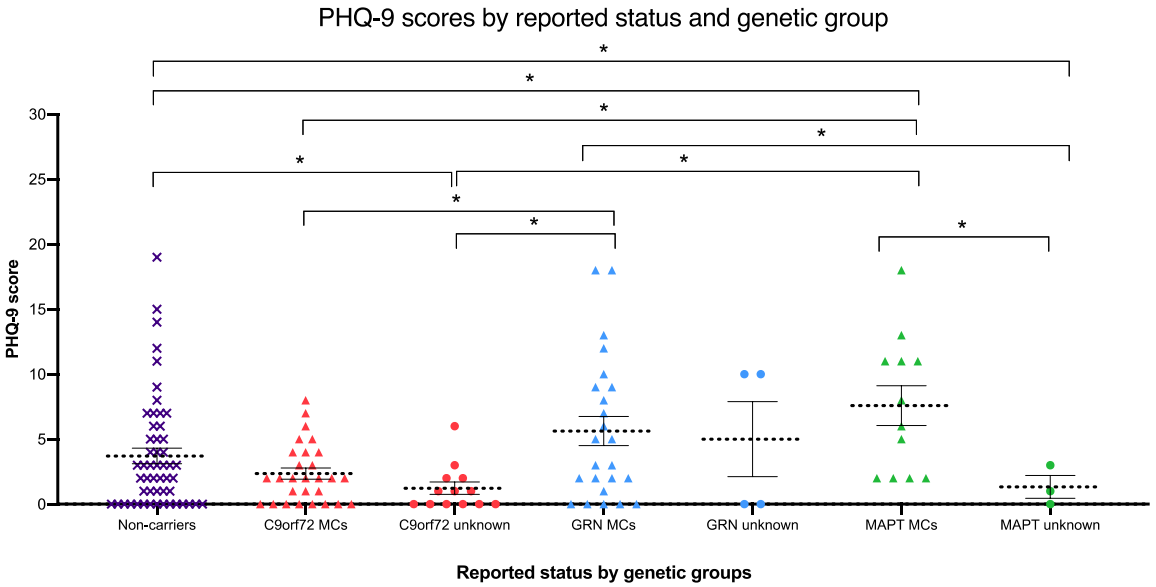
There was a significant effect of reported status on PHQ-9 score (p<0.01). Pairwise comparisons revealed that both non-carriers and mutation carriers scored significantly higher than those with unknown status (mean difference = 2.95, p=0.04 and mean difference = 2.13, p<0.01 respectively). No other significant differences were observed.

When reported status was stratified by genetic group, there was a significant effect of gene and status on PHQ-9 score (p<0.001). Pairwise comparisons revealed that *MAPT* mutation carriers scored significantly higher than non-carriers (mean difference = 3.70, p=0.02), *C9orf72* mutation carriers (mean difference = 5.13, p<0.01), *C9orf72* unknown status (mean difference = 5.81, p<0.001) and *MAPT* unknown status (mean difference = 5.57, p<0.01). *C9orf72* mutation carriers scored significantly lower than *GRN* mutation carriers (mean difference = -3.66, p=0.01). The *C9orf72* group with unknown status scored significantly lower compared to non-carriers (mean difference = -2.11, p=0.01) and *GRN* mutation carriers (mean difference = -4.34, p<0.01). The *MAPT* group with unknown status scored significantly lower than non-carriers (mean difference = -1.87, p=0.02) and *GRN* mutation carriers (mean difference = -4.10, p<0.01).

Figure 8 a-b show the distribution of PHQ-9scores across reported status groups.



a)



b)

Figure 8 a-b - Scatter plots demonstrating the distribution of PHQ-9 scores across reported status groups. Horizontal dotted lines show the mean PHQ-9 score for each group and asterixis indicate significant comparisons. Asterisks denote p<0.05.

3.4.4.2. Does biological status affect PHQ-9 score?

There were no significant differences in PHQ-9 score between biological status groups (mutation carriers vs non-carriers).

There was a significant difference in PHQ-9 score when stratified by biological status and genetic group (p<0.001). *C9orf72* mutation carriers scored significantly lower than

non-carriers (mean difference = -1.63, *p*=0.02), *GRN* mutation carriers (mean difference = -3.69, *p*<0.01) and *MAPT* mutation carriers (mean difference = -4.22, *p*<0.01). There was also a significant gender difference observed in PHQ-9 scores, with males scoring significantly lower compared to female participants (mean difference =-1.49, *p*=0.04).

Figure 9 a-b show the distribution of PHQ-9 scores across biological status groups.

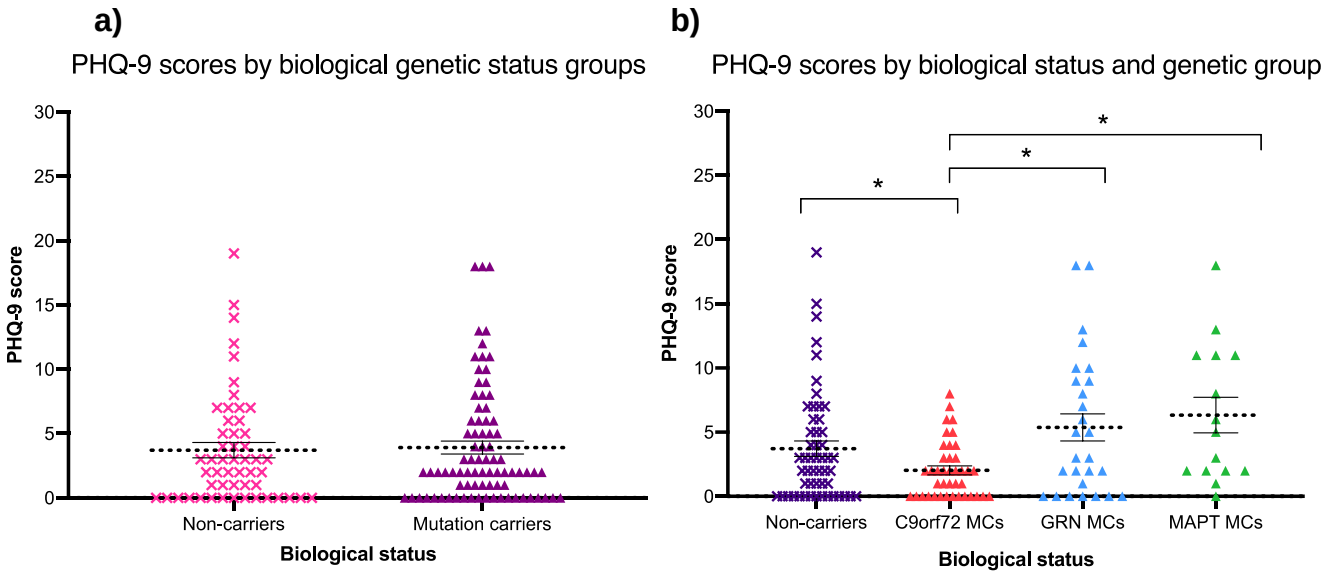


Figure 9 a-b - Scatter plots demonstrating the distribution of PHQ-9 scores across biological status groups. Horizontal dotted lines show the mean PHQ-9 score for each group and asterixis indicate significant comparisons. Asterisks denote p<0.05.

3.4.4.3. Do years to parental onset correlate with PHQ-9 score?

A Spearman correlation revealed no correlation between years to parental age at onset and PHQ-9 score.

Table 27 - PHQ-9 mean differences between groups, p-values and confidence intervals for each comparison within linear regression models

Model	Comparisons	Mean difference	*p*-value	95% confidence interval	
				Lower	Upper
Reported status	*Non-carrier vs unknown*	2.95	0.04*	0.20	5.69
	Mutation carrier vs unknown	2.13	<0.01*	0.73	3.53
	Mutation carrier vs non-carrier	-0.82	0.59	-3.76	2.13
	Male vs female	-1.12	0.12	-2.54	0.31
	Years in education	0.03	0.74	-0.17	0.24
Biological status	*Mutation carriers vs non-carriers*	0.32	0.67	-1.15	1.78
	Male vs female	-1.40	0.07	-2.89	0.09
	Years in education	-0.00	0.98	-0.21	0.21
Gene group and reported status	*C9orf72 mutation carriers vs non-carriers*	-1.43	0.06	-2.92	0.06
	GRN mutation carriers vs non-carriers	2.23	0.10	-0.40	4.86
	MAPT mutation carriers vs non-carriers	3.70	0.02*	0.51	6.88
	C9orf72 unknown vs non-carriers	-2.11	0.01*	-3.72	-0.50
	GRN unknown vs non-carrier	-0.02	0.10	-5.63	5.59
	MAPT unknown vs non-carriers	-1.87	0.02*	-3.49	-0.25
	GRN mutation carriers vs C9orf72 mutation carriers	3.66	<0.01*	1.07	6.25
	MAPT mutation carriers vs C9orf72 mutation carriers	5.13	<0.01*	2.07	8.19
	C9orf72 unknown vs C9orf72 mutation carriers	-0.68	0.39	-2.21	0.85
	GRN unknown vs C9orf72 mutation carriers	1.41	0.62	-4.18	7.01

	MAPT unknown vs C9orf72 mutation carriers	-0.44	0.60	-2.11	1.22
	MAPT mutation carriers vs GRN mutation carriers	1.47	0.45	-2.34	5.28
	C9orf72 unknown vs GRN mutation carriers	-4.34	<0.01*	-7.06	-1.62
	GRN unknown vs GRN mutation carriers	-2.25	0.46	-8.26	3.77
	MAPT unknown vs GRN mutation carriers	-4.10	<0.01*	-6.49	-1.72
	C9orf72 unknown vs MAPT mutation carriers	-5.81	<0.001*	-9.02	-2.60
	GRN unknown vs MAPT mutation carriers	-3.72	0.24	-9.93	2.50
	MAPT unknown vs MAPT mutation carriers	-5.57	<0.01*	-8.87	-2.27
	GRN unknown vs C9orf72 unknown	2.09	0.47	-3.52	7.71
	MAPT unknown vs C9orf72 unknown	0.24	0.80	-1.64	2.11
	MAPT unknown vs GRN unknown	-1.86	0.52	-7.53	3.82
	Male vs female	-1.25	0.08	-2.66	0.15
	Years in education	-0.04	0.72	-0.24	0.17
Gene group and biological status	*C9orf72 mutation carriers vs non-carriers*	-1.63	0.02*	-2.98	-0.29
	GRN mutation carriers vs non-carriers	2.06	0.092	-0.33	4.45
	MAPT mutation carriers vs non-carriers	2.58	0.08	-0.26	5.43
	GRN mutation carriers vs C9orf72 mutation carriers	3.69	<0.01*	1.39	6.00
	MAPT mutation carriers vs C9orf72 mutation carriers	4.22	<0.01*	1.51	6.92
	MAPT mutation carriers vs GRN mutation carriers	0.52	0.77	-2.92	3.97
	Male vs female	-1.49	0.04*	-2.88	-0.11
	Years in education	-0.06	0.58	-0.26	0.15

3.4.5. Genetic Psychosocial Risk Instrument (GPRI)

The mean GPRI score across all groups was 45 (SD = 11.17). The original GPRI measure used a threshold score of 50 to identify those individuals in need of psychosocial referral. Thirty-nine percent of participants in this study met GPRI criteria for psychosocial referral.

GPRI means and standard deviations are displayed below in Table 28 stratified by demographic groups.

Table 28 – Genetic Psychosocial Risk Instrument (GPRI) mean scores and standard deviations by demographic characteristics

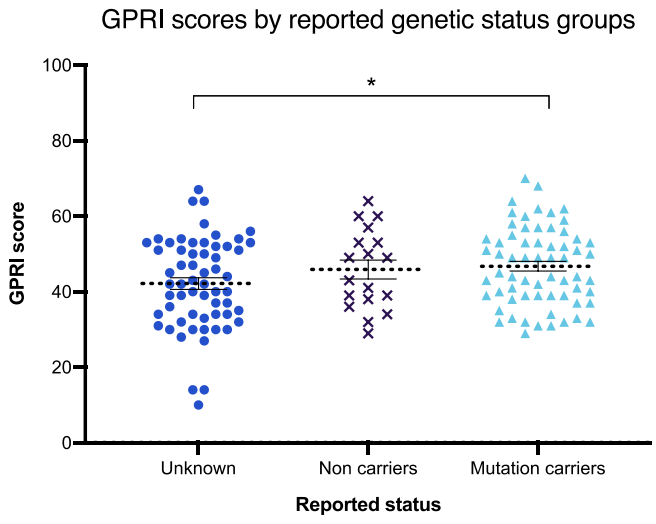
		N	GPRI score	
			Mean	SD
Reported status				
	Unknown	59	41.93	12.00
	Known non-carrier	18	45.89	10.56
	Known mutation carrier	64	46.75	10.29
Biological status				
	Non-carrier	54	44.57	11.96
	Carrier	86	44.84	10.83
Gender				
	Female	80	47.44	10.61
	Male	60	41.20	11.06
Genetic group				
*Those at-risk of *TBK1* were excluded from this analysis as there were too few to make meaningful conclusions	*C9orf72*	73	43.03	10.48
	GRN	47	44.47	10.69
	MAPT	22	50.73	13.09

3.4.5.1. Does knowing status affect GPRI score?

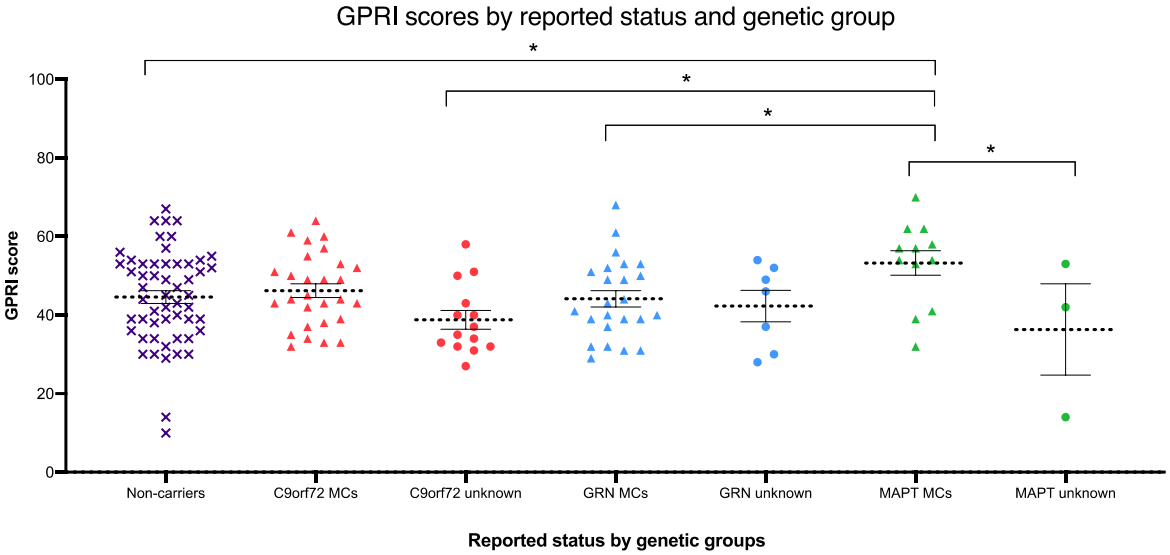
There was a significant effect of reported status on GPRI score (p<0.001). Pairwise comparisons found a significant difference in GPRI score between known mutation carriers and those with unknown status, with mutation carriers scoring significantly higher (mean difference = 4.15, p=0.34). There were also significant effects of gender, with males scoring significantly lower than females (mean difference = -5.85, p<0.01) and years in education (p=0.01).

When reported status and genetic group were combined, there was a significant difference between genetic groups, between genders, with females scoring higher than males (mean difference = 5.38, p<0.01) and a significant effect of years in education (p=0.01). Pairwise comparisons found that *MAPT* mutation carriers scored significantly higher compared to non-carriers (mean difference = 8.11, p=0.16), *GRN* mutation carriers (mean difference = 8.66, p=0.02), *C9orf72* with unknown status (mean difference = 12.44, p<0.01) and *MAPT* with unknown status (mean difference = 17.47, p=0.01).

Figure 10 a-b show the distribution of GPRI scores across reported status groups.



a)



b)

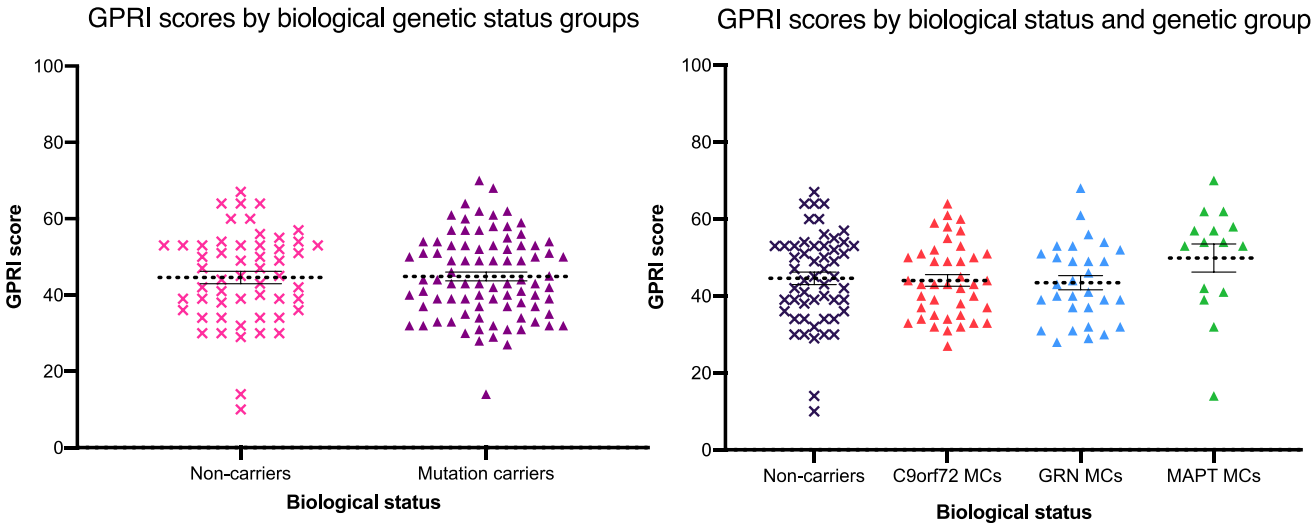
Figure 10 a-b - Scatter plots demonstrating the distribution of Genetic Psychosocial Risk Instrument (GPRI) scores across reported status groups. Horizontal dotted lines show the mean GPRI score for each group and asterixis indicate significant comparisons. Asterisks denote p<0.05.

3.4.5.2. Does biological status affect GPRI score?

There was no significant difference in GPRI score between biological status groups (mutation carriers vs non-carriers). There was a significant effect of gender, with males scoring significantly lower than females (mean difference = -6.47, $p<0.01$). There was also a significant effect of years in education ($p=0.02$).

When stratified by biological status and genetic group, there was no effect of gene group and biological status on GPRI score. As above, there was a significant effect of gender (mean difference =-6.25, $p<0.01$), with males scoring lower compared to females, and a significant effect of years in education ($p=0.03$).

Figure 11a-b show the distribution of GPRI scores across biological status groups.



a) **b)**

Figure 11 a-b - Scatter plots demonstrating the distribution of Genetic Psychosocial Risk Instrument (GPRI) scores across biological status groups. Horizontal dotted lines show the mean GPRI score for each group and asterixis indicate significant comparisons. Asterisks denote p<0.05.

3.4.5.3. Do years to parental onset correlate with GPRI score?

A Pearson correlation revealed no correlation between years to parental age at onset and GPRI score.

Table 29 - Genetic Psychosocial Risk Instrument (GPRI) mean differences between groups, p-values and confidence intervals for each comparison within linear regression models

Model	Comparisons	Mean difference	*p*-value	95% confidence interval	
				Lower	Upper
Known status	*Non-carrier vs unknown*	3.96	0.17	-1.77	9.69
	Mutation carrier vs unknown	4.15	0.03*	0.32	7.98
	Mutation carrier vs non-carrier	0.18	0.95	-5.41	5.78
	Male vs female	-5.85	<0.01*	-9.46	-2.23
	Years in education	0.65	0.01*	0.16	1.13
Biological status	*Mutation carriers vs non-carriers*	0.65	0.73	-3.03	4.34
	Male vs female	-6.47	<0.01*	-10.12	-2.83
	Years in education	0.56	0.02*	0.08	1.04
Gene group and known status	*C9orf72 mutation carriers vs non-carriers*	1.43	0.56	-3.39	6.24
	GRN mutation carriers vs non-carriers	-0.55	0.83	-5.67	4.58
	MAPT mutation carriers vs non-carriers	8.11	0.02*	1.52	14.70
	C9orf72 unknown vs non-carriers	-4.33	0.17	-10.58	1.91
	GRN unknown vs non-carrier	0.63	0.90	-9.11	10.37
	MAPT unknown vs non-carriers	-9.36	0.14	-21.76	3.04
	GRN mutation carriers vs C9orf72 mutation carriers	-1.97	0.51	-7.85	3.90
	MAPT mutation carriers vs C9orf72 mutation carriers	6.68	0.07	-0.42	13.79
	C9orf72 unknown vs C9orf72 mutation carriers	-5.76	0.10	-12.63	1.11
	GRN unknown vs C9orf72 mutation carriers	-0.79	0.88	-10.97	9.38

	MAPT unknown vs C9orf72 mutation carriers	-10.79	0.10	-23.55	1.98
	MAPT mutation carriers vs GRN mutation carriers	8.66	0.02*	1.26	16.05
	C9orf72 unknown vs GRN mutation carriers	-3.79	0.29	-10.76	3.19
	GRN unknown vs GRN mutation carriers	1.18	0.82	-9.00	11.36
	MAPT unknown vs GRN mutation carriers	-8.81	0.17	-21.49	3.86
	C9orf72 unknown vs MAPT mutation carriers	-12.44	<0.01*	-20.67	-4.22
	GRN unknown vs MAPT mutation carriers	-7.48	0.19	-18.62	3.67
	MAPT unknown vs MAPT mutation carriers	-17.47	0.01*	-30.10	-3.94
	GRN unknown vs C9orf72 unknown	4.97	0.36	-5.78	15.71
	MAPT unknown vs C9orf72 unknown	-5.03	0.45	-18.28	8.23
	MAPT unknown vs GRN unknown	-9.99	0.19	-25.14	5.16
	Male vs female	-5.38	<0.01*	-9.06	-1.71
	Years in education	0.65	0.01*	0.16	1.13
Gene group and biological status	*C9orf72 mutation carriers vs non-carriers*	-0.32	0.88	-4.70	4.05
	GRN mutation carriers vs non-carriers	-0.05	0.99	-4.99	4.89
	MAPT mutation carriers vs non-carriers	4.63	0.14	-1.54	10.79
	GRN mutation carriers vs C9orf72 mutation carriers	0.28	0.92	-4.94	5.50
	MAPT mutation carriers vs C9orf72 mutation carriers	4.95	0.13	-1.43	11.34
	MAPT mutation carriers vs GRN mutation carriers	4.67	0.18	-2.10	11.45
	Male vs female	-6.25	<0.01*	-9.93	-2.57
	Years in education	0.54	0.03*	0.06	1.03

3.5. Discussion

The aim of this chapter was to investigate the lived experience of at-risk individuals, and the psychological consequences of being at-risk of fFTD, using the GPRI*plus* questionnaire. This study also aimed to investigate the impact of biological genetic status and known genetic status on standardised measures of mental health in order to better understand the factors that may contribute to depression and anxiety in those at-risk of fFTD.

The main findings of this study are explored below.

3.5.1. The sample

The findings of this study reveal important demographic information regarding the at-risk population. Firstly, those from families affected by the *MAPT* mutation learnt of their risk at a younger age compared to other genes. This is likely due to the earlier age at onset observed in *MAPT* compared to *C9orf72* and *GRN*. It is not uncommon for people to learn of their risk, particularly of *MAPT*, as children or young adults, often as a parent becomes affected. This may be protective for some as they are able to adjust over time, however, there also may be added challenges due to growing up with a parent affected with FTD. Therefore, this may indicate a need for support for children living at-risk, as well as to aid parents managing risk disclosure to children.

This study revealed a higher proportion (58%) of individuals who had undergone predictive testing and thus knew their own genetic status, compared to the 20% reported in the literature (Craufurd et al., 1989; Quaid et al., 2008). There are a number of possibilities for this; firstly, those who engage in research may be more likely to desire predictive testing and may display certain personality characteristics e.g., they may be more likely to be 'information gatherers'. Secondly, it may be that the pathways for recruitment employed, created a high chance of a biased sample. Through recruiting via neurogenetics clinics, it is likely that those who test positive are most likely to engage in research. As such, the findings of this study and other cohort studies should be extrapolated with caution, as the sample may not be reflective of the whole at-risk community. On this note, 76% of those who underwent predictive testing, tested positive for an FTD-causing genetic mutation, considerably higher than the expected

50%. This likely demonstrates the effect of recruitment from neurogenetics clinics on bias within the sample. It follows that those who test positive for a genetic mutation during predictive testing are more likely to be offered, and engage in research participation, compared to those who are non-carriers. However, the sample within this study demonstrates increased ecological validity compared to similar studies within the literature due to the inclusion of 'unknown status' individuals. As much of the literature relies on samples derived from genetics clinics, this group is often overlooked despite making up the majority of those living at-risk. So, despite being underrepresented in the sample, the mere inclusion of this group within this study allowed for a much deeper understanding of the at-risk experience as a whole.

3.5.2. Predictive testing and understanding of risk

Of the sample within this study, around 10% reported to have genetic counselling but did not go on to have predictive testing. This suggests that for these individuals, genetic counselling helped them to realise that testing was not the right decision for them at this moment in time. However, 13% of those who had predictive testing reported that they did not receive genetic counselling. This may indicate confusion regarding the distinction between genetic counselling and testing, however it may also suggest that recommended procedures regarding predictive testing are not being followed. In line with MacLeod et al's (2013) gold standard predictive testing recommendations, predictive testing must involve genetic counselling.

Around half of those who had predictive testing considered it for less than six months, while the remaining half considered this decision for between six months and over three years. This indicates two subsets of individuals, those who are certain that they want predictive testing and require little time to decide, and those who may be more unsure and require more decision-making time. This emphasises the importance of genetic counselling for both groups. For those certain of their decision, genetic counselling may be important to thoroughly consider and weigh-up the, potentially negative, aspects of predictive testing which may have been overlooked. Similarly, those who have considered testing for a longer period may require more information or support from a genetic counsellor or geneticist in order to be confident in their decision.

The reasoning surrounding predictive testing decision-making was consistent to that reported in the literature in HD, with relieving uncertainty, allowing for future planning and informing children as the most important factors in pursuing predictive testing (Craufurd et al., 1989; Fanos et al., 2011; Steinbart, 2001a; UK Huntington's Disease Prediction Consortium et al., 2016). Reasoning against predictive testing were similar to those reported in HD, emphasising the fear of an adverse psychological response (Craufurd et al., 1989) and concern regarding symptom searching (Fanos et al., 2011) with the addition of the statement regarding lack of treatment.

The majority of untested participants indicated good understanding of their risk, rating it at 50%. However, around a third of participants perceived it to be higher or lower than 50%. This could be due to misunderstanding or a lack of information regarding their genetic risk. However, it may also support the idea of the individual's perception of their own risk reported in the literature, where those perceiving themselves as higher risk may base this on subjective information such as a 'feeling', likeness to their affected parents or the genetic information of their siblings (i.e., if siblings test negative, remaining un-tested siblings may believe this increases their likelihood of being a mutation carrier). Similarly, those perceiving their risk as lower than 50% may base this on factors such as surpassing their parent's age at symptom onset.

3.5.3. Mental health symptoms

3.5.3.1. Compared to general population statistics and normative data

The findings of this study suggest a similar prevalence of mental health diagnoses as demonstrated in the general population. Although almost 50% of participants reported having emotional problems in the past, 27% had a diagnosed mental health problem, which is slightly below the lifetime prevalence of common mental health disorders recorded in the general population (Steel et al., 2014).

Contrary to this, 10% of participants scored ten or above on the GAD-7 measure, indicating moderate anxiety. This is higher than the 5% observed using the GAD-7 in the general population (Löwe et al., 2008) and also higher than the prevalence of Generalised Anxiety Disorder (GAD) in the general population (5.9%) (McManus et al.,

2016). Similarly in this study 4% of participants scored 15 or above, compared to 1% in the general population (Löwe et al., 2008) suggesting increased prevalence of anxiety in those at-risk of fFTD compared to those in the general population. A similar pattern is seen in results from the PHQ-9 measure of depression symptom severity with 13% participants scoring ten or above compared to 5.6% using the PHQ-9 in the general population (Kocalevent et al., 2013). The prevalence of depression within the general population is 3.3%, demonstrating an almost four-fold increase within the at-risk population (McManus et al., 2016). Furthermore, reports of suicidal ideation were elevated within the at-risk population (11%) compared to the lifetime prevalence reported in the general population (9% - [Nock et al., 2009]). Taken together, these findings may suggest a higher prevalence of moderate to severe anxiety and depression symptoms in those living at-risk of fFTD. However, the findings explored above regarding diagnosis of mental health disorders suggest that this may be undiagnosed. Therefore, one may conclude that despite a higher prevalence of anxiety and depression observed in those living at-risk comparatively to the general population, this may be underdiagnosed due to a reluctance to pursue non-specialised psychological support. This is supported by results from the GPRI measure which found that almost 40% participants met criteria for psychosocial referral, suggesting an even greater need for psychosocial support than observed using standardised measures commonly used in primary care (GAD-7 and PHQ-9). This may suggest that there are additional elements to the fFTD at-risk experience, not captured by measures such as the GAD-7 and PHQ-9. Therefore, the GPRI may be a useful addition within neurogenetics and cognitive neurology clinics to identify those patients who require additional support.

Within at-risk fFTD

Within those at-risk of fFTD, a high percentage (37%) rated their mental health as worsening since learning of their risk, while 11% felt it changed for the better. This suggests a need for psychological support from the earliest point of intervention, ideally prior to predictive testing. A smaller percentage (22%) felt their mental health worsened following predictive testing while 26% felt it changed for the better, supporting the idea within the qualitative literature, that there is an element of relief following predictive testing. However, despite a smaller percentage feeling that their mental health worsened following predictive testing, mutation carriers were also found to be at a

significantly higher risk of suicidality, reinforcing the need for psychological intervention.

3.5.4. Standardised measures

3.5.4.1. GAD-7 and PHQ-9

There was both a significant effect of status knowledge and biological status found on anxiety score on GAD-7. *C9orf72* known carriers were significantly less anxious compared to non-carriers and *GRN* and *MAPT* known carriers, while *MAPT* known carriers were significantly more anxious comparatively to non-carriers and those with unknown status in *C9orf72* and *MAPT* families. *GRN* known carriers also were significantly more anxious compared to those with unknown status in C9 and *MAPT* families. A similar effect was seen within biological status, with *C9orf72* mutation carriers being significantly less anxious than other groups, and *MAPT* mutation carriers significantly more anxious.

A similar pattern was observed in results from the PHQ-9, with *MAPT* known mutation carriers demonstrating significantly increased depressive symptoms compared to known non-carriers and *C9orf72* known mutation carriers, while *C9orf72* mutation carriers demonstrated significantly fewer depressive symptoms compared to *GRN* known mutation carriers. Again, *C9orf72* and *MAPT* individuals with unknown status demonstrated fewer depressive symptoms compared to non-carriers and *GRN* known mutation carriers. Similarly, when looking at biological status, *C9orf72* mutation carriers demonstrated fewer depressive symptoms compared to non-carriers and all mutation carriers.

These findings are contrary to findings reported by Devenney et al., (2018) who report increased prevalence of psychiatric disorders in *C9orf72* kindreds, suggesting that those at-risk of *C9orf72* mutations may be at increased risk of depressive and anxiety disorders, among other diagnoses. However, the pattern of increased anxiety and depression in *MAPT* mutation carriers supports prior findings of increased depressive disorder ‘not otherwise specified’ in *MAPT* mutation carriers (Cheran et al., 2018). There are a number of possible explanations for this effect, however, due to a lack of literature exploring such symptoms in this population, it is challenging to disentangle

the effect of biological status from status knowledge.

It is possible that both biological status and knowledge of status affect depression and anxiety symptoms differently. Biologically, it may be concluded that *MAPT* mutation carriers are predisposed to increased anxiety symptoms, while *C9orf72* mutation carriers may possess protective factors from both anxiety and depressive disorders. Similarly, knowledge of carrier status may exacerbate this effect, increasing depression and anxiety within mutation carriers, and protecting non-carriers and those with unknown status. It is likely that there is a more complex gene and environment interaction at play, however due to the exploratory nature of this analysis, further research will be required to understand this.

Alternatively, increased anxiety in *MAPT* mutation carriers and decreased anxiety and depression in *C9orf72* mutation carriers may be indicative of early prodromal symptoms of FTD. Literature suggests changes may be observed neuroanatomically in *C9orf72* up to 20 years prior to symptom onset and up to five years prior on psychometric testing. Therefore, it is possible that *C9orf72* mutation carriers may demonstrate decreased insight, highlighted here in diminished awareness of mental health symptomatology, prior to symptom onset. Similarly, as suggested by Cheran et al., (2018), *MAPT* mutation carriers may display early dysfunction of neural networks involved in emotion, manifesting as early mood changes.

These findings are contrary to recent findings by Samra et al., (2023), who found that depression and anxiety symptoms were common across all genetic groups. However Samra et al., (2023) also found that these symptoms increased in frequency as symptom severity increased. Therefore, one possible explanation for the findings within this study may be that the *MAPT* sample may have been, on average, closer to symptom onset comparatively to *C9orf72* and *GRN* groups. Similarly, the *C9orf72* group may have been further from symptom onset. This study used years to parental age at onset as a marker of proximity to onset as this is often what individuals use as a benchmark when predicting their own age at onset, therefore I felt that it was a better measure of an individual's perception of their proximity to onset. However, as this is not a great biological measure of proximity to onset (Moore et al., 2020), future research should replicate this analysis with the inclusion of a measure of FTD disease severity e.g. Clinical Dementia Rating Dementia Staging Instrument plus National

Alzheimer's Coordinating Center Behaviour and Language Domains (CDR plus NACC FTLD, Knopman et al., 2011; Miyagawa et al., 2020).

Furthermore, those who choose to undertake predictive testing may possess personality traits or characteristics that predispose them to increase depression or anxiety, leading those who have knowledge of their mutation status to be increasingly predisposed to mood disorders comparatively to those who do not know their status. The qualitative literature in FTD, HD and other hereditary neurogenetic disorders often discusses an intolerance to uncertainty as a leading factor in pursuing predictive testing. Within the Acceptance and Commitment therapy model, an intolerance to uncertainty may be described as experiential avoidance. Those who have not had predictive testing and instead have chosen not to know their mutation status may have increased tolerance to uncertainty as they have chosen to accept a highly uncertain situation, and therefore they may be able to respond more flexibly to challenging thoughts and feelings surrounding their risk, leading to reduced anxiety and depressive symptoms. Therefore, the ability to tolerate living at-risk may act as a protective trait regarding anxiety and depression. For non-carriers, the knowledge that they do not carry the mutation may reduce this effect, while in mutation carriers this knowledge may exacerbate the existing predisposition.

3.5.4.2. GPRI

A slightly different pattern of findings was observed on the GPRI measure. Known mutation carriers scored higher, indicating increased need for psychosocial referral. As above, *MAPT* known mutation carriers scored higher compared to other genetic groups, however *C9orf72* mutation carriers did not score significantly lower. There was also no effect of biological status. This suggests that there is an element captured in *C9orf72* known mutation carriers using the GPRI that is not observed using GAD-7 or PHQ-9 measures. In addition, this also supports the findings above regarding an increased need for psychosocial support within *MAPT* mutation carriers in particular. There was also a significant effect of years in education observed within the GPRI model, this may indicate years in education as a protective factor for psychological wellbeing and need for psychosocial referral. This is a concept that is supported by literature looking at predictive testing adjustment in familial AD and FTD (Galluzzi et al., 2022), with higher education associated with a greater ability to deal with genetic

counselling and testing. This effect is also observed more generally in the population, again with higher educational level resulting in reduced frequency and severity of depression and anxiety symptoms (Belo et al., 2020; Kondirolli & Sunder, 2022). As this sample has a high average level of education, this might indicate a potential greater need for psychosocial support within the at-risk FTD population.

3.5.5. Lack of support

Despite the need for psychological support demonstrated above, the vast majority of participants in this study reported having no support while living at-risk. Furthermore, many individuals quoted support from their friends and family in response to this question and as such, the number of individuals accessing formal or professional support is likely even lower. In contrast, a large proportion had explored counselling, which may be indicative of a need for further support. However, as this juxtaposes the lack of support reported above, this may be due to many people misunderstanding counselling to mean genetic counselling, rather than psychological therapy.

3.5.6. The effect of gender

There was a significant effect of gender observed throughout analysis of data, with females consistently scoring higher than males on standardised measures (GAD-7, PHQ-9 and GPRI), as well as receiving more mental health diagnoses, and experiencing significantly more suicidal ideation. Females were also significantly more likely to have counselling than males, suggesting they are not only predisposed to experience more mental health problems, but also may be more aware of their mental health. This is an effect that is well documented in mental health literature (Riecher-Rössler, 2017) and therefore the replication of this finding may increase the reliability of the findings of this study as it indicates a robust design and sample.

3.5.7. COVID-19 considerations

As data was collected during the COVID-19 pandemic, I had concerns that mental health symptoms may be exacerbated by the global pandemic. I stopped data collection for several months and re-started it with added questions regarding people's

feelings towards the impact of the pandemic on their mental health. Those who reported a detrimental impact of COVID on their mental health were asked to complete the questionnaire at another date. There were too few responses to these COVID-19 related questions to analyse within this study. Despite taking every measure to minimise the confounding effect of the COVID-19 pandemic on this study there are several concerns that remain. Firstly, there was an overall increase in reports of anxiety and depression during the COVID-19 lockdown (Weich, 2022), as well as a significant increase in distress (Pierce et al., 2020) which may have influenced the data within this study despite my best efforts. In particular, as the study relied on self-report, those with low mental health literacy may not have recognised the impact of measures such as lengthy self-isolation and reduced social contact on their mental health, as well as the impact of COVID infection itself. Similarly, the pandemic may have brought a range of other stressors, such as the inability to see symptomatic family members due to vulnerability, the deterioration of affected relatives during lockdown periods, concern for affected family members of COVID infection and for some, the passing of family members from COVID infection. These factors may also have had a significant impact on mental health and, in particular, GAD-7 and PHQ-9 scores which investigate the frequency of symptoms within the past two weeks. Furthermore, as discussed in Chapter 4 in more detail, certain events may increase the relevancy and saliency of an individual's genetic risk, for example, having children. The pandemic may also have 'artificially' increased the relevancy and saliency of genetic risk for participants within this study as the pandemic itself, concern for symptomatic relatives and sensationalism within the media may have triggered increased health-related anxiety, therefore potentially artificially inflating reports of mental health symptoms within this study.

In addition to the above issues regarding the confounding nature of the COVID-19 pandemic, there were also subsequent issues experienced regarding the design, participant recruitment and data collection. The study was not initially designed for online data-collection, however following the onset of the pandemic, the design required alteration to facilitate online data-collection. Despite this change, data collection was hindered by the rather chaotic experience of the pandemic and COVID lockdowns, at this point research participation was not at the forefront of many participants' minds or priorities. In addition, many people were on furlough from employment thus not regularly monitoring email. It took many months for the Dementia

Research Centre to begin research study activity and recruitment was slow due to reluctance in some participants as well as comprehensive safety protocols within the department to control the spread of infection. While recruitment in the UK was slow and often stagnating, the GENFI site in Milan were unable to continue recruitment and data collection prior to the end of this study due to the strict disease control measures in Italy and redeployment of many medical professionals. As such the COVID-19 pandemic impacted this study significantly in many ways, which cannot be ignored when interpreting such findings.

3.5.8. Limitations

There are several limitations to this study to be explored. Firstly, the static timepoint of data collection for the GAD7 and PHQ9 is a limitation of the study as it shows only a snapshot of participant's current mood. This may overlook patterns of peaks and troughs in depression and anxiety symptoms that occur at specific timepoints throughout the at-risk journey. Therefore, longitudinal analysis with a larger sample size may be more informative and sensitive to any potential changes. Additionally, the study design relied on self-report measures which, despite being a commonly used methodology, may create issues in FTD due to the lack of insight observed in symptomatic individuals. Secondly, when investigating the influence of biological status on anxiety and depression symptoms, it is impossible to remove the knowledge of an individual's status, therefore making it extremely difficult to disentangle these effects. Due to sample limitations, it was not possible to conduct the analysis on unknown status individuals alone, however future research may benefit from the use of a larger cohort of unknown individuals to investigate this effect further. Finally, as there were significant gender differences observed throughout the analysis, another limitation of the study may be that the sample was biased towards female participants. In addition to this, two participant's gender identity was incongruent to their biological sex, with one transgender individual and one participant identifying as non-binary, i.e., not identifying as male nor female, (however they indicated their preferred gender from the options provided). Although there were too few gender non-conforming individuals within this sample to create any significant effects, future research should be mindful of gender identity when designing such questionnaires and analyses.

There are also a number of confounding variables that complicate the assessment of

mood in at-risk individuals. As discussed previously, the at-risk experience is complex, with individuals often playing numerous roles within the family, simultaneously concerned with their own risk, the risk of others within the family, including children, and often also taking on a caring role for symptomatic family members, most commonly their parent. The role of caring for a person living with FTD comes with its own challenges, distinct from those of other neurodegenerative conditions (Tookey et al., 2022). In particular, personality changes and disinhibition can be particularly distressing for loved ones. In my time as a researcher in the Dementia Research Centre, caregivers often described the symptomatic individual as becoming a fundamentally different person. Added to this, is the experience of childhood development in a family affected by fFTD. Behaviour modelled by symptomatic, or prodromal individuals in early life may also impact how the at-risk person behaves and interprets the world, and therefore impact their mental health and wellbeing. Social learning theory (Bandura & Walters, 1977) posits that behaviour is learnt by observation and imitation other's behaviour. For individuals developing in fFTD families, some behaviours modelled during childhood may be inappropriate, undesirable, or simply unusual, due to the sociocognitive and behavioural symptoms exhibited in FTD. As such this influences their perception of the world around them through imitation of such behaviours, potentially impacting mood and wellbeing in adult life. Furthermore, due to the heterogeneous presentation of FTD, mood disorders may be difficult to disentangle from the mood symptoms see in symptomatic or prodromal FTD. Future research may benefit from the addition of an FTD symptom severity measure, however such measures do not currently distinguish the nuanced differences between these presentations. Therefore, the complexity of the at-risk FTD experience creates a number of confounding factors to acknowledge in understanding the findings presented in this chapter.

3.5.9. Clinical implications

There are significant clinical implications resulting from this work. Primarily, this study has provided evidence to support the need for increased availability of psychological support for individuals living at-risk of fFTD. This evidence may be used in order to aid the development of specialist psychological services for those living at-risk and may guide clinicians in their approach to asymptomatic individuals. To my knowledge, this

is the first study of its kind in familial FTD and as such it provides increased understanding for the FTD community regarding the experience living at-risk. The findings may also help to guide future research within the field to further this understanding and answer the questions posed above.

3.5.10. Future research

As this was an exploratory study, there is scope for lots of further development in terms of future research. Future research should employ longitudinal methods in order to investigate whether symptoms of anxiety and depression are static throughout the at-risk experience or wax and wane over time, in accordance with the relevancy and saliency hypothesis. It would also be pertinent to investigate whether the mental health implications of living at-risk are limited to depression and anxiety or more wide-ranging. Furthermore, in order to identify whether the mood symptoms identified in this study are associated with FTD prodrome, future research may further stratify participants by FTD symptom severity, or assess whether each GAD-7 and PHQ-9 element maps onto symptoms of FTD.

3.5.11. Conclusions

In summary, prevalence of depression and anxiety diagnoses were found to be higher within those at-risk compared to reports in the general population and a high proportion of those living at-risk met criteria for referral for psychosocial intervention. This suggests that there is a need for psychological support targeted towards this group. Both knowledge of mutation status and biological genetic status had significant effects on depression and anxiety, suggesting a gene and environment interaction to further elucidate this phenomenon. Clinical implications resulting from this study may involve the development and increased availability of specialist psychological support for individuals living at-risk of fFTD. It is important the experience of living at-risk is further understood in order to allow people to live well at-risk. As previously mentioned, many people are at-risk for much of their lives and as such is important to reduce the psychological burden associated with this wherever possible.

Chapter 4. Using qualitative interview to understand the at-risk experience and support needs in familial FTD

4.1. Chapter overview

Following on from Chapter 3 outlining anxiety, depression and need for psychosocial support in individuals at-risk of fFTD, this chapter aims to further explore this lived experience. While the quantitative data in Chapter 3 demonstrates some of the psychological difficulties associated with living at-risk, it is not able to provide insight into why this might occur, those factors that are most challenging, and how they might be overcome when applying psychological intervention. This study aimed to gain a richer and more in-depth description of the feelings and experiences of living at-risk, as well as to evaluate support needs, using qualitative semi-structured interviews. This study was carried out with a view to developing a tailored psychological intervention for use in the at-risk population. In order to do this, further context was required regarding the emotions experienced and the trajectory of the at-risk journey to determine key areas where intervention may be beneficial. Evaluation of support needs, existing support, barriers and facilitators allowed for improved understanding of what was needed from an intervention for this group, and aided design to maximise accessibility. Another goal of this study was to characterise the holistic at-risk experience, including those who have, and have not had predictive testing, something that to date, has often been overlooked but has important implications regarding improved wellbeing while at-risk.

4.2. Introduction

There has been little research into the psychological impact of living at risk of FTD. There is, however, a larger literature base examining the at-risk lived experience in other autosomal dominant neurodegenerative diseases, predominantly Huntington's disease (HD). The literature outlined in Chapter 3.2 demonstrates inconclusive findings regarding the psychological effects of living at-risk, however qualitative studies provide a richer, more detailed analysis, and wholistic view of this lived experience. Although many have focused on the predictive testing experience and impact of status disclosure, rather than the whole at-risk journey, they literature describes an impact of risk and carrier status on various aspects of life, including mental health, career and education, romantic relationships (Gong et al., 2016; Quaid et al., 2008) and having children (Fahy et al., 2023; Gong et al., 2016; Tillerås et al., 2020).

4.2.1. What factors affect saliency of being at-risk?

Not everyone experiences living at-risk in the same way, and the associated psychological effects may fluctuate over time due to various factors. Prior to predictive testing, the idea of life as a mutation carrier may become part of an individual's core identity and sense of self, leading to biographical disruption following disclosure of a negative predictive test, as a key part of the individual's core identity now requires redefinition in accordance to this new information (Tillerås et al., 2020; Williams et al., 2000; Winnberg et al., 2018). Factors such as stage in life, family history, other life events and beliefs about risk may increase the saliency and biographical disruption of genetic status at certain times in a person's life (Cox & McKellin, 1999; Etchegary, 2011; Kenen et al., 2003). Those at-risk do not necessarily ruminate on their risk continuously over time but rather, there are numerous factors that lead to their risk both increasing and decreasing in relevance and subsequent impact over time (Cox & McKellin, 1999). Etchegary (2011) argues that when risk is of low relevance it may cause minimal disruption and be paid little attention, however when highly relevant it may become salient and biographically disruptive (Kenen et al., 2003). Factors relevant to the saliency of genetic risk included stage of life (youth vs nearing onset or approaching marital and reproductive decisions), family history, unique life events (such as the breakdown of a relationship) and cognitive beliefs about risk (Etchegary, 2011).

4.2.2. What is the effect on mental health?

Many people will experience negative emotions regarding their risk. These include powerlessness, anxiety, depression, fear, hopelessness, isolation and loneliness (Forrest Keenan et al., 2007; Gong et al., 2016; Tillerås et al., 2020). Strong negative emotions were reported in response to both positive and negative predictive test results. In addition to this, mutation carriers have been found to be at increased risk of suicide (Tillerås et al., 2020). Mixed emotions including relief, joy and guilt are often experienced by non-carriers. Relief and joy may be felt due to their own negative mutation status, occurring simultaneously alongside worry about other family members, leading to feelings of survivor guilt (Tillerås et al., 2020; Williams et al., 2000; Winnberg et al., 2018). Uncertainty is also commonly reported in this group as there is both uncertainty regarding genetic status and the onset of symptoms (Quaid et al., 2008; Tillerås et al., 2020). An excerpt from Binedell et al's (2008) study describes the uncertainty of living at-risk of HD like *"living on a ticking time bomb. You don't know when you're going to go off*". This study also found, in accordance with Wexler's (1979) findings, that those who requested predictive testing reported uncertainty to be significantly more stressful in comparison to those who did not request predictive testing, despite demonstrating no differences in ability to cope with the uncertainty (Binedell et al., 2008). Those at risk of HD also report searching for symptoms in themselves, with some reporting looking for symptoms from childhood (Tillerås et al., 2020). The onset of symptoms is also reported as a source of anxiety and uncertainty for many with regards to the timing of symptom onset, phenotypic expression and for those with unknown status, whether symptoms will onset at all (Cox & McKellin, 1999; Hayes, 1992; Kessler, 1993; Kessler & Bloch, 1989; Wexler, 1979).

4.2.3. Is living at-risk an exclusively negative experience?

Although there are many negative emotions associated with living at-risk, positive elements are also experienced. Individuals at-risk state that they found that their risk helped motivate them to live their lives in the present and many held on to hope for a favourable mutation status, as well as hope for future curative treatments and a meaningful life, regardless of whether or not they developed HD (Tillerås et al., 2020). Uncertainty has been argued as a key component to preserving hope as without uncertainty, for some individuals who test positive for the mutation, there can be no

hope (Quaid et al., 2008). Some studies suggest that the completion of predictive testing, despite potential negative outcomes (i.e. mutation carriership) provides relief from some of the uncertainty and that living with a positive result is often easier than living with uncertainty (Novak & Tabrizi, 2010; Tibben et al., 1993). Increased appreciation for time has also been described following receipt of a positive predictive test (Gong et al., 2016).

4.2.4. How do people cope with living at-risk?

Taking into consideration the significant challenges of living at-risk reported above, how do people cope with living at-risk? Avoidance, assimilation, problem solving, planning and gaining certainty were described as methods by which those at-risk of HD attempted to cope (Binedell et al., 2008; Forrest Keenan et al., 2007; Tibben et al., 1993). Binedell et al. (2008) reported a tendency, although non-significant, for those who did not pursue predictive testing to adopt more avoidant coping styles. Those with strong support networks and relationship attachments, as well as those who knew of their risk from a young age were found to cope more successfully with their risk and the associated challenges (Forrest Keenan et al., 2007).

One specific way in which people may attempt to cope with living at-risk is to predict their own carrier status. This may provide a feeling of clarity, reduce uncertainty, and allow planning for what they perceive to be the 'worst-case scenario'. People may do this in particular ways, e.g. based on the parent that they feel they are most alike (Forrest Keenan et al., 2007). A number of studies propose that this prediction of genetic status may lead to biographical disruption when an individual receives a test result incongruent to that which they predicted (Bury, 1982; Tillerås et al., 2020; Williams et al., 2000; Winnberg et al., 2018). A recent study by Tillerås et al., (2020) found that, in line with Forrest Keenan et al., (2007) many individuals at-risk of HD anticipated their genetic status, regardless of whether they chose to request predictive testing. Participants commonly predicted mutation carriership, anticipated symptom onset and planned their lives according to this assumption. Wexler (1979) found that 75% of people at-risk of HD felt certain that they were a mutation carrier, with the remaining 25% being aged around mid-30s and therefore assuming that symptom onset had passed them by. Wexler reported 'magical and unrealistic explanations' for the assumption of mutation carriership, including bad luck and being unlucky on

lotteries, as well as based on birth order, believing elder siblings to be more at-risk. In addition, Wexler argues that most commonly, participants predicted their status in order to exert control over an uncertain situation and alleviate the passivity of waiting for symptoms to onset.

Despite the literature detailing the at-risk HD experience, there have been no studies exploring this in fFTD. While some elements of this experience may be similar, it is unclear what may be extrapolated from the HD literature for use in fFTD. In addition, although there has been a considerable amount of research into fFTD in recent years, FTD causing genes were discovered much more recently compared to HD, therefore less is known about fFTD, e.g., it is currently not possible to predict age at onset reliably for individuals at-risk of fFTD. Meanwhile, in HD, CAG repeat length is associated with disease penetrance, age at onset, rate of disease progression and disease duration, providing those at-risk with added information regarding their future (Langbehn, 2022). In comparison with HD there are key differences in disease presentation and predictability in fFTD. fFTD has wide phenotypic heterogeneity, ranging across motor, language, behaviour and psychiatric led presentations. There is also an older average age at onset observed in FTD, with average age at symptom onsetting of 49.5 in FTD compared to 40 in HD (Moore et al., 2020; Myers, 2004). Therefore, those at-risk of fFTD may live longer with the knowledge of their risk. Thus, there may be more uncertainty experienced, for a prolonged period, for those living at-risk of fFTD. Furthermore, much of the HD literature focuses on the experience of those who have received predictive genetic testing, largely investigating the mutation carrier experience. Anecdotally, within the cohort studied at UCL, around 80% of those at-risk choose not to have predictive testing, therefore this literature may miss key parts of the at-risk experience due to a bias towards the minority of at-risk individuals who know their mutation status.

Overall, in order to best support those living at-risk of FTD, this experience needs to be explored and understood further. The aim of this study was to use semi-structured qualitative interviews to explore the feelings, experiences and support needs while living at-risk of fFTD.

4.3. Methods

4.3.1. Participants and recruitment

Participants were 16 asymptomatic individuals at-risk of fFTD, recruited from the GENFI study cohort at UCL. For the purpose of this study, at-risk status was characterised by having a first degree relative with a genetically confirmed diagnosis of an FTD syndrome. At-risk individuals included asymptomatic confirmed mutation carriers, non-carriers and those with unknown status. Participants were classified as asymptomatic on the basis of expert neurologist review, aided by MRI imaging, neuropsychometry and clinical assessments. A purposive sampling method was used based on a sampling matrix, to ensure that there was suitable distribution across mutation status groups (unknown, known mutation carriers and known non-carriers), and across gender (Ritchie et al., 2003). A goal of three to five participants within each mutation group was set, leading to an eventual sample size of 16.

Initial invitation to the study was provided to eligible participants via email, with information regarding the purpose of the study and topics covered. Interested participants were then able to arrange a convenient time for interview via email or phone. In order to participate in the study the participant also needed to be proficient and confident communicating in English.

4.3.2. Demographics

Nine participants were female and seven were male, with ages ranging from 30 to 60 years (M= 39.9, SD=7.87). The age that participants learnt of their risk ranged from 12 to 55 (M=32.6, SD=10.80) and the mean time since participants learnt of their risk was 7.3 years (SD=6.25). The majority of participants' affected parents were deceased at the time of interview (n=12), with the remaining four receiving care either in the home or from a specialist centre. Twelve participants had undergone genetic testing, of which seven had received a confirmatory test of a known pathogenic mutation and five were found not to possess the mutation. The remaining four had chosen not to pursue genetic testing at this point in time, and therefore their status remained unknown.

Table 30 shows participants' demographic characteristics.

Table 30 – Demographic characteristics

Participant number	Gene in family	Genetic status	Sex	Age at interview	Age found out about risk	Relationship status	Symptomatic parent
1	*GRN*	Carrier	F	34	24	Married	Deceased
2	*GRN*	Non-carrier	M	42	'Mid-late 30s'	Engaged	Deceased
3	*C9orf72*	Carrier	M	40	37-38	Single	Full-time care
4	*MAPT*	Non-carrier	M	34	26	Long-term partner	Receiving care in the home
5	*C9orf72*	Unknown	F	60	55	Single	Deceased
6	*C9orf72*	Carrier	F	56	54	Married	Deceased
7	*GRN*	Unknown	F	40	33	Married	Deceased
8	*GRN*	Non-carrier	M	42	33	Married	Deceased
9	*MAPT*	Unknown	M	38	12	Married	Deceased
10	*GRN*	Non-carrier	F	30	24	Long-term partner	Deceased
11	*C9orf72*	Carrier	F	34	32-33	Married	Full-time care
12	*GRN*	Non-carrier	F	38	34	Married	Deceased
13	*C9orf72*	Carrier	F	38	34-35	Single	Deceased
14	*MAPT*	Carrier	M	37	22	Married	Deceased
15	*C9orf72*	Carrier	F	34	~32	Married	Cared for by spouse at home
16	*MAPT*	Unknown	M	41	30	Married	Deceased

4.3.3. Procedures

Semi-structured interviews were conducted in order to explore participants' lived experience of being at-risk of fFTD. The interview schedule was developed with a view to identifying information relevant for future intervention design (further information regarding intervention design can be found in Chapter 5). This interview schedule was then tested by an expert by experience who offered feedback on question wording and clarity and any key information that may have been missed. This feedback was then incorporated to form the final interview schedule.

Prior to beginning the interview participants were introduced to the study and the wider focus of the project. The procedures of the interview, and subsequent data handling were outlined and the participant's right to pause or withdraw from the interview was emphasised. Participants were reminded that their data would remain confidential and be analysed in an anonymous manner, however any concerns regarding risk to themselves or others would be reported to the study PI, in accordance with departmental procedure. Participants gave verbal consent for the interview to be recorded and were offered the opportunity to ask any questions prior to commencement of the interview. The interview explored the impact of living at-risk of FTD, including, where applicable, their experience and impact of genetic testing. Support received, barriers and facilitators to support and support wanted were also investigated (see Appendix 2 for the interview schedule). Prior to ending the interview participants were offered a final opportunity to share any additional information they felt was relevant to the study. Interviews took place between August and October 2020 and lasted for between 30-90 minutes.

4.3.4. Materials

Due to this project falling under the period of COVID-19 lockdown, interviews were conducted and recorded virtually using Zoom (Zoom Video Communications Inc., 2021) and Microsoft Teams (*Microsoft Corporation*, 2020). Recordings were transcribed using Trint software (*Trint*, 2021, https://trint.com).

4.3.5. Analysis

An inductive and reflexive approach to thematic analysis was taken in analysing the

data in line with the model outlined by Braun and Clarke (2006, 2019), meaning that analysis was approached without preconception and the researcher's bias was acknowledged throughout. Bracketing was used to mitigate the effects of researcher bias and preconceptions prior to approaching the study (Tufford & Newman, 2012). Prior and throughout interviewing and analysis, I reflected upon my own assumptions regarding the lived-experience I had observed. I reminded myself and the participant of this when introducing the study by stating that I was approaching the interview with the goal to learn about their personal experience. I took a critical realist epistemological approach to analysis. Critical realism can be used in this context to explain how and why particular events or phenomena occur in natural settings (Sturgiss & Clark, 2020). Critical realism was chosen as this analysis set out to further understanding of the experience of living at-risk of fFTD and explain why those feelings outlined within this experience may occur.

NVivo 12 Pro software (*NVivo*, 2018) was used to aid the coding procedure, this was first done by CG and reviewed by an independent rater (CF). Themes were explored both across participants and also between genetic groups. Themes were then reviewed by CVG and JCS.

In line with Braun and Clarke's model, the following six steps were used to inform analysis;

1) data familiarisation, through the process of transcription, listening to recordings and reading interview transcripts and initial note taking.

2) coding; assigning sections of the transcript with codes to identify the relevant information and labelling common ideas within the interview.

3) codes were then combined to generate themes encompassing wider ideas that run throughout the data, in accordance with the research question.

4) researchers reflect on and review the codes and themes that have been generated from the data, keeping in mind how their own bias may influence analysis

5) definition of themes, ensuring that themes are clear and labelled accurately and succinctly.

6) reporting results, outlining themes and any important sub-themes identified within the analysis, using direct quotations where necessary to illustrate relevant or important ideas and summarising the data in response to the research question.

A large amount of rich data was obtained through this project. As a result, a number of research questions were employed in analysis to ensure important details were not lost. The main two research questions were as follows;

1. **What are the feelings and experiences of living at-risk of fFTD?**

2. **What are the support needs while living at-risk of fFTD?**

The results of these analyses are detailed below. However, during the interview information was also gathered regarding a third research question: What is the predictive testing experience like in fFTD? This will be discussed further and results outlined in Chapter 7.4.2.

4.4. Results

4.4.1. Research question 1: What are the feelings and experiences of living at-risk of fFTD?

There were six themes derived from data regarding the feelings and experiences of living at-risk of fFTD. The main themes were; *(i) The reaction to learning about risk or status – 'it's like ups and downs all the time', (ii) the journey to finding out about your risk, (iii) The value of information – 'I'm a bit more in control if I've got the knowledge', (iv) coping, (v) how risk influences life and, (vi) The 'whirlwind' of emotions experienced throughout the at-risk journey.*

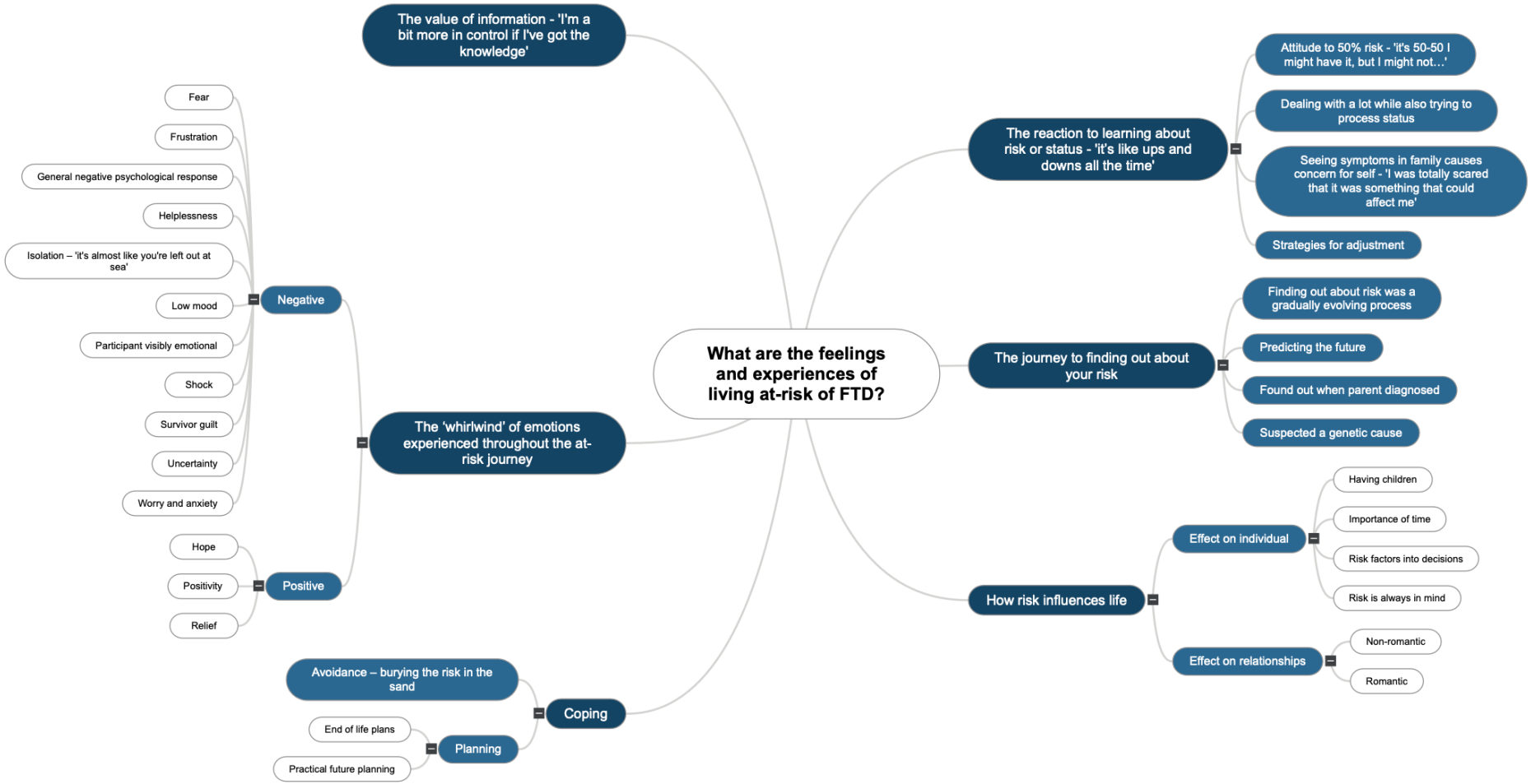


Figure 12 - Mindmap describing the main themes and subthemes generated regarding the feelings and experiences in at-risk FTD

Theme 1: The reaction to learning about risk or status – *'it's like ups and downs all the time'*

Most participants contributed to this theme, regarding their reaction to learning about either their risk of fFTD or their genetic status following predictive testing and how this changes over time as the disease progresses in loved ones and individuals come closer to potential symptom onset. The excerpt below demonstrates how one individual began feeling positive and empowered, becoming informed about their risk and involved in the fFTD community, however over time this has become increasingly difficult.

> *Oh God, it's like ups and downs all the time. At the beginning, I almost felt kind of, I felt quite positive, like, you know, I know this information, great, empowered. I want to kind of do what I can. And then, and then what I found quite difficult was, I realised over the last few years, being immersed in the world of FTD when it is this reality, I actually found it really difficult. I'd say I'd gone on a steady decline in terms of my mental health related to FTD… it feels more and more impactful as time has gone on.* (Participant 1)

a) Attitude to 50% risk – *'it's 50-50 – I might have it, but I might not…'*

One sub-theme discussed by many participants was their attitude towards being at 50% risk of fFTD. This could be broadly classified into positive and negative reactions. Participant 15 (below) notes how difficult it was to be informed about the genetic mutation in their family.

> *A huge part of me that just wishes we didn't know, and that life carried on and then you just forget about it.* (Participant 15)

A few individuals who felt they reacted negatively to news of their risk spoke of how they struggled to cope with the information and found it devastating.

> *At first [I dealt with it] quite badly. I didn't know how to, I kind of became very selfish and kind of rejected everybody around me.* (Participant 3)

However, some individuals spoke of how they were able to cope with this difficult information with a level of optimism, holding onto hope that they don't carry the gene,

feeling reassured by understanding their risk, and noting that there may be many other challenges ahead in life that may potentially change their life that they are not informed about in advance.

> *So the way I've kind of coped with it is to think, well, you know, it's 50-50. You know, I might have it, but I might not… I just think there is a possibility- the possibility that I haven't got it is something that I prefer to have rather than a total affirmation. However, obviously, if I got tested and I didn't have it, that would completely free me up from work and everything. But it's just too much of a Russian roulette situation, I think.* (Participant 7)

b) Dealing with a lot while also trying to process status

Another thread that arose with several participants was that they were dealing with a lot in their life whilst also trying to process their genetic status, making the situation more challenging. In particular, many people were caring for or supporting symptomatic family members, often parents, while undergoing genetic testing, as well as supporting their wider family through the adjustment process.

> *And I think just it was also like the timing of it, like obviously there's no good time, but when everything is going on with like the person that you're caring for and things are really hectic there, and sort of, you're dealing with like police and fall teams and like, you know, and local councils and various sort of benefits and things and trying to kind of get things sorted.*
> *So it was just like it was just a constant of like that in my day to day and trying to, like, sort out the whole mess it was. And the genetic counselling sort of process was like sort of slotted into that.* (Participant 11)

c) Seeing symptoms in family causes concern for self – *'I was totally scared that it was something that could affect me'*

Seeing symptoms in family members also caused concern for many individuals due to their awareness of the devastation of FTD and how difficult it is to see loved ones experiencing distressing symptoms. For many this extended to a realisation that this could also be in their own future.

> *I saw my dad really struggling to breathe in hospital… I saw them both*

suffering great discomfort, and it was quite disturbing to see it.
And there was a sense of horror of the disease to some extent that I just I was totally scared that it was something that could affect me. (Participant 6)

d) Strategies for adjustment

A final sub-theme generated with regards to one's reaction to learning about their risk or status was the way in which people adjusted to this information. A few individuals mentioned that they had worked on using acceptance to adjust.

I've accepted it, I've accepted it to a degree that, you know, I might not, I might not live to a certain age. (Participant 14)

A small number of participants also spoke of using information in order to aid adjustment. They found information empowering and felt more in control by becoming as informed as possible.

I trawled the internet for everything I could find on C9orf-. I feel better by being informed. So I found out everything, everything I could about it, how, how, what the penetrance of it was, the age of onset was supposed to be between the age you parents were affected. (Participant 6)

Around half of participants spoke of time as an important factor in adjustment. Many expressed how it took a lengthy time to come to terms with the information, however eventually it became easier.

Probably two years, I'd say. I mean, it wasn't something that I could just do overnight, and I don't even, I couldn't even really put a point on when that was, you know, all of a sudden you just sort of start to think, OK I just made my peace with it a bit really because I didn't want it to define the rest of my life, you know, and that, it was a bit of a-, I got to a point where I felt like I was making a choice to be sad
…but it did take a long time, did take a long time. (Participant 12)

Theme 2: The journey to finding out about your risk

All participants described the theme of their journey to finding out about their risk. Several mentioned how they learnt about their risk formally following the diagnosis of

their parent but for many this journey involved suspecting a genetic cause and gradually learning information over time.

a) Finding out about risk was a gradually evolving process

Around half of participants found out about their risk through a gradually evolving process over time as information regarding their family history was uncovered, as well as information regarding their parent's diagnosis.

> *you see your parents doing it and you think, 'oh, well, you know, there is a risk of it'. So your perception of that risk increases over time until you get to your knowledge that it would be a 50/50 risk. And so in doing that you probably sort of subconsciously process it and then think of the implications and then really what it means.* (Participant 8)

However, for some this was not the case, and the news of their genetic risk came as a surprise.

> *I didn't realise there were genetic forms of dementia. So yeah, that was a bit of a shock.*(Participant 10)

b) Suspected a genetic cause

Several participants also spoke of how they had suspected a genetic cause based on their family history and research they had carried out.

> *I'd done enough Googling about dementia and I'd come across FTD and I'd seen that it was, there was a chance for it to be genetic. And because we had a line of two people before mum who had dementia, I was starting to think hmm this seems a lot about my nan. So I didn't know, that wasn't a, you know, 'you are at risk'. I didn't know exactly at that point, but I would say by then I was very suspicious.* (Participant 12)

c) Finding out that you are at-risk - Predicting the future

Another sub-theme that arose from the ten participants was 'predicting the future'. This encompassed how individuals spent time thinking about their future and postulating about their genetic status prior to undergoing testing. Six individuals assumed that they were gene carriers with only one assuming they would not carry the gene.

I kind of knew, before all the testing happened, I had it. Just a sixth sense kind of thing. (Participant 13)

A number of individuals noted that their status felt linked to their sibling's despite often understanding that each were individually at 50% risk. Some were so convinced of their positive status that they were unprepared for a negative result during predictive testing.

it always seemed to me that either me or [sister] would have to get it. Therefore if I didn't. Which I think is scientifically not true. I mean.
…So I was sort of convinced that if I wasn't positive that [sister] would be. (Participant 4)

I think it was quite confusing. I think I was just also I was so convinced I was going to have it that all my thoughts had been so rigidly for that outcome that I didn't really know how to process [my negative status] - I certainly wasn't like happy, I didn't sort of think 'oh good my...', you know, which is, seems a bit ridiculous, but that was very much how it was I think. I was depressed and confused and frightened for what it meant for my sister. It just wasn't what I expected. (Participant 4)

A number of individuals also described that they felt like they would rather be the gene carrier than their siblings, some feeling as though their life circumstances meant there were fewer negative consequences to this, or that they would be more resilient than their siblings. Some also felt protective towards their siblings and that they would rather carry this burden than their siblings potentially become affected in future.

Part of me wanted to, given that I've got sisters, to be if anyone's going to have it I'd prefer to be me. [Participant gets visibly emotional]…Yeah, I mean, so part of me, was just sort of a bit sort of, I I guess there was a little bit of me that was a bit angry. (Participant 8)

Theme 3: The value of information – 'I'm a bit more in control if I've got the knowledge'

The third theme explored in this analysis was 'the value of information'. A few

individuals spoke of how they looked for information, however one noted a general lack of information. One individual explained that the effortful nature of having to seek out information made the experience more difficult and another found information pamphlets at the point of parental diagnosis to be overwhelming.

> *I got through it by just trying to learn as much as I could because I'm one of those people that feel like then I'm a bit more in control if I've got the knowledge…when you've got to dig for that information, when you're already in a dark mental place, that doesn't help, you know* (Participant 12)

Theme 4: Coping

The theme of coping was split into two main subthemes; avoidance – burying the risk in the sand and planning.

a) Avoidance

Many participants coped with the knowledge of their risk or status by burying their head in the sand, putting it to the back of their mind or putting it away 'in a box' as, one individual explained, that they would not be able to cope with thinking about it all the time.

> *I was just playing dumb to it really, just playing, yeah just playing- burying my head in the sand.* (Participant 14)

One individual described that this was the only way they knew how to cope and had generally been a successful coping mechanism for them.

> *I kind of bury things, I put things in boxes and I just put them to the back of my head …[I] put it in a box, put a lid on it and don't think about it* (Participant 13)

Few participants used alcohol as a coping mechanism, with one describing that this had been particularly destructive in their life at the time.

b) Planning

Aside from overt avoidance of their risk, over half of participants used planning as a

coping mechanism. Participants spoke of planning far into the future and one individual planned their life with the assumption that they carried the genetic mutation. A small subset of participants spoke about end-of-life plans. One individual made funeral plans in order to relieve their family of this burden and to allow them to grieve when the time came.

> *I also kind of, was very morbid with it and even planned my own funeral just because I thought, that's one thing that's so difficult on people and if it's already done then it helps take away that stress and they can then just mourn*. (Participant 10)

Some participants expressed interest in assisted dying, despite being illegal in the UK. For these individuals, the prospect of being able to go to somewhere like Dignitas should they become affected, was a comfort. However, both noted that they would no longer be eligible for this should they become affected with FTD symptoms.

> *I made up my mind that I would go, if I did get motor neurone disease that I would be going to Dignitas. So that's a kind of, a comfort to know that, you know, there is a way out… if I got FTD, I probably wouldn't do that because, you know, you have to be of kind of sound mind to be able to make these decisions.* (Participant 5)

One individual spoke of a plan to take their life prior to their parental age at onset however as life has progressed and since they have become married, this is a more challenging prospect. They also noted that memory and executive functioning difficulties may pose problems in terms of carrying out the plan at a suitable time. This individual was particularly concerned with the future care burden on their family, as they had cared for their parent and did not want their loved ones to have to care for them in the same way. However, they also noted that the plan to take their own life would also hurt their loved ones.

> *You know, it's, unfortunately obviously in the UK, you haven't got that, that capability of ending your life, have you? … Legally.*
> *… I think that you should be allowed because you can do it, you can go abroad can't you, but you've got to be of sound mind when you're making that decision. But I'm never going to be of sound mind, you know, I'm going*

to be all over the place.
Before I met [wife], my, my plan was always, it was going to be before 40, so it was going to be something like 47, 48, I was going to end my life.
…But obviously I got [wife] to think about now, you know… that's the one thing that I find very difficult to come to terms with really, yeah.
And then you're going to hurt people as well aren't you? That's the thing you're going to hurt people if you stay, and you'll hurt people if you go. It's difficult. (Participant 14)

In addition, several individuals described practical future planning, including housing, finances, insurance and creating a care plan. This was done with mutation carriership in mind and with the aim to relieve the burden of planning and decision making from their loved ones.

I want to make sure that if I do have it, that when I go, [son] is financially set so, and so is my other half so that they don't need to worry. (Participant 10)

Participants described finding their 'forever home' and purchasing more affordable homes so that they would be able to leave their family without the burden of mortgage payments. Future care needs were also considered when finding a home, ensuring that there would be space for a bed downstairs if they were to experience mobility problems in future. Financially, participants planned shorter term pensions and ensured that debts were paid far in advance of potential symptom onset, again to ensure financial stability for their loved ones. In terms of care plans, participants outlined their desires for future care and discussed their decisions with partners and family members to ensure that they feel confident that they are making the right choices once they no longer have capacity to advocate for themselves.

And [husband] and I have a lot of discussions about sort of the do's and don'ts if I get it, and the- how I want the care to sort of progress because one of the great things is that I won't care at the time. But I'd like him to know he's making the right choices. (Participant 7)

However, one individual explained that although they use planning as a coping mechanism in their general life, they feel unable to plan for their future as a mutation carrier as there is nothing they can do to control it.

> *I'm a control freak. So if I know I've got to do something, I will plan and I'll plan and I'll plan and then I will plan for failure. And then. But with this, I can't-, there's nothing I can do.* (Participant 13)

c) Talking

A small number of participants also spoke of talking as a coping mechanism, speaking openly with their support network, particularly their partner.

> *I spoke really openly about it with my husband, we spoke about it quite a lot. We weren't married at the time, this was before we got married. And because it felt quite important to be quite practical about at that stage, because we were sort of coming towards maybe moving in and then getting engaged and then having children. So each of those processes were kind of different things of, 'okay, hang on, how does this impact us now?* (Participant 1)

Theme 5: How risk influences life

Participants referenced how their risk had influenced how they live their life. This was further subdivided into a number of sub-themes; the effect on the individual, and the effect on both romantic and non-romantic relationships. Some individuals did not feel as though their risk had changed how they live their life, a few felt as though they had become more health conscious, and some felt it had influenced their career.

a) The effect on the individual

Participants referenced the effect being at-risk had on themselves. This included having children, the importance of time, factoring risk into decision making and their risk always being in their mind.

Around half of individuals reported that their genetic risk influenced their decision-making process regarding having children, while some had already had children prior to learning of their risk. Participants demonstrated differing views and choices regarding reproductive decision making, some felt strongly that they did not want to have a child at-risk, and some no longer wanted to have children at all following learning of their positive status.

Just, I couldn't have a child knowing my mum passed it to me, I could potentially pass it on, it's just too much of a guilt. And knowing that I have the faulty gene is just a no no. (Participant 13)

One individual, however, felt that their risk spurred them on to have children, so that they would not leave their partner alone should they become affected in future.

The second hope, I was like, well if I have a family and I know I haven't passed it on then my husband's got some support for when I'm poorly …because if I was positive I might not be around for very long and my husband was going to have to deal with me being poorly and then be left on his own for the rest of his life. (Participant 12)

Many participants pursued preimplantation genetic diagnosis (PGD) in order to have children that did not have a risk of fFTD themselves, however some also chose to have children without reproductive intervention.

I was having children, I was starting a family. I didn't want that start to the family life to be totally about my dad's illness. (Participant 7)

Those who had children prior to learning of their risk were not able to make this choice and some reported feeling guilt towards their child's risk.

it was it was quite terrifying. Not so much for myself, but obviously because I had my kids. I was worried that obviously, whatever I had I'm going to pass to them. And there's not a thing I could have done about it, especially because the year my eldest was born, was the year that you found out exactly what the Progranulin gene and all that was kind of discovered. So that means that I had no way of avoiding her, potentially being it passed on to her. (Participant 2)

Although they would not change the decision they made regarding having children, one individual said that their status may have contributed towards them not having any more children in future. This was an emotive topic for many and source of frustration, in particular for those whose family remained in the hands of PGD.

I'm not getting any younger and we want children and that's delayed

everything, so you know, it's not been an easy year, well two years actually, it's been a longer process… if I didn't have the gene then we could, you know, crack on. Whereas our life is now in the hands of other people … I keep harping back to the whole children thing, but we'd already started the process in our life and then it just had to stop. Dead. Because I couldn't live with the guilt of having a child knowing that I had a 50% chance. Yeah, sorry I'm getting quite emotional now. (Participant 15)

Most participants also referenced the 'importance of time. This included a positive approach to life at risk with a view to making the most of life. Many participants felt motivated to do things sooner rather than waiting for the right time, live their life now, enjoy it while they are healthy and able and ensure a good work-life balance.

living this life could end soon and that being kind of like kind of turning that into a fuel to live the life that I wanted to live, now, like now and always. (Participant 9)

I'm doing everything that I want to do. Like the life which I lead now is… it's pretty much my dream life in many ways…if you knew the date you were going to die, you'd want to squeeze in and squeeze as much juice out of life as possible. (Participant 16)

Many participants also described how their view of their risk changed over time. Several saw their life as having a clear end date, usually around the time that their parent or other family members became affected. Some individuals also drew similarities to cancer and terminal diagnoses, explaining that dementia is not often thought of as such but an FTD diagnosis, or even for some a positive predictive test can be considered as such. Some participants also described how their perception of their risk changed and became more real over time. Some of those who learned of their risk at a young age reported a lack of concern for their risk at first, however as they have got closer to estimated symptom onset they have become increasingly concerned, some spoke of a ticking clock or feeling as though they were living on borrowed time as they got older and potentially surpassed their parent's age at death.

[I] definitely think age has made a big difference because at 24, when you're looking at 60, as you know, this can happen at 60…Obviously, I've got

closer to the age. And it all becomes a bit more real...So I'd say the last couple of years its suddenly felt like it's come, come up to my, my present much more. It's like, oh okay it's here… And then like my dad dying made quite a difference because suddenly it was, you know, we're next now. He was almost that buffer, you know… You know, it feels much more, it feels much nearer. (Participant 1)

However, one individual explained that they had lived their life with an expected end date and recently they have come to the realisation that they may surpass this and have had to adjust their thinking and plans accordingly.

I think the most recent thing has actually been a bit of a realisation that I have been living under that kind of like picturing my life ending at like 40ish, kind of thing, when it might not now. And actually that kind of adjusting to the idea of I might be here for a long time is kind of like the more recent thing…now I'm thinking don't make decisions as if I'm only going to be here for like two to five years, make decisions as if you're going to be here for 20, 30. (Participant 9)

Around half of participants referenced factoring their risk or status into making decisions, including re-evaluating life choices and priorities with their risk in mind and exercising caution within their decisions. For example, regarding financial decisions, some participants exercised greater caution in order to ensure they were protecting their family for a future in which they were to become affected.

I decided not to sort of take risks on that because I thought, OK, I'll just-, I want to play safe, make sure my family's looked after, not get the biggest mortgage I possibly can on that. (Participant 8)

Participants also reported keeping their risk in mind when making big life decisions such as retirement, pensions and buying a house.

Everything you do, everything I tend to do, you know, the big decisions have got to be, that's in the back of my mind. (Participant 14)

However, as Participant 5 states, although risk is accounted for, it is not always the driving force in these decisions.

I made the decision to retire early. It does. It does kind of come into that in a way, because you just think, well, you know, if I've only got a limited time So it does kind of influence decisions, but not totally. I wouldn't say that was the main influence. (Participant 5)

Similarly, around half of participants spoke of their risk always being on their mind. One participant explained that at the beginning of their at-risk journey it was always on their mind, and another struggled to think of anything else.

it really it massively infected like my well-being because… I couldn't think of anything else… Whenever I saw my dad, I saw what I'd become and whenever I, you know, whenever I was going out and like people were having a really nice time, I was just like 'oh I can't' so I stopped going out to a lot of events and I stopped… I wasn't in the right frame of mind and like all I felt like was bursting into tears. (Participant 11)

However, the majority of those whose risk was always on their mind reported that it was in the back of mind, suggesting that although their risk was not necessarily currently a priority, it was a constant burden to carry, regardless of resilience or positivity.

it does invade every part of our lives though, it's always there in the back of your mind. But whether you know, whether you have it or not, it's always going to be there. So, it's not fun, not remotely fun…knowing we're at risk it's just more in the back of our minds it's always lurking in the background more than it was. (Participant 15)

it puts like a bit of a black cloud, not a black cloud, it's not even, it's always there in the back of your mind, in some ways. And I'm a very positive, upbeat person. So it's not, it's not like I'm walking around with a huge rain cloud over me all the time. But it is, it's kind of there in the back of your mind a bit. (Participant 16)

b) The effect on relationships – non-romantic

In terms of the effect risk had on relationships, most participants referenced an effect on non-romantic relationships. Primarily this focused on the at-risk individual as a

caregiver for symptomatic relatives, but also extended to supporting siblings, the non-affected parent and wider family system. Although many people learned their own genetic status during their affected parent's disease, their parent remained the focus and some reported being unable to process this information while they cared for their parent.

> *I think the at-risk part before kind of knowing I had the gene, didn't faze me at all because it was secondary to my dad's diagnosis so I think that was very much what the focus was. So, yes, so that part really went over my head.* (Participant 1)

One participant described mourning for their affected parent, despite them still being alive.

> *I done all my morning when my mum was alive. As terrible as that is.* (Participant 10)

A few participants explained that their affected family members passing away or going into full time care relieved some stress and caregiver burden, particularly the implication for their own genetic status as they were no longer confronted with FTD on a regular basis.

> *So I suppose within the first year, certainly since my mum and my uncle have died, it's been a lot easier because I'm not faced with, you know, at the moment I don't have FTD or motor neurone disease in my life. So that is much, much easier than actually when my mum and my uncle both had MND because, you know, I was faced with it every day, every time I- you know, all the, all the time. It was like preoccupying my whole life.* (Participant 5)

A small number of participants described a strain on their family as a result of fFTD and one referenced the specific challenges posed by behavioural variant FTD.

c) The effect on relationships –romantic

Some individuals reported a strain on romantic, long-term relationships and two participants found that their risk creates difficulty in new relationships. A few individuals

experienced the breakdown of romantic relationships following learning of their positive genetic status, due to unsupportive partners.

> *I split up with my ex because of it, he couldn't handle what the future would hold, and I was, we were going through a bad patch and I kind of said, well, if you can't deal with it today, how are you going to deal with it if I'm ill? And, yeah we split up.* (Participant 13)

Participant 13 explained the difficulty of entering into romantic relationships due to the potential burden a partner would face in future. They explained that those who marry prior to learning of their genetic status promise to support their partner in sickness and in health, however as they already know their status they will not allow themselves to form romantic relationships.

> *how can I get in a relationship and know that that person could potentially have to care for me, I- [shrugging gesture]…I won't allow people into my world because I just think I know I'm going to be ill. And how can I expect someone else to have that burden.* (Participant 13)

However, it is important to note that several participants found their partner to be very supportive, which was extremely important in their at-risk experience. This is described in more detail below regarding support needs while at-risk.

Theme 6: The 'whirlwind' of emotions experienced throughout the at-risk journey

Participants spoke of the wide-ranging emotions they experienced as part of their personal at-risk journey. There were a complex range of emotions demonstrated, highlighting the emotional burden of living at-risk of fFTD. These emotions have been broadly split into two sub-themes; positive affect and negative affect.

a) Negative affect

All participants reported experiencing negative emotions during their time at-risk. Firstly, over half of participants spoke of a general negative psychological response, using phrases to suggest overwhelming and diverse emotion; *'a rollercoaster of emotions'* (Participant 10), *'a whirlwind'* (Participant 10), *'a cocktail of emotions'*

(Participant 11) and *'a big burden'* (Participant 14). Similarly Participant 12 described poor sleep and a lack of focus, as well as being in '*a dark mental place'*. In addition to this, several participants became visibly emotional during the course of the interview, suggesting an enduring emotional burden relating to the topic.

Most participants experienced low mood while at-risk, with many explicitly discussing a diagnosis of depression, while others expressed sadness, and general low mood, being unable to enjoy social activities and being constantly tearful. For some this was due to the idea, or reality of being a mutation carrier.

> *So if I tried to talk, I would just burst into tears. And I was just constantly. I'd probably say, like every day I was just on the verge of tears and like, anything could set me off…during that time…I did, yeah, cry a lot.* (Participant 11)

A few participants spoke of going to a 'dark place'.

> *I spent a number of days just sitting there crying…there were days where I kind of went into a deep, dark hole…I kind of went into the attitude of what's the point then? If I'm going to die in 30 years and I'm already started to go then what's, yeah, kind of what's the point…I did go back on anti-depressants for a while.* (Participant 10)

> *it is a really dark, really dark, really lonely place.* (Participant 12)

Around half of individuals spoke about struggling with the uncertainty associated with FTD. Some chose to minimise uncertainty by undergoing predictive testing as this was preferable to the feeling of 'not knowing'.

> *Some people say to me, do you, are you glad you know? 100% I'm glad that I know, yeah, you know. Because the worst thing is not knowing. I think that's a killer.* (Participant 14)

This was the same regardless of predictive test result.

> *the uncertainty of it was worrying both of us really. But that's why I think I was preparing myself so much for having it…Being uncertain was worse*

than knowing, even though it was a positive result. (Participant 3)

However, some still found the uncertainty of phenotype and age at onset to be challenging.

> *And it's not like someone says, 'oh, you're going to catch this, and you catch this at this set age'. So, you know, right I can set my life up to that point…you never know and how it's going to affect you…its such a, such a nasty disease in itself that it's not like you can even prep yourself for what's going to come round the corner.* (Participant 2)

Most participants made reference to a feeling of worry or anxiety. The cause of such worry or anxiety was wide ranging, including genetic status of themselves, siblings and children, receiving predictive testing results, worry about what the future holds for themselves and their family and worry about symptom onset.

> *you're not worried just for yourself, as I said, you're worried for your partner and the rest of your family, the people that are going to have to deal with you. So I have my result, my brother doesn't, so I'm now worried for him. Because he doesn't know.* (Participant 15)

The predictive testing experience was a source of great anxiety for many, some participants reported analysing changes in the geneticists behaviour and body language to gain clues as to their status. Participant 11 describes their anxiety during the predictive testing process.

> *I was just sort of nervous, I just had the pitted feeling in my stomach the whole time and sort of praying to like getting sort of anxiety, sort of rising and attacks*. (Participant 11)

Some individuals began analysing their behaviour for signs of symptom onset and convinced themselves they were becoming symptomatic.

> *I'd sort of convinced myself that that I was going to get dementia. And in fact, I could convince myself that I saw early signs of it in myself. So when I, you know, forgot a word or, you know, left the door open, you would attribute it to that. And, you know, then I was sort of starting to sort of think*

about, OK, if it's starting now, you know, how quickly is it going to go? And that that actually got me very down at the time. (Participant 8)

However, others, like Participant 9, who had known about their risk since a young age, reported not feeling particularly worried about it.

[I] can imagine that having a big impact [on] how I felt because I didn't feel like, I didn't- you know I knew it was bad, but I didn't feel like worried about it. (Participant 9)

Some participants reported survivor guilt either in themselves or their gene negative siblings. This arose where one sibling was found to be mutation negative, while another's status may remain unknown, or they may be a mutation carrier. This led to guilt regarding the negative individual, and by extension their children, achieving the desired outcome while their sibling and their family continue to face a difficult future ahead. For one individual whose sibling was still at-risk, they explained that they understood what their sibling was going through, however felt guilty that they were unable to fix it for them. In addition, some individuals felt guilt for feeling relieved or happy after receiving their predictive test result.

I think my sister felt worse knowing that she didn't have it. And she she's confused as to not being happy, I think. And she, I think she feels worse knowing that I have got it. (Participant 3)

Participant 4 describes that they felt as though they should have been the gene carrier in place of their sibling.

I was sort of convinced that if I wasn't positive that [sister] would be. So I felt rather. I felt terrible I felt very much like I'd sort of not absorbed it. And I should, you know, I should be the one. (Participant 4)

Several individuals felt fear, largely towards their genetic risk and the potential of being a gene carrier. For others this extended to a fear for their children's future, of becoming affected and leaving their family to struggle and a fear of death. Some felt fearful as they understood the future that lay ahead as a result of caring for their parent, and others spoke of a fear of the unknown. It is possible that both are the case due to the unpredictability of FTD.

there's this paralysis that sets in, I think, when you get the, it's not so much the diagnosis it's the fear of the diagnosis. And suddenly, like your life has- hits this fork where there's this kind of terrible stark future. I think it's just that you know, your, the experience of being a carer or the experience of living in fear of a diagnosis or having your sibling at risk and knowing what the future holds and knowing that you will have a role probably in that future difficulty, it makes you terrified and it makes you very angry. It's terrifying because it's so unknown. (Participant 4)

Anger and frustration were also felt as part of the at-risk experience, some individuals felt anger and spoke of frustration. Frustration often referred to waiting times and lengthy predictive testing processes, as participants felt as though their life was left on hold during this time.

It's not so much knowing that I have the gene, it's the waiting that, that, that ma-, it doesn't make us anxious, it just, it's frustrating. And you know, you have too much to drink and your discussion becomes very negative very quickly because your-, it's just frustration coming out…but the overwhelming emotion was just frustration that our life was put on hold for a year, well longer now. (Participant 15)

This was also felt towards a lack of understanding of what they were going through and the frustration of struggling to articulate the experience.

it's an additional stress to you if you can't get people to understand or you can't articulate what you're going through or what your family is going through, which just makes you feel more frustrated. (Participant 4)

Anger was often referred to as part of the predictive testing process and experience, some who had a bad experience of predictive testing felt angry towards this and didn't want their family members to have this experience. Some felt angry towards their negative status, alongside survivor guilt as they felt a burden of how they were to tell their family who were still struggling and also that they were not able to protect their siblings from their risk.

I guess there was a little bit of me that was a bit angry. And then also maybe

angry at myself for being relieved about it. (Participant 8)

Another participant felt anger towards themselves within their caregiving role for with their difficult thoughts and feelings towards their affected parent. Participant 4 explains this experience.

> *I think I realised I felt probably very angry or very, quite self-hating of myself for being angry and not being able to articulate it or feeling things which I thought were very unworthy things to think, I guess. But then actually discovering that this nice lady next to you was saying the same terrible, terrible things made you realise that you were part of some bigger process, that it was a kind of shared thing… you weren't sort of alone in this whole process.* (Participant 4)

Helplessness was mentioned by around half of individuals. Some people felt as though they can't control their risk or status and there is nothing they can do about it, for some this felt negative, however others felt that this removed some anxiety and allowed them not to ruminate on it.

> *Do I want to live the rest of my life feeling like a victim? Or do I just say I can't control this like it is, if it's going to happen, it's going to happen.* (Participant 12)

Some individuals also felt helpless as they were unable to plan for the future.

Individuals also spoke of a feeling of isolation while at-risk as they felt as if no one understood their experience and that they were left to cope with it alone, without support. Participant 2 explained their experience of isolation while at-risk.

> *I kind of became very selfish and kind of rejected everybody around me because obviously I felt like it was something that I had to do on my own and no one else can understand because obviously it is something very personal. I wouldn't commit to anything, so if someone said 'oh do you want to go...' I'm like no, no holidays because, you know, because obviously if I have got this, then everything's got to change, even though it wouldn't affect me straight away. But to me everything will change straight away. And that's a lot.* (Participant 2)

Participant 6 articulates their feelings towards being left to cope alone, without support.

> *I do feel all at sea really…it's almost like you're left out at sea.* (Participant 6)

However, sharing the at-risk or mutation carrier experience with a sibling was helpful in combatting this feeling of isolation for some.

> *When I when I told my family about it, I found out that [sister] had it as well then. So I kind of didn't feel alone.* (Participant 14)

Around half of participants spoke of shock as part of the at-risk experience, for some this was shock towards their parent's diagnosis and a genetic mutation being identified in their family, there was also shock when receiving predictive testing results.

> *I did feel a little bit kind of shocked, although I was prepared. I was a little bit shocked when I found out, especially when I saw it on black and white, I think, more than when she told me, especially 'cause she seemed devastated, the geneticist telling me.* (Participant 3)

However, others reported that they were not surprised when they were told of their risk 'officially' as they felt like their knowledge had gradually increased over time for many years.

> *That was the first time I found out but it, it was kind of like, it had been simmering for a while. I think, I don't remember that being a surprise or anything. I think I kind of had guessed that…it certainly wasn't like, 'oh my word we thought this was going to be all fine for us'. So it wasn't, it sounds like I'm really downplaying it, but it wasn't like a shock.* (Participant 9)

b) Positive affect

Conversely, many participants also experienced positive emotions in relation to their genetic risk. Around half individuals mentioned the idea of hope, with some specifying hope for future clinical trials in fFTD. By extension, hope towards clinical trials allowed for hope for participants' children who may also be at-risk and family members who are gene carriers or who do not know their status.

> *I think it's a lot more positive if like with the drug trials going on that it's giving hope …there is possibly going to be a cure one day…there is a light at the end of the tunnel for this whole process.* (Participant 10)

Similarly, hope for clinical trials and recent progress in this field motivated Participant 12 to have predictive testing and take an element of control over their risk.

> *You know, and then I'm kind of like, well maybe there's a chance if I know that what's wrong with me, that I can be involved in clinical trials and maybe because it's genetic they might be able to do something about it. So you get that bit of hope that enables you to think, right well I'll build on that hope that maybe they can do something about it.* (Participant 12)

A few individuals, however, felt that they had no hope, Participant 1 specifies how it felt dangerous to have hope as a mutation carrier due to the potential for disappointment should trials be unsuccessful.

> *I have found it more difficult to think about the trials even now, because I think. I still, I don't want to let in the hope. I don't want to allow myself to think about the possibility that it won't happen, because that's not it doesn't feel helpful for me in terms of managing and kind of preparing myself, I think I would find it much harder to be hoping for something and then it not, it not happen. I think that would be quite, quite difficult to overcome. (Participant 1)*

Similarly Participant 7 felt that there is currently too little to be hopeful for when at-risk of FTD, due to both the autosomal dominant nature and lack of successful treatment.

> *Hope is a massive thing. You know, being 99 percent likely to pop your clogs means you've got a one percent chance of survival. And I think at the moment, that's just not there. So there is nobody that reverses the effects of FTD, you know.* (Participant 7)

Many individuals also felt an element of positivity towards their risk and used it as a motivating factor to live life to the fullest.

Participant 1 and Participant 10 expressed how they became more conscious of

ensuring they were enjoying life and making the most of it.

> *I think I'm much more aware of enjoying life, enjoying what I have.* (Participant 1)

> *I went a bit like Dead Poets Society of I'm going to seize the day, kind of thing.* (Participant 10)

Meanwhile Participant 12 felt that they viewed predictive testing as a positive factor as this allowed them to begin the process of having a family and used the positive elements of being at-risk to aid the psychological adjustment process.

> *I almost put a positive plan in my head together of how, if I had it, what was my life going to look like and what was I going to do about it?...And for me, that, I tried to really focus on the positive things to get me to a place where I could go, 'do you know what, I'm not, I'm choosing not to be sad about this now'…But I think the having a family thing has enabled me to give more of a positive spin to it than say other people.* (Participant 12)

Participant 14 stated that they look at their mutation carrier status as a largely positive influence in their life as it allows them to make informed decisions.

> *So now, 90% I see it as a positive thing, if I'm honest with you…Because I can make decisions clearer…So I just see it as positive because everything I do, I do it with that in mind. So then it's all, I'm making the right decisions. If that makes sense.* (Participant 14)

Participant 9 reiterated the sentiment of seeing their risk as almost wholly positive as they were able to analyse ways in which their risk could be helpful to them. They note that they are able to be more appreciative of the life they have lived and see the joy in everyday experiences where, if they were not at-risk, they may not have been as grateful.

> *I was like, 'this is my scenario, this is my situation. How is that a helpful thing to me?'…somewhere in the last five years, I'd started to come to the conclusion this was almost wholly positive…I'm 38 now, there's plenty of better men than me who died younger than this. And I've had a flipping ball,*

you know… I think there's things that I appreciate now that I might have had the same life and I don't think I would have appreciated them the same way…So I think I'd kind of come to think of it almost like a pure good, because I- it started to matter less to me how long I was living and how the quality of the life that I was living was. (Participant 9)

Finally, some participants felt relief having had predictive testing, regardless of genetic status. As detailed above, *"not knowing was much worse than knowing"* (Participant 3), therefore for some individuals there was a sense of relief once this element of uncertainty was removed. Participant 15 explains that they felt relief due to the ability to make informed decisions for their future, despite the information that they carry the genetic mutation.

I mean there was a huge sense of relief and it wasn't just for me it was for my husband as well…So it wasn't the result we wanted obviously, but knowing we could make decisions about our life…both of us were just so relieved. And you've had a year's worth of tension just sort of weight lifted off your shoulders. (Participant 15)

As expected, relief was also felt at negative status. Participant 8 describes how their worries were immediately lifted on finding out that they were mutation negative.

I don't have the gene. So it was it was immediately sort of lifted and then you realise that everyone forgets to close the door, everyone trips over their words. And that those things I was looking at were, you know, not really there. And the worries I had about financial and family, you know, just immediately don't exist from that, from that point onwards…its just one less thing to worry about because you feel like it's hanging over you basically. And so you just have that kind of cloud kind of lift with that. (Participant 8)

4.4.2. Summary of the feelings and experiences of living at-risk

In summary, the feelings and experiences of living at-risk, discussed within this study encompassed individual's reaction to learning of their risk, which fluctuated over time. Positive and negative reactions were experienced regarding the perception of 50%

risk, with some optimistic and reassured by their understanding of their risk, while others felt devastated by the news. There were also many additional challenges relating to fFTD, on top of the individual's risk that made the experience more complex, including caring for or supporting symptomatic family members and the wider family. Many participants also found the symptoms observed in symptomatic loved ones to be confronting and related this to their own future. Acceptance, information gathering, and time were all important factors in aiding adjustment to genetic risk. Information regarding risk was often gradually learnt over time, and many suspected an underlying genetic cause, however for others it came as a surprise. Prior to predictive testing, participants often assumed their genetic status, and planned for life as mutation carriers. Many felt their status was linked to that of their siblings and felt that they should bear the burden of a mutation carrier in place of their siblings. Information was considered extremely valuable; however, a lack of accessible information was noted. Coping strategies outlined were avoidance and planning, including end-of-life plans, financial plans and practical planning with symptom onset in mind. The effect of genetic risk on the individual referred to the influence of living at-risk on decision-making, especially reproductive decisions, the importance of time in terms of motivation to live life in the present and in their view of their risk as they approached their parent's age at symptom onset. Risk was also reported to always be on their mind, whether in the forefront or at the back of their mind. Being at-risk also impacted non-romantic relationships with symptomatic relatives remaining the focus within the family. Romantic relationships were difficult for single participants, however those in long-term relationships often reported their partner to be supportive. A whirlwind of feelings and emotions were experienced, both positive and negative. These were low mood, anxiety and worry, uncertainty, fear, survivor guilt, anger, frustration, helplessness, isolation, shock, relief, hope and positivity.

4.4.3. Research question 2: What are the support needs while living at-risk of FTD?

There were seven themes derived from data regarding the support needs while living at-risk of fFTD. Main themes included; *(i) the presence or absence of support, (ii) the types of support received, (iii) the impact of support, (iv) barriers to accessing support, (v) facilitators for support, (vi) support wanted, and (vii) the importance of understanding specific difficulties.*

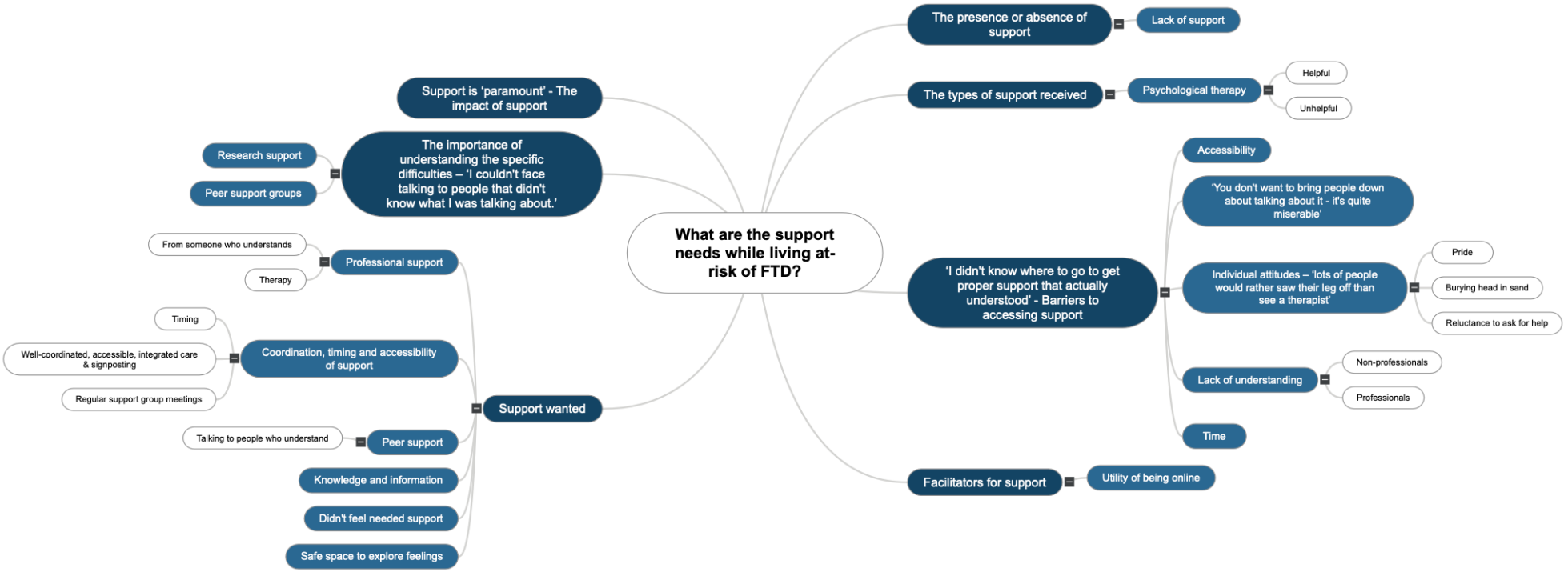


Figure 13 - Mindmap to display themes and subthemes generated regarding the support needs while living at-risk of fFTD

Theme 1: The presence or absence of support

Most participants contributed to the theme regarding the presence or absence of support.

a) Lack of support

Many participants felt that they experienced a lack of support offered to those at-risk of fFTD.

> *No formal support so I've never gone to genetic counselling, I've never been offered anything actually really, beyond kind of like, obviously we go to the research.* (Participant 7)

Participant 11 describes how they were unable to access support due to administrative mistakes.

> *But actually, the way, sort of, I found out like this was the letter. And actually they hadn't filled in…they hadn't filled in the telephone or the fax or the department information. So actually the letter sort of said, like, you know, don't hesitate to contact me on the number above, but there wasn't a number to call. And yeah so we didn't have any follow up from, from them.* (Participant 11)

However, one individual did feel well supported regarding their risk due to contacts at a specialist centre.

> *Looking back I did feel quite supported anyway like I, obviously, my sister was very instrumental, but, the, you know, we spoke a lot to the doctors and to the Dementia Research Centre. We had quite a kind of, continuous dialogue, so I was very lucky.* (Participant 4)

Theme 2: The types of support received

a) Psychological therapy

Despite a general lack of support as mentioned above, over half of participants attempted to seek specialised support. Participants largely received standard

psychological talking therapy as provided by local psychological services. Participants reported both helpful and unhelpful aspects to this support. For some, CBT was helpful to an extent, allowing for exploration and validation of their experience, and facilitating acceptance.

> *I think like so the CBT probably helped me understand that it was a massive deal to go through and that everything that I was going through at the time was an awful lot for one person to go through at one time. So I think it kind of helped me realise that and accept that, that that was, you know, that it was alright to be emotional because it was shit. So I think CBT probably did help in the sense of just like accepting it was ok to feel what I was feeling.* (Participant 11)

Participant 14 explains how CBT helped them to understand the workable and unworkable actions they were making, creating a space for them to challenge their behaviour.

> *I went and got some CBT, cognitive behavioural therapy. Yeah so I've seen a gentlemen, local…I thought that was pretty good because its more to do with making you think about your action, making you think about stuff and answering your own questions in a way, that's the kind of therapy that I was given, like, you know. So that was good… it just made me question myself, challenge myself. So everything I was doing, I was kind of 'am I doing the right thing here?'…rather than just, like I say, going on self-destruct and kind of just not really caring…Kind of, kind of centres you a bit and humbles you a bit, you know.* (Participant 14)

Participant 4 also explains that therapy provided a listening and empathetic ear to their problems, allowing them a space to express their difficulties and frustrations in a healthy way.

> *I found it very useful to go and just like talk and motor mouth and come to try and, you know, work out what I was actually trying to say by blathering completely incoherently…I think as well because I was, I didn't really have anyone directly to talk to the time…I think you just need that thing that therapists are paid for anyway to, just to listen. Sort of empathetically…And*

that, to me, was quite clarifying, really. And you know, healthier than drinking or doing any other useful things like that. (Participant 4)

However, unhelpful aspects included things such as the lack of knowledge from the counsellor or psychologist regarding fFTD. Participant 1 explains how educating the therapist felt like a waste of time and money.

one of the things I struggled with, with the support, with the counselling I was having at the time was they didn't know anything about it…I don't want to spend my therapy time informing you about this in order for you to support me, because that's a complete waste of my time. Like, you're catching up to me and it was taking so long to catch up to my level of knowledge about this, that, you know I'm paying you, so, frankly, I can't afford that. So I think that it would have been very different if I was speaking to somebody who already had that background knowledge that didn't have to say, 'have you thought about diet and lifestyle?' and you go... [shakes head]. (Participant 1)

Some individuals also found a point at which sessions reached the limit of helpfulness as many techniques were not appropriate for the specific challenges of FTD. Participants 11 and 8 discuss the limited nature of the psychological support they were able to access.

I think we sort of agreed during those sessions that actually like the sort of techniques and things that she was giving me, weren't appropriate at that point in time, because the emotion was too high, that even just trying to, you know, not think about it for a short period of time, it was too difficult because it was just too overwhelming…but it didn't really give me anything at that point in time to kind of help me deal with it…I think it was, it wasn't specific enough or it didn't have, like she didn't have an understanding, obviously, about anything because it's so, you know, it's rare …I didn't really feel it was going anywhere. (Participant 11)

I was offered some kind of, you know, talking, sort of, therapy, then. As you know, the sort of standard you get from the GP. Which I think I did one or two…that felt kind of a little bit sort of generic and because it was a, sort of,

a specific worry. (Participant 8)

Theme 3: Support is 'paramount' - The impact of support

Several participants discussed the impact of support on their wellbeing. Support was considered extremely important in adjusting to living at-risk and working through the challenging emotions that arise as a result of this.

> *I think it. It probably make- made me less inward looking in terms of, rather than looking for solutions within my own concerns or whatever and trying to find my own answer to everything. It allows you to be a bit more proactive I guess and progressive…you don't feel as kind of trapped and like shackled up by, by your kind of fears and your doubts and your kind of guilts. You sort of, you feel less, you know, less trapped by it, I think.* (Participant 4)

Participant 15 explains the importance of their support network in providing a space to talk and express emotions.

> *Having that support and being able to vocalise stuff, if you don't have that support network that's there, I just don't know how people would, would deal with it. I really don't. … vocalising is what, for me is what's needed, being able to cry…being able to vocalise and having that support network there was hugely important.* (Participant 15)

Theme 4: 'I didn't know where to go to get proper support that actually understood' - Barriers to accessing support

All participants spoke of barriers to support. This theme was broken down into a number of subthemes to categorise the barriers discussed; *accessibility, 'you don't want to bring people down about talking about it - it's quite miserable', individual attitudes - 'lots of people would rather saw their leg off than see a therapist', lack of understanding, and time.*

a) Accessibility

Accessibility of support and information was a barrier for most participants. Participants were not aware of available support that may be suitable for them and did

not know how to go about accessing useful support.

> *I didn't know where to go to actually get, like, proper support that actually understood.* (Participant 11)

However, some were reluctant to use the internet as they were worried that they may come across scaremongering or unpleasant information. Therefore, it required time and effort to find information and support.

> *I refused to go on to Google and start typing in to find stuff, because Google can be a very scary place if you start typing things like that….through this all I think there has been times where we've needed a bit more support, but yet there wasn't, there wasn't much … or there was nothing to kind of help us at that time.* (Participant 10)

Similarly, there was a lack of local support which resulted in a London-centric view of support services as those outside London either had to travel to attend RDS [Rare Dementia Support] support group meetings or they were not able to attend.

> *We have to come to London for that because of where we are in the country. And I imagine there would be people that are put off by that…I don't feel like the familial like seminars are often enough, like once a year doesn't feel like enough but I understand that it's all, you know, charity funding and things and you, the money has to go somewhere doesn't it at the end of the day.* (Participant 12)

Furthermore, accessing information was challenging for some as they found it hard to navigate multiple websites, access basic lay summaries and found that the medical jargon in research papers created a barrier to them learning more.

> *you have to really search for it. It's not very accessible. I don't think. So you actually have to actively, kind of dig in to, you know…you have to press this link and that link and … all that sort of thing. And I'm not very good at reading medical papers… You know, for anybody who's not bloody qualified in neurology, it doesn't make much sense… it's really difficult for lay people to get their heads round it, really. And I'd consider myself a fairly intelligent,*

educated person… I don't think there's enough kind of basic information that's readily accessible to people who don't understand the kind of neurological stuff. (Participant 5)

b) 'You don't want to bring people down about talking about it - it's quite miserable'

Another theme regarding barriers to support was the difficulty talking about risk to others. Participants reported that discussing their risk was difficult to navigate within the family as they were conscious of sibling's and parent's feelings on the matter, in particular they did not want to trigger feelings of guilt in their parent. Some also kept their genetic status secret from their family for a long time to protect siblings from feeling pressured or burdened by this information.

Participant 14 explains that they initially kept their genetic status private from family members, however once they disclosed this information, siblings were able to support each other through a shared experience.

So I kind of went in my shell a bit then, and I didn't like people knowing my business and so probably for about a year or so, I just didn't tell anyone like, you know…didn't even tell my family… when I told my family about it, I found out that [sister] had it as well then. So I kind of didn't feel alone. In a way. (Participant 14)

Although many people felt that they wanted to talk to others at-risk who understood their experience, some individuals felt conscious of other's choices and opinions as they understood that they are highly personal and may align with each other's values.

I felt a bit awkward talking, not awkward, but like I was just like conscious that like, you know, she had found out she had the mutation and she had already got kids already and that they therefore had a 50% chance. So I didn't want to make her feel worse for like talking about those things because like I have a choice now about children whereas she doesn't. (Participant 11)

Finally, some participants were discouraged from speaking with their support network

as they were mindful of lowering the mood of the conversation by bringing up an emotive topic.

> *I probably talked to [best friend] a lot and a couple of my other friends know, but it's really difficult because you don't want to bring people down about talking about it because it's quite miserable. So you tend to sort of maybe talk about it after a glass of wine and that's never sensible.* (Participant 7)

c) Individual attitudes – 'lots of people would rather saw their leg off than see a therapist'

Individual attitudes also served as barriers to accessing support. Around half of participants spoke of individual attitudes as barriers, and these occurred not only in participants but also were observed within family members also at-risk. Firstly, many people at-risk 'bury their head in the sand', meaning they avoid information and prefer not to engage with their risk through genetic testing, research or support groups, therefore creating a barrier to accessing support. Secondly, some male participants stated that they dislike asking for help.

> *I would be, you know, with my legs falling off and having a heart attack before I, sort of, thought about troubling somebody for help.* (Participant 16)

Similarly, a number of participants referenced pride as a barrier to support. Participant 4 highlights that pride is often a particular issue for men.

> *I'm aware that most people, I think particularly men, run a mile if you suggest therapy. But I'm aware that lots of other people would rather saw off their leg than go to see a therapist.* (Participant 4)

Participant 14 describes how pride was an initial barrier to support, however once they were able to overcome this, they were able to access helpful support.

> *At first maybe I wouldn't have done it because, again it's stupid male pride thing, isn't it? Like, you know, 'I don't need that and I don't need someone talking at me and lalala'... It was only once I kind of accepted it for what it was, then I went in and like I say, when I went in for the session, and I'm paying as well so I thought…I'm paying for it I'm going to get as much out*

> *of it really…then I kind of broke down those barriers a bit…and accepted the help. But yeah, I think with a lot of men… you think … 'I don't need the help' and that but everyone needs help you know, it is what it is.* (Participant 14)

Participant 2 suggests that a way to overcome pride as a barrier may be by ensuring support is widely offered and suggested when discussing risk with medical professionals.

> *I know British people generally are very, very I don't need anything, I can soldier on and my arms falling off, I can soldier on! Until the last point when they can't soldier on then they ask for support. But if someone sometimes says, do you need any help? There might be some support I get for you. That's when, you know, depending, I suppose, on a case by case basis, if someone seems like they are struggling more than that's potentially when, I don't know, mental support and, you know, that kind of thing can step in to give them that counselling as such.* (Participant 2)

One participant also expressed a distrust and fear of judgement from professionals as a personal barrier.

> *I'm quite a closed book, so I'm not the kind that will go 'I need help' or 'I need to talk about this' because I keep it all inside…I was brought up as you don't talk to people, you don't talk to professionals, so when you've had that ingrained in you from such a young age it's very difficult to say 'I need help' or 'can I talk to someone'…And I always feel like I'm being judged, that's part of me, so to kind of expose myself to someone, I struggle.* (Participant 13)

d) Lack of understanding

Most participants expressed a lack of understanding as a barrier to accessing support. This was described as an issue when accessing support both from healthcare professionals and also non-professions such as friends. Within the public, participants described a lack of understanding of non-Alzheimer's dementias and misconceptions of the umbrella term of dementia. This created barriers for some when wanting to

discuss their risk, as at-risk individuals often did not want to educate people on the complexities of FTD and found it frustrating when people drew comparisons with older age dementias.

> *You know, a lot of people you talk to go 'oh yeah my nan's got dementia', you're like, she's not 58 though is she?...it's such a weird thing that no one really understands unless they've lived it or seen it really, not truly.* (Participant 12)

Furthermore, participants explained that often people struggled to understand FTD, genetics and what this means in terms of risk. Some individuals also felt as though people were not able to understand the difficulties they face unless they have been through something similar.

Participant 4 explains that despite having a network of supportive friends, they struggled to understand the experience of being at-risk and were surprised that a mutation negative test result still resulted in challenging emotions.

> *unless you kind of experience [it]…it's very hard to explain it to people. Both the kind of genetic risk as a thing and also FTD as a condition because people are so sort of blinded by Alzheimer's and assume like dementia is just this kind of single condition that-. People could kind of, were supportive in terms of they understood it was a difficult time and they were giving of their time to sort of be supportive. But, it's never quite, doesn't quite hit the spot in the sense that you need to talk to people who really kind of understand you…my friends didn't really understand it. I think my friends were a bit sort of confused why I was-, yeah I think they thought it* [their negative genetic test result] *was going to be a great celebration.* (Participant 4)

Participant 9 also explains that people's reaction to speaking about risk can have an impact on how you view it yourself and this may have a negative impact on your wellbeing.

> *I think this is it, because, like, if I tell someone else and let's say if I tell someone in my life that this is the, this is my scenario, they will be like, 'oh*

my God, that is so bad, how do you-' you know? And then if I'm, if all I've got is what I'm thinking and then the people who react to what I'm thinking, if that's all I've got to go on to judge how I should be reacting, then I would be like in a flipping tailspin… it is a funny thing though, because I mean, I would feel weird if someone was like, 'oh right well never mind'. (Participant 9)

Similarly, there was also a lack of understanding within healthcare professionals. Participants reported that within general medicine, and even some specialist services, many healthcare professionals did not have any, or had very limited knowledge of FTD. This created a barrier for some, particularly when seeking mental health support as it is both emotionally and time consuming to educate the mental health provider prior to beginning support. Both participant 10 and 12 felt that this was a barrier in accessing support.

I didn't want to go to see someone, have to explain this, which they might not understand what it is, and then to have to take longer to try and process it, because I'm having to explain to them what it is and how it affects someone. So I just, I kind of just dealt with it myself. (Participant 10)

I couldn't, I couldn't face talking to people that didn't know what I was talking about. (Participant 12)

However, others such as Participant 14 felt as though a lack of knowledge in professionals was not a barrier as they were seeking support to help themselves. Participant 14 explains how their therapist said that they had knowledge of FTD but it became clear that this was not the case so Participant 14 brought FTD information resources to assist their therapy process.

I think he said yes, but I don't think, I don't think so. To be honest with you, because it's such, quite a rare thing, isn't it?...the second time I went, I took like one of the fact sheets I got from the Internet...I kind of put [the lack of knowledge of FTD] to one side really, you know because I was there to try and help myself like. (Participant 14)

e) Time

Finally, time was also considered a barrier to accessing support, as well as a barrier in terms of processing emotions. As reported above, at-risk people often have lots of things going on when they first learn of their own risk, most commonly an unwell parent. Therefore, there may be limited time in which to focus on their own feelings and emotions at this time. Participant 11 describes this experience.

> *I didn't have the time to kind of like, try and just let the emotions flow or anything.* (Participant 11)

Participants reported that it was time consuming to research suitable therapy modalities, as well as a time commitment to engage in therapy alongside work and family life.

> *I generally work Monday to Fridays and…you work Monday to Friday and you work, would be the same kind of hours. So, you know, obviously, not everyone's got that access in the evenings or the weekends. So that that's something that's going to be the only thing that would standing in my way and stand in quite a lot of other people's ways.* (Participant 2)

Similarly to above, at-risk individuals were also conscious of wasting their time on therapy that was not suited to their circumstances.

Theme 5: Facilitators for support

a) Utility of online support

The main facilitator for support discussed by participants was the utility of online support. As this study was conducted during the COVID19 pandemic many people had already adjusted to online working and therefore people felt more comfortable accessing support online. Some participants identified finding time to travel to in-person appointments as a barrier, this is a particular problem in the at-risk community as largely, they tend to be of working age and may also have young families, therefore online support provided a way to overcome this.

> *I feel like I would be comfortable doing therapy over online. So I think that that's something that would be not a barrier because actually, yeah, getting somewhere, fitting the time in, would, would be a potential barrier.*

(Participant 1)

Similarly, participant 11 acknowledged that online support may provide greater access to specialists who are understanding of the challenges living at-risk of fFTD brings.

> *actually having these as virtual is probably easier like you know in a sense of time out, like not having to travel…there's never going to be like a psychologist who knows everything that's like around the corner sort of thing, that I can go to face to face so actually like the advent of virtual meetings and things like that is actually a lot more positive because you can obviously reach more.* (Participant 11)

Theme 6: Support wanted

When asked what participant's support needs were throughout the at-risk experience there were a number of subthemes that arose including; professional support, better coordination, timing and accessibility of support, peer support, knowledge and information and those that did not need further support. In addition to these subthemes, participants expressed need for a safe space to explore their feelings and open-up emotionally. Some participants wanted local support and some also expressed a need for specific support targeted for FTD.

a) Professional support

Most participants wanted professional support, some of which specified they wanted support from professionals who understand. Several participants wanted psychological support from professionals who understood FTD and the challenges of living at-risk, while others wanted a point of contact to ask questions when needed.

Participant 8 explains that it would be difficult to engage with a therapist without specialist knowledge of FTD, but a small number of specialist FTD mental health professionals would be helpful.

> *when you're talking to someone generally about how you feel if they don't know the sort of, more about the specifics of the condition, you tend to think, 'well, you just don't know'. Now, it might be that the condition and the, sort of, the mental stuff is separate, but it would be nice if someone could talk*

> *about the two things together…I think having someone that was sort of, you know, trained in, you know, whether it's sort of psychotherapy, whatever it's called, but also the condition…I think would be super useful… But just having that, sort of, specialist resource that knows the condition, knows some of the practical answers to some of the practical questions.* (Participant 8)

Several participants also expressed a need for access to therapy or guidance on suitable types of therapy and recommended therapists.

Participant 1 discusses how therapy would be useful in reflecting during the genetic counselling process.

> *in some ways, I wonder whether people should be kind of forced to undergo some actual intensive therapy before they find out because I just think it would have opened up more questions. You know, I went in there with my one mindset… I wasn't asked anything that would shift me from that…If I'd maybe been challenged on it a little bit maybe it would have just helped me kind of reflect in a different way. But at the same time, you know, it is that, are we kind of trying to take away people's freedom of knowledge in terms of, you know, it's kind of your right to find out.* (Participant 1)

Theme 7: The importance of understanding the specific difficulties – 'I couldn't face talking to people that didn't know what I was talking about.'

All participants acknowledged the importance of people in their lives who understand the specific difficulties faced living at-risk of fFTD. This support came in a number of ways; from research teams, peer support, and from a network of supportive partners and family members.

Most participants noted the importance of support through their participation in research studies and their engagement with the research team. Some found the process of research participation encouraging, receiving updates regarding research breakthroughs and clinical trial progress.

> *I come to see you guys I found that's helped a lot, you know. I almost see it as a weekend down in London, you know…it's good because if can also show that you're not alone, in a way…the kind of positivity and the news from the first time and the last time, honestly it's massive because obviously with the, with the developments it's - … last time we came down, me and [sister] came back and we were buzzing. So it's, to us, it's good coming down. It's- that's helped a lot.* (Participant 14)

Many participants emphasised their personal connection with the research team, feeling like the team feel like part of their family.

> *The thing is, is like [study co-ordinator], yourself and even [study PI]… you know, you are kind of, like me and my sister have looked at you as like an extended member of the family because obviously you've been there and been the support all through my mum and all through the last couple of years you've been there and we've probably seen you more regularly than quite a few of my cousins and stuff.* (Participant 2)

For some the personal element and rapport with the research team helped them to feel more connected to the research, but also more comfortable with their participation which might otherwise feel daunting.

> *it just helps you feel in touch, whereas I think I might feel quite lost if I wasn't in GENFI…you and the team, you and [study PI], actually you're very, very good at making it feel like we matter…[sister] and I have talked about how it's kind of like a little family…the personal effect actually helps. I think if you were very, very clinical and sort of 'you are patient 372', then I don't think I'd enjoy it.* (Participant 7)

Peer support was another important element for many, who spoke of the importance of peer support, acknowledging peer support groups specifically.

Peer support groups provided access to professionals who understand fFTD, but most importantly, they provided access to others with the shared lived experience of being at-risk and in a family affected by FTD. Below Participant 4 explains how attending peer support groups was helpful in terms of understanding that they were not alone in

experiencing challenging thoughts and feelings with regards to their at-risk status and also caregiving experience. This helped them with emotional adjustment to the situation and reduced the guilt and negative self-talk they were experiencing.

> *talking to people who were saying exactly the same things that you'd been saying or thinking the same things that you'd been thinking about. That sort of support is what's really kind of critical, I think…The process, I think I went through was immediate, sort of, appalled that I wasn't such an individual thinker…and actually everyone else was saying exactly the same thing. It was a bit galling…I think I realised I felt probably very angry or very, quite self-hating of myself for being angry and not being able to articulate it or feeling things which I thought were very unworthy things to think, I guess. But then actually discovering that this nice lady next to you was saying the same terrible, terrible things made you realise that you were part of some bigger process, that it was a kind of shared thing and, you know…you weren't sort of alone in this whole process. That you weren't, that, you know, other people had got through it and survived, as it were…that that was probably the most helpful thing I had.* (Participant 4)

Participant 3 also describes how helpful it was to meet others who were both mutation carriers and non-carriers at support group events as they had never met anyone else going through the same experience.

> *I remember the first time, I met a couple of people that were there. And one of them had the gene and one didn't. And that was really helpful to meet someone else that did have the gene and that didn't show any symptoms yet, but they almost were in the same boat kind of thing. And that was really helpful. And I think they're the only person I've actually met so far that I knew that actually had the gene.* (Participant 3)

Other participants found peer support from friends useful, and some formed friendships with other at-risk individuals they had met at support groups who they met with to share the burdens they were carrying. One individual described how they enjoyed being able to spend time with their affected parent alongside an at-risk friend as they knew that this person understood FTD and would not be judgemental.

Furthermore, many participants acknowledged a support network, largely consisting of supportive partners and family.

Supportive partners were important in providing a listening ear and emotional support when needed but also in approaching life challenges as a team, particularly in relation to having children. Participant 14 describes how integral their partner's support has been.

> *I talk to my wife about it a lot…because she's a good listener…my wife like honestly I couldn't get someone better sup-, better support than [wife]. Honest to God she's fantastic. So if ever I need to talk, her ears are always open, you know?...And it's good because when I'm talking to her …she's not trying to be like, 'everything's OK lalala', you know, she just like listens to me …and even asking questions…like 'how are you feeling?' … It's that kind of thing, you know.* (Participant 14)

Others found peer support from family members who were also living at-risk. Two individuals mentioned that they had been given a great example by other family members that it was possible to live a normal life at-risk. While others spoke to their siblings and other at-risk family members in order to support each other reciprocally.

4.4.4. Summary of the support needs while at-risk

To summarise the support needs of the at-risk population, first the absence of support was established. Of those who sought support, most received talking therapy through local psychological services. This was often helpful to an extent, allowing exploration and validation of the challenges faced, however limited in its application to the specific problems associated with living at-risk. The lack of knowledge regarding FTD from mental health professionals also further limited this experience. Despite a general lack of support, the support received was considered *'paramount'* with regards to wellbeing and adjustment to genetic risk. Barriers to accessing support discussed were accessibility, the difficulty of discussing risk with others, individual attitudes, lack of understanding and time. Support was inaccessible due to a lack of awareness of available and suitable support and not knowing how to find this. Information was also deemed inaccessible due to medical jargon. Talking about risk with others was difficult

due to concern for feelings of other family members, as well as the choices and circumstances of at-risk peers. Individual attitudes referred to qualities such as pride, a dislike of asking for help and a tendency to avoid the topic. Lack of understanding of FTD in both healthcare professionals and the wider public was also considered a barrier due to the need to educate those responsible for providing support. Time was a barrier due to the complex and busy lives of those at-risk who often have caring responsibilities for symptomatic family members and children, as well as typically being of working-age. The main facilitator discussed was online support, to reduce the need for travel to in-person support and increasing access to those in a wider geographical area. Participants expressed a desire for professional, psychological support from individuals who are familiar with FTD, better coordination, timing and accessibility of services, peer support and improved access to information. Finally, the importance of understanding the difficulties of living at-risk of fFTD was emphasised. Participants acknowledged the importance of support they had received from research teams, peers and supportive partners and family members, who understood the specific challenges faced.

4.5. Discussion

This is the first study to extensively explore the lived experience and support needs of individuals living at-risk of fFTD. Prior studies in FTD have focused on the experiences of caregivers, spouses and person living with dementia, as well as a very limited number of studies into the experience of those who have undergone predictive genetic testing. Therefore, this is the first study to investigate the experience of those living with 50% risk of FTD, alongside asymptomatic known mutation carriers and non-carriers.

In relation to the first research question regarding the feelings and experiences of living at-risk six themes were identified: *the reaction to learning about risk or status – 'it's like ups and downs all the time', the journey to finding out about your risk, the value of information – 'I'm a bit more in control if I've got the knowledge', coping, how risk influences life and, the 'whirlwind' of emotions experienced throughout the at-risk journey*.

Seven themes were also generated in relation to the support needs while living at-risk: *the presence or absence of support, the types of support received, the impact of support, barriers to accessing support, facilitators for support, support wanted, and the importance of understanding specific difficulties.*

4.5.1. The feelings and experiences of living at-risk

4.5.1.1. Linking findings to existing literature in hereditary neurodegenerative diseases

The findings of this research support the extrapolation of many aspects of the at-risk HD experience. Despite Wexler's research taking place in HD in the late 1970s, their findings and suggestions for practice bear resemblance to the findings in this study in FTD, over 40 years later. Wexler described many issues that remain important in the field of fFTD to this day, including prediction of status, symptom searching and uncertainty – *"the ambiguities of limbo were psychologically more difficult to bear than the certain knowledge that they were carrying the HD gene".* This demonstrates how far research needs to come in order to improve the lived experience of individuals at-

risk of inherited neurodegenerative diseases, and in particular FTD.

In line with the HD literature, this study found that uncertainty played a role in the at-risk experience, both as a source of anxiety but also as a driving factor in pursuing predictive testing. As discussed by Binedell et al., (2008) and Wexler (1979) in HD, although some individuals tolerated the uncertainty of life at-risk well, others found the extent of unknowns to be very challenging and sought to gain certainty where possible.

The search for certainty, for some led to survivor guilt and subsequent biographical disruption, as the majority of individuals predicted their status to be that of a mutation carrier and planned their life as such (Bury, 1982; Tillerås et al., 2020; Williams et al., 2000; Winnberg et al., 2018). Due to uncertainty and high levels of anxiety, some individuals made extensive plans for their future. For those who subsequently learnt of non-carrier status, this may have caused biographical disruption, as discussed in HD, as their plans for the future focused around life as a mutation carrier. As proposed by Etchegary (2011), the relevancy of risk or genetic status may wax and wane over time, increasing saliency and biographical disruption when highly relevant and decreasing when less relevant. This study found that many reported that, initially, their own risk was not a priority due to their parent's diagnosis and caring responsibilities. As such this information was not highly relevant or biographically disruptive. However, saliency appeared to increase with major life events, such as having children (Participant 15) and also as people neared the age at which they expected symptoms to start.

In addition, a key part of the lived at-risk experience was the complex variety of emotions experienced. Six participants became emotional and tearful on recounting their experience, demonstrating the persistent heightened emotion that may be experienced despite some years living with this risk or mutation status. For many, FTD remained integral to their family system, with either affected family members or siblings and cousins who may be still living at-risk or mutation carriers. Therefore, even for those who are no longer at-risk due to a negative predictive test, they still live in a world where FTD is present and challenging. Negative emotions reported were consistent with many of those experienced in HD, including anxiety, depression, fear, hopelessness, isolation and loneliness (Forrest Keenan et al., 2007; Gong et al., 2016; Tillerås et al., 2020). An increased risk of suicidality has also been reported in HD

(Tillerås et al., 2020). Although this was not an intended topic of discussion in this study, two participants discussed a desire to pursue assisted dying as part of their end-of-life plans, despite acknowledging that this would be difficult due to diminished capacity following FTD symptom onset. The illegality of such end-of-life care in the UK was understood, but participants stated that they may consider this option should certain circumstances be met. To date, assisted dying is permitted under certain criteria in countries such as Canada, Australia, some European countries, and some US states, and it remains a much-debated topic elsewhere, including in the UK. Due to legal factors and a lack of literature, this is not a commonly discussed topic within the FTD community, however such findings may open further discussion in future.

The findings of positive emotions and positive views of risk were surprising, despite also mirroring literature in HD. As reported by Tillerås et al., (2020) and Gong et al., (2016) some individuals were able to repurpose their risk as a motivating factor within their life, encouraging them to live the life that they desire, and live in the present moment. Participants described living their desired life now, as should they wait for the 'right moment', symptoms may onset and they may be less able to appreciate the experience. In line with HD findings, hope was important for many, and there were many things to be hopeful for in the current state of FTD research, with clinical trials in progress and successful treatments hopefully on the horizon (Tillerås et al., 2020).

Another theme that bore resemblance to HD literature was that of coping mechanisms. Avoidance, problem solving, planning and gaining certainty were reported in HD (Binedell et al., 2008; Forrest Keenan et al., 2007; Tibben et al., 1993). All elements above were also observed in this study. One may argue that all such coping mechanisms include an element of experiential avoidance, both of uncertainty and anxiety. All involve ways of escaping the distress associated with living at-risk and many people may employ such coping mechanisms without being cognisant of the underlying avoidance. While burying one's head in the sand or gaining certainty via predictive testing are more overt ways in which to avoid uncertainty, anxiety and distress, problem-solving and planning are often used to protect in case of the 'worst-case scenario'. This avoids feeling the uncomfortable feelings associated with living at-risk. Although, avoidance is not always pathological, the reliance on avoidance in this context indicates that at-risk individuals may benefit from increased psychological

flexibility perhaps using models such as acceptance and commitment therapy (ACT). However, it is important to note that due to the self-selected sample studied here, the lived experience of these participants may not be representative of the general at-risk experience. One may expect that the participants in this study may have employed coping mechanisms focusing more on gaining certainty and planning due to their engagement in research and FTD community, whereas those who choose not to explore research or predictive testing may employ more overt avoidance mechanisms.

Outside the HD literature, literature regarding early-stage young-onset dementia (YOD) and elements of the family and caregiving experience also mirror the findings of this study, suggesting, as outlined in this data, that the at-risk experience is not limited to the individuals own genetic risk, but more so a holistic experience encompassing many different roles. Qualitative studies of the family and caregiving experience for people living with a diagnosis of YOD discuss key themes of denial and avoidant coping mechanisms, as well as 'living in the moment' (García-Toro et al., 2020; Lai et al., 2023; Wiggins et al., 2023). The general lack of support received by families affected by YOD, may therefore lead to more avoidant coping mechanisms. Avoidant coping mechanisms were also observed in children and young-adults with parent's affected by YOD. Therefore, taking a more psychological perspective, children in families affected by YOD may develop avoidant coping skills through modelling avoidant behaviour in their affected parent or other family members, as per social learning theory (Bandura & Walters, 1977), and rely heavily on this throughout life, including when managing their own genetic risk. Other threads commonly reported in the YOD literature were anxiety and frustration, particularly towards long waiting times for diagnosis and support, as we observed regarding predictive testing and PGD within this study (Lai et al., 2023; Wiggins et al., 2023). Similarly to the findings reported in this study, relief was experienced when diagnosis was finally received, potentially relieving some uncertainty, as in predictive testing (Lai et al., 2023; Shiba et al., 2022). A systematic review of qualitative studies of children with parents with YOD found a significant emotional impact of parental diagnosis, including depression, anxiety, substance use and other psychiatric illnesses, alongside uncertainty for both themselves, regarding their genetic status and risk, as well as their parent's disease trajectory (Wiggins et al., 2023). Wain et al., (2009) also studied siblings of individuals living with YOD and found a subset of 28% participants who worried often or very often

about their own risk of YOD, and this subset of individuals were also prone to symptom seeking behaviour and increased mental health effects relating to their risk. Multiple studies also reported a lack of understanding of FTD, as reported in this study. This included understanding within the general population, and trivialisation by family and friends, as well as a lack of knowledge and support from healthcare professionals (Bruinsma et al., 2022; Shiba et al., 2022). Furthermore, similarities can also be drawn between our findings and those regarding support needs for YOD. In line with our findings, studies in YOD suggest a need for in-depth advice and information, information regarding research and clinical trials, as well as education resources (Dratch et al., 2023; Stamou et al., 2021). Additionally, as we found in this study, the YOD literature also reported a need for clearer pathways to support and support resources, such as links to psychologists with specific knowledge and experience of FTD (Dratch et al., 2023).

Although significant overlap has been described with those at-risk of HD and YOD, there are several novel findings reported here. This study provides insight into the feelings and experiences of living at-risk, outside of the predictive testing experience, allowing the voice of those who have not had predictive testing to be heard. Therefore, it provides a more comprehensive overview. It is particularly important to understand the underpinnings of the feelings reported in order to better understand those factors that are important to those at-risk and determine how best to provide support. For example, here I report the effect of the lack of support following fFTD risk disclosure on feelings of isolation and frustration and anger felt towards negative experiences within clinical services, and negative predictive test results. Although the presence of uncertainty seems to be a shared experience across hereditary neurodegenerative diseases, there are arguably more unknown factors in relation to FTD risk, e.g., the significance of intermediate repeat expansions, prediction of age at symptom onset and expected phenotypic expression. Therefore, although shared, this work highlights the significant effect of this increased uncertainty on those at-risk of fFTD. To my knowledge, this is the first description of the at-risk experience across the time course and provides evidence for the fluctuation of the at-risk experience over time, increasing in saliency and relevancy as people near the age at which their parent became symptomatic. In addition, the importance of risk relating to reproductive decision making, is a novel finding. Participants described a range of different perspectives

regarding having children, however for many, their genetic risk was an extremely important factor in their decision making. Finally, this is the first study to describe the effect of living at-risk of FTD on end-of-life plans, in particular highlighting views and desire for suicide, and/or assisted dying in mutation carriers to alleviate the care burden on family members. This provides important insight into the psychological challenges of those at-risk as they approach symptom onset, and suggests a need for improved support for both the individual and their family at this point.

4.5.2. The support needs while at-risk

In addition to the feelings and experiences of living at-risk of fFTD, the findings of this study highlight the complexity of the lived experience for individuals at-risk of FTD and importance for improved psychosocial support. This is the first study to explore the support needs of the at-risk population in depth. Participants identified a lack of support, along with barriers and facilitators for support, and suggested ways in which support could be developed to suit the needs of the at-risk population. Primarily participants desired better access to professional support and support from professionals who had an understanding of FTD, this also was reflected in barriers discussed, as some participants decided against pursuing support due to the likelihood that the clinician would not understand the difficulties they were facing. In the UK there is currently no provision for specialist mental health support for those living at-risk of fFTD and existing in-person peer support remains London-centric owing to the niche nature of the disease. As such support for those living at-risk is limited. Accessibility to support and information resources was also identified as an area for improvement, suggesting that clear pathways to suitable support and lay information would be beneficial to the at-risk community. Peer support was also identified as support that had been important in the at-risk journey for many, especially due to the fact that this provides access to others who intimately understand this shared lived experience.

4.5.3. Limitations

Although the findings of this study are largely in accordance with similar literature across young-onset neurodegenerative disease, there are some limitations to be acknowledged. In particular, as described above, due to the self-selected, highly

engaged samples seen in cohort studies, this experience may not be representative of the holistic at-risk experience. Due to participant's engagement in research, it is highly likely that they have better access to FTD specialist clinicians and academics through their engagement with the research team. As the findings of this study suggest, this is a supportive experience and provides greater access to psychoeducation, clinical trials and support services, compared to those available through less specialist healthcare pathways. Therefore, this should be considered when reviewing the support experienced and the support needs outlined in this study. Similarly, the reasons behind the sample's increased engagement may lead them to differ from other subsets of the at-risk community. Firstly, it is possible that this group are more engaged in the world of FTD due to finding the experience particularly challenging and therefore being forced to seek out opportunities for support. Conversely, as discussed above, they may be more supported due to their engagement in research and subsequent connection to professionals who may be able to support in various ways. Finally, this group of individuals may also be more fused with the identity and label of being at-risk compared to those not engaged in research. Furthermore, there are a number of commonly mentioned limitations associated with cohort studies, including biases towards highly educated, white, middle-class individuals. All of which must be acknowledged in the interpretation of this study.

Similarly, in addition to participant bias, researcher bias must be explored. While the researcher attempted to remove implicit biases where possible using bracketing, there are number of elements where researcher biases may play a role in this research. Additionally, the bracketing process would have been improved with the aid of an independent individual to discuss and outline potential biases and assumptions. Firstly, the researcher was well-known to participants, having worked with many participants for a number of years prior to this study. This may be interpreted through both positive and negative lenses. The researcher had a strong rapport with the participant group which allowed some individuals to feel more comfortable and open when discussing highly emotive and personal experiences. One participant expressed that they only felt comfortable participating in the study as they had an existing relationship with the researcher and had met them in person. However, this may have also dissuaded people from participating in the study if they were concerned about

judgement or may have felt embarrassed opening-up to someone that they knew well and would continue to interact with in future. Similarly, due to the nature of familial research, the researcher was not only well known to the participant but also to other family members, including siblings and cousins, meaning some may have held back on the information they disclosed, particularly regarding family issues. Another participant noted that although they understood that information would not be disclosed due to ethical reasons, they were conscious of the fact that the researcher knew their siblings when discussing these difficult topics.

4.5.4. Future research

As this study is the first of its kind, future research is necessary to develop a literature base exploring further, in depth, the experience of living at-risk of fFTD. This study uncovered a plethora of data, and the field would benefit from many of the themes identified being explored in more detail. In particular, further investigation is needed to identify the similarities and differences between the 'pure' at-risk experience and that of mutation carriers and non-carriers. Engaging at-risk individuals outside traditional research contexts, such as through cognitive neurology or memory clinics may also allow for a more representative view of the lived experience. The field may also benefit from evaluation and development of support services to identify where changes can be implemented in healthcare provision, and ensuring specialist support for those who require it. Cross-cultural collaboration will also be important in ensuring acknowledgement of cultural differences in this lived experience, allowing for development of support that serves the entire at-risk community. There has been a movement within the past few years towards ensuring and supporting people to live well with dementia, and this is supported by the UK government's 10 year 'dementia plan'. It is clear from the findings of this study and the literature discussed above, that post-diagnostic and at-risk support for families affected by YOD and inherited YODs such as fFTD require significant improvement (Stamou et al., 2021). Therefore, future research and clinical work should address this by developing resources to promote living well at-risk, as well as with dementia diagnoses.

4.5.5. Clinical implications

Clinical implications of this work include the identification of key areas for change in

existing support for those at-risk of fFTD, as well as providing key building blocks for the development of more specialist psychological support resources. Barriers and facilitators identified in the study will also help to ensure support provided is better suited to the needs of the population. Furthermore, the study identified an important area for improvement in healthcare professionals; a lack of understanding of FTD. This suggests further awareness and training may be required for healthcare professionals who may work with families affected by FTD, and the importance of support services facilitated by professionals who are well versed in supporting people through the associated challenges.

4.5.6. Conclusions

Overall, the findings of this study are largely in line with the literature in HD and YOD, however there are key novel elements to this study that build on these existing findings such as the exploration of support needs. Furthermore, as findings were largely in line with those in HD in particular, this may allow for future extrapolation and collaboration with the HD research community to work towards greater understanding and more appropriate support across both of our patient groups. This work provides a greater understanding of the lived experience of at-risk individuals and outlines specific support needs in order to inform development of tailored psychological support. This is important as this study also identified the many challenges and difficult emotions experienced while at-risk, alongside a lack of understanding within the general population and many healthcare professionals. Therefore, while simultaneously furthering understanding of living at-risk, this study also identifies need for better psychological support and key areas for improvement in existing support systems. Importantly, the findings outlined here provide information regarding those aspects within the at-risk experience that require additional support, providing topics and targets for intervention. Additionally, the barriers, support needs and facilitators identified provide guidance in terms of intervention design, to ensure support designed is relevant and accessible to those for which it is intended. This will be further explored in Chapter 5, where this data will be utilised in the systematic development of a tailored psychological intervention for those at-risk.

Chapter 5. Development of a tailored psychological intervention for those at-risk of familial frontotemporal dementia

5.1. Chapter outline

This chapter employs the use of the MRC complex intervention development framework to guide development of an intervention specifically tailored for those at-risk of fFTD. The findings described in Chapter 3 and a review of existing literature in hereditary neurodegenerative diseases provide a rationale for such an intervention, and findings from Chapter 4 provide a theoretical basis for intervention, target components, and inform design in order to maximise feasibility and acceptability. The main aim of this being to develop a novel, tailored psychological intervention using a rigorous development framework and person-centred approach.

5.2. Introduction

5.2.1. Complex interventions

Complex interventions such as psychological therapies, are defined as interventions containing several interacting components, with a number of complex behaviours required by both the deliverer of the intervention and the individuals receiving it (Craig et al., 2008). Complex interventions also may target a number of groups within the intervention, with several varied outcomes measured (Craig et al., 2008). However flexibility within the intervention programme, allowing for tailoring to individual's needs is also important, as well as creativity and an iterative approach, creating an openness for change within the development process (Craig et al., 2008; O'Cathain et al., 2019). When developing and evaluating complex interventions, a rigorous framework should be followed to allow for interventions founded in a robust theoretical and empirical evidence base (Skivington et al., 2021).

5.2.2. Context

A core component of intervention development, according to Skivington et al., (2021), is identifying the context for the intervention and defining how the proposed intervention may interact within this. As discussed throughout this thesis, the at-risk fFTD experience can be challenging in a number of ways, namely, the uncertainty regarding genetic status, disease onset and phenotype, an inability to plan for the future and the complex emotions evoked. The process of predictive testing can be difficult for some of those who choose to go through it, as it confronts many of the worries and challenging emotions regarding risk. In addition to the effect of risk on the individual themselves, there are also often complex concerns regarding those other family members who may be at-risk, including current and future children, as well as often the added challenge of caring for a symptomatic family member and dealing with emotions that their disease process evokes. Therefore, the context within which this intervention takes place is one of complex, often overwhelming, emotional and practical difficulties.

5.2.3. Background and rationale for the intervention

As identified and discussed in detail in Chapter 3 and Chapter 4, living at-risk has a profound impact on the mental health and wellbeing of certain individuals. This is evidenced by the qualitative data outlining the emotions experienced while at-risk, including anxiety, depression and isolation (see Chapter 4.4.1). Many participants indicated prior or ongoing diagnoses of common mental health problems and statistics regarding GAD-7 and PHQ-9 scores indicated that 10 to 13% scored in the moderate to severe ranges respectively, meeting validated thresholds for 'caseness' and as such, indicating a possible need for psychological intervention (see Chapter 3.4). Similarly, 38% individuals met criteria for psychosocial referral on the GPRI questionnaire, suggesting that more individuals than identified using standardised measures of depression and anxiety, required psychosocial support. This support need is echoed in HD literature, with intervention recommended for families impacted by HD (Maxted et al., 2014) and talking therapies identified as the preferred method of intervention (Theed et al., 2018). Similarly, Crook et al., (2022) identified a number of support and information needs in individuals affected by familial FTD and ALS. These included improved clarity, additional genetic counselling appointments if necessary, and the availability of additional support options with clear a clear pathway to access it, as well as improved and clear follow up plan, and follow-up support from the clinical genetics service. When considered together, this evidence identifies a gap in support for individuals at-risk, with those who choose not to have testing remaining unsupported, and some of those who undergo predictive testing requiring further support throughout and following result disclosure. For some, psychological support accessed via NHS talking therapies may be appropriate, providing more general psychological tools, for application when emotions become challenging. However, for others who struggle more with specific worries or concerns regarding being at-risk of fFTD, including the genetic element, and the challenges of living in a family affected by FTD, which can be confronting in itself, more specialist support may be needed. However, the literature base regarding psychological intervention in the context of those with genetic risk of fFTD, or in fact other hereditary neurodegenerative disorders, is limited. Therefore, further exploration is needed in order to determine the suitability of therapeutic models, as well as assessment of feasibility and acceptability for use in this area.

5.2.4. MRC complex intervention development framework

The MRC complex intervention development framework outlines four main processes within the development and evaluation of complex interventions (see Figure 14 adapted from Skivington et al., 2021). These processes are; development or identification of an intervention, feasibility, evaluation and implementation (Campbell, 2000; Craig et al., 2008; Skivington et al., 2021). These processes are dynamic and iterative, and as such one may re-visit prior phases as they progress through the framework. This chapter will focus specifically on the development phase of the intervention. The development phase refers to either the development of a new intervention, or adaptation of an existing intervention for use in a new context (Skivington et al., 2021). This phase of development should be grounded in empirical evidence, and outline a theoretical approach to the problem (Skivington et al., 2021). This phase involves three key components; identification of an evidence base, identification or developing theory and modelling process and outcomes (Craig et al., 2008). Skivington et al., (2021) also outlines some core elements for consideration throughout the process of development and evaluation. These are: context, definition, refinement and testing of programme theory, engagement of stakeholders, identification of key uncertainties, refinement of the intervention and economic considerations.

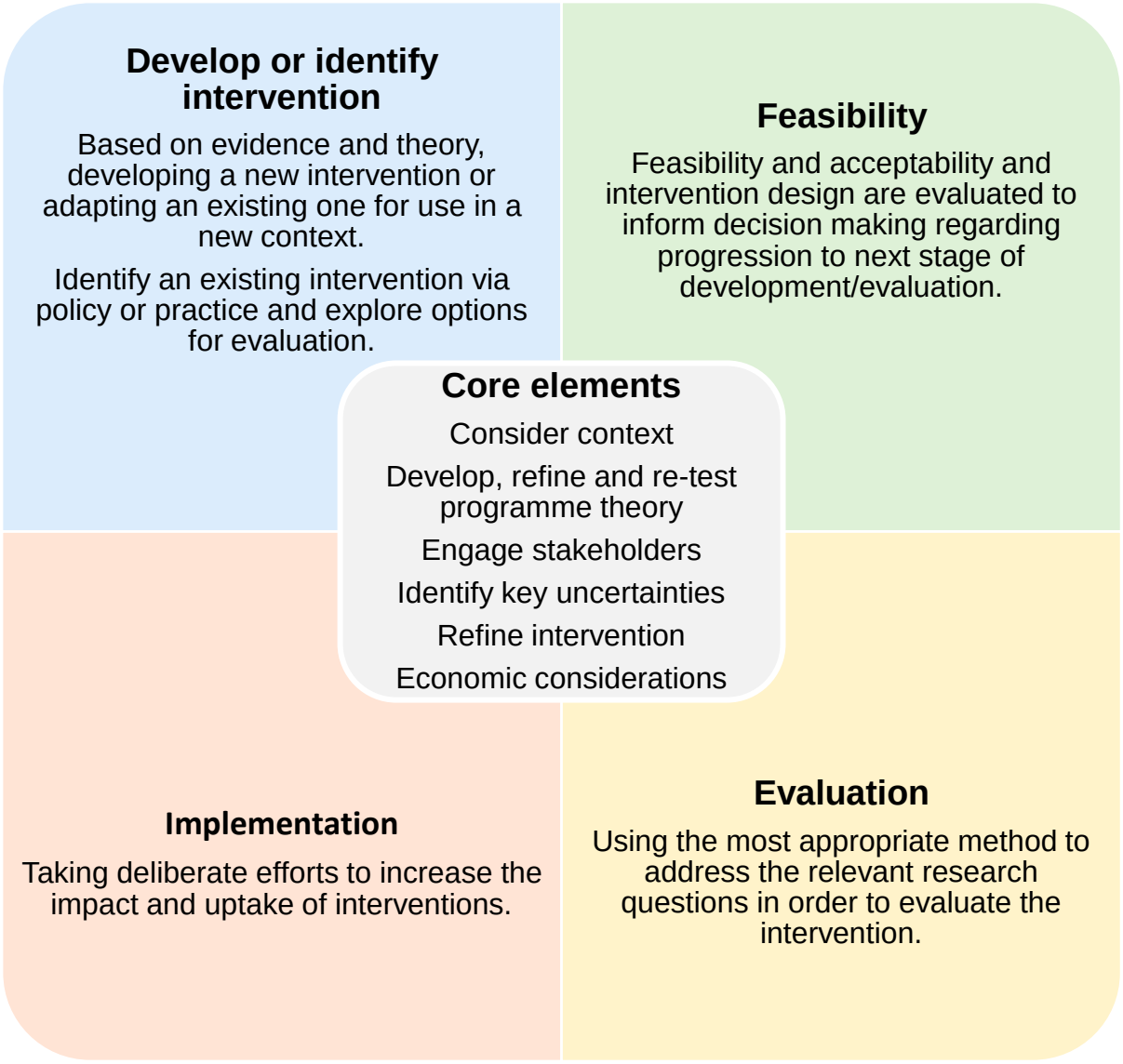


Figure 14 - MRC complex intervention development framework, adapted from Skivington et al., 2021

Within the boundaries of the MRC complex intervention development framework, a person-centred approach and a co-production model were also employed in order to ensure that the intervention was specific to the community it is intended to serve, enhancing ecological validity of the intervention by ensuring it meets the needs expressed by the population itself.

5.2.5. A person-centred approach to co-production in intervention development

Co-production refers to a *"collaborative model of research that includes stakeholders*

in the research process" (Oliver et al., 2019; Ramage et al., 2022). Ramage et al., (2022) outline the integrated knowledge translation model of co-production, in which individuals with expertise relating to the area of intervention, for example, healthcare workers, policymakers and those with lived experience, collaborate with researchers throughout the development process. This model involves using this group of stakeholders, referred to as 'knowledge users' to consider barriers to intervention, identify intervention targets, elements for inclusion and prioritisation, and useful outcomes. This group are referred to throughout the process in order to refine the intervention.

A person-centred approach takes a detailed look at the intervention target users and the context in which they will interact with the intervention. This can be used to complement broader intervention development frameworks, such as that described above, to ensure a relevant and engaging intervention that is sensitive to the lives and experiences of those for whom it is designed (Yardley et al., 2015). As the person-centred approach utilises stakeholder engagement throughout, this enhances the feasibility and acceptability of the intervention, and promotes investment in the intervention within the target population (Yardley et al., 2015).

The person-centred approach to intervention development involves three phases (see Table 31 below, adapted from Yardley et al., 2015); intervention planning, intervention design and intervention development, and evaluation of acceptability and feasibility. The intervention planning stage consists of synthesising qualitative data on experience of similar interventions, as well as systematically gathering qualitative data regarding views of the proposed intervention, relevant lived experience and barriers and facilitators regarding the intervention. Investigation of the lived experience, beliefs and needs of the target population allows for identification of specific intervention components likely to be important and salient (Yardley et al., 2015). Such investigation in the current context is reported in Chapter 4. This chapter will report on the next element of the design phase, whereby themes derived from the qualitative data are used to create guiding principles for the intervention, including key objectives and the features required to meet objectives. The final phase employs the use of stakeholder review of intervention components and takes an iterative approach to modify and refine the intervention in order to maximise acceptability, prior to feasibility and

acceptability testing.

Table 31 - Activities relevant to applying the person-based approach at each stage of intervention development and early evaluation, adapted from Yardley et al., 2015

Stage of intervention development and evaluation	Specific person-based approach activities	Other relevant activities undertaken as part of intervention development
1. Intervention planning	• Utilise qualitative data regarding experience of similar interventions • Carry out qualitative research into views of the intervention, prior experiences, barriers and facilitators	• Consult experts and stakeholders • Examine theory and evidence from relevant prior trials • Observe intended intervention context
2. Intervention design	• Identify key issues, needs and challenges for the intervention to address, using the qualitative themes generated from the planning stage • Create guiding principles including: - Key objectives for intervention - Key features the intervention must include in order to meet these objectives	• Map out behavioural determinants and behaviour change techniques • Depict mechanisms of action within the intervention using a logic model
3. Intervention development and evaluation of acceptability and feasibility	• Optimise acceptability and feasibility by observing reactions to each intervention element and modifying where required • Study intervention usage using longitudinal mixed method case studies	• Develop procedures for intervention • Pilot intervention using mixed methods

5.2.6. Aims

Those at-risk of fFTD have been found to have increased risk of depression and anxiety, among other common mental health problems (Chapter 4.4). My Qualitative research reported above also describes several support needs, expressed by those at-risk of fFTD that require addressing, including a need for psychological support, however no specialised psychological interventions exist to target this.

As described above, the Medical Research Council (MRC), has outlined a rigorous framework for the development and evaluation of complex interventions (Campbell, 2000; Craig et al., 2008; O'Cathain et al., 2019; Skivington et al., 2021). This chapter describes the application of the MRC complex intervention framework, using a person-centred approach and co-production model, in the development of an acceptance and commitment therapy-based intervention for use in familial FTD.

5.3. Methods

The methods used within each stage of the MRC complex intervention development framework are outlined below, with the addition of elements derived from the person-centred approach and co-production model.

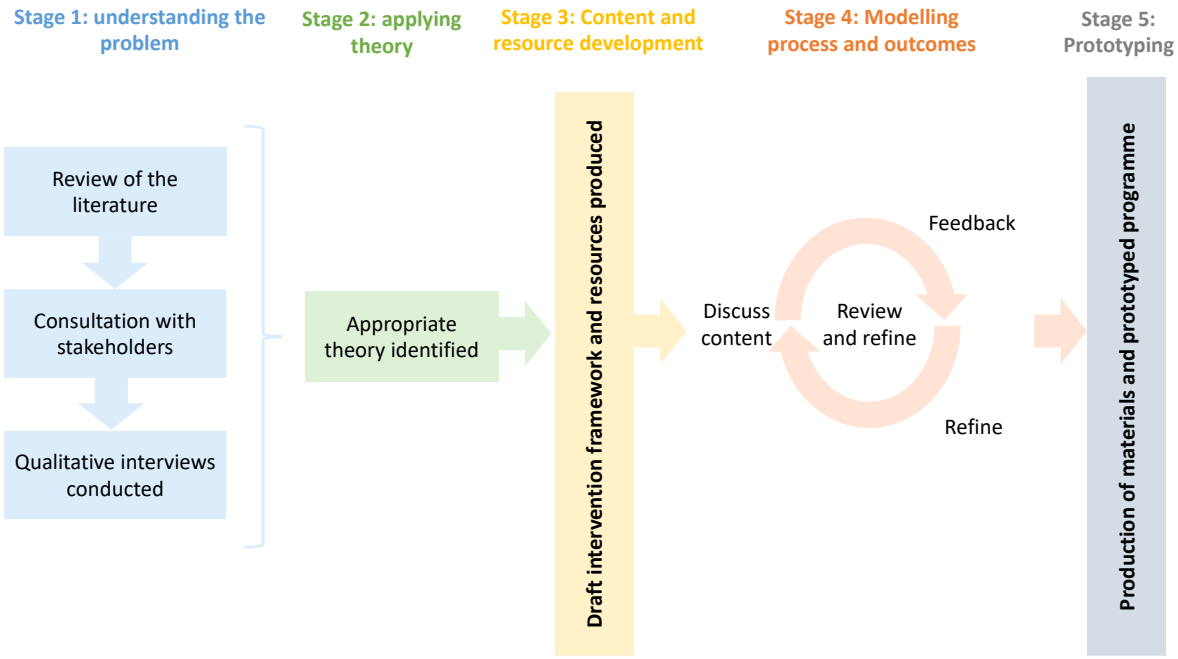


Figure 15 - A logic model describing the overall process of intervention development across five key phases

5.3.1. Stage 1: Understanding the problem

Within stage 1, a review of the literature was employed, along with a qualitative investigation of the at-risk lived experience, support experience, support needs and barriers and facilitators to support. A preliminary consultation with stakeholders was also carried out to assess initial perspectives and psychological support needs.

5.3.1.1. A rapid scoping review of the existing evidence base

A rapid scoping review of existing literature was performed with a view to identifying any existing psychological interventions used in hereditary neurodegenerative disorders. Scoping reviews are a systematic method of gathering evidence on a particular topic and identifying knowledge gaps (Tricco et al., 2018). Therefore, this

method of review was chosen due to the limited existing literature on this topic, in order to identify interventions that had previously been employed within this population. In addition, the few existing studies were not suitable for more rigorous systematic review, due to being small, often underpowered, feasibility studies rather than randomised control trials, and few studies existed in neurodegenerative diseases outside of HD. The aims of this review were threefold:

1. To identify whether there is need for a new intervention.
2. To identify the acceptability and feasibility of such interventions and what affects have been observed.
3. To determine whether there any learnings that can be taken forward into developing a novel intervention for at-risk FTD.

Search procedure

Databases searched included: PubMed, PsychINFO, CINAHL and clinicaltrials.gov for identification of any ongoing randomised control trials. Search terms included: *psychological intervention, psychological therapy, mindfulness, acceptance and commitment, cognitive therapy, frontotemporal dementia, Huntington's disease, motor neuron disease, motor neurone disease and amyotrophic lateral sclerosis.* Filters limited search results to papers published in English. Search strings used are detailed in Appendix 4. Bibliographies were hand-searched to retrieve any additional relevant studies omitted from database searches.

Inclusion criteria

Criteria for inclusion within the review were studies detailing the use of any model of psychological therapy within individuals presymptomatic, asymptomatic or at-risk for familial FTD, HD or MND/ALS.

Exclusion criteria

Exclusion criteria included studies unrelated to the topic of interest, those not investigating the specified disorders and those investigating symptomatic individuals or caregivers. Duplicate studies and review papers were excluded, as well as abstract-only papers and those for which full-text was unavailable. No criteria were set for

publication dates.

5.3.1.2. Qualitative semi-structured interviews

Sixteen semi-structured interviews were conducted to understand the impact of living at-risk of FTD, including, where applicable, their experience and impact of genetic testing, support received, barriers and facilitators to support and support wanted (see Appendix 2 for the interview schedule). The interview schedule was developed with a view to identifying information relevant for intervention design. Participants were offered a chance to share any additional relevant information before the interview was terminated. Interviews took place between August and October 2020 and lasted for between 30-90 minutes. See Chapter 4.3.3 for further details regarding the methods used in this study.

Use of qualitative themes in intervention development

Themes derived from semi-structured interviews were used to outline key issues, needs and challenges for the intervention to address. They were also used to define guiding principles for the intervention, as well as key features required to meet intervention objectives.

5.3.1.3. Stakeholder consultation

Stakeholders were engaged at an early stage in planning using a Rare Dementia Support familial FTD support group meeting as an initial focus-group to identify attitudes towards the intervention, as well as what was felt necessary, useful and desirable in terms of support.

5.3.2. Stage 2: Identification of an appropriate theoretical approach

Following the procedures of the ‘understanding the problem’ stage, an appropriate theoretical approach was identified based on the ‘problems’ discussed within the qualitative data, as well some of the barriers and facilitators expressed. A programme theory was articulated in order to outline the mechanism by which the intervention may

work.

5.3.3. Stage 3: Content and resource development

Findings from stages 1 and 2 were combined to create an initial intervention programme draft. Core intervention components identified in stage 2 of development were approached using ACT resources (Harris, 2019b) to identify suitable processes from the ACT model. Core intervention components were developed into intervention modules encompassing an introductory section, to introduce the relevant ACT process, using metaphor to link this to the lived experience of at-risk FTD. Following the introductory section, a strategies section was outlined linking the relevant concept with actionable activities and exercises. A framework for intervention delivery was outlined, based on the barriers and facilitators identified in stage 1.

5.3.4. Stage 4: Modelling process and outcomes

The objectives of the modelling process were: to ensure the therapeutic materials were easy to use, clear, and appropriately tailored to the needs of at-risk individuals, and to assess the feasibility of the program in theory. Draft intervention framework and module outlines were presented to various stakeholders, with feedback requests depending on their area of expertise.

5.3.4.1. Expert by experience stakeholders

Expert by experience stakeholders were asked to assess appropriateness of topics, language used and the theoretical feasibility for use in this group. Experts by experience were engaged via project update presentations in Rare Dementia Support familial FTD support group meetings. An additional focus group of five experts by experience were approached via their involvement in GENFI to provide additional feedback on detailed review of the framework, content and proposed materials. As part of the person-centred approach employed throughout the development process, this group of experts by experience were also invited to share their personal lived experience relevant to specific intervention modules through video, audio or written testimonials. Two expert by experience testimonials were included in the final intervention.

5.3.4.2. Professional stakeholders

Academic and clinical professional stakeholders were consulted from within the Dementia Research Centre (DRC) and Psychology and Language Science (PALS) departments at UCL regarding ACT exercises employed within the module outlines to gauge appropriateness of the resources used, and suggestions were requested regarding additional resources from ACT and other therapeutic models, that clinicians have found to be effective when working with individuals within this population and other similar groups.

The intervention framework and outline were also presented to clinical and academic professionals specialising in dementia and non-pharmacological interventions at the Alzheimer's Association International Conference (AAIC) in July 2022. Feedback was requested following the presentation.

A core team of research psychologists, a clinical psychologist, a consultant neurologist and a counselling psychologist were consulted to decide on a list of suitable outcome measures. This core team also reviewed detailed scripts written for each module and designed a framework and process for face-to-face check-in sessions.

5.3.4.3. Feedback and intervention refinement

Stakeholder feedback was incorporated, and relevant amendments made, in order to refine the intervention design.

5.3.5. Stage 5: Prototyping

A prototype intervention was constructed between January 2022 and June 2023. A website to host the intervention was built using Wordpress (wordpress.com), and tested by core intervention team members, as well as extended team members from the DRC and PALS at UCL. Introduction and strategy videos for each therapeutic module were developed using Animaker (animaker.com) and voice-over applied. Additional ACT and psychoeducation materials and worksheets were created, or adapted. Psychoeducational materials were filmed in collaboration with clinical specialists at the DRC, and a 'day in the life of a research visit' video was filmed around the DRC and Queen Square, in collaboration with GENFI research assistants. Videos

were edited using iMovie (Version 10.3.5, Apple Inc© [mobile application software, available from apple.com/uk/app-store/]) and royalty free background music sourced from Pixabay (pixabay.com). Outcome measures were uploaded to Qualtrics (Qualtrics, 2021, Provo, Utah, USA) and tested by core team members to ensure accessibility and readability.

A feasibility study was designed in collaboration with core team members, however this is not included within this thesis.

5.4. Results

5.4.1. Stage 1: Understanding the problem

5.4.1.1. A rapid scoping review of the existing evidence base

A rapid scoping review of the literature regarding psychological intervention in fFTD, HD and familial MND/ALS, yielded 212 articles, of which eight met inclusion criteria. A flowchart of the selection process is depicted below in Figure 16. See appendices 5 and 6 for a more detailed breakdown of articles screened across databases and reasons for exclusion.

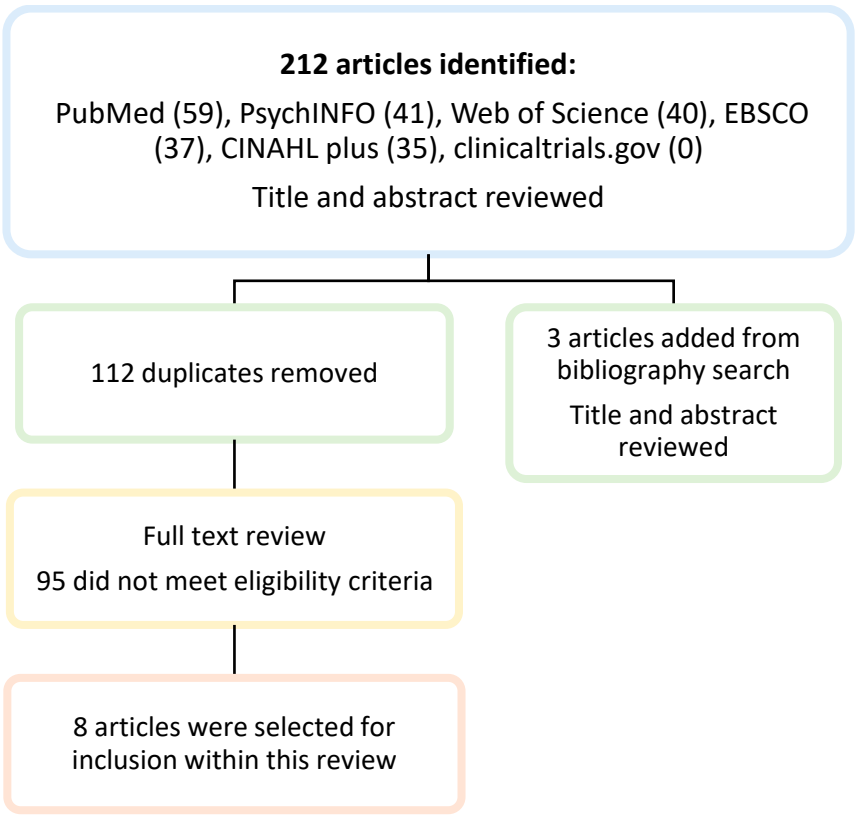


Figure 16 - Selection of articles included for review

For characteristics of the studies and interventions included for review see Table 32. Therapeutic models reported were mindfulness based cognitive therapy (MBCT), narrative therapy (NT), cognitive behavioural therapy (CBT), mindfulness-based stress reduction (MBSR) and psychoeducation. The two MBCT articles reported the same study with one describing the qualitative arm in more detail. Similarly, both NT

articles reported the same intervention with one study in HD non-carriers and the other in a mixed group of HD mutation carriers and their partners. All interventions were carried out in HD except for one study in fFTD. As all interventions were feasibility studies, pilot studies or case studies, few reliable conclusions can be drawn regarding the efficacy of such intervention models. Therefore, this review describes the intervention programmes employed, as well as any relevant quantitative or qualitative findings, including acceptability and feasibility.

Table 32 - Characteristics of studies included within review

Study	Sample	Study design	Intervention	Main intervention components	Programme design	Main findings
Eccles et al., 2020 and Eccles et al., 2021	Pre-manifest mutation carriers (n=14)	Feasibility study	MBCT	- Core cognitive therapy principles with mindfulness practices & meditations - Non-judgement towards thoughts and feelings (de-centring) - Focus on being present in the moment - Up to one hour daily home practice is expected	Group format 8 x 2-hour sessions over 8 weeks Outcomes measures at: Pre and post intervention, 3 month and 1 year follow up	Eccles et al., 2020 - Two participants dropped out after the first class – 1 stated that this was because they disliked the intervention - All participants positively appraised the experience of mindfulness and most enjoyed the classes - Participants enjoyed meeting other HD mutation carriers - Most intended to continue practicing mindfulness following completion of the course - Participants successfully learnt mindfulness skills - Levels of depression were low at baseline therefore there was little room for improvement Eccles et al., 2021 - Participants found the group format beneficial as they were “all in the same boat”, however reported concern over the potential involvement of symptomatic individuals - Mindfulness anchored them in the present, rather than fearing the future and de-centring helped recognition of unhelpful thoughts which in turn could prevent mood worsening - Mindfulness had positive benefits regarding relationship with the self and others. Reports included feeling calmer and less stressed, less anxious, fewer checking behaviours, less irritability and less persistent low mood - Flexibility in response to thoughts and emotions reduced overwhelm and participants felt more able to cope - The course also helped to open discussions with others about their wellbeing - Although longer formal practices decreased, at one year follow up most participants were still using formal practices

MacLeod et al., 2018	HD non-carriers (n=9)	Pilot study	NT	- Externalising - Group agenda setting - 'The Tree of Life'	Group format 1 x 2-hour session	- Levels of anxiety and depression were below threshold levels for caseness both pre and post intervention, despite 'problems' being reported during the session - All participants were positive about their experience, specifically finding the following factors useful; the safe space to talk about emotions, emphasis on positive coping and the sense of community - All participants indicated interest in taking part in the session again, and would recommend it to others
Stopford et al., 2020	HD presymptomatic mutation carriers (n=6) & 2 partners	Pilot study	NT	- The same intervention as reported by MacLeod et al., 2018 above	As above	- As above levels of anxiety and depression were low before and after the session - Participants described the session positively, emphasising safety and comfort and felt that it was beneficial, enjoyable and reassuring - Having an organised space and time for these discussions was considered helpful and the structure of the session helped facilitate natural conversations - Participants emphasised the helpfulness of the peer support element in reflecting on their own and other's ways of managing situations - Participants reported improved confidence and optimism and recognised their own existing coping mechanisms
Silver, 2003	HD mutation carrier (n=1)	Case study	CBT	- The aims and methods of CBT were introduced and general types of thought distortions were examined - An activity diary with ratings (out of 10) of how much achievement and pleasure was felt in relation to the relevant task - Thought records were	9, weekly sessions plus a follow up session 4 weeks following therapy completion	- There were observed reductions in both anxiety and depression throughout the course of therapy and at 6 month follow up - The individual reported improved emotional regulation, reduced intrusive thoughts regarding symptoms of HD and improved confidence managing HD diagnosis

				used to organise thoughts and evaluate biases - Historical re-analysis and strengthening alternatives to her negative belief system - Homework activities and reading from self-help books		
A'Campo et al., 2012	Symptomatic HD (n=29), partners (n=22) & pre-manifest mutation carriers (n=12), partners (n=8)	Pilot study	The patient education programme for HD (PEP-HD)	- Adapted from manual for PD - Information - Self monitoring - Health promotion - Stress management - Management of anxiety and depression - Social competence - Social support - evaluation	Group sessions of 4-7 8 two-weekly sessions of 90 mins	- The programme was rated as good overall, and the stress management session was felt to be most valuable - Participants felt the content was suitable and clear, and useful in every-day life - Improvements were observed in coping strategies, with increased seeking of social support - However the qualitative benefit was not reflected in scores on standardised measures of behaviour, anxiety and quality of life
Velissaris et al., 2023	Presymptomatic HD (n=9), very early symptomatic HD (n=1)	Feasibility study	MBSR	Standard MBSR protocols were used with adaptations for HD	8, weekly 2-hour sessions Single group	- Generally positive experiences were reported regarding structure and content, but there were reservations about practice expectations - There were statistically significant improvements in observing and non-judgement of inner experience - Qualitative feedback indicated successful development of mindfulness skills, increase ease of mindfulness practice, engagement with sensory experience, awareness of thoughts and emotions and awareness of options for responding rather than reacting - Participants also reported reduction in preoccupation with future HD worry, and increased hope for the future

						- The course was considered feasible and acceptable due to a high attendance and completion rate and engagement with session content and practices, however 3 were lost to drop out (2 because uncomfortable with attendance and homework expectations)
Poos et al., 2022	N = 13 Presymptomatic fFTD mutation carriers Those at 50% risk – unknown status	Pilot study	MBSR	Standard MBSR protocols were used, without adaptation	8 sessions of 2-hours 2 groups of maximum 8 participants Mixed online and in person due to COVID-19	- Statistically significant reduction in anxiety was observed immediately post-intervention and in depression and anxiety at 2 month follow up - All participants reported satisfaction with the course, wanted to continue applying the skills they had gained and would recommend it to others - There was a positive response to switching from physical to online sessions - Participants reported that the course was relevant in dealing with fears and uncertainty associated with FTD, and that the peer support element was helpful - Successful application of mindfulness skills were reported to reduce tension and stress, to notice pleasant situations, to calm down when upset, view situations form a positive perspective, realise thoughts are not fact, to view thoughts from a distance and stop unhelpful reactions

Mindfulness based cognitive therapy (MBCT)

The intervention reported using MBCT employed a standard MBCT protocol (except for omission of the all-day session), which was implemented without changes, and was delivered via group format, as is recommended in MBCT (Eccles et al., 2020, 2021). The MBCT intervention included core cognitive therapy principles with the addition of formal and informal mindfulness practices, such as the body scan, mindful breath, and mindful movement. Mindfulness practices are intended to encourage present moment awareness while cognitive techniques focus on non-judgemental noticing of thoughts and feelings, allowing them to recognise and disengage from those that are unhelpful, a metacognitive process referred to as de-centring. There were significant challenges reported regarding recruitment to the intervention, with geographical restriction due to attendance in-person, the group design, along with the belief that mood symptoms related to HD onset and therefore psychological intervention would not be beneficial, all contributing factors (Eccles et al., 2020). The authors concluded that the intervention was feasible for use in this group without adaptation, as all participants (except for two early dropouts following session 1), completed the required number of sessions, however they suggest that due to low levels of distress reported, other mindfulness based therapeutic models such as MBSR may be more beneficial. The intervention was also found to be acceptable, as participants demonstrated mindfulness skills, good attendance to sessions and continued to practice mindfulness following the intervention. All those who completed the course reported that they found it worthwhile and benefits included skills for the future, a reduction in stress and an increased sense of calm (Eccles et al., 2021). Thematic analysis of qualitative data highlighted the perceived benefit of the group in creating a common ground and sense of community among participants, however concern was expressed regarding the inclusion of symptomatic people within the group (Eccles et al., 2021). Specific mindfulness practices were acknowledged as particularly helpful regarding managing HD-relevant challenges, noting that the ability to de-centre from a stressful event, e.g., being with symptomatic family members, allowed them to prevent their mood from worsening. For many this led to increased self-compassion. Mindfulness practices were also perceived to improve relationships with both the self and others, including being less anxious, fewer checking behaviours, reduced irritability and less persistent low mood. Flexibility in responding to difficult

thoughts and emotions helped reduce overwhelm and improve coping. At one year follow up, most participants reported continuation of informal practices, especially in stressful situations. Noticing breath and anchoring in the present moment were noted as particularly useful. Authors concluded that de-centring allowed participants to relate to their experience in a different way, seeing thinking as an ongoing process that can be observed and reflected upon to change their response.

Narrative therapy (NT)

Two studies also reported the application of narrative therapy in post-test genetic counselling follow up for individuals testing negative for the HD gene (MacLeod et al., 2018) and positive (Stopford et al., 2020), with the addition of one symptomatic individual to the mutation carrier study. Both studies used a group format with one two-hour narrative therapy session facilitated by the genetic counsellor and a clinical psychologist. Similarly to de-centring in MBCT, a key principle of narrative therapy is externalising - the separation of 'the problem' from the individual (MacLeod et al., 2018). Facilitators used 'double-listening' whereby they would listen to the individual explain their problem, but also to their response and the contextual factors surrounding it in order to reveal existing coping skills and values. The session began with group agenda setting, followed by an adapted 'Tree of Life' exercise. This exercise uses the tree as a metaphor, facing hazards such as storms or disease, with HD being considered a 'storm' in this context. Participants provided examples or stories relating to the different tree parts. Roots represented background, the ground was daily life, the trunk represented skills and coping mechanisms, the branches were hopes, the leaves symbolised important individuals and the fruits were the gifts others had made to their lives. The facilitator then invited discussion around these important descriptions and the group reflected on the qualities highlighted and how these connect them. The completed tree then provides an alternative vantage point from which to view their reflections. Despite 'problems' associated with HD, and emotions they evoke being discussed in the session, measures of depression and anxiety remained below threshold levels for caseness. However, the intervention was deemed acceptable with participants reporting positive benefits including providing a safe way of talking about powerful emotions, emphasising positive coping and creating a sense of community (MacLeod et al., 2018). Participants reported interest to participate in

another similar session and would recommend the experience to others (MacLeod et al., 2018). Specifically, participants felt their confidence and optimism was increased within their personal lives, relating to group participation and HD research (Stopford et al., 2020). Re-discovery of existing coping mechanisms also helped to recognise agency in managing symptoms of low mood (Stopford et al., 2020).

Mindfulness based stress reduction (MBSR)

Two studies employed the use of MBSR in presymptomatic HD (Velissaris et al., 2023) and presymptomatic and at-risk FTD (Poos et al., 2022). Both required eight, weekly group sessions, however the latter utilised mixed online and in-person delivery due to the COVID-19 pandemic. Velissaris et al., (2023) adapted standard MBSR protocols to presymptomatic HD by asking participants to reflect upon their lived experience, however many of such changes reported were accommodations for early or prodromal HD cognitive symptoms e.g., slower pace of delivery with added repetition. Conversely, Poos et al., (2022) used standard MBSR protocol without adaptation. The MBSR protocol is an eight-week group intervention with weekly two to 2.5-hour sessions and an all-day session at six to seven weeks, although shorter sessions of 90 minutes and omission of the all-day session is permitted (Vibe et al., 2010). Standardised core elements are included across sessions such as mindfulness practices like the body scan, attention and breath-work, exercises relating to awareness of sensations within the body, and using breathing as an anchor for attention (Vibe et al., 2010). Information is provided relating to stress, stress management and the application of these resources, and discussion facilitated. Participants also reflect on their experience of their practice. A core tenet of this approach is development of an accepting and non-reactive response to personal experience (Vibe et al., 2010). Both studies reported feasibility and acceptability of this intervention within the relevant populations, including strong engagement with the session content and practices (Velissaris et al., 2023) and an intention to continue applying the skills learnt through the course . This was reflected to an extent at follow up, although frequency of practice had decreased (Velissaris et al., 2023). Statistically significant improvements were found regarding the mindfulness skills of observing and non-judgement of inner experiences (Velissaris et al., 2023). In HD, no statistically significant differences were observed in terms of depression and anxiety (Velissaris et

al., 2023), however in FTD there was a significant reduction in anxiety both immediately and at two month follow up, and a significant reduction in depression at two month follow up (Poos et al., 2022). Qualitative analysis also suggested the improved emotional regulation as a result of increased non-judgemental acceptance of emotions, enabling them to react more thoughtfully (Velissaris et al., 2023). Importantly, Velissaris et al., (2023) reported reduced intrusive HD rumination, less preoccupation with future worries and increased focus on present life experience.

Cognitive behavioural therapy (CBT)

One case study reported the use of CBT with an individual struggling following a positive predictive test for HD (Silver, 2003). Due to the nature of a case report, there are a number of confounding factors identified, contributing to the psychological distress observed, namely adverse childhood experiences, a history of sexual abuse, alcoholism and challenges with acceptance of sexual identity. The nine session CBT intervention used, targeted the individual's negative automatic thoughts and core belief systems about themselves. Thought diaries and a visual representation of the case formulation helped the individual to understand how their problems interacted and lead to the use of unhealthy coping mechanisms e.g., alcohol use. Thought and activity diaries aided recognition regarding the impact of identified 'triggers' and the lack of time spent on pleasurable activities, as well as organisation and evaluation of biases within these patterns of thought. Over time the individual reported improved ability to 'answer' these negative automatic thoughts. Further cognitive behavioural techniques address a core belief of abnormality and historical re-analysis was used to strengthen alternative beliefs. Following therapy sessions, mood improved with scores of depression and anxiety falling into normal range. The effect of these sessions remained at six month follow up. In addition to the effect seen on standardised measures, there was an improvement in general mood, increased control felt over anxiety and depressive episodes and a reduction in thoughts of being symptomatic of HD, as well as increased confidence regarding their ability to cope with the HD diagnosis. Although this study demonstrates successful application of CBT to negative automatic thoughts regarding genetic status and symptom onset, it is limited due to the specific nature of this individual's life experiences.

Psychoeducation

Another study adapted a patient education programme manual for Parkinson's disease for use in HD (A'Campo et al., 2012). The programme integrated cognitive-behavioural techniques within its psychoeducational approach. The core programme targets generic coping strategies including playing a proactive role in seeking information about the disease, self-monitoring body, behaviour and mood, pleasant activities and relaxation, stress management (involving cognitive restructuring), managing and preventing depression and anxiety, social competence and self-advocacy, and asking for social support. The final session provides an opportunity to rehearse skills and evaluate the session. Materials were specifically adapted for issues identified in HD. The study reports application in a small group setting for presymptomatic HD mutation carriers, partners and individuals living with a diagnosis of HD. The programme was well-rated, and the content found to be acceptable. Participants found the stress management session most useful and reported application of the programme in daily life. Improvement in wellbeing and coping strategies were observed. Although lacking in a clear theoretical basis, this intervention provides evidence for the efficacy of cognitive restructuring and psychoeducational materials tailored to the challenges faced by a particular group.

Discussion

The purpose of this review was to identify which intervention models had been used with individuals at-risk of hereditary neurodegenerative diseases and whether there is a need for a novel intervention. The acceptability and feasibility of such interventions, and adaptations for use within this population provided learnings to be taken forward into future intervention design.

This review identified six psychological interventions reported within this population, and only one specifically focusing on at-risk fFTD. This intervention was designed for in-person delivery, with consequent implications for feasibility, particularly considering the barriers for at-risk individuals reported elsewhere in this thesis (Chapter 4.4.3) suggesting in-person intervention may pose additional challenges regarding engagement. Therefore, this gap identified within the literature suggests that it is important to develop such an intervention for this particular population.

Limitations to note within this review include the exclusion of studies without English

as a first language, limiting generalisability. Additionally grey literature was not reviewed, and one researcher conducted selection and review of papers, increasing likelihood of bias within this process. Methodologically, scoping reviews are also limited due to a focus on breath across the topic, rather than depth of information (Tricco et al., 2016). Although this method was chosen for this reason, this remains a limitation as it lacks the depth provided by other review methods, such as systematic review, which provide additional detail to evaluate the studies reviewed e.g., quality assessment.

Overall, all methods of intervention reported were deemed feasible and acceptable for use in presymptomatic individuals at-risk of HD and FTD. Although few reliable comparisons can be made between the reported studies, due to their exploratory nature, there are a number of common threads throughout which can be used to inform the design of a novel intervention. Firstly, all interventions used group designs except for the singular case study. While there were extremely positive responses to this in terms of creating a sense of community and peer support (Eccles et al., 2020, 2021; Poos et al., 2022; Velissaris et al., 2023), this design may also give rise to a self-selection bias as reported by Eccles and colleagues (2020, 2021). Although group formats may provide added benefit for those who enjoy it, it may also exclude many from participation. Due to the relative rarity of these conditions, it is therefore important to aim for improved inclusivity in intervention design, potentially with the addition of optional peer support components to provide similar benefits, without the dichotomising aspects of group therapy. Secondly, qualitative benefits were not captured quantitatively with the standardised measures used, suggesting a need for the development of specific measures to quantify this experience. Finally, all studies reported acceptability of the intervention by the majority, if not all, participants, with many indicating their approval and recommendation of the intervention. This suggests that, due to the underserved nature of this group, any intervention aimed at improving the psychological experience is likely to be well-received. Therefore, due to a clear need for and benefit of such intervention, further development will be necessary to allow for wider clinical application. Importantly, there were several key intervention features employed across multiple approaches that were reported to be beneficial in this group. De-centring in MBCT and MBSR, externalising in NT and to an extent, cognitive restructuring used in cognitive-behavioural approaches, all centre around

the idea of the individual being separate to their thoughts. Further to this, multiple approaches used this idea in combination with non-judgemental noticing of difficult thoughts and feelings to aid acceptance and a more thoughtful and flexible response. Therefore, this common thread of the observing-self, facilitating improved flexibility of response to challenging stimuli, may be a key mechanism warranting further exploration within this group. This mechanism is a key component of Acceptance and Commitment therapy (ACT), and other third-wave CBT approaches. Additionally, feasibility evidence provided by one study using mixed in-person and online intervention delivery points towards the utility of online intervention, which may be particularly suited towards removing barriers for the at-risk population.

5.4.1.2. Qualitative semi-structured interviews

As reported in Chapter 4.4, themes and sub-themes were derived from thematic analysis of semi-structured interview data. Those relevant to intervention development are reported in Table 33 and Table 34 below.

Table 33 - A brief explanation of relevant themes and subthemes generated from qualitative data regarding the feelings and experiences of living at-risk of fFTD

Theme	Subthemes	Explanation
The reaction to learning about risk or status – 'its like ups and downs all the time'		This theme related to the fluctuation in the challenges associated to being at-risk or learning one's mutation status. There were many factors that mediated participant's reaction and perception towards this information over time, including the added challenges of having an affected relative, as well as coming closer to potential symptom onset over time. Strategies used to aid in adjustment to risk and status information were acceptance, information gathering and time.
How risk influences life – the effect on the individual	Risk is always in mind	Many participants mentioned their risk being always in their mind, particularly at the beginning of their at-risk journey, some struggling to think of anything else. Even when not considered a priority, risk remained in the back of participant's minds.
The value of information – 'I'm a bit more in control if I've got the knowledge'		Participants reported searching for information, as well as noting a general lack of lay information regarding FTD and genetic risk. This information was valuable in adjustment to risk and status information but the process of searching for relevant information, and using the internet, was stressful and overwhelming.
Coping	Avoidance – burying the risk in the sand	The two main coping mechanisms participants used for managing their emotions relating to their risk were avoidance and planning. Avoidance referred most commonly to 'burying their head in the sand', or 'putting it in a box', but for some alcohol was also used.
	Planning	Participants tried to plan for the future, often with the assumption of being a mutation carrier. This usually encompassed practical planning for the future, including housing, finances, insurance and future care planning. Occasionally this also included funeral and end-of-life

		plans.
The ‘whirlwind’ of emotions experienced throughout the at-risk journey	Negative: fear, frustration, helplessness, isolation, low mood, shock, survivor guilt, uncertainty, worry and anxiety Positive: hope, positivity, relief	A wide range of positive and negative emotions were experienced while at-risk. There was a general negative response reported, with reports of being in a ‘dark place’ and speaking of the challenges and experiences associated with their personal journey evoked high levels of emotion, with many participants becoming visibly emotional. The uncertainty of being at-risk posed significant challenges and triggered worry and anxiety. This uncertainty commonly related to genetic status, the age symptoms may onset and potential phenotype that might be experienced. Worry, anxiety and fear also extended to wider family members and children, as well as symptom searching for signs of onset. Survivor guilt was common in non-carriers, feeling as though they should have carried the genetic mutation in place of their sibling. Frustration was felt towards waiting times and lengthy predictive testing processes as well as the lack of understanding of FTD and the challenges associated with being at-risk. Anger often related to poor predictive testing experiences, as well as with regards to their mutation status and caregiving role. Helplessness was articulated due to the lack of control over risk and status, and the inability to plan due to uncertainty. Isolation was experienced due to the lack of understanding of fFTD and the uniqueness of this lived experience. For some there was also shock when receiving information regarding their risk of fFTD. Positive emotions included hope for future clinical trials, and hope that a treatment would be available for children and other at-risk family members. Many also used their risk as a positive and motivating factor to live life to the fullest while well, as well as being able to have a greater appreciation for life. Relief was also common following predictive testing regardless of test result.

Table 34 - A brief explanation of relevant themes and subthemes generated from qualitative data regarding the support needs while living at-risk of fFTD

Theme	Subthemes	Explanation
Lack of support		There was a general lack of support available to individuals at-risk, this was further confounded by the inaccessibility of follow up support from clinical services.
'I didn't know where to go to get proper support that actually understood' - Barriers to support	Accessibility, individual attitudes, lack of understanding in professionals and non-professionals	There were a number of subthemes categorising barriers to accessing support, these included accessibility, individual attitudes, a lack of understanding, not wanting to bring people down by talking about it, and time. Participants weren't aware of support that would be suitable for their circumstances and didn't know how to go about finding support. Accessing information was also challenging, particularly finding lay summaries, and medical jargon created a further barrier in learning more about their risk and FTD. Individual attitudes such as pride, avoidance and a reluctance to ask for help were also common personal barriers. Finally, lack of understanding from both healthcare professionals and within their personal support network towards fFTD and the challenges of being at-risk created barriers in terms of talking about their problems and pursuing professional support. Regarding professional support, as many participants knew that counsellors and healthcare professionals were unlikely to understand FTD, they did not want to try accessing support through these routes as it would require them to spend significant time explaining the complexities of familial FTD.
Facilitators for support	Utility of online support	The main facilitator mentioned was the utility of online support. As the majority of at-risk individuals are of working age, and often have work and family commitments, as well as child-care challenges, online support was expressed as preferable in order to fit support around their busy lives. Similarly, as fFTD is a rare dementia, specialist support services are focused around London, therefore online support provides the opportunity for those outside this geographical area to access support.
Support wanted		Participants reported wanting professional support, better coordination, timing and accessibility of support and clinical services, peer support, increased knowledge and information, a safe space to

		explore feelings and support targeted for FTD. Professional support was specified as support from professionals who had an understanding of fFTD, as well as a point of contact to ask questions and clarify information. A number of participants also reported wanting access to therapy, or guidance on how to find suitable therapy.

5.4.1.3. Stakeholder consultation

Initial stakeholder consultation at a Rare Dementia Support familial FTD support group in 2019 identified general interest in psychological intervention, and a lack of support experienced by individuals at-risk. However, there was resistance and criticism expressed towards CBT methods due to personal experiences that were perceived as unhelpful due to the limitations of the techniques used, as well as therapists with little or no knowledge of FTD.

5.4.1.4. Guiding principles of the intervention

Intervention design objectives and key features were described based on the information derived from review of the literature and analysis of qualitative data, see Table 35. The key objectives of the intervention refer to the context specific needs, issues or challenges that have been recognised (Yardley et al., 2015). The key features of the intervention refer to the characteristics the intervention design must contain in order to meet the defined objectives (Yardley et al., 2015).

Table 35 - Guiding principles for intervention development: key objectives and key features

Key objectives:	Key features for intervention design:
Improvement of at-risk individuals' quality of life and wellbeing by supporting adjustment to genetic risk information and mutation status, using a bespoke non-pharmacological intervention	Implementation of evidence-based therapeutic methods to target positivity, and negative consequences identified within thematic analysis.
To increase accessibility to psychological support for at-risk FTD	Flexible and time-efficient design, hosted online to increase accessibility and flexibility.
To ensure the intervention targets the needs of the population it aims to serve	Stakeholders will be involved throughout the development of the intervention through the use of a person-centred approach to co-production. The intervention will contain modules

	focused around key issues identified in qualitative interview of individuals at-risk.
To provide support from professionals who understand familial FTD and the challenges of living at-risk	Materials will be tailored specifically for use in fFTD, employing knowledge from stakeholders specialising in familial FTD, as well as experts by experience. There will be a face-to-face component to the intervention to allow for contact with professionals and the opportunity to ask any personal questions. Professionals carrying out the intervention will be well-versed in fFTD.

5.4.2. Stage 2: Identification of an appropriate theoretical approach

An appropriate theoretical underpinning was identified on the basis of the qualitative themes identified. The acceptance and commitment therapy (ACT) model was chosen to underpin the intervention. Reinforcing this decision, ACT has been used successfully in the context of chronic physical health conditions. It also has specific elements that will target a number of issues within at-risk individuals identified in Chapter 4. Therefore, ACT was felt to be a suitable model, and provides a novel approach to addressing wellbeing in at-risk fFTD. Elements of second wave cognitive behavioural therapy (CBT) and guided problem solving were also employed where appropriate. Below I provide a background and brief summary of the ACT model and detail how the chronic health condition literature adds further support to the use of ACT for individuals at-risk of fFTD. Chronic health conditions may be considered analogous to the at-risk lived experience due to the lack of available ‘cure’, and long-term nature, which much like genetic risk, must be lived alongside throughout life.

5.4.2.1. Acceptance and commitment therapy (ACT) background

ACT is a 'third wave' cognitive behavioural therapy designed as a transdiagnostic approach based on common core processes thought to account for psychological suffering. ACT takes the perspective that human suffering is a result of normal psychological processes and is inevitable (Hayes et al., 2009). Hayes argues that, as human suffering is a universal process, it may have originated as an evolutionary adaptation, proposing the idea of 'destructive normality'; the idea that ordinary psychological processes can lead to destructive psychological results. Core processes involved in psychological suffering include cognitive fusion and experiential avoidance. When these core pathological processes dominate, unworkable action increases (that which does not work towards a rich and meaningful life) and as such there is increased disconnection from values. This process leads to increased psychological rigidity. ACT is based on the aim of accepting that which is out of your control and increasing psychological flexibility to live in a way which is guided by one's values (Harris, 2009, 2019a). The ACT model is based on the core goal of improving psychological flexibility, the ability to be present in the moment, be open to the spectrum of private experiences and act in a value-directed manner. This can be further divided into a number of sub-processes; contacting the present moment, acceptance, defusion, self-as-context, values, and committed action (Graham et al., 2016; Hayes et al., 2006; Herbert et al., 2022). The concept of contacting the present moment refers to non-judgemental awareness and experience living in the here-and-now, rather than being caught up in future worries or past pain. Acceptance is the ability to allow both positive and negative private experiences, such as thoughts, feelings or sensations, to occur without making effort to avoid or change it and without it pulling you away from what you value in life. Defusion, the antithesis to the process of cognitive fusion, is a skill or process referring to detachment and separation from thoughts, feelings and emotions, aiming to decrease belief in these private experiences as an absolute truth, but rather allow for a more flexible response. Self as context is the concept that an individual is not the content of their thoughts or feelings, but rather a conscious observer of this private experience. Values are the things that make life rich and meaningful, specific to the individual. They are characteristics that form guiding life principles. Finally, committed action refers to value-directed behaviour. The ACT model utilises these sub-processes

in order to provide new ways of responding to challenging experiences, thoughts and feelings, reducing cognitive fusion and experiential avoidance. While reducing suffering is not the primary aim of ACT, this is often experienced as a by-product.

5.4.2.2. Rationale for the use of ACT in the context of individuals at-risk of fFTD

A number of systematic and meta-analytic reviews have provided support for the effectiveness of ACT as a psychological intervention with some even concluding that it outperformed traditional CBT (Hacker et al., 2007; Powers et al., 2009; Ruiz, 2012). There have been a number of randomised control trials (RCTs) demonstrating ACT's efficacy in reducing depressive symptoms (Ataie Moghanloo et al., 2015; Bohlmeijer et al., 2011; Kohtala et al., 2015; Lappalainen et al., 2015; Østergaard et al., 2020; Zettle & Rains, 1989) and anxiety symptoms (Brown et al., 2011; Roemer et al., 2008; Zargar et al., 2012). There is also a small amount of literature to suggest that ACT may be useful in reducing guilt (Ataie Moghanloo et al., 2015) intolerance to uncertainty (Gharashi et al., 2019), fear (Johns et al., 2020) and also may positively impact quality of life and life satisfaction (Forman et al., 2007; Lappalainen et al., 2021).

More specifically, living at-risk is a long-term experience, often lasting for a large proportion of an individual's lifetime and involving complex psychological responses including increased uncertainty, anxiety, depression, and a reduction in quality of life and wellbeing. Much of which overlaps with the lived experience of those with chronic health conditions, therefore we may also look to literature utilising ACT in this area. A review of several systematic reviews and meta-analyses revealed evidence for the effectiveness of ACT in improving quality of life and health related psychological distress, in a range of chronic health conditions including HIV, cancer, epilepsy and chronic pain (Graham et al., 2016; Herbert et al., 2022). A meta-analysis of ACT interventions in individuals with cancer reported a reduction in psychological distress and increase in quality of life (Zhao et al., 2021), while a systematic review of ACT in advanced, late-stage, incurable cancers revealed a number of studies finding a significant reduction in depressive symptoms and psychological distress, as well as one study detailing a significant improvement in anxiety, sleep and health related

quality of life (Li et al., 2021). A reduction in depression and anxiety was also seen following ACT intervention for caregivers of individuals with palliative stage cancers (Yıldız et al., 2023). A systematic review of ACT intervention in chronic pain also reported eight randomised control trials (RCTs) utilising online ACT intervention successfully, concluding that this is an effective mode of delivery (Van De Graaf et al., 2021). A three year follow-up study to an RCT using acceptance and values based action in chronic pain found that significant improvements in emotional and physical functioning were maintained in at least one domain (Vowles et al., 2011). There is also evidence supporting a significant improvement in mental health related quality of life, and symptoms of depression and anxiety in individuals with fibromyalgia (Wicksell et al., 2013), as well as enhanced adjustment to a multiple sclerosis diagnosis (Gillanders & Gillanders, 2018; Graham et al., 2016).

This model differs from the second wave, 'traditional' model of CBT in several important ways that make it more suitable for use in this context. Firstly, second wave CBT sees changing personal beliefs and "maladaptive" thought processes as the central process in therapy. Whereas ACT's process of psychological flexibility allows for more flexible engagement with these thought processes or emotions, reducing the direct impact of thoughts or emotions on behaviour (Graham et al., 2016). As many of the concerns and worries affecting those living at-risk are realistic and rational, they pose a challenge for more traditional CBT methods, and as such the ACT model as a whole, and more specifically acceptance of such uncertainties, and the encouragement of value-directed behaviour may provide a novel and effective therapeutic approach. For this reason, many argue for the use of ACT over alternative therapeutic models in the context of chronic conditions (Graham et al., 2016), which I hypothesise may extend to include those living with genetic risk.

5.4.2.3. Programme theory

Based on the above information sources a logic model was created in order to depict an initial programme theory as to how an intervention may meet the objectives outlined. A programme theory describes the mechanisms and causal pathways by which the content of the intervention affects change on the outcomes and goals identified (O'Cathain et al., 2019). The programme theory is dynamic and will be refined throughout the long-term course of the intervention, outside the scope of this

thesis, and will be part of later evaluation using the MRC guidance for complex intervention framework (O'Cathain et al., 2019). This programme theory is articulated below using a logic model (Figure 17).

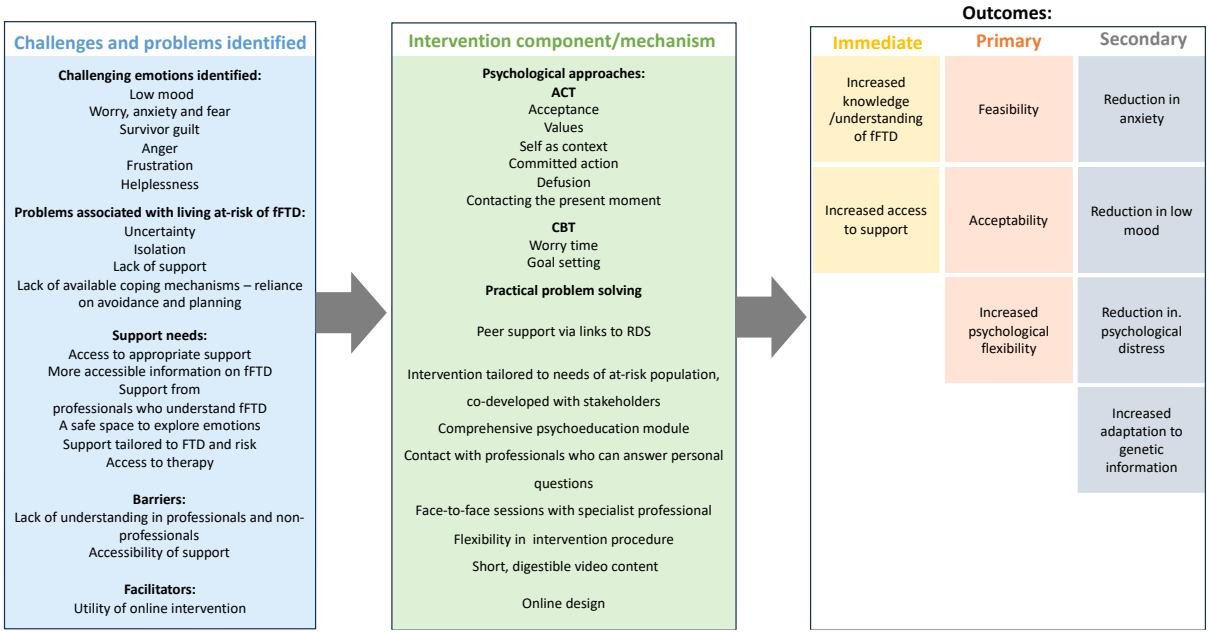


Figure 17 - A logic model depicting the programme theory used in intervention development

5.4.3. Stage 3: Content and resource development

Based on the information gained from stage 1 and 2 of the development process, content and resources were developed. A summary of the intervention, proposed structure and a framework for intervention delivery are outlined below, as well as a summary of content for each proposed module.

5.4.3.1. Intervention summary

The intervention comprises of several online sessions spanning over a suggested length of eight weeks, with additional psychoeducational videos and three face-to-face check-in sessions. The programme follows a modular design, which participants complete at their own pace, except for check-in sessions which occur at the beginning, middle and end of the course. There are between seven and 10 modules depending on the individual's genetic status, covering a number of issues including general anxiety and low mood, rumination about risk or positive genetic status, survivor guilt, being 'worried well' (i.e., false concern that symptoms are starting), uncertainty,

making the most of life at-risk, practical planning and problem solving, decision making while at risk, frustration, anger and isolation. Module content is delivered via short, animated videos to maximise accessibility and reduce overwhelm. Animations were used to help visualisation during mindfulness exercises, illustrate metaphors and to aid understanding of difficult concepts such as heritability, as well as to make content more engaging and minimise drop-out. Clinically related psychoeducation topics were delivered using direct-to-camera interview style videos with a fFTD specialist consultant neurologist to explain the clinical elements of the disease. The psychoeducation modules were designed to provide a comprehensive knowledge of fFTD and fill any knowledge gaps experienced by less engaged or researched participants, again to maximise accessibility. As the experience is not the same across all mutation status groups, a variety of modules are provided depending on mutation status, however qualitative data revealed more overlap than expected so some modules are shared while some are specific to certain mutation groups. Face-to-face check in sessions are conducted by a psychologist with expertise working in rare dementias, with comprehensive knowledge of fFTD and the associated challenges, as well as the ability to answer specific questions relating to FTD and genetic risk. These check-in sessions provide the individual contact with a specialist professional, an opportunity to ask questions and a safe space to explore more personal experiences and emotions, allowing for further personalisation of the intervention.

5.4.3.2. Initial intervention framework:

See Figure 18 below for an initial framework outlining the modules and structure of the intervention. Modules are arranged in a hierarchy, so participants must complete the psychoeducation and introduction modules and the first check in before subsequent modules are unlocked as they move further through the intervention.

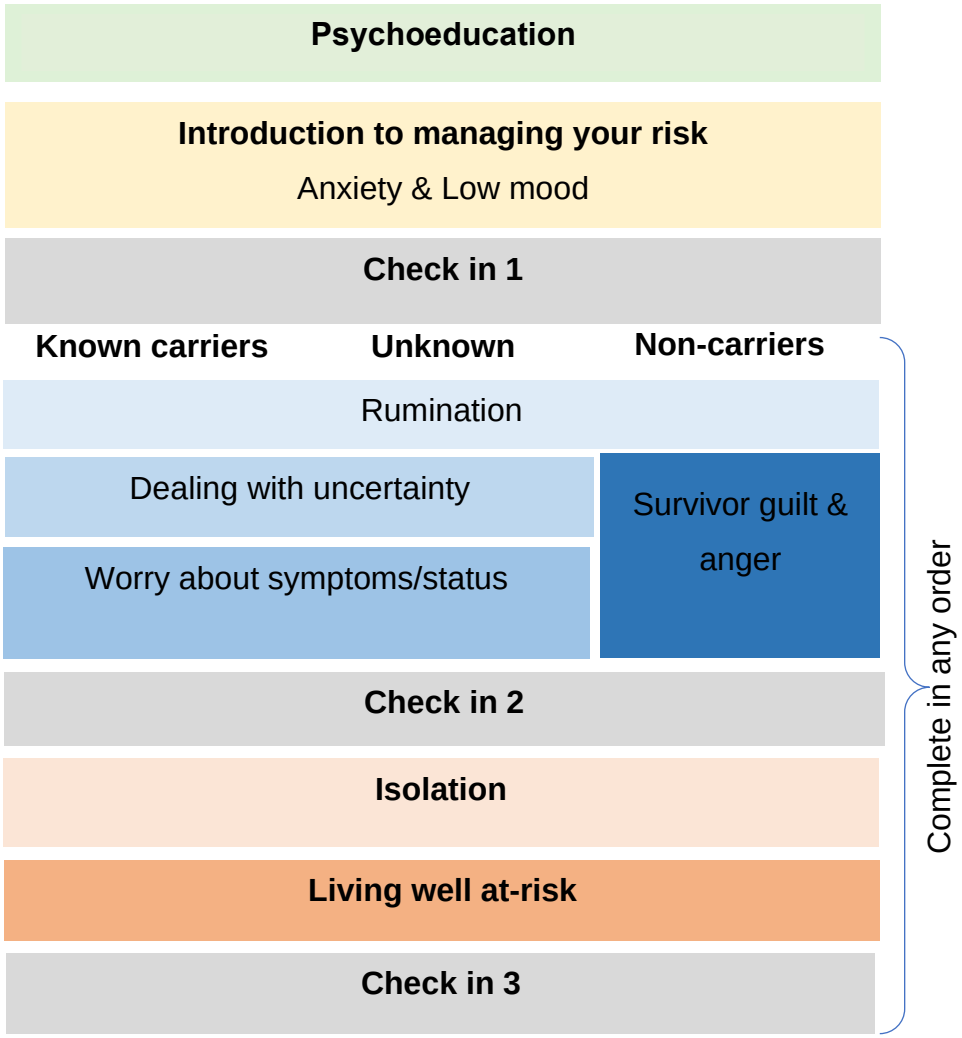


Figure 18 - An initial structure for intervention delivery

5.4.3.3. Module outline and programme mock-up

An outline of the proposed modules and example mock-up of the intervention website were created for stakeholder review (Figure 19 a-e).

a)

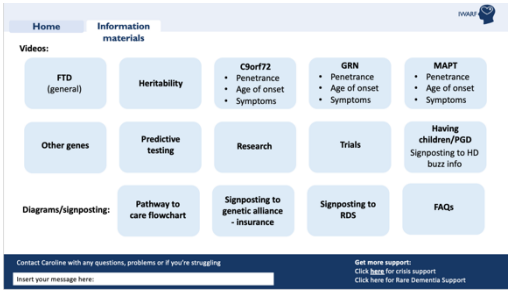
b)

Figure 19 a-e - Example 'mock-up' of proposed web-design

On the intervention homepage is an introductory video, demonstrating how to navigate through the intervention and use the website.

c)

Module 1: Psychoeducation

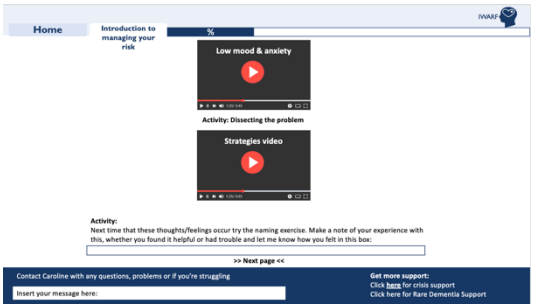


The psychoeducation module is designed to ensure a core knowledgebase for all of those participating in the intervention. This covers key aspects and in a digestible and engaging way, and allows for core, important information to be accessed easily and stored in one location. A common comment throughout qualitative interviews was the difficulty of searching for information resources and the challenge of understanding academic papers and medical jargon. Therefore, each video covers a key concept, to aid finding relevant information, and is delivered as a lay summary of the topic. Videos cover frequently asked questions, as well as ‘higher level’ topics like penetrance, to help people to understand their risk thoroughly. Videos within this section are longer compared to therapeutic module videos as it was important to ensure all relevant information was covered. Core videos include a general introduction to FTD, heritability, research and a ‘day in the life’ of a research visit walkthrough, information on predictive testing and PGD, and a summary of the current state of clinical trials. There are also gene-specific videos that provide information on issues like penetrance, age at onset and commonly experienced phenotypes. There are links and signposts provided throughout to relevant resources including a link to sign up to Rare Dementia Support, links to organisations like the Genetic Alliance (Genetic Alliance

UK, n.d.) for legal and insurance advice, and to FTD research studies across the world. There are also flowcharts to illustrate NHS pathways to common clinical services, such as how to access predictive testing, and how to get PGD including average estimates of the timeline of each process. Information regarding what to do if you are concerned about symptom onset which is a common source of concern as people near their parent's age at symptom onset.

Module 2: An introduction to managing your risk

d)



e)

The introduction to managing your risk module is available to all participants and requires completion to allow progression to further elements of the intervention programme. This module requires completion as its purpose is to introduce core ACT concepts that will be referred to throughout future modules. All elements of the ACT hexaflex are covered across five pages within the module, introducing the concepts of acceptance, values, cognitive fusion and defusion, contacting the present moment, self as context and committed action, focusing around the common problems of worry and low mood.

Videos, as throughout the remaining therapeutic content, last around two to three minutes, with the first video introducing the concept covered using metaphor and linking to the fFTD experience. The second video on each page describes strategies to work on in order to change the way the individual responds to their thoughts and feelings. Strategies used here included drawing the choice point to identify values, practicing non-judgemental noticing and naming, and guided leaves in the stream and dropping anchor meditations.

Check in 1:

This check-in will be web-based, using a platform such as Zoom to facilitate a face-to-face style meeting. A semi-structured virtual therapy session will then be carried out, this will be specific to the individual but adapted from a set of ACT intervention tools that have been specifically tailored for use in this context.

This may include:

- Discussion of areas of importance for participant
- Discussion of experience of modules so far and 'homework' activities
- Drawing the choice point and discussion of towards and away moves / the dinner party exercise (imagine at a dinner party with people you care about – what would you like them to say about you?)
- Discuss workability – if you let being at-risk dictate what you do and hook you, does it take you towards or away from the life that you want?

Modules 3 to 6 - Specialist modules

Specialist modules are unlocked following the completion of check-in one and can be accessed in any order. Depending on the individual's specified mutation status, modules include managing rumination, dealing with uncertainty, worries about symptoms or status, and survivor guilt and anger (for non-carriers only).

The dealing with uncertainty module focuses on acceptance of uncertainty, and contacting the present moment as much of the anxiety experienced relating to uncertainty is regarding the future. Values are built upon, and acceptance strategies used, as well as dropping anchor.

Again, the rumination module applies the concepts covered in the introductory module, using acceptance, defusion and mindfulness techniques as well as the addition of 'worry time' used in traditional CBT.

The worry about symptoms and status module focuses on the unreliability of our own observations into our own behaviour, to discourage over-analysis of potential symptoms, many of which are normal in isolation. This module emphasises changes relating to FTD as progressing over time, rather than occasional mental lapses that

happen relating to common issues like lack of sleep, hormones or a period of depression. Strategies used within this module include peer support in reviewing concerns about symptoms, as well as a reminder to practice self-compassion.

For known non-carriers, the survivor guilt and anger module attempts to validate the complex emotional experience of being mutation negative. Strategies focus on values clarification to identify and carry out committed action, as well as acceptance of mutation status and the new role within the family, and defusion from guilt and negative self-talk. It also attempts to reframe feelings of guilt and anger as a reminder to practice self-compassion.

Check in 2:

The same process as check in 1 will be followed here, however sessions will be designed around the specialist modules clients completed in module 3.

Potential topics include:

- Discussion of experience of modules so far and 'homework' activities
- Review of the choice point and identification of committed action including practical planning, problem solving and factoring risk into decision making

  Optional:
- Address any specific issues expressed by the individual

Modules 7 and 8

Modules 7 and 8 are unlocked following the completion of check-in 2 and cover isolation and living well at-risk. The isolation module introduces the Rare Dementia Support team and what they offer in terms of familial FTD support, as well as a testimonial provided by an individual living at-risk describing their experience of using the Rare Dementia Support familial FTD support group. This aims to reduce isolation by way of peer support. Similarly, living well at-risk focuses on the positive aspects of living at-risk identified from qualitative interview, such as appreciating and making the most of life while well, and uses SMART goals to define relevant committed action to move towards personal values. This section also includes a testimonial regarding lived experience of living well at-risk and using genetic risk as a positive force in life.

Final check-in

The final check-in session follows the same process as previous check ins, with a view to carrying forward the skills learnt throughout the intervention. Goals are revisited and a 'staying ok' plan created. Referrals for additional support, or to be seen in a cognitive neurology clinic are also covered.

Follow up:

Referrals to a cognitive neurology clinic will be made where necessary and possible, as well as contact to GP if necessary. All materials will remain available to participants following completion of the intervention programme. See Appendix 7 for full materials provided to experts by experience for review.

5.4.4. Stage 4: Modelling process and outcomes

Stakeholders reviewed the materials provided and the intervention design and content was amended based on feedback provided.

5.4.4.1. Expert by experience stakeholders

One expert by experience returned feedback following review of intervention materials, while lack of response was taken to mean the remaining four experts by experience did not have any comments. Minor amendments were made based on these suggestions e.g., language was modified to improve accessibility such as using 'worries that won't go away' in place of psychological jargon like 'rumination'. Feedback was positive regarding the theoretical acceptability of the intervention (see quote below). It was felt that content was appropriate, and the design was easy to navigate.

> *"I am very impressed with the content - I have tried cognitive therapy which helped with other anxieties in my life at the time but I felt it didn't work for where you know you are at risk and have no choice/way of resolving that. The proposed strategies in your [intervention] acknowledge the risk and don't try to suggest the anxieties are inappropriate but gives suggestions on how that anxiety can be managed or accepted - but never ignored or trivialised. "It may never*

happen" has been offered to me in the past as a strategy -not appropriate if you know you carry the gene."

5.4.4.2. Professional stakeholders

Professional stakeholders provided and signposted to resources that may aid the delivery of more difficult concepts and reviewed the structure of module content, as well as scripts for proposed content delivery. Minor amendments to the module structure and some language used within the intervention content was made. A prototype video was also reviewed by professional stakeholders to determine theoretical acceptability of content delivery using this method. Professional stakeholders and core team members also aided in the refinement of proposed outcome measures, ensuring that key features of the intervention were assessed, while accounting for questionnaire length and burden on intervention users.

On consultation with the core team regarding check-in sessions, it was decided that a structured format would allow for more consistent application in future, with multiple psychologists able to follow instructions, without the need for specialist training. A 'future toolkit' section was also added to aid use of skills following the end of the intervention. Information regarding clinical trials updates were removed in order to futureproof the intervention.

5.4.5. Stage 5: Prototyping

Following the modelling stage, a final prototype intervention was created for feasibility testing (as stated above, due to time constraints within this research feasibility data is not presented). See https://tinyurl.com/Virtual-appendix for a virtual appendix of video content and worksheets included within the intervention, as well as a guided walkthrough of the intervention website. Outcome measure questionnaires were selected based on challenges and outcomes described in the logic model depicted above (Figure 17). Outcome measure questionnaires and check-in session materials can be found in appendices 8 and 9.

The intervention framework and structure remained consistent following the modelling stage. Finalised content of each module and check in is summarised below. Following discussion with the core intervention development team, a safeguarding and risk

mitigation strategy was also outlined, in line with departmental procedures more detail on this is provided below.

5.4.5.1. Finalised web design

The intervention website was built using Wordpress to allow for easy modification in future. It is optimised for use on desktop, as well as tablet and smartphone. Administrators can monitor progress and are notified when a user fulfils criteria for check-in, and is able to unlock subsequent modules following completion of check in.

A footer consistently appears throughout the website and offers the opportunity to send a message to administrators with any problems or questions. There are also links to NHS crisis resources and RDS throughout. See Figure 20 for a screenshot of the footer, and Figure 21 for examples of the module web-design.

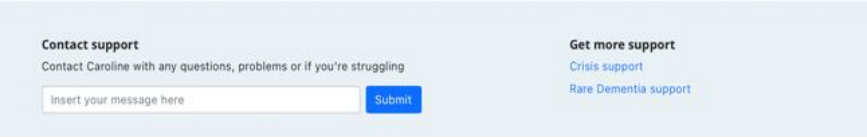


Figure 20 - Intervention website support footer

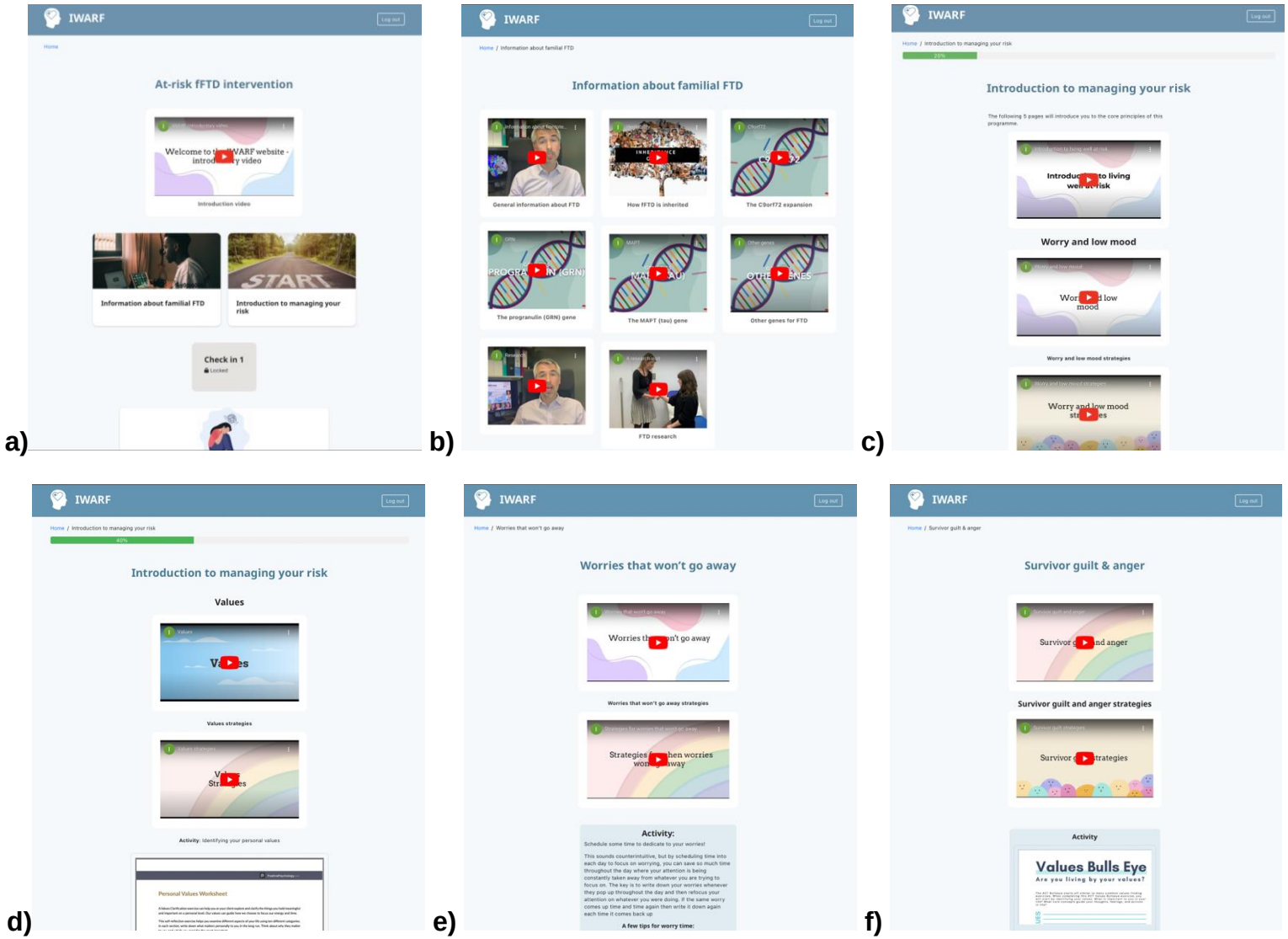


Figure 21 a-f - Example web-design and module content

5.4.5.2. Finalised module content

A summary of the finalised content across psychoeducation and therapeutic modules can be found in Table 36and Table 37.

Table 36 - An outline of psychoeducation module content

Module	Content
Psychoeducation General FTD information	• An introduction to dementia • Where FTD affects us in the brain and how this affects behaviour, personality, language and cognition • Brief overview of genetics in familial FTD • Variants, phenotypes and symptoms in FTD
Heritability	• 30% of FTD is genetic • The main genes; *MAPT*, *GRN* and *C9orf72* • Families with a history of FTD but no identified pathogenic mutation • Autosomal dominant inheritance • We can't predict inheritance based on physical or personality characteristics • Predictive testing • Penetrance – mutation carriers are very likely to develop FTD at some point
Gene specific information: *C9orf72* *GRN*	All: • Explanation of mutation name and abbreviations • Symptoms and phenotypes associated with each particular gene • Age at onset • Mutation penetrance

MAPT Other genes	• Disease mechanisms and how clinical trials might target them
Research	• The research currently happening in familial FTD • A summary of active FTD research studies worldwide • Those eligible to participate in research studies • The main aim of these studies is to better understand FTD so that we can find a cure • What research participation often involves and why • A summary of FTD Prevention Initiative
A research visit	This video is a guided walkthrough of a typical research visit day at the DRC
Genetic testing	• Brief recap of heredity and risk • Explanation of predictive testing • How to get predictive testing in UK (NHS) • Explanation of predictive testing and genetic counselling process • Support following predictive testing result

Having children when at-risk of fFTD	• Explanation of each assisted fertility technique
	  ○ Prenatal testing
	  ○ Preimplantation genetic diagnosis (PGD)
	  ▪ Exclusion testing
	  ▪ Eligibility criteria on NHS

Table 37 - An outline of therapeutic module content, informational videos, strategies employed and follow-on activities

Module	Content		
	Introductory video	**Strategies and activities included**	**Follow-on activities**
An introduction to managing your risk			
Worry and low mood	• Validation of feelings of anxiety and low mood • Radio doom and gloom analogy	• Continuation of radio doom and gloom analogy • Non-judgemental noticing and naming • Observe but don't engage • Leaves on the stream guided meditation	Dissecting the problem worksheet (Harris, 2019b)
Values	• Explanation of values • The idea of holding psychodynamic labels, and the labels of being at-risk or FTD, lightly • Your values are more important than any label • Introduction to the choice point to identify values	• Identifying your personal values using the personal values worksheet (© 2023 PositivePsychology.com B.V.) • Worked example of the choice point using 'Sarah' who is at-risk	The choice point exercise (Harris, 2019b)
Getting caught up in difficult thoughts and	• Cognitive fusion in at-risk fFTD • How being caught up in thoughts and feelings can lead	• Noticing and naming development – naming the story	

feelings	us away from values – quicksand metaphor • How we can practice defusing from difficult thoughts and feelings	• Modified guided compassionate hand meditation with added physical warmth of rubbing palms together	
Avoidance and coping	• Explanation of avoidance in fFTD • Why we avoid • Why avoidance can sometimes be unhelpful • Link to avoidance in fFTD – commonly burying head in the sand or overpreparing • Analogy of mind being like a computer to explain how our mind misinterprets rules e.g. must avoid negative thoughts or feelings • How this becomes a vicious cycle	• Analogy of the emotional storm brewing • Dropping anchor guided meditation	Debrief questions following a guided meditation
Dealing with uncertainty	• A summary of the uncertainty in at-risk FTD • validating how difficult this is due to the rationality of the worries • Coping mechanisms commonly used: problem	• Explanation and example of how we lack control over our thoughts and feelings e.g. don't think about pink elephants • What is in our control? ○ Connect with values	

	solving and avoidance – and why these often won't work in this case • We need to stop struggling and live alongside these worries without getting caught up in them	○ What can we problem solve? • Practice living alongside worries – notice the story your mind is telling you and practice one of the exercises we've already covered: leaves on the stream, observe breathe expand and allow, and the compassionate hand • Reminder to live in the present moment – emphasis on importance of enjoying life while well – brief dropping anchor	
Worries that won't go away (previously rumination)	• Validation of common worries in at-risk people and how they might become overwhelming • Creative hopelessness - pushing away paper analogy/example • Workability – what happens if your thoughts and feelings run your life? • Focus on living with them rather than trying to make them go away	• Responding flexibly • Reminder of leaves on the stream exercise, or alternatively observe, breathe, expand and allow meditation with contacting present moment at the end	Worry time

Worry about symptoms or status	• Validation of difficulty being at-risk around symptomatic people
	• Symptom searching – counterproductive as there is a limited benefit of early diagnosis while there no successful treatment trials
	• Living at-risk means a lot of plans already in place, and family equipped for care
	• We're not accurate observers of our own behaviour
	• Normalisation of occasional lapses in thinking, or unusual behaviour – hard to disentangle other reasons for this from risk
	• FTD symptoms are prolonged and progress over time
	• Reminder to see doctor if serious concern regarding symptoms
		• Stepped plan to manage worry about symptoms
		  ○ Discuss concerns with someone who knows you well
		  ○ Opportunity to discuss friendship/relationship too
		• Progressive change over time
		• Monitoring too regularly is likely to be unhelpful
		• Use these discussions or thoughts as a reminder to practice self-compassion – brief reminder of the compassionate hand exercise
		• Ask GP for referral to neurologist if concerned about symptoms or feel this would be helpful in management of worries
			Symptom review template

Survivor guilt and anger	• Validation of the emotional challenges of being a non-carrier • Lack of understanding of the	• Assess values using the choice-point – what happens when you're caught up in feelings by guilt and anger?	Values bullseye exercise (Harris, 2019b)

	negative side of a negative result • Disconnect from services that previously supported • The purpose of emotions in communication, behaviour and what is important – so these emotions can help us realise our values	• What would you do differently if these emotions didn't have so much control over you • Setting SMART goals as committed action • SMART goal example • Work on living with the new-role and knowledge – start with acknowledging the painful thoughts and feelings • Validate the pain – you are human! • Disarm the critic – non-judgementally name the feeling/name the story • Make room for your pain – observe, breathe, expand and allow • Respond to yourself with compassion • Reframing as a reminder to practice self-compassion	
Managing isolation with support	• Introduction to the direct support team at Rare Dementia Support (RDS) • How to get in touch • What RDS can offer	• Support group member testimonial explaining how being part of the support group was helpful for them and their family	Rare dementia support sign up link and contact details

	• Introduction to RDS direct support team members • Explanation of the familial FTD support group • Who is invited to attend • Group members are welcome to talk about fundraising or anything they would like to present that might be relevant to the group • Topics covered include; research, clinical trials updates, clinical presentations and Rare Dementia Support projects		
Living well at-risk	• Working on living alongside the challenges of being at-risk might help to make room for some positivity • Expert by experience testimonial of positive aspects of risk	• Remember the pillars of good mental health: exercise, eating well, sleeping well, connecting with others • Remain connected to values – values reflection exercise: imagine loved ones giving a toast about you • What changes do you need to make in order to be that person • Make some SMART goals that	

		reflect this • Remember to regularly practice grounding yourself in the present moment to ensure you're living in the here and now	
Future toolkit		• Ground yourself in the present moment e.g. dropping anchor • Defuse from difficult thoughts and feelings e.g. naming the story • Practice making room for difficult thoughts and feelings e.g. observe, breathe, expand and allow/the compassionate hand • Act flexibly guided by your values • Self-compassion – hold yourself kindly	

5.4.5.3. Finalised check-in procedure

A revised check-in session outline was created based on discussions within the core intervention team. The framework for these sessions remains the same across all sessions, allowing exploration of experience of modules so far and an opportunity to go over an activity together, clarify concepts that were difficult, or ask questions. The facilitator and intervention user finish the session by completing a worksheet together to summarise the session, set aims or goals to work towards before next session and schedule the subsequent check-in session (if appropriate). Participants are given the option of brief breathing space exercises to begin and end the sessions. See Figure 22 below for an outline of the session structure, full scripts and worksheets can be found in Appendix 8.

Check-in outline

- Hello and agenda setting (5mins)
- Offer a 3 minute breathing exercise

PART 1: 15 minute discussion about experience of the modules and follow-on activities so far

- Which modules have you mostly accessed so far?

PART 2: 15 minutes to go through an activity or exercise together: [select together based on responses to above]

- Discussion regarding anything we are going to aim to do between now and next time
- Complete a worksheet to summarise the session (10 mins)
- Optional: Offer a 3 minute breathing exercise to close the session
- Schedule next check in session
- Goodbye

[Final check in also will include a discussion regarding onward referrals for support, or to see a neurologist in clinic regarding symptom onset]

Figure 22 - Outline of check-in session agenda

A safeguarding procedure was developed with the core team in line with departmental policy. Crisis resources were included throughout the website in order to be easily accessed in an emergency. Alerts were set using Qualtrics workflow to alert the team if an individual indicated suicidal ideation or self-harm on outcome measures. Intervention users are informed of the safeguarding procedure during the onboarding process, and should risk be indicated throughout outcome measures, via the message box, or during check-ins, a team member will respond with urgency. Senior clinicians (JR- consultant neurologist and JCS – consultant clinical psychologist) must be

informed following disclosure of risk. Appropriate follow up will then be discussed with the intervention user prior to implementation.

5.4.5.4. Outcome measures for feasibility study

As stated above, initial outcome measures were suggested based on information gleaned from review of the literature and qualitative data described in Chapter 4. This provided the basis for the logic model depicted above (Figure 17), and outcome measures were selected based on the challenges identified for intervention, and potential outcomes outlined. Outcome measure questionnaires are completed preceding and following the intervention. Quantitative measures include; Acceptance and action questionnaire 2 (AAQ-2) measure of psychological flexibility (Bond et al., 2011; Hayes et al., 2004), GAD-7 (Spitzer et al., 2006) and PHQ-9 (Spitzer et al., 1999) measures of anxiety and depression severity, ICECAP-A measure of wellbeing (Al-Janabi et al., 2012), Impact of Event Scale revised (IES) measure of psychological distress (Weiss & Marmar, 1997), DQ5 measure of distress (Batterham et al., 2016), Psychological Adaptation to Genetic Information Scale (PAGIS) modified (Read et al., 2005), EuroQol EQ5D-5L measure of health status (Herdman et al., 2011). The Impact of Event Scale was selected as a measure of distress based on the HD literature suggesting significant intrusion and avoidance following receipt of genetic status information (Timman et al., 2004). See Appendix 9 for full questionnaires. A short semi-structured qualitative interview will then be carried out a short time (3 weeks) following intervention completion in order to explore feasibility and accessibility in more detail.

5.5. Discussion

This chapter describes an empirical, theoretical and person-centred approach to development of an ACT based psychological intervention for individuals living with genetic risk of fFTD, in accordance with MRC complex intervention development and evaluation guidelines. This is the first ACT-based intervention and second psychological intervention developed for use in this population, despite literature and additional findings reported within this thesis expressing a demand for psychosocial intervention for this group. The use of qualitative data to develop an intervention grounded in the lived experience and support needs of the intended intervention users, allowed for specific barriers to be addressed in intervention design to ensure maximum accessibility.

The initial phase of development, as defined by the MRC framework, was an in-depth review of the existing literature. As this was limited, the literature search covered other similar hereditary neurodegenerative disorders. This initial information gathering stage also involved semi-structured qualitative interview, and stakeholder consultation to better understand the lived-experience and therefore identify potential target focus of the intervention, as well as support needs to aid intervention design. The person-centred approach was used to develop guiding principles in the form of key objectives and design features, based on the evidence gathered in the preliminary stage. The subsequent development of preliminary materials and intervention structure was guided by this evidence. The use of a person-centred approach required continued stakeholder review from both experts by experience and clinical and academic stakeholders at each stage of development, allowing the intervention to be progressively refined over time. A final prototype intervention was then reported, in preparation for feasibility evaluation.

Qualitative data, and evidence from the literature in at-risk fFTD identified uncertainty as a key factor underpinning the challenges associated with living at-risk. Although intervention components focused around low mood and anxiety, as well as survivor guilt and anger, the mechanisms derived from the ACT hexaflex aim to increase psychological flexibility and as such re-frame the way in which individuals respond to the difficult thoughts and emotions experienced as a result of their risk. In particular, acceptance and defusion techniques were utilised in order to defuse form the negative

thoughts associated with being at-risk, and practice living alongside the feeling of uncertainty, in turn reducing rumination. Self as context emphasised the distinction between the at-risk label and the individual, helping them to separate their thoughts and feelings relating to their risk from their view of themselves. Values were identified to guide committed action towards living well at-risk, as well as recognising and reducing experiential avoidance. Contacting the present moment was also an important tool to practice living in the present. In addition to ACT mechanisms, components of CBT such as worry time were used in the context of reducing rumination, as well as goal setting and practical problem solving where appropriate.

Themes derived from analysis of qualitative data identified a number of barriers, including accessibility of information and appropriate support, time constraints, as well as a lack of understanding of fFTD. These were overcome by the inclusion of a psychoeducation module, as well as short-video delivery of content and a flexible design, allowing users to work through the intervention at a pace that suits their life. The lack of understanding from professionals was addressed using a tailored approach, linking back to familial FTD throughout content delivery, as well as the addition of face-to-face sessions with a specialist psychologist. To address time constraints, as well as geographical limitations and to increase accessibility, the intervention was designed to be completed entirely online. This approach also minimises the resources needed for delivery at a larger scale in future. Links and information regarding peer support, as well as information and signposting regarding clinical pathways were incorporated within the design to reduce isolation and reduce the need for information gathering.

The use of the MRC framework allowed for a systematic approach to intervention development, grounded in robust synthesis of evidence (Richards et al., 2022). Due to the lack of literature in fFTD and similar disorders, this approach allowed for identification of a suitable theoretical approach to target key ‘problems’ reported in qualitative interview, based on the evidence-base for ACT in other healthcare areas, such as advanced cancers and chronic pain. This provided a robust rationale for the application of this theoretical approach within the at-risk group. The thorough and iterative nature of the development process, allowed for the prevention of future problems, maximising potential for feasibility and acceptability.

The UK Department of Health (Yates et al., 2014) recommends service-user involvement in clinical trials. The use of the person-centred approach throughout the development of this intervention allowed for appropriate tailoring of intervention content, ensuring that it is fit for its intended purpose. Additionally, as this is an underserved group, this process allowed for increased understanding and validation of the challenging lived experience and provides evidence on which future interventions can also be developed.

However, despite the use of best practice guidelines in development of this intervention, efficacy at full-scale evaluation is not guaranteed, particularly as there is no evidence-base for the application of the therapeutic mechanisms used, within this niche. Although a person-centred approach was employed to ameliorate this, the subset of 16 individuals sampled for semi-structured interview are unlikely to represent the views and needs of the whole at-risk population. An iterative approach will be necessary throughout further development and evaluation stages in order to address any issues that arise and ensure best fit for purpose.

5.5.1. Limitations

The main limitation of the study reported in this chapter is the lack of acceptability feasibility data to support the implementation of this intervention design and provide further evaluation of the components and materials developed. This is due to several factors, firstly due to the lack of literature or resources regarding ACT intervention within similar populations, the development phase, particularly the development of intervention materials, was lengthy. A programme had to be created to address the key themes identified for intervention, in a way which was digestible and appropriate. Further to that video resources were also time consuming to create and there were a number of setbacks regarding web-design, with glitches identified during the user testing process. Unfortunately, due to personal circumstances, I was unwell for a substantial period of 2022 and as such required a significant period of sick leave, further delaying intervention development. Therefore, the feasibility study was not able to be completed prior to the completion of my PhD studies. This is a significant limitation as, although reviewed by stakeholder, there is not yet evidence evaluating the acceptability of the therapeutic model and intervention design, or feasibility of use for this population. Further to this, there is no evidence to suggest a meaningful

difference in outcome measures, which will be assessed with future RCT, however preliminary feasibility and acceptability data may provide insight into the suitability of outcome measures. Outcome measures were selected as an initial suggestions and further review of the literature is required to finalise the most appropriate measures. On this note, the AAQ-2 was originally selected as a measure of psychological flexibility, to determine gain of 'ACT skills', due to its popularity and the minimal burden it presents. However, further review of the literature revealed major limitations and criticism of the psychometric properties of this scale (Cherry et al., 2021; Vaughan-Johnston et al., 2017). In particular, there is evidence to suggest that the AAQ-2 is limited in its reliability and construct validity (Rochefort et al., 2018; Tyndall et al., 2019; Vaughan-Johnston et al., 2017). Therefore, alternative measures should be considered.

Further to this, another limitation was the lack of response from experts by experience during the modelling stage of development. As this stage took place during the COVID-19 pandemic, there were mitigating circumstances relating to participant responses however the assumption that no response indicated a lack of feedback may be incorrect. This is a limitation as it limits the person-centred approach at the later development stage, meaning that issues relating to acceptability of content, design may arise in future evaluation.

5.5.2. Clinical implications

There are significant implications regarding the development of this intervention, which at its core, aims to increase accessibility of psychological support to those at-risk of fFTD. Future application of the intervention within NHS services has remained important throughout the development process, with the aim to target at-risk individuals as early as possible by intervening at the point of risk disclosure within tertiary cognitive neurology and memory clinics, as well as alongside predictive testing and genetic counselling within neurogenetics clinics. The online nature of the intervention increases the cost-effectiveness of intervening in this way, increasing the feasibility of implementation within these services. Clinical geneticists and neurologists were consulted from the early stages of the development of the intervention with these future applications in mind. A goal of this intervention was also long-term reduction in anxiety, depression and distress within at-risk individuals, as well as increased adaptation to

genetic information. A further implication of this, if successful would be a reduced burden on NHS talking therapies which are currently in high demand. Therefore, the provision of a more specific, bespoke intervention may free up resources within general mental health services. Finally, aside from application within fFTD, the similarities identified with other hereditary rare dementias reported throughout this thesis suggest potential application of this intervention for other individuals living with genetic risk, with minor amendment of video content. The qualitative data reported as well as scoping review of the literature also provides a basis for other interventions to be built upon in future.

5.5.3. Future research

Due to the limitations identified in this study, there are lots of implications for future research. Firstly, a feasibility study will be the next stage in the development and evaluation of this intervention. A feasibility study protocol has been designed and has received ethical approval, with recruitment expected to take place as soon as possible. Future refinement of the intervention will be guided by the findings of this study and grant funding has been secured for a further RCT following this. As described above, amendment of video content may also allow for application of the intervention design and amended materials in other rare dementias, however future research is required to investigate this further.

5.5.4. Conclusions

Overall, the MRC complex intervention development and evaluation framework was a useful tool for systematic and rigorous application of empirical and theoretical evidence in development of a tailored ACT-based psychological intervention for individuals at-risk of fFTD. A person-centred approach aided in grounding intervention content and target components within the lived experience of fFTD, as well as identifying important barriers and facilitators for intervention design. As a novel approach to psychological intervention within this group, further evaluation is needed to ensure feasibility, acceptability and efficacy for future clinical application.

Chapter 6. Developing a tailored diagnostic testing protocol for use in frontotemporal dementia

6.1. Chapter overview

This chapter uses a Delphi consensus methodology to provide expert recommendations regarding to whom diagnostic testing should be offered, and amendments to the current HD protocol regarding how this should be carried out. Diagnostic testing in FTD is a key element of the at-risk experience as this is often the point at which many people learn of their risk. Diagnostic testing to provide confirmation of a genetic mutation within the family is also critical to allow for future predictive testing for those at-risk. However, due to the lack of guidance regarding this process in FTD, unnecessary barriers may be formed which pose challenges for future generations, as well as for the individual themselves. This will also become increasingly important as clinical trials progress to ensure timely diagnosis and early access to available treatments.

6.2. Introduction

Despite two decades of research into both familial and sporadic FTD, the discovery of the causative link between the three most common FTD genes was relatively recent in comparison to other genetic disorders (*MAPT*, Hutton et al., 1998, *GRN*, Baker et al., 2006; Cruts et al., 2006, *C9orf72*, DeJesus-Hernandez et al., 2011; Renton et al., 2011). The progress of research within the realm of FTD has not been reflected in the development of an FTD-specific protocol for genetic testing, therefore, much is still extrapolated from diseases such as Huntington's disease. The 'gold standard' for both predictive and diagnostic genetic testing for neurodegenerative conditions such as FTD was originally developed for use in HD. This protocol is largely applicable to FTD however there are a number of issues specific to genetic testing in FTD that are not addressed.

6.2.1. Diagnostic testing issues in FTD:

1. The challenge of testing for FTD-related genes

The introduction of next generation sequencing (NGS) was transformative for diagnostic testing as NGS sequencing panels provide a much more efficient way to test for FTD-related mutations compared to the previous method of single gene testing. Many laboratories now offer 'dementia' or 'FTD/ALS' NGS panels which often include the *MAPT* and *GRN* genes amongst many others. However, few of these panels contain a standardised list of genes. This poses a challenge as local panels require regular review to ensure all genes with strong evidence for pathogenicity are included within their panel. Whole genome sequencing is likely to soon supersede NGS panels and would identify mutations which have only recently been associated with FTD.

Similarly, *C9orf72* expansions are not easily identified using NGS. Repeat primed PCR (RP-PCR) is used by many laboratories to detect hexanucleotide repeat expansions. RP-PCR may then be followed by Southern blotting which is considered the 'gold standard' for confirming repeat expansions such as that in *C9orf72.* A large multicentre study by Akimoto et al. (2014) found that only five of 14 laboratories were able to achieve concordant results with Southern blotting using PCR alone. Therefore, they suggest that due to the high risk of misgenotyping using only PCR and the clinical

consequences of this misgenotyping, Southern blotting should always be used to confirm RP-PCR results in a clinical setting. However this method is costly, time consuming and requires large, high quality DNA samples (Akimoto et al., 2014; Cleary, 2016) and as such, many laboratories use only RP-PCR, without the confirmatory Southern blotting procedure.

2. Special circumstances; challenges in interpreting pathogenicity of FTD-causing genetic mutations:

The American College of Medical Genetics and Genomic (ACMG) guidelines (Richards et al., 2015) are commonly used to interpret pathogenicity of a variant, however there are a number of points specific to FTD that are also important to consider when determining pathogenicity.

Firstly, the repeat length at which a *C9orf72* expansion is pathogenic remains unclear. In the initial studies of *C9orf72*, an expansion length of >30 repeats was considered pathogenic, although it was noted that most symptomatic patients had repeat lengths ranging from hundreds to hundreds of thousands of repeats (DeJesus-Hernandez et al., 2011; Renton et al., 2011). In contrast, in healthy controls the vast majority of people have repeat lengths of <20, most commonly 2-8 repeats (Ng & Tan, 2017). An 'intermediate' length expansion was initially considered to be between 20 and 30 repeats with possible pathogenicity e.g. expansions of 20-22 repeats were found in five people with FTD, three of which had a modified Goldman score of two suggesting a strong family history (Gomez-Tortosa et al., 2013). Another study showed a higher frequency of psychiatric presentations in intermediate expansion carriers (Ng & Tan, 2017), and several studies have demonstrated an association with atypical parkinsonian syndromes (Cali et al., 2019; Cannas et al., 2015; Schottlaender et al., 2015). In a cohort of 354 pathologically confirmed CBD cases, there were significantly more *C9orf72* repeat expansions found compared to controls (3.7% vs 0.52%) using a minimum cut off of 17 repeats, however, no expansions larger than 29 repeats were detected (Cali et al., 2019). A post-hoc analysis found that *C9orf72* repeat length as low as 10 was associated with CBD, indicating that intermediate repeat expansion length may be a risk factor for CBD, with increasing risk with higher repeat sizes (Cali et al., 2019). However, uncertainty remains over their significance, and the lower limit of pathogenicity, which poses a challenge when 'intermediate' expansions are

identified in clinic. Crook et al., (2019) report a case in which highly discordant repeat length results were obtained via differing laboratories using RP-PCR and Southern blotting procedures. Expansion lengths of between >15 to 28 were recorded and interpretations provided by laboratory thresholds included inconclusive, intermediate, negative (<30 repeats) and pathogenic. However, the expansion was not detected by Southern blotting. These findings emphasise the lack of clarity regarding the discovery in patients of *C9orf72* expansion lengths that are not clearly pathogenic (i.e., those that are not in the thousands to hundreds of thousands) and the authors highlight the impact that this may have on the individual, their children or potential children as a result of increased uncertainty, confusion and potential psychological risk.

Secondly, in addition to the pathogenicity problem in *C9orf72* repeat expansions, there are also a number of issues in interpreting pathogenicity of some progranulin mutations. Studies have demonstrated the association between pathogenic *GRN* mutations and low levels of progranulin in CSF (Ghidoni et al., 2008), plasma (Finch et al., 2009; Galimberti et al., 2018; Ghidoni et al., 2008) and serum (Sleegers et al., 2009). However, there is currently no definitive cut-off level to determine pathogenicity. With the commonly used Adipogen ELISA, levels of 61.5 (Ghidoni et al., 2012) or 71 (Sellami et al., 2020) have been used in plasma or serum. However, there is some overlap around 55-85 between controls and *GRN* mutation carriers. No cut-off level for CSF has been identified but some cases have been shown to have low CSF but normal serum progranulin levels (Wilke et al., 2016). Similarly, multiple missense mutations have been reported in *GRN*, many of which have unclear pathogenicity and can have variable progranulin levels in blood or CSF. Functional biological studies have been carried out to investigate pathogenicity in only a small number of such mutations e.g. *A9D* and C105Y (Karch et al., 2016; Mukherjee et al., 2008). 'Normal' progranulin levels are observed with a number of missense *GRN* mutations (suggesting they are not pathogenic) while others give rise to 'intermediate' progranulin levels lying somewhere in between 'normal' and the much greater reduction seen in loss of function *GRN* mutations. More recent research suggests many missense variants may be risk factors for dementia without being directly pathogenic (Redaelli et al., 2018).

Thirdly, although uncommon, a number of families with more than one pathogenic mutation have been reported. This has been most commonly reported in families

carrying a *C9orf72* expansion alongside another mutation in *GRN* or *MAPT* (Lashley et al., 2014; van Blitterswijk et al., 2013). However, in reality, dual mutations are likely to be more prevalent than currently reported as many centres do not test for additional mutations once a *C9orf72* expansion is detected. There are also reports in the literature of dual mutations in rarer genes, for example dual *C9orf72* and *TARDBP* mutations (Origone et al., 2015). This phenomenon, although rare, poses difficulties for genetic counselling of family members, and in the practice of sequential genetic testing with *C9orf72* expansion testing followed by NGS sequencing only if the initial test is negative.

Lastly, diminished capacity to consent for diagnostic testing and communication problems may pose an increased problem in FTD compared to other neurogenetic disorders (Crook et al., 2021). Therefore, there may be increased burden on family members regarding diagnostic testing decision-making, not limited to the diagnostic test itself but also regarding storage of samples for future testing. Issues may arise in particular when family are not in agreement regarding these factors and, as such, care must be taken to counsel families throughout the decision-making process.

Therefore, this study aimed to provide clarity on the above issues by developing expert consensus recommendations for diagnostic testing in FTD using a Delphi methodology.

6.3. Methods

6.3.1. Delphi consensus methods

6.3.1.1. Participants

Participants were members of either the GENFI Investigators Group or the UK Predictive Testing Consortium. All participants were either neurologists, clinical geneticists or psychiatrists with a specialist interest in either FTD or neurogenetics. Twenty-three GENFI principal investigators (all of whom were consultant neurologists, clinical geneticists or psychiatrists), were initially invited to participate. International participants also recommended suitable collaborators to participate who were either neurologists or local geneticists associated with the study at their site. Eleven clinical geneticists were also invited to participate via the UK-based geneticists from the UK Predictive Testing Consortium. The introductory invitation to participate was followed by two subsequent reminders. Those who did not respond following the final reminder email were excluded, resulting in a final panel of 18 neurologists, three psychiatrists and seven clinical geneticists. Three panellists dropped out throughout the duration of the study: one neurologist and two clinical geneticists. For distribution of professionals across each round see Table 38. Experts also indicated their professional area of interest; FTD (n=20), neurogenetics (n=16) or both FTD and neurogenetics (n=8).

Table 38 - Panellist distribution across professional specialism

	Neurologists	Psychiatrists	Geneticists	Total
Round 1	18	3	7	28
Round 2	17	3	6	26
Round 3	17	3	5	25

6.3.1.2. Procedures, design and survey development

The Delphi technique was employed to determine consensus amongst a group of experts. The Delphi process comprised of three rounds **(**Figure 23). The topic was first

discussed during an investigator meeting of the GENFI consortium in 2019 and a number of key questions were identified which were used to develop the first questionnaire. In Round 1 of the questionnaire, participants were asked to answer a total of 20 questions from a selection of multiple-choice options. A free-text answer 'other' option was also available. The questionnaires used and adapted throughout the study can be found in appendices 15 to 17. Family history was quantified using the modified Goldman score, outlined in Table 39 (Beck et al., 2008; Rohrer et al., 2009).

Table 39 - The modified Goldman score

Modified Goldman score	Family history description
1	Autosomal dominant family history
2	Three or more family members with FTD but not meeting criteria for autosomal dominance
3	One first degree relative with young onset dementia
3.5	One first degree relative with dementia onsetting over the age of 65
4	No family history

In Round 2, all multiple-choice options with less than 10% uptake were removed and one additional option was added as suggested by participants (see appendices 10 to 14). The percentage of respondents who selected each option in the previous round was highlighted and participants received individualised questionnaires indicating their previous response. They were then asked to reconsider their answer based on this information.

Although consensus was achieved on a number of items, a third questionnaire round was carried out as this is reported to be an optimal number of rounds to achieve a consensus (Iqbal & Pipon-Young, 2009; Vogel et al., 2019). Here, all items that had achieved consensus were removed and again, items with less than 10% uptake were removed. The percentage of respondents who selected each option in the prior round was highlighted and each participant saw their previous response indicated and were asked to reconsider based on the information provided. Throughout the study, for each round, participants were given three opportunities to respond. As demonstrated in

Figure 23 below, three participants failed to respond between round one and round three. Missing data was clarified for incomplete responses. A number of geneticists objected from responding to questions outside their area of specialism. For these questions the analysis was adjusted accordingly to maximise the utility of the data gathered.

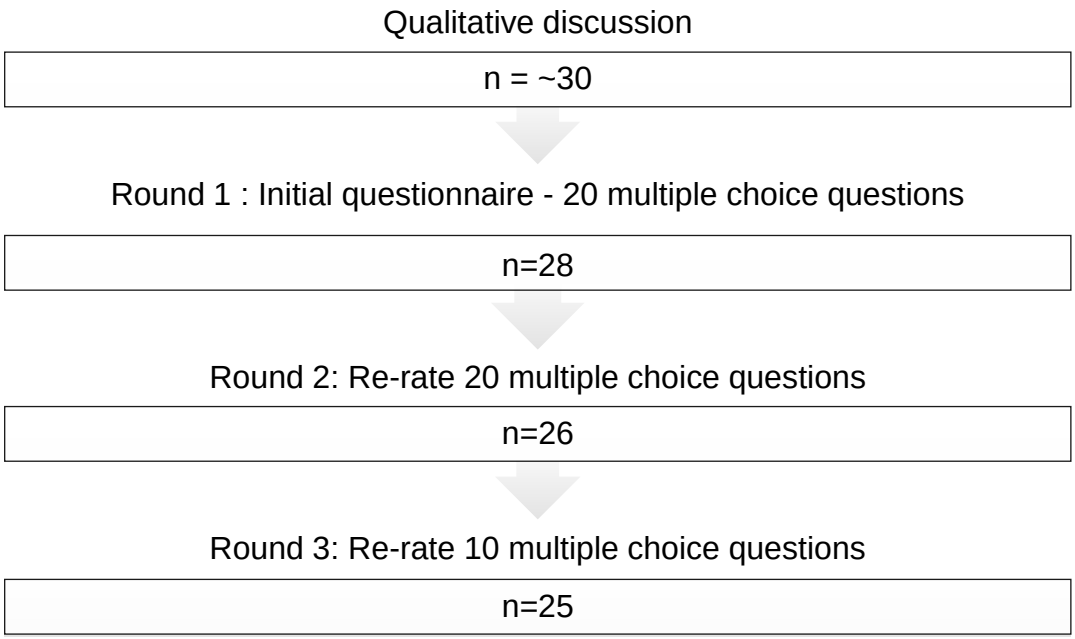


Figure 23 - Flow chart demonstrating the Delphi procedure and number of participants and questions at each stage

6.3.1.3. Analyses

Questionnaire responses were summarised after each round using descriptive statistics, computed using Microsoft Excel (*Microsoft Excel*, 2018). The percentages of experts who chose each multiple-choice response were calculated for each item (see appendices 10 to 14 for responses across all Delphi rounds). Criteria for strong consensus was determined to be the answer selected by >80% respondents and moderate consensus was >70%. The literature suggests that consensus of >70% is an adequate level of agreement (Vogel et al., 2019). Free-text data informed the development of the subsequent questionnaire iterations.

6.4. Results

Consensus results are reported following three rounds of questionnaires. According to the Delphi methodology consensus was not achieved during the first round. In Round 2, strong consensus (>80%) was achieved for eight items and moderate consensus (>70%) for two additional items. At round three all items reached strong or moderate consensus, except for three diagnoses; lvPPA, CBS/PPA overlap and PSP and one further item regarding minimum symptoms for diagnostic testing. Age was not a factor in the final consensus results. See appendices 10 to 14 for full results after each questionnaire round.

Regarding to whom diagnostic testing should be offered based on phenotype, age and family history, it was recommended that diagnostic testing is offered to all individuals presenting with the following phenotypes: bvFTD, FTD-ALS, bvFTD/PPA overlap syndrome, nfvPPA, lvPPA with negative AD biomarkers and PPA-NOS. For diagnoses of svPPA and CBS, it was recommended to offer diagnostic testing to individuals with a modified Goldman score of 1 to 3.5, indicating a first degree relative with a dementia diagnosis over the age of 65. Experts also recommended that those with late onset psychosis and schizophrenia with a modified Goldman score of 1-2 should be offered diagnostic testing.

Consensus above 70% was not met for lvPPA with unknown biomarkers, lvPPA with positive AD biomarkers, PSP and CBS/PPA overlap. However, as these items still achieved over 60% consensus, they may be used as suggestions rather than guidelines.

Table 40 - Percentage consensus for whom diagnostic testing should be offered, based on phenotype and family history

Phenotype	All	Goldman score of 1-3.5 (at any age)	Goldman score of 1-3 (at any age)	Goldman score of 1-2 (at any age)
BvFTD	83%			
FTD-ALS	92%			
bvFTD/PPA overlap	70%			
nfvPPA	76%			
svPPA		72%		
lvPPA (AD biomarkers unknown)			60%	
lvPPA (AD biomarkers positive)				64%
lvPPA (AD biomarkers negative)	80%			
PPA-NOS	80%			
CBS		76%		
PSP				64%
CBS/PPA overlap				60%
Late onset psychosis/ schizophrenia				73%

In addition, participants were asked whether blood or CSF progranulin levels should be used to supplement guidelines for determining pathogenicity in *GRN*. Eighty-two percent recommended that low blood or CSF *GRN* levels should be considered supportive of pathogenicity but not definitive.

When asked whether we should consider minimum criteria for diagnostic testing in prodromal FTD, experts did not meet the consensus threshold, however 64% were in agreement that patients should display minimal cognitive and/or behavioural impairment, displaying at least one symptom described in the Rascovsky criteria.

6.4.1.1. Proposed FTD diagnostic testing recommendations

The recommendations outlined below may be considered supplementary to those described by Craufurd et al., (2015), for diagnostic testing in FTD. Additional adaptations to Craufurd et al's (2015) guidelines are also described.

When should we consider diagnostic genetic testing?

Recommendations refer to those supported by the consensus threshold, guidelines refer to those items that did not meet 70% consensus but clinicians may consider using their discretion on a case by case basis.

Proposed FTD recommendations
Recommendations (RECs) 1-3: 1. Experts recommend that diagnostic testing is offered to all those given the following clinical diagnoses regardless of family history: - Behavioural variant FTD - FTD-ALS/MND - Behavioural variant FTD/Primary progressive aphasia overlap syndrome - Non-fluent variant primary progressive aphasia - Logopenic aphasia (once AD biomarkers are confirmed to be negative) - PPA-not otherwise specified 2. Experts recommend that diagnostic testing is offered to those with the following diagnoses, with a family history of a dementia diagnosis over the age of 65 (mGS 1-3.5) - Semantic variant primary progressive aphasia - Corticobasal syndrome 3. Experts recommend that diagnostic testing is offered to those with the following diagnoses, with a family history involving 3 or more family members with FTD but not meeting criteria for autosomal dominance (mGS 1-2). - Late onset psychosis or schizophrenia
GUIDELINE 1: Clinicians may want to consider offering diagnostic testing to those with a diagnosis of progressive supranuclear palsy or corticobasal syndrome/primary progressive aphasia overlap with a family history involving a 1 first degree relative with young onset dementia (mGS 1-3). However please note that this did not meet consensus threshold and therefore should be considered on an individual basis and at the

discretion of the clinician.
GUIDELINE 2: Clinicians may want to consider a minimum symptom threshold for diagnostic testing, with individuals requiring minimal cognitive and/or behavioural impairment, displaying at least one symptom outlined by the Rascovsky criteria to qualify for diagnostic testing. However, this should be considered on an individual basis and predictive testing protocols may often be most appropriate, particularly due to the additional counselling element and should be employed in situations where there is doubt regarding the appropriateness of diagnostic testing.

How should diagnostic testing be carried out?

From Craufurd et al., (2015), amendments highlighted in **bold**: Where **FTD** seems possible, the neurologist may suggest proceeding with genetic testing. It is best to inform both the patient and immediate relatives about the hereditary nature of the disease before carrying out the test. If the diagnosis is confirmed, the clinician must recognise the needs of the entire family as well as the index patient and ensure that family members can access appropriate genetic counselling services.
Clinicians should always offer follow-up to the patient and **their** family. The opportunity to participate in research such as the **GENFI or ALLFTD studies** provide the patient with a sense of purpose and may also offer future opportunities to participate in clinical trials. Family members may want to access genetic counselling, and the neurologist should be aware of the nearest genetic counselling unit and be able to provide details of the lay organisation for support (**e.g. RDS, AFTD** or other local organisations).

Additional recommendations/considerations:

REC 4: Low blood or CSF *GRN* levels should be considered supportive of pathogenicity but not definitive and may be used in conjunction with ACMG guidelines to determine pathogenicity of variants of unknown significance.
Lack of insight – adapted from Craufurd et al., (2015): Commonly in **FTD**, the person living with **FTD** may have little insight into their own symptoms, thus their partner or family members often suspect the diagnosis before the individual acknowledges their symptoms themselves. In some cases, family may have prompted the referral. Therefore, such individuals may be unprepared for the diagnosis, affecting their ability to provide informed consent. The diagnostic and genetic testing process requires care and sensitivity and exploration of the individual's understanding of the situation may be necessary prior to proceeding with genetic testing. An additional appointment and/or offering additional support before diagnostic testing may help.

Adapted from Craufurd et al., (2015):

Checklist before diagnostic genetic testing

- Has the test been requested by a neurologist or psychiatrist with relevant experience?
- Has the patient been appropriately counselled about the implications of genetic testing and possible test outcomes?
- Has the neurological examination shown evidence of motor symptoms?
- Have the patient's family or caregiver been included in discussions about the diagnostic genetic test and hereditary implications of **FTD**?
- Has the family been informed about the option of referral for genetic counselling?
- Has appropriate informed consent for diagnostic genetic testing been obtained by the patient/legal representative/person with parental responsibility?
- Is the laboratory to which the sample is being sent accredited and do they have experience of performing **FTD** genetic testing?
- Have full clinical details, contact details of the requesting clinician and evidence that

consent has been obtained noted on the laboratory request card?

- Has the timescale for expecting a result been made clear to the patient family and the laboratory?
- Has a face-to-face appointment with the person requesting the genetic test been arranged to give the result?

Checklist following a genetic diagnosis of FTD

- Has a plan for follow-up been discussed with the patient and his/her family?
- Have details of the lay organisation been provided?
- Have options to participate in research been discussed?
- Do the patient's relatives wish to be referred for genetic counselling?

6.5. Discussion

This study uses expert opinion to develop guidelines for diagnostic genetic testing in fFTD. Recommendations build upon those used as a ‘gold standard’ for testing in HD, allowing for the added uncertainty and unpredictability seen in fFTD, due to variable age at onset, phenotypic heterogeneity and other ‘special circumstances’ discussed above.

6.5.1. Summary of main findings

This study achieved consensus on all but a small number of items, including diagnoses of lvPPA, CBS/PPA overlap and PSP and a question regarding minimum symptoms for diagnostic testing. Most of those which met consensus, did so at a level of over 80% indicating strong consensus within the group of experts.

The results of this study highlight that it is important to offer testing to those phenotypes commonly observed in fFTD. Experts were in agreement that diagnostic testing should be offered to all of those presenting clinically with a bvFTD or FTD-ALS diagnosis. Despite these phenotypes both occurring sporadically, they are the most common phenotypes observed within familial FTD. As diagnostic testing occurs in those who have already developed symptoms, therefore it may be reasoned that in these cases, if the individual and their family would like to proceed with it, diagnostic testing would cause minimal harm, but should a mutation be identified, this may be important information for other family members. Similarly, although there is currently no treatment for FTD, identifying individuals in the early stages of the disease with a genetic cause may allow them, in future, to participate in clinical trials or receive potentially disease modifying treatments.

Similarly, the panel of experts recommended that testing should be offered to those with a late onset psychosis or schizophrenia diagnosis who displayed a strong family history of FTD-related disorders, which may include FTD, MND, Parkinsonism and late onset psychiatric diagnoses. A strong family history was classified either as an autosomal dominant history (modified Goldman score of one) or familial aggregation of three or more family members with dementia including FTD/PSP/CBS/ALS (modified Goldman score of two). Although adult-onset psychiatric diagnoses alone

are not necessarily indicative of FTD, many individuals with FTD are misdiagnosed with a primary psychiatric illness, therefore diagnostic testing may be a helpful tool to ensure the correct diagnosis and care for those with a strong family history of FTD related disorders.

The expert panel also recommended that low blood or CSF progranulin levels may be considered supportive of pathogenicity, used in conjunction with ACMG guidelines for determining pathogenicity, however low progranulin levels should not be considered definitive of pathogenicity. As discussed above, there is no set cut-off to determine pathogenic progranulin levels, and missense mutations often demonstrate variable progranulin levels, some lying between 'normal' and clearly pathogenic levels. Levels can also vary depending on whether they are measured in blood or CSF (Wilke et al., 2016). However functional biological studies have been carried out for only a small number of mutations . Therefore, although progranulin levels can provide useful information in support of pathogenicity, they should not be considered definitive.

The recommendations for diagnostic testing provided within this study take into account work in HD (Craufurd et al., 2015), as well as more recent work in ALS and FTD (Crook et al., 2022). Crook and colleagues also used a modified Delphi methodology to identify diagnostic testing recommendations which are complementary to those outlined in this study. They identified a number of recommendations relating to the diagnostic test counselling procedure, for example, the presence of a consistent healthcare provider, information provided in various formats and a flexible and family centred approach to diagnostic testing. They detail much of the content that a healthcare provider should cover while counselling a family ahead of diagnostic testing. This fits well with the recommendations provided within this study, which largely focus on ensuring clarity regarding eligibility for diagnostic testing. Therefore, it may be useful in future to combine both resources to form a combined FTD and ALS diagnostic testing protocol.

Age was not considered a factor in any of the final consensus results. This may be due to a number of factors; firstly there is a variable age at onset observed across fFTD, most commonly ranging between the ages of 49 to 65 years (Moore et al., 2020). This large variability in onset may pose a challenge in applying age-related boundaries in genetic testing guidelines and may increase the risk of individuals outside these

arbitrary age brackets not being offered appropriate genetic testing. Similarly, studies (Moore et al., 2020) suggest that there is age related penetrance observed in *GRN* and *C9orf72*, therefore age cut-offs favouring young-onset dementia (i.e. under the age of 65) may disadvantage those where age-related penetrance is an issue. Finally, as age at onset within families is not predictable, aside from in *MAPT* mutations, age boundaries for genetic testing may be seen as arbitrary and as such creating barriers to accessing appropriate and important clinical care and support. The additional qualitative data explored within this study highlights the importance and emotive nature of genetic testing for families affected by fFTD, therefore it is important that the relevant services are as accessible as possible, hence the importance of defining guidelines for testing.

6.5.2. Evaluation of the Delphi methodology

The Delphi methodology utilised in this study provides many advantages that made it a suitable method for creating expert recommendations. Firstly, it provides anonymity and encourages reflection, allowing for collaboration of a diverse group of expert panellists. As FTD is a niche field of research, this method allowed for collaboration of experts from across the globe, both allowing for cross-cultural perspectives but also facilitating investment of clinical professionals within the field, in the subsequent guidelines generated. Due to the consensus nature of the methodology, a 'best-fit' scenario is generated, reducing the noise in the data and reducing the impact of dominant individual's viewpoints. This is particularly advantageous over other consensus methods such as in-person discussion, as within academia there may be a social desirability bias towards senior clinicians and academics, leading panellists to conform rather than indicate their true opinion. Furthermore, the reflexivity of the method, reflecting using feedback over multiple rounds of questionnaires, increases the validity of the findings (Donohoe & Needham, 2009; Fink-Hafner et al., 2019; Hsu & Sandford, 2007).

Although supporters of the Delphi methodology argue that group decisions, specifically those made by informed expert opinion, are more reliable than decisions made by a single person, particularly where there is minimal literature or historical context regarding the problem in question (Franklin & Hart, 2006) this methodology is not without its limitations. The lack of active discussion involved in the process may limit

the responses given, particularly as there is limited opportunity to share reasoning behind decision-making with other panellists. Similarly, the development of the initial questionnaire can be subjective and may limit or bias responses due to the choices offered. This study attempted to overcome this limitation by developing the initial questionnaire from a group discussion on the topic and allowed qualitative feedback in the first iteration of the questionnaire so that panellists could make their own suggestions or provide reasoning which could be accounted for in the following iteration.

6.5.3. Limitations

Despite best efforts to limit any limitations within this study, there are a number to be addressed. Firstly, although the panel encompassed experts from across the UK, Europe and Canada, the judgements made by the panel may not be representative of other countries and cultures and therefore not generalisable, particularly as it takes a particularly 'Western' stance towards medicine and healthcare. Additionally, due to a focus on NHS systems, the implementation of these recommendations may not be possible within the constraints of other healthcare systems. Furthermore, the overrepresentation of neurologists in the expert panel may have led to recommendations that are unrealistic for application within a genetic counselling or testing real-life scenario. There may also be limitations in terms of clinical and laboratory capacity for carrying out such tests, making the implementation of the above recommendations challenging. Furthermore, working with family systems raises the problem of discordant views regarding testing, which can complicate the diagnostic and predictive testing experience, particularly when the symptomatic individual lacks capacity to make this decision themselves. There are also complex ethical issues regarding the right to know the genetic information of family members when this impacts an individual's risk, as has been discussed in the high court of late. Additionally, there are further constraints relating to the rights and counselling of estranged family members, or those who cannot attend appointment due to geographical distance. Therefore, this process can be 'messy', and while the above recommendations are intended to assist this process, it also requires careful consideration on a case-by-case basis, with the option of DNA storage for future analysis potentially existing as a suitable compromise in these difficult situations. A

strength of this study was the panel size, as this exceeded the lower limit of 12 described in the literature (Vogel et al., 2019), drop out between questionnaire rounds was also very low. The use of the Delphi methodology in this study also allowed for a collaborative and cross-cultural approach to developing recommendations, allowing experts to make suggestions for changes and providing a method by which to find a best-fit solution to these complex problems.

6.5.4. Future work

Future work would be beneficial in the development of this field. Future research evaluating the implementation of the above recommendations will determine whether benefits are observed in patient experience and begin the process of generating an evidence-base for clinical practice. In addition, future work including non-western cultures and non-UK healthcare systems will improve application outside the UK and Europe, allowing for more uniform patient experience across the fFTD community.

6.5.5. Conclusions

Overall, this study uses a Delphi consensus methodology to explore the genetic testing experience in fFTD and provide expert recommendations for diagnostic testing. Healthcare professionals should be educated on the complexities of counselling individuals affected by fFTD and remain mindful of the psychological impact this may have. The recommendations outlined in this chapter provide a framework within which healthcare professionals can evaluate complex situations and ensure that best-practice is followed. Following the implementation of these recommendations within clinical neurogenetics services, future work should investigate whether improvements in patient experience are observed. Further work will also be needed to address whether the application of such recommendations in different healthcare systems is feasible.

Chapter 7. Developing a tailored predictive testing protocol for use in frontotemporal dementia

7.1. Chapter overview

Following on from the diagnostic testing recommendations presented in Chapter 6, this chapter outlines expert consensus recommendations for predictive testing. In addition to this, qualitative data was employed to provide a patient perspective to predictive testing, and guidelines for predictive testing. The findings outlined in Chapter 3 and Chapter 4 of this thesis demonstrate the psychological challenges associated with living at-risk, and for some predictive testing is a key part of this experience. The current predictive testing protocol used as a 'gold standard' in hereditary neurodegenerative diseases was designed for HD, although there are likely many overlapping aspects covered within this protocol, therefore also may be issues regarding the application within FTD. For example, these guidelines may be implemented in a less rigorous manner due to the need for extrapolation, and healthcare professionals unfamiliar with fFTD may also lack resources and information to thoroughly counsel those at-risk. Anecdotally, some participants seen within GENFI report difficult experiences with predictive testing, suggesting there is variation across services. Therefore, due to the significance of predictive testing for many at-risk individuals, and the potential psychological implications of this experience at an already emotionally challenging time, it is important to ensure a supportive and comprehensive predictive testing experience. Therefore, the aim of this chapter was to consult experts within the field, using a Delphi consensus methodology, as well as thematic analysis of qualitative interview data regarding predictive testing experiences, to inform the development of FTD predictive testing recommendations, and adaptation of existing 'gold standard' guidelines. The overarching goal of this is to improve the predictive testing experience and provide more well-rounded and supportive services in order to further improve wellbeing of those living at-risk of fFTD.

7.2. Introduction

Genetic counselling is recommended prior to predictive testing (MacLeod et al., 2013) and a detailed cost-benefit discussion is had to assist the individual's decision making. There have been a small number of studies that have looked at people's reasoning around testing with the most common factors in people who choose to have testing being: to know if children were at risk, financial and family planning, reducing uncertainty and anxiety and concern about developing symptoms (McRae et al., 2001; Steinbart, 2001b). Reasons for not having predictive testing included maintaining hope and the inability to cope with the psychological consequences of knowing they will develop the disease in the future (McRae et al., 2001). While predictive testing may relieve uncertainty, allow planning for the future, and inform decision-making regarding reproduction for some, there are also many limitations to undergoing this procedure (McRae et al., 2001; Steinbart, 2001). As fFTD research moves closer to identifying potential disease modifying treatments, requests for predictive testing are increasing (Amador et al., 2021; Crook et al., 2022).

The main limitation of undergoing testing is that once the result is disclosed, there is no way to remove this information. Adverse psychological reactions are also a risk to consider as this is difficult to predict as discussed in Chapter 3.2. A further issue is the uncertainty and lack of information available regarding disease onset (i.e. what age they will develop symptoms) and the presentation that an individual can expect (i.e. what symptoms they may develop) (Fong et al., 2012).

7.2.1. Predicting age at onset

Age at onset remains difficult to predict in genetic FTD in comparison to many other neurodegenerative conditions, and can be between 20 years of age and 90. Moore et al. (2020) recently showed that although age at symptom onset in an individual significantly correlated with both their parental age at onset and mean family age at onset across all three main FTD causing genes, the correlation was weak for *C9orf72* and *GRN* mutation*s,* and only relatively strong for *MAPT* mutations (r=0.45 for parental age at onset and r=0.63 for mean familial age at onset).

Both *GRN* and *C9orf72* mutations show age-related penetrance, with onset being seen

into the 90s (Gass et al., 2006b; Moore et al., 2020; Murphy et al., 2017b). The *C9orf72* expansion has also been found in 0.15% - 1.2% of healthy older individuals (Beck et al., 2013; Galimberti et al., 2014). *MAPT* mutations are generally fully penetrant although onset can be into the 80s on rare occasions with some incomplete (likely age-related) penetrance reported (Anfossi et al., 2011; Moore et al., 2020; Munoz et al., 2007; Rossi et al., 2008; Van Herpen et al., 2003).

7.2.2. Prediction of phenotype

As previously discussed in the introductory chapter, numerous clinical phenotypes can exist within the same family and it cannot be predicted in advance which phenotype an individual may develop. This can be of concern within families at-risk of *C9orf72* expansions, who are unable to predict if they will develop FTD, MND or FTD-MND which can cause a significant burden when planning for the future.

There are also more complex issues such as variants of unknown significance, an unknown mutation but autosomal dominant family history, and genetic anticipation, that it might be pertinent to discuss with a patient. However, currently these issues are difficult to address owing to lack of conclusive findings within the literature (Fong et al., 2012). Furthermore, considering the lack of currently available treatment for FTD, knowing one's genetic status would not have an impact on an individual's medical treatment or provide clinical benefit while living asymptomatically. Genetic privacy may also be an issue to some, particularly in countries without a national healthcare system. The Genetic Information Non-discrimination Act prohibits genetic information being used to discriminate in terms of health insurance and employment in the US and in addition to this federal legislation, many states also have their own legislation (Fong et al., 2012). Therefore, discussing this issue during genetic counselling may put patients at ease regarding the wider impact of their genetic status.

As discussed above, there is a large amount of uncertainty and unpredictability associated with predictive testing in FTD which differs from diseases like HD which are more well understood. It is important to ensure predictive testing processes are standardised in order to ensure the best, evidence-based practice for patients and their families. Receiving genetic information is a psychologically challenging experience which, as stated above, may have adverse psychological effects, therefore it is

imperative that clinicians remain cognisant of this risk and take measures to limit this wherever possible. Therefore, both patients receiving genetic testing and health-care professionals involved in genetic counselling and testing, may benefit from an FTD-specific protocol to address some of these issues. As such, this study aimed to develop a tailored genetic testing protocol for use in FTD by use of expert opinion through a Delphi consensus methodology and using semi-structured interview to incorporate the patient perspective.

7.3. Methods

7.3.1. Delphi consensus methodology

For Delphi methodology, see Chapter 6.3.1.

7.3.2. The patient perspective of predictive testing - qualitative methods

A more detailed explanation of the methods employed in the qualitative arm of this project can be found in Chapter 4.3.

7.3.2.1. Participants and recruitment

Participants were a subset of the sample outlined in Chapter 4.3.1 who had undergone predictive testing. Twelve individuals were recruited from the GENFI cohort at UCL. Seven individuals were identified as mutation carriers, with the remaining five, found not to possess the genetic mutation (non-carriers).

Participants were recruited by email as this study took place during the COVID-19 pandemic. Project details were outlined, following which, a number of individuals identified themselves as interested in participating. There was an underrepresentation of non-carriers within the initial sample and as such, a number of known non-carriers were approached and offered the opportunity to participate.

For participant demographics see Chapter 4.3.2.

7.3.2.2. Procedures

Semi-structured interviews explored the lived experience of being at-risk of fFTD. This study utilises a subset of this data, focusing on the predictive testing experience. Participants were specifically asked to outline their experience of predictive testing and the impact that this had, (for the full interview schedule see Appendix 2). Interviews took place in mid-late 2020 and lasted for between 30-90 minutes.

For a more detailed description of the procedures used within this study see Chapter 4.3.3.

7.3.2.3. Materials

As described in Chapter 4.3.4, interviews were conducted virtually due to COVID-19 lockdown. Both Zoom (Zoom Video Communications Inc., 2021) and Microsoft Teams (*Microsoft Corporation*, 2020) were used to host and record the interview sessions. Transcription was aided by the use of Trint software (*Trint*, 2021, https://trint.com).

7.3.2.4. Analyses

An inductive and reflexive approach to thematic analysis was used, following the methodology outlined by (Braun and Clarke, 2006). NVivo 12 Pro software (*NVivo*, 2018) aided the coding and thematic analysis procedure. A subset of codes were reviewed by an independent rater and themes derived were reviewed with JCS.

As above, a more detailed description of the analytic procedure can be found in Chapter 4.3.5.

7.4. Results

7.4.1. Delphi consensus

As in Chapter 6, findings are reported following three questionnaire rounds and a minimum of 70% is required to achieve consensus.

Participants were presented with a number of vignettes of an asymptomatic individual with a family history of FTD, presenting to clinic requesting predictive testing. They were asked what they would do in these four scenarios – how would they proceed with testing?

"An asymptomatic person with a family history of FTD but no known genetic mutation in the family at present…"

Scenario 1 –*… and a living, affected relative who is able and willing to consent to diagnostic testing.*

Eighty-five percent of experts recommended performing diagnostic testing on the affected relative, independent of their family history, to ascertain whether a mutation is present and then offering predictive testing to the asymptomatic individual.

Scenario 2 - … *and a living, affected relative who is unable to consent to diagnostic testing.*

Eighty-one percent of experts recommended performing diagnostic testing on the affected relative, independent of their family history, to ascertain whether a mutation is present *if they are able to assent to having a blood or saliva sample taken and the family are all in agreement* and then offering predictive testing to the asymptomatic individual.

Scenario 3 - … *and no living affected relative but a sample of DNA or tissue is stored from a non-living affected relative. The family are in agreement with testing.*

Eighty-four percent of experts recommended performing diagnostic testing on the affected relative's stored sample, independent of their family history, to ascertain whether a mutation is present and then offering predictive testing to the asymptomatic

individual.

Scenario 4 - … *and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member*

Eighty-eight percent of experts recommended not offering predictive testing in this circumstance i.e. no blind predictive testing of individuals.

Scenario 5: … *and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD. E.g., only fixed tissue available, no DNA has been able to be extracted.*

Eighty-eight percent of experts recommended performing targeted predictive testing in this circumstance, based on the underlying characteristic pathology e.g., 1) presence of dipeptide repeats in the brain would lead to testing for *C9orf72*; e.g., 2) presence of TDP-43 type D pathology would lead to testing for VCP.

7.4.2. Qualitative results – the patient perspective

There were five themes relating to the process of genetic testing and PGD. These themes describe the stages of predictive testing; deciding whether to get tested, preparation and expectations for genetic testing, the process of testing, receiving the genetic test result and preimplantation genetic diagnosis. The content of these themes are summarised below.

Theme 1: Deciding whether to get tested

All participants spoke about the decision regarding predictive testing. Some were advised against or discouraged from testing in some way, however around half felt strongly that they wanted to know their status.

> *The only thing that I was certain of when I found out she had it was I wanted to get tested.* (Participant 10)

Most participants mentioned factors they considered when making their decision to have predictive testing. These included family support, practical implications of knowing their status and whether they would feel better or worse for knowing. Some

individuals spent time deciding whether to go through the testing process, with one initiating counselling in order to help make their final decision, whereas others made the decision quickly.

Many individuals noted reasons in favour of predictive testing, including clarity, future planning, peace of mind, to understand the impact on family and children, to allow for having a child without the gene. A few individuals noted that they would be motivated to have predictive testing if clinical trials looked hopeful. Some individuals also noted reasons against having predictive testing, these included that they felt comfortable not knowing, the length of time one would potentially live with the knowledge of their positive status, the potential to overthink possible symptoms and question judgement and the lack of treatment available.

Theme 2: Preparation and expectations for genetic testing

Most participants spoke of their preparation and expectations for predictive testing. Around half of individuals expected psychological counselling as part of the predictive testing process. Some expected psychological support to automatically be in place throughout the testing process, while others expected more mental health support or simply more support in general. Many participants expressed that genetic counselling was not what they expected. Some individuals felt that the label of 'genetic counselling' was inappropriate as it implied more of a talking therapy style of support, rather than the psychoeducation that was provided. In addition, a few individuals felt that they did not receive adequate information during genetic counselling about what to expect from predictive testing.

Theme 3: Process of testing

Almost all individuals described problems with the predictive testing experience. Practical problems included disorganised appointments, accidental disclosure of results to GP and issues with follow up appointments. For some, this created additional stress and frustration, due to their already heightened emotional state at uncovering their risk. The length of predictive testing was an issue for ten individuals who felt that the process was too lengthy and waiting times were too long, both in terms of appointment waiting times and the 'cooling off period'. This was a source of frustration for some who were eager to find out their result and for those who needed to begin

PGD. Meanwhile a few participants felt that the length of predictive testing was suitable, with one stating that the ‘necessary slowness’ ensured the decision wasn’t rushed.

> *I mean, I felt, the one thing it was very useful for was I didn't feel like I was rushing into something that I would potentially regret. I did feel like the necessary slowness of it. I think it was once a month, I could be, it might have been once every fortnight but it, it seemed, it went on for a long time. And there was enough time in between sessions for these internal thoughts I was having and conversations I was having with friends, family and stuff or my sister. To. To influence what I was thinking about between each session, so I'd sort of, it wasn't like it was one once a day for a week. It was. There was enough time. So it was actually weighted quite well, I think. It was just it wasn't a sort of like session one; 'oh my God, I've never really thought about this I really need to think about it'. So in that sense, it was quite, that was probably the best thing about it.* (Participant 4)

Many participants noted negative experiences during the predictive testing process. Many of whom had issues during genetic counselling, feeling as though they did not gain information from this experience. In addition, a small number of participants stated that they had little or no counselling. Over half of individuals felt that they had a bad experiences in predictive testing, largely referring to the psychological difficulty of the process and the negative implications for their mental health and wellbeing. Disorganisation, miscommunication and disconnect between services were also issues in this experience.

Over half of individuals also mentioned positive experiences during predictive testing, this included feeling that it was thorough and helpful and ensuring that they considered a range of factors prior to testing.

Many participants also offered improvements for the predictive testing process. Suggested improvements included better management of expectations in terms of predictive testing, genetic counselling and time scales. It was also suggested that there was a need for greater clarity and depth of information given in counselling. Participants wanted more support throughout the predictive testing process and some

felt that they would benefit from the process being quicker.

Theme 4: Receiving the genetic test result

A number of participants had negative experiences receiving the results of their predictive test. Some individuals felt that they were not adequately prepared to receive their result and their expectations were not met in terms of the time frame in which they expected to receive their result. A few individuals reported poor delivery of results, including lack of compassion, poor timing and receiving results by letter. One individual noted that the counsellor's body language and behaviour was different in the appointment in which they received their results, leading them to assume they were going to receive an unfavourable result.

Most individuals spoke of their emotional reaction to their predictive test result. Some felt confused at their result and at the range of emotions they experienced. A small number of individuals also described having a difficult time adjusting to their genetic information, both positive and negative. Some individuals described negative reactions to their status, these were largely those who had received news that they were mutation carriers. While others also spoke of positive reactions to their status, largely those with negative status.

Theme 5: Preimplantation genetic diagnosis (PGD)

Around half of participants mentioned PGD, often linked with the predictive testing experience and experienced some of the same difficulties as with predictive testing, including waiting, frustration and administrative problems. One individual said that the information regarding PGD provided by their geneticist was helpful.

7.4.3. Proposed FTD predictive testing recommendations

MacLeod et al.,'s (2013) recommendations for predictive testing in HD provide comprehensive guidance for the predictive testing procedure. These recommendations are largely applicable in FTD with only some minor amendments, a table displaying MacLeod's HD recommendations amended for use in FTD can be found in Appendix 18.

The recommendations described below can be considered supplementary to

MacLeod’s original recommendations, based on the findings outlined above.

Additional recommendations:

Who should be offered predictive testing? Special circumstances

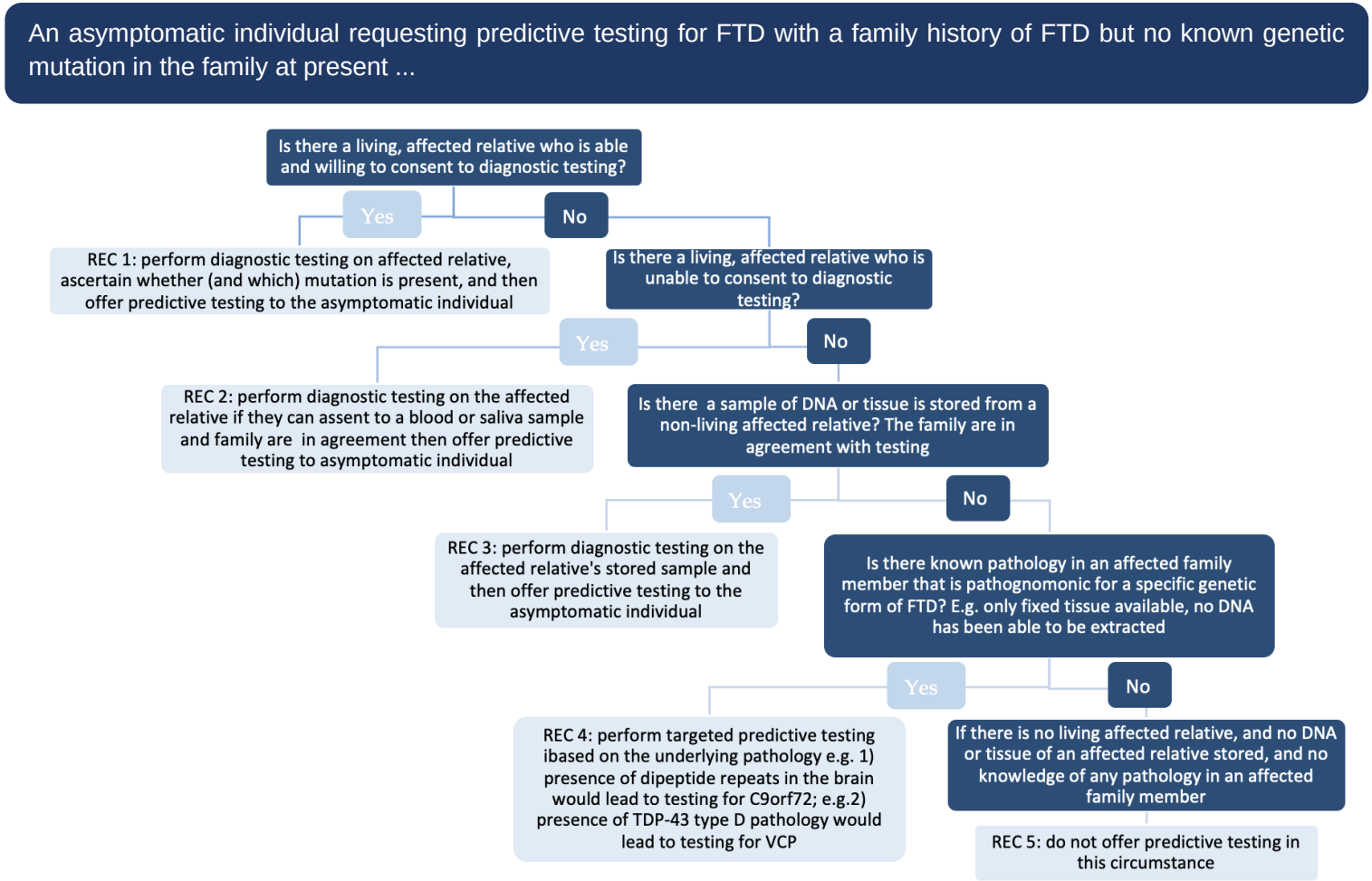


Figure 24- Decision-tree showing predictive testing recommendations for various special circumstances

How should predictive testing be carried out? The patient's perspective:

Pre-test
1. Minimisation of administrative issues
2. Management of expectations a. Expected timelines and waiting times should be clearly communicated to patients wherever possible to minimise frustration. b. Patients should be fully informed regarding the purpose and procedures involved in genetic counselling. There should be transparency regarding the support available throughout the genetic counselling process.
Counselling procedure
3. Access to counselling and/or specialist psychological support should be available in tandem with predictive testing for FTD. There should be clarity regarding how to access this support and participants should be informed of this at the beginning of the predictive testing process.
4. Predictive testing and genetic counselling should be tailored to the individual wherever possible: a. During the first genetic counselling session, a timeline for future appointments should be agreed with the patient, for some it may be appropriate to have fewer sessions or a shorter period between appointments due to other time-sensitive issues such as PGD. Therefore, it is important to assess on a case-by-case basis. b. As above, the length of the 'cooling off' period should be discussed and agreed with the patient, again to minimise frustration. For some a shorter cooling off period may be appropriate if they have communicated certainty on their decision throughout the counselling process, while those who remain undecided may request a longer period to make their final decision. **c.** The content of genetic counselling should be tailored to the individual's

knowledge base. The counsellor should assess the patient's baseline knowledge and what they would like to understand through the counselling process. For some, it may be pertinent to cover the basic elements FTD psychoeducation and heritability, such as possible phenotypes and potential age at onset. Others may already be well-read on such information and prefer a higher-level of understanding, with the guidance of a professional who may be able to help them understand more complex issues.

5. Genetic counselling should prepare patients for the wide-ranging and often turbulent emotions experienced following predictive testing and provide them with tools to manage this experience.

Test result

6. Delivery of results:
    a. A rapport should be built during the counselling process so that genetic counsellors can understand how best to approach result disclosure for the individual they are working with. They should consider their body language and maintain their 'routine' behaviour where possible as patients may be analysing this non-verbal behaviour to attempt to predict the result they may receive.
    b. Regardless of outcome, patients should be reminded of the range of emotions they may experience and a plan should be made for follow up and additional support if needed.
    c. If not already in progress, patients should be offered psychological support.

Follow-up

7. Follow-up should be considered a priority;
    a. At least one follow-up appointment should be scheduled during the final genetic counselling session or following the delivery of the genetic result.
    b. Follow appointments should be in-person wherever possible, however video or phone appointments may also be suitable.

c. If a patient does not attend their follow up appointment, contact should be made via email or letter to provide contact details for follow up support.
8. Connect to support and research a. Regardless of test outcome, patients should be connected to available research studies e.g. GENFI (UK, Europe and Canada) and ALLFTD (US), genetic counsellors or geneticists may refer patients directly to the study, or provide contact details for the patient to self-refer. b. Regardless of test outcome, patients should be linked to appropriate support services e.g. Rare Dementia Support (UK) and AFTD (US). c. Regardless of test outcome, patients should be provided information on how to access further psychological support if necessary.

7.5. Discussion

This study uses expert opinion and patient perspectives to develop guidelines for predictive genetic testing in fFTD. Recommendations provide important additions to the 'gold standard' designed for use in HD, allowing for a more comprehensive counselling experience, and addressing current issues in predictive testing highlighted by experts by experience.

7.5.1. Summary of main findings

The vignettes presented to the panel covered scenarios that ranged from relatively common to more unusual scenarios that may present to clinic. Notably, there was strong consensus to recommend targeted predictive testing in cases where characteristic pathology has been identified post-mortem, for example, if dipeptide repeats were identified in the brain, targeted testing for *C9orf72* may be carried out and TDP-43 type D pathology would provide evidence for targeted testing for a *VCP* mutation. These vignettes range from typical situations presenting to a neurogenetics clinic, to some of the more complex and unusual clinical scenarios. Therefore, the expert recommendations may provide useful guidance for healthcare professionals who may have limited experience with FTD families, as well as providing guidance for practice and discussion when presented with more complex cases. Many clinical geneticists remain cautious regarding targeted predictive testing due to the potential of uncovering indeterminate findings. This is often due to the difficulties of counselling families regarding indeterminate results, as well as the impact that these results may have on the individual, such as increased uncertainty and anxiety. There is likely a fine line between being risk averse for the benefit of the patient and creating barriers to accessing predictive testing. The results from this study regarding this particular scenario were largely driven by expert neurologists rather than geneticists or genetic counsellors, highlighting differing opinions dependent on medical specialism. This suggests that implementation of such recommendation may be met with resistance by some geneticists who favour a more cautious approach to predictive testing, however the presentation of this data may open conversation between clinical geneticists and neurologists to assess this on a case-by-case basis.

Thematic analysis of qualitative data highlighted a number of issues regarding patient

experience of predictive testing. The themes identified in this study can be further collated into four main areas for improvement in the predictive testing process, detailed below. It is important to note that 50% of individuals expressed positive views regarding parts of the predictive testing experience, indicating that it helped them to thoroughly consider their decision. Such recommendations for improvement should be viewed as an opportunity to improve clinical practice and patient experience, rather than as criticism of existing services.

7.5.1.1. Meeting expectations

Results from this thematic analysis indicated that expectations for genetic counselling were not met. This resulted from patient's lack of understanding regarding the process of genetic counselling and its distinction from psychological therapy or counselling. It is important that expectations are met in terms of what patients may expect from genetic counselling to ensure their engagement in the process. This may be done by early clarification of genetic counselling as a psychoeducation based reflective exercise to support the decision-making process. Some participants found the term 'genetic counselling' elicited confusion; therefore, it may be useful to exercise caution when using this term with patients, but rather outline the process in lay-terms instead.

Similarly, data revealed a need for better management of expectations in terms of timescale. This was reported across the predictive testing process and specifically when receiving results. Patients became frustrated at the lack of clarity regarding timescale of their counselling appointments and when they might expect to receive their result as this had a direct impact on other clinical care such as PGD. For those nearing the boundary of NHS age-related eligibility for PGD this was a source of stress and frustration. In addition, it is important to remember that the information revealed from predictive testing for fFTD is particularly emotive, therefore the time when waiting to receive results may be particularly anxiety inducing for some individuals. Therefore, where possible, as opposed to omission of this information, patients may benefit from increased transparency from clinical genetics services on when they might expect this information and may appreciate updates on delays if appropriate.

7.5.1.2. Need for psychological support

This qualitative data also highlighted the importance of psychological support in tandem with genetic counselling, as recommended by both MacLeod et al. and Crook et al. (Crook et al., 2022; Crook et al., 2022; MacLeod et al., 2013). Some patients found the process of predictive testing to be particularly psychologically challenging and had negative implications for their mental health and wellbeing. Negative emotions were also reported regarding the predictive testing experience as well as confusion at the emotions experienced on receipt of their genetic result. In addition, administrative problems and disorganisation of services added an extra element of distress to the already emotive experience. It is to be expected that predictive testing for fFTD is an emotionally charged experience, however, measures can be taken to mitigate this. Services may consider working with specialist mental health professionals, or local community mental health services in order to offer coordinated psychological support throughout predictive testing. Clear pathways to support should be signposted throughout appointments and information provided regarding specialist services such as Rare Dementia Support and GENFI who may be able to provide more specialist and ongoing support.

7.5.1.3. Administrative problems

Disorganisation, miscommunication and disconnect between services were reported as issues that created difficulties in the predictive testing experience. Unfortunately, NHS services in the UK are experiencing challenges regarding underfunding and understaffing, therefore many of these issues may result from systemic problems within the NHS as a whole. However, in order to improve the patient experience, an effort should be made to streamline services, ensuring effective communication between GPs, cognitive neurology clinics, clinical genetics services and other relevant services such as specialist fertility clinics. Patients reported that they found administrative issues difficult to manage due to the added demands of caring for symptomatic family members and managing their own risk. Therefore, attention should be paid to the impact of administrative errors on the patient and assistance may be provided from administrative staff to help resolve such issues.

7.5.1.4. Individualisation

Finally, some patients may benefit from greater individualisation during predictive testing. For example, some patients reported the length of predictive testing to be suitable, while some found it to be too lengthy. For those who found the process to be too lengthy it became less useful and more a source of frustration and 'jumping through hoops'. As mentioned above, for those who required their predictive testing result for further care (e.g., PGD) this was also a source of frustration, particularly due to lengthy waiting times for initial appointments. Therefore, it may be helpful to address these issues with the patient directly and create a dialogue to reflect throughout the process, ensuring both the patient and the genetic counselling requirements are satisfied.

Similarly, some patients expressed that they felt they did not gain information from genetic counselling and that they would have appreciated greater clarity and depth of information. Firstly, this highlights the importance of assessing the patient's baseline knowledge, in order to clarify any errors and assess where further information is needed. As this data was gathered from participants involved in a large cohort study, the sample may be biased towards particularly engaged individuals, therefore they may represent a subset of individuals more inclined to engage in their own research and information gathering regarding fFTD. In addition, a limitation of cohort studies in general is that the sample tends to be of more educated individuals, as such, the individuals in this study may have had a higher educational level and therefore increased opportunity to gather information on fFTD. For more educated or well-researched patients, a higher level of knowledge may be desired, however this may also present difficulty as much remains unknown about fFTD. In such cases the guidelines presented above may provide literature and insight into more specialist issues within fFTD to support healthcare professionals who are unfamiliar with fFTD in having these discussions.

Furthermore, this study also highlights the importance of compassionate delivery of predictive testing results. There should be an emphasis on sensitivity when disclosing such information, particularly as some individuals noted that the clinician seemed distressed at providing this information. Others also analysed body-language and the clinician's behaviour to try to predict whether they would be receiving positive or

negative information. It is important for clinicians to take care and consideration regarding the manner in which they feel it most appropriate to approach this. It may be helpful to be led by the patient themselves, observing their behaviour in prior sessions and building a suitable rapport in order to understand the most appropriate delivery.

The qualitative findings reported in this study, regarding the predictive testing experiences in fFTD are supported by findings reported by Crook et al., (2022) who conducted a qualitative study into genetic testing experiences in FTD and ALS in Australia. In accordance with the findings of this study, they found a lack of information and support, minimal pre and post-test counselling and inadequate follow up, suggesting that the issues highlighted within this study are not limited to UK predictive testing procedures, but rather are indicative of flaws within fFTD genetic testing process worldwide. Crook et al., (2022) also identified support and information needs for genetic testing in FTD and ALS that overlap with the recommendations derived from the data within this study; including greater clarity of information provided, clearer pathways to access genetic testing and further support, information regarding genetic testing timeframes, a clearly defined follow up plan and procedure, as well as access to psychological support. This provides further support to the recommendations for predictive testing outlined within this thesis and suggests clinical implications reaching outside the boundaries of the UK and NHS healthcare systems.

It is clear from the qualitative data analysed alongside this study, that there is room for improvement within the genetic testing experience. It is important within this era of patient-centred care, and in line with the NHS constitution and values, that this lived-experience is accounted for, and the data used to develop services that serve and support this population appropriately. Many healthcare professionals lack experience and knowledge regarding FTD, therefore, for example when counselling those at-risk, they may lack confidence due to the many complexities discussed above (Crook et al., 2022; White et al., 2020). Therefore, the expert consensus recommendations outlined in this study may provide much-needed clarity on some of the difficult topics and scenarios that may arise when dealing with FTD families. This increased clarity and confidence may, in turn, translate directly into a smoother and more positive experience for patients which is vital given that this is often a difficult and distressing

time. The implementation of this protocol may also help to create a more uniform genetic testing experience across services. Clinicians will also recognise that living at-risk of fFTD, undergoing genetic testing and receiving genetic information, whether positive or negative, is a highly challenging and emotional time for not only the individual themselves, but also their family and loved ones. Therefore, it is imperative that genetics services create a supportive and sensitive, patient-centred environment within which to explore these issues.

7.5.2. Limitations

As with all qualitative research, there are limitations regarding the sample studied. The themes outlined within this study are not necessarily representative of the predictive testing experience across different services. Anecdotally, there is high geographical variability observed regarding predictive testing experience, with some services being well equipped to manage rarer conditions such as fFTD. Therefore, findings may be limited in terms of application across services, however the recommendations remain important in guiding counselling and predictive testing procedures. In addition, the application of the patient perspective recommendations outlined within this study may be limited by healthcare resources, or may simply be difficult to apply e.g., minimisation of administrative issues. One issue that arose when presenting these findings to clinical geneticists, were variants of unknown significance. Many geneticists were uncomfortable carrying out genetic tests where there was a possibility of uncertain findings as they are unable to counsel individuals on what this means, therefore increasing the individual's uncertainty, rather than reducing it. Therefore, while such uncertainty exists, geneticists may be reluctant to implement such recommendations. Therefore, further collaboration with clinical genetics services is required.

7.5.3. Future work

As with the diagnostic testing recommendations in Chapter 6, evaluation will be required to determine whether the implementation of these recommendations within predictive testing clinics leads to an improvement in patient experience, as well as evaluating application across cultural groups and settings. In addition, in order to address the application of recommendations in a clinical setting further collaboration

with clinicians and genetics services will be required. The findings regarding assisted suicide were a novel finding that has not yet been discussed within at-risk FTD, therefore further research will be crucial in understanding this within this group in order to safeguard individuals and ensure suitable support is in place. Further work is needed to integrate tailored psychological support interventions such as that outlined in Chapter 5, within predictive testing services, and reliably identify those individuals who require additional support e.g. using the GPRI*plus* questionnaire as described in Chapter 3. This further work is important to ensure a well-integrated and connected service and reduce the frustration felt by patients with regards to a disconnect between different aspects of their care.

7.5.4. Conclusions

Overall, the predictive testing experiences presents a number of challenges, both from the perspective of healthcare professionals in terms of determining how to manage more difficult predictive testing scenarios, and also from the patient perspective. Data obtained from qualitative interview regarding the predictive testing experience suggested a number of areas in which the patient experience may be improved. These were, management of expectations, accessibility and integration of psychological support, individualisation of the counselling process and management of administrative issues. Recommendations outlined provide additional guidance to that currently used for HD, providing insight and information on important topics to cover when counselling those at-risk of fFTD, and providing signposting to services such as RDS and AFTD that can offer additional support. Findings highlighting the need for psychological support during the predictive testing process support findings reported in Chapter 3 and 4 and suggest that due to current guidelines being designed for HD, this protocol is not followed consistently across services. Therefore, the FTD-specific protocol outlined here has important implications for predictive testing experience in fFTD. The use of these guidelines will hopefully provide improved confidence to those counselling individuals at-risk of fFTD, providing them with the resources required to provide comprehensive counselling. In turn, I hope that this will improve the experience of predictive testing for patients. Future integration of predictive testing with tailored psychological interventions as outlined in Chapter 5 will also ensure a more well-rounded, informational and supportive experience.

Chapter 8. Investigating autistic traits and schizotypy in the presymptomatic phase of FTD

8.1. Chapter overview

Previous chapters within this thesis have explored affective problems in at-risk FTD, however there are also a number of neuropsychiatric and developmental features observed quantitatively in symptomatic FTD, and anecdotally in presymptomatic FTD. These features include overt psychiatric features such as hallucinations and delusions, along with more subtle problems with social skills, communication and emotional expression. Understanding the association of such features with the presymptomatic phase of FTD is important in characterising the FTD prodrome and in ensuring the suitability and accessibility of psychological intervention to improve wellbeing in this group. Therefore, this chapter describes a small exploratory study which is the first of its kind in FTD, aiming to investigate broad autism phenotype and schizotypal traits in presymptomatic FTD mutation carriers, including the association with proximity to symptom onset.

8.2. Introduction

The frontotemporal dementias exhibit wide phenotypic heterogeneity, including the presence of neuropsychiatric features in around 46% of mutation carriers, particularly within *C9orf72* expansion carriers (Ducharme et al., 2017; Samra et al., 2023). These neuropsychiatric features can include hallucinations, delusions and paranoia and often lead to a misdiagnosis of late-onset schizophrenia or psychosis (Ducharme et al., 2020). These symptoms in FTD can be categorised into three domains; affective symptoms, 'psychotic' symptoms, and 'other' symptoms including agitation, irritability and hypersexuality corresponding to the core behavioural features of bvFTD (Samra et al., 2023). Neuropsychiatric features have been reported most frequently in *C9orf72* symptomatic mutation carriers (Snowden et al., 2015), with evidence of more frequent and severe visual, auditory and tactile hallucinations, and delusions, in *C9orf72* compared to *GRN* and *MAPT* mutations (Samra et al., 2023). Less commonly there is also evidence of neuropsychiatric features within other mutations. Schizophrenia and visual hallucinations have also been reported in *GRN* (Momeni et al., 2010; Shinagawa et al., 2014) and altered sense of humour in occurs more frequently in *MAPT* compared to other mutations (Samra et al., 2023).

8.2.1. Neuropsychiatric features prior to FTD symptom onset

Neuropsychiatric features may not be limited to the symptomatic phase of FTD. There is a growing body of evidence to suggest the presence of these features, although less frequent and severe, in prodromal, and asymptomatic mutation carriers (Samra et al., 2023), preceding typical FTD symptom onset by one to 30 years (Kaivorinne et al., 2013; Kertesz, 2009; Shinagawa et al., 2015) . A recent international cohort study found neuropsychiatric symptoms occurring in 18% asymptomatic mutation carriers, 71% of those in the prodromal phase of FTD and 89% of those with a symptomatic diagnosis of FTD, with highest frequency in *C9orf72*, followed by *MAPT* and then *GRN* (Samra et al., 2023). Within the prodromal stage of FTD, anxiety, depression, irritability, impaired sleep, visual hallucinations, agitation, euphoria, aberrant motor behaviour, hypersexuality and altered sense of humour are all observed significantly more frequently compared to controls (Samra et al., 2023).

8.2.2. Is there a developmental element to fFTD?

Although the link between psychiatric symptoms and frontotemporal dementia has been a source of interest for over 20 years, the mechanisms behind it remain unclear (Gregory et al., 1998). Similarly, it remains to be understood why FTD symptoms onset at a particular point in adulthood, despite the presence of pathogenic mutations from birth. The question has been posed as to whether there may be a developmental element to the disease, particularly in *C9orf72*. Currently there have been no studies involving children at-risk of FTD, therefore data on this is limited, however brain atrophy has been identified among *C9orf72* mutation carriers up to 20 years prior to disease onset, suggesting changes occurring within the brain long before FTD symptoms occur (Rohrer et al., 2015). Further to this hypothesis, Lulé et al., (2020) found that presymptomatic *C9orf72* carriers demonstrated verbal fluency deficits in comparison to *SOD1* carriers and non-carriers. These deficits were significantly associated with changes in white matter structure in the inferior frontal and orbitofrontal areas, independent of age or expected time to symptom onset. This led them to suggest a potential developmental disorder in *C9orf72* carriers due to an association suggested between cognition, white matter alterations and early CNS development and the significant role that the *C9orf72* protein may potentially play in CNS development (Kiernan et al., 2019; Luu et al., 2011; Yeh et al., 2018). There is also evidence in support of a neurodevelopmental model of schizophrenia, with studies suggesting potential genetic associations which may disrupt developmental processes and in turn lead to psychotic symptoms (Fatemi & Folsom, 2009). This developmental hypothesis may therefore provide an explanation for the early changes observed in prodromal and even presymptomatic FTD, suggesting that there may be associations with developmental disorders such as autism spectrum disorder (ASD) and psychiatric disorders however further exploration is needed.

8.2.3. The relationship between FTD and developmental disorders

ASD is a neurodevelopmental disorder defined by social and communication differences and ritualistic, repetitive behaviours (Hurley et al., 2007). As stated by Devenney et al., (2018), many of the characteristic features of ASD overlap with those

deficits observed in FTD, such as impaired executive functioning, language and social cognition differences, and apathy, with key distinctions being the progressive changes in functioning observed in FTD, and the developmental nature of ASD vs adult-onset nature of FTD. Studies have also found autism to be highly heritable, Folstein and Rutter (1977) described a collection of milder autistic traits, bearing resemblance to the characteristic features of autism in non-autistic relatives of autistic individuals. These differences in social skills, communication ability and personality traits are known as the broad autism phenotype (BAP). Social traits characteristic of the BAP include decreased interest in reciprocal social interaction and focus on special interests within conversation (Gerdts & Bernier, 2011). Personality traits refer to 'aloofness', restricted emotional expression, rigidity and difficulty adjusting to change, while communication abilities refer to appropriate communication in social situations, or pragmatic language (Gerdts & Bernier, 2011). These BAP traits map onto to the three core domains of ASD as outlined by the DSM IV (Bell, 1994); social difficulties, stereotyped-repetitive behaviours and social language differences. The overlapping of BAP and neuropsychiatric features observed in symptomatic FTD, and family members, may suggest the presence of BAP traits in early FTD, maybe even in the presymptomatic phase.

Increased prevalence of developmental disorders such as ASD have been found in *C9orf72* probands (43% compared to 10% in non-*C9orf72* families, Devenney et al., 2018). However as this study utilised retrospective family history interview and did not carry out DNA sequencing, it is unclear whether such findings were associated with gene carriership (Devenney et al., 2018). Another theory, aside from the developmental hypothesis outlined above, may be that the increased prevalence of psychiatric disorders within these families may be attributed to the unique stresses of growing up either with a symptomatic parent or within a family at-risk of FTD, likely witnessing the disease progress in family member(s). Devenney argues that autism spectrum disorder (ASD) and FTD should be more closely studied as the triad of behavioural changes in ASD including impaired social cognition, language and obsessive or repetitive behaviours, mirrors common changes seen in those affected by FTD, however there has been no research on this to date.

8.2.4. The relationship between FTD and psychiatric diagnoses

In addition to the association with developmental disorders, psychiatric diagnoses have been also found to have increased prevalence in *C9orf72* kindreds, including psychotic disorders and schizophrenia (Devenney et al., 2018). Primary psychiatric diagnoses such as bipolar disorder and schizophrenia have also been identified in prodromal FTD mutation carriers, which resolved upon FTD symptom onset (Block et al., 2016; Gregory, 1999). Schizophrenia has many characteristics overlapping with the neuropsychiatric symptoms in FTD, such as affective symptoms, diminished emotional expression, psychotic symptoms including hallucinations and delusions, changes in motivation, altered cognition, executive functioning, attention and sleep (Patel et al., 2014). Mild and subclinical, schizophrenia-like symptoms have long been described in individuals prior to a clinical diagnosis, and in relatives of those with a schizophrenia diagnosis (Bleuler, 1950). This is now referred to as schizotypy or schizotypal traits. Schizotypy refers to personality characteristics and interpersonal difficulties which occur on a continuum with schizophrenia and may be suggestive of a vulnerability for schizophrenia (Matthews, 2012; Porac, 2016). These traits occur within the general population and include unusual perceptual experiences, odd beliefs, unusual speech, social anxiety, paranoia, and in isolated cases, psychotic symptoms (Walter et al., 2016). Schizotypy is also thought to be heritable, due to traits found in relatives of individuals with schizophrenia, however there is also increased prevalence of schizotypal traits within genetic conditions (Walter et al., 2016).

Taken together, the hereditary nature of ASD and schizotypy, and increased prevalence alongside psychiatric diagnoses in prodromal FTD and *C9orf72* family members suggests the presence of a relationship that may explain the presence of such features in FTD, however this is yet to be understood. As outlined above, neuropsychiatric symptoms are common in FTD, particularly within the *C9orf72* expansion. Many of the neuropsychiatric symptoms typically observed in FTD also overlap with those of ASD and psychiatric disorders such as schizophrenia and may be observed as an increased prevalence of subclinical traits within this population. Anecdotally, while working in fFTD, I observed that some presymptomatic individuals displayed characteristics qualitatively similar to ASD and schizotypy such as reported

difficulties with social interaction, rigidity, executive functioning difficulties and odd perceptual experiences. This felt particularly evident in those at-risk of *C9orf72,* which was unsurprising given the neuropsychiatric features observed in some symptomatic *C9orf72* carriers. I also observed when taking family histories, that the *C9orf72* group had increasing ASD diagnoses in young people, as well as historic 'adult-onset' schizophrenia diagnoses in mutation carriers who often deceased at an early age, indicating a likely psychiatric-led FTD presentation. The literature reported here suggests that there may be an association between developmental and psychiatric disorders, and FTD, and this thought was catalysed by Devenney et al., (2018) findings of increased prevalence of ASD and psychiatric diagnoses in *C9orf72* kindreds. However as, aside from the work by Devenney et al., there is such limited literature on psychiatric and developmental features in presymptomatic FTD, it was clear that further exploration was necessary. In particular, by investigating subclinical traits, this may identify a clearer picture of such features in those at-risk of fFTD. Therefore, this study aims to explore the presence of schizotypal and BAP traits in individuals within the presymptomatic phase of FTD. Should an association exist between fFTD, ASD and schizotypy, there may be potential barriers for the implementation of psychological interventions in this population. For example, rigid thinking and strong preference for routine may pose additional challenges for people when engaging in psychological intervention aiming to change thought processes and increase flexibility in responding to emotions and difficult situations (Leung & Zakzanis, 2014) . Alexithymia, i.e. difficulty describing emotional experiences, is also not uncommon in ASD, which, if identified in this group, would be an important factor to consider when adapting and using intervention within this group, as much of the content presented in Chapter 5 involves noticing and naming of emotions (Pantazakos, 2023). As such, it is important to understand the presence or absence of such traits to make relevant adjustments and ensure appropriate accessibility (Pantazakos, 2023).

8.3. Methods

8.3.1. Participants

Participants were asymptomatic individuals recruited from UCL's local GENFI cohort at-risk of a known pathogenic mutation in *MAPT*, *GRN*, or an expansion in *C9orf72.* Ethical approval was granted by the University College London Hospital research ethics committee. As described in Chapter 2.2.1 all GENFI participants undergo genotyping to confirm their genetic status.

A number of responses were excluded due to unavailability of genetic information (BAPQ n=11 and sO-LIFE n=12). Several participants were also excluded due to symptomatic status (BAPQ n=7 and sO-LIFE n=5) as the symptomatic subgroup was too small for analysis. One individual at-risk of *TBK-1* was excluded because, as a single case of this mutation, their data and genetic status would be identifiable. Following exclusion of the above responses, there were 99 BAPQ and 96 sO-LIFE responses.

8.3.2. Study design and procedures

All participants underwent the standardised GENFI assessments as detailed in Chapter 2.2.1. In addition, participants completed two self-report measures of neuropsychiatric and developmental traits; the Broad Autism Phenotype Questionnaire (BAPQ) and Short Oxford-Liverpool Index of Feelings and Experiences (sO-LIFE). Informant report was also obtained for the BAPQ, however this is not included within this study due to a small sample size. Participants completed the BAPQ using pen and paper during their research visit and the sO-LIFE was completed online using Limesurvey (Limesurvey GmbH. LimeSurvey: An Open Source survey tool. LimeSurvey GmbH, Hamburg, Germany. URL http://www.limesurvey.org), either prior, during or within 12 weeks following the research visit. Data collection for this study began in May 2021 and continued until April 2023. Participants were followed up via email to provide missing data-points, or re-complete the questionnaire at a later date if there were extensive data missing, or over 12 weeks had passed since initial data was collected.

8.3.3. Materials

Broad Autism Phenotype Questionnaire (BAPQ)

The BAPQ (Hurley et al., 2007) is a 36-item questionnaire used to detect traits associated with the broad autism phenotype (BAP). Items ask participants to rate the frequency of each statement on a 6-point scale where 1 refers to a very rare occurrence and 6 indicates that the statement applies very often. A total score can be calculated for the BAPQ as well as categorisation by three 12-item subscales: aloof, pragmatic language and rigid. The BAPQ was designed to measure social personality, rigid personality and language differences, and subscales correspond to the DSM IV (Bell, 1994) domains of autism; social difficulties, stereotyped-repetitive behaviours and social language differences (Hurley et al., 2007). The aloof personality subscale refers to a lack of interest or enjoyment in social interaction, rigid personality is defined as little interest, or difficulty adjusting to change, and the pragmatic language subscale measures differences in the social aspects of language, resulting in communication difficulties, or problems holding a reciprocal and fluid conversation (Hurley et al., 2007). 80% sensitivity and specificity is reported for the total BAPQ score, with above 70% for all subscales and above 80% for two of three subscales (Hurley et al., 2007).

Short Oxford-Liverpool Index of Feelings and Experiences (sO-LIFE)

The sO-LIFE is an abbreviated 43 item version of the 104 item O-LIFE questionnaire, both of which have been validated as measures of schizotypal traits (Mason et al., 1995; Mason & Claridge, 2006). Items are designed to assess normal personality variation related to schizotypy rather than clinical symptoms of schizotypal personality disorder, making it suitable for use in this study (Polner et al., 2021). Items are assessed in terms of presence or absence. Both the sO-LIFE and full O-LIFE consist of four subscales: unusual experiences, cognitive disorganisation, introvertive anhedonia and impulsive non-conformity. The unusual experiences subscale (UE) contains 12 items and measures ‘positive schizotypy’ traits, i.e., the occurrence of odd perceptual experiences such as hallucinations, magical thinking and odd beliefs. Cognitive disorganisation (CD, 11 items) taps into attention and concentration difficulties, decision making and social anxiety. The impulsive non-conformity subscale (IC, 10 items) assesses impulsive, anti-social and eccentric behaviour. Finally,

introvertive anhedonia (IA, 10 items) refers to reduced enjoyment in social and physical sources of pleasure and avoidance of intimacy. This is thought to be associated with negative schizophrenia symptoms and negative schizotypy. Higher scores indicate increased expression of schizotypy. sO-LIFE has been shown to have high test-retest reliability across all subscales, good internal consistency across unusual experiences and cognitive disorganisation subscales, and convergent validity has been demonstrated by correlation with subscales measuring the same dimension (Polner et al., 2021).

FTD symptom severity

The Clinical Dementia Rating scale (CDR) plus National Alzheimer's Coordinating Centre FTLD component (CDR plus NACC FTLD) was carried out in accordance with the standardised GENFI assessment protocol in Chapter 2.2.1, as part of the clinical assessment. The CDR consists of six domains encompassing memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care. The NACC FTLD component includes the addition of behaviour and language domains (Knopman et al., 2008). Clinicians assess each domain, using semi-structured interview with the patient and an informant, on a five-point scale where 0 is no symptoms present, 0.5 is questionable or mild symptoms, 1 is mild impairment, 2 is moderate impairment and 3 is severe impairment (Miyagawa et al., 2020). Two scores are subsequently calculated. The sum total across all domains creates a sum of boxes score, while a global score can be calculated using published procedures (Knopman et al., 2008; Miyagawa et al., 2020). Global scores exist on the same five-point scale from 0-3. The CDR plus NACC FTLD has been found to successfully identify early FTD symptoms (Miyagawa et al., 2020).

8.3.4. Analysis

Statistical analysis was performed using STATA 16 software (16.1, StataCorp LLC, College Station, TX). Histograms and Shapiro-Wilk tests were used to determine whether distribution of the data was normal for BAPQ and sO-LIFE total scores, as well as for each subscale.

8.3.4.1. Demographics

Statistical differences between mutation status groups were assessed for each demographic characteristic. Independent sample t-tests and Mann-Whitney U tests measured differences between mutation status groups and age, years in education, years to parental age at onset and CDR NACC FTLD sum of boxes score. One-way ANOVA and Kruskal-Wallis tests measures differences between genetic groups (non-carriers, *C9orf72* mutation carriers, *GRN* mutation carriers and *MAPT* mutation carriers) for the above characteristics. Sex differences and FTLD global scores between mutation status groups were investigated using chi-squared tests.

8.3.4.2. Threshold and normative value analysis

Cut-off scores described by Hurley et al., (2007) provide thresholds for BAP diagnosis. Frequency of BAPQ scores above these thresholds were computed. Chi squared tests were used to compare the frequency of BAPQ scores above and below threshold levels, between mutation carriers and non-carrier controls, and between gene groups (non-carrier controls, *C9orf72* mutation carriers, *GRN* mutation carriers and *MAPT* mutation carriers).

As sO-LIFE does not have threshold levels, comparisons were computed based on mean scores reported within normative datasets for each subscale (Mason et al., 2005). Kruskal-Wallis tests were carried out to assess differences between mutation carriers, non-carriers and normative means, while Mann-Whitney U tests specifically looked at the difference in subscale scores between mutation carriers and normative values.

8.3.4.3. Comparing mean total scores between mutation carriers and non-carriers

Mann Whitney U tests were used to investigate differences in BAPQ and sO-LIFE scores between mutation status groups (mutation carriers vs non-carriers), due to non-normally distributed data. This was replicated for each subscale.

8.3.4.4. Linear regression

Separate linear regression models were conducted to analyse the difference in BAP and schizotypal traits between genetic groups and compared to non-carrier controls, with test score as the dependent variable and gene group included within the model. Sex and FTD symptom severity (using the CDR plus NACC FTLD) were included as covariates in the model. Sex differences have been reported within the literature describing each measure (Hurley et al., 2007; Mason et al., 2005; Sasson et al., 2013), and FTD symptom severity was used as an indicator of proximity to, or progression of FTD symptoms.

For those measures where residuals were not normally distributed, bootstrapping was used with 2000 replications. The assumptions of linear regressions (normality of residuals, linearity, homoscedasticity, little or no multicollinearity, independence and appropriate model specification) were tested and fulfilled. Exploratory post-hoc pairwise comparisons were also computed to allow further insight into any significant associations between gene groups.

8.3.4.5. Correlational analyses

Spearman correlations were carried out to assess the relationship between BAPQ total and subscale scores, sO-LIFE total score and subscale score and indicators of proximity to onset: CDR plus NACC FTLD global scores, years to parental age at onset and age.

8.4. Results

8.4.1. Demographic characteristics

Thirty-four non-carrier controls and 62 mutation carriers participated in the sO-LIFE questionnaire, while 33 non-carriers and 66 mutation carriers responded to the BAPQ. Mutation carriers were further subdivided by the affected gene within their family (Table 42). See Table 41 for further demographic information. Five participants included within BAPQ analysis had one missing data point, as did two participants for sOLIFE. This data was not removed for analysis due to the minimal effect that one missing data-point had on each participant's overall scores.

Table 41 - Demographic characteristics for BAPQ and so-LIFE participants

	BAPQ	**sO-LIFE**
N	99	96
Gender (F : M)	53 : 46	52 : 42
Mean years in education Range	16 (2.5) 10-24	16 (2.5) 10-24
Mean age (SD) Range	43 (10.8) 22-75	43 (11.8) 23-76
Mean parental AAO Range	56 (8.6) 34-75	56 (8.4) 34-75
Mean years to parental AAO Range	15 (10.7) -11-35	14 (11.0) -22-35

Table 42 - Number of participants and distribution by sex, across genetic mutation groups for BAPQ and sO-LIFE

	BAPQ		**sO-LIFE**	
	Total N	F : M	Total N	F : M
Non-carriers	33	14 : 19	34	16:18
C9orf72 mutation carriers	37	21 : 16	34	20:14
GRN mutation carriers	13	8 : 5	13	8:5

MAPT mutation carriers	16	10 : 6	15	10:5

8.4.1.1. BAPQ

Demographic characteristics of age (p=0.09), years to parental age at onset (p=0.69), years in education (p=0.27) and sex (p=0.12) were not significantly different in mutation carriers compared to non-carriers. No significant differences were also observed between genetic groups (age p=0.39, years in education p=0.71, and sex p=0.45). There was a significant difference in years to parental age at onset p<0.05, with the *MAPT* group being significantly closer to parental age at onset (mean [M] = 7.80, standard deviation [SD] = 10.34) compared to non-carriers (M=15.17, SD=12.13), *C9orf72* (M=15.61, SD=8.80) and *GRN* (M=18.00, SD=9.83). There were no significant differences in CDR plus NACC FTLD sum of boxes scores between mutation status groups (p=0.25), however there was a significant difference between genetic groups (p=0.02). For CDR plus NACC FTLD global score, there were no significant differences between mutation carriers and non-carriers (p=0.11), however there was a significant difference between genetic groups (p<0.01). For sum of boxes and global scores across groups see Table 43.

8.4.1.2. sO-LIFE

No significant differences were identified between mutation carriers and non-carriers, and between genetic groups for years to parental age at onset (p=0.72, p=0.16), years in education (p=0.16, p=0.56) and sex (p=0.18, p=0.56). CDR plus NACC FTLD sum of boxes scores were also not significantly different between mutation status and genetic groups (p=0.24, p=0.06). There were no significant differences observed between mutation carriers and non-carriers for CDR plus NACC FTLD global score (p=0.36), however there was a significant difference between genetic groups (p=0.04). For sum of boxes and global scores across groups see Table 44. There was a significant difference in age between mutation status groups (p=0.03), with the non-carrier group being significantly older (mean [M]=47.56, standard deviation [SD]=14.38) than mutation carriers (M=41.26, SD=9.48). However, age was not significantly different by mutation groups (p=0.21).

8.4.1.3. FTD symptom severity

Participants were assigned a CDR plus NACC FTLD global score of 0, 0.5, 1, 2 or 3 based on the outcome of their assessment. For BAPQ participants 36% mutation carriers and 55% non-carriers received scores of 0 and 52% and 30% respectively received scores of 0.5. A small percentage of individuals received scores of >1 without having received a symptomatic diagnosis (12% and 15%). For sO-LIFE, 33% mutation carriers and 53% non-carriers scored 0, while 60% and 41% respectively scored 0.5. Again, a small percentage of 5% and 6% scored >1. CDR plus NACC FTLD sum of boxes mean scores, and frequency distribution across scoring categories are represented in Table 43 for BAPQ and Table 44 for sO-LIFE.

Table 43 - CDR plus NACC FTLD mean and standard deviation of sum of boxes scores, and frequency of global score categories for BAPQ participants across each genetic group

	BAPQ				
	SOB M (SD)	Frequency of global scores			Total N
		0	0.5	>1	
Non-carriers	0.76 (1.20)	18	10	5	33
All mutation carriers	0.82 (0.78)	24	34	8	66
C9orf72 mutation carriers	0.47 (0.52)	17	19	1	37
GRN mutation carriers	0.81 (0.13)	5	3	5	13
MAPT mutation carriers	1.07 (0.73)	2	12	2	16

Table 44 - CDR plus NACC FTLD mean and standard deviation of sum of boxes scores,

and frequency of global score categories for sO-LIFE participants across each genetic group

	sO-LIFE				
	SOB M (SD)	Frequency of global scores			Total N
		0	0.5	>1	
Non-carriers	0.62 (1.05)	18	14	2	34
All mutation carriers	0.69 (0.76)	22	37	3	62
C9orf72 mutation carriers	0.47 (0.52)	15	19	0	34
GRN mutation carriers	0.81 (0.13)	5	6	2	13
MAPT mutation carriers	1.07 (0.73)	2	12	1	15

8.4.2. BAPQ

8.4.2.1. BAPQ threshold analysis

There were no significant differences in frequency of scores above and below BAPQ cut-offs between mutation carriers and non-carriers (p=0.18). Cohen's d was calculated as a measure of effect size (d=0.03), and indicated a small effect. There were also no significant differences between non-carriers, *C9orf72* mutation carriers, *GRN* mutation carriers and *MAPT* mutation carriers (p=0.08).

8.4.2.2. BAPQ score comparisons between mutation carriers and non-carrier controls

No significant differences were observed between mutation carriers and non-carriers for BAPQ total score (p=0.89) and all subscales (aloof p=0.85, pragmatic language p=0.86 and rigidity p=0.41).

8.4.2.3. BAPQ scores between genetic groups

There were no significant differences in BAPQ total scores between genetic groups, as well as when compared to non-carrier controls. However, there was a significant

effect of CDR plus FTLD NACC sum of boxes (p=0.02). Again, there were no significant differences in aloof subscale scores between genetic groups and compared to controls, however there was a significant effect of both sex (p=0.02) and CDR plus FTLD NACC sum of boxes (p<0.01). No significant differences were found on the pragmatic language subscale between genetic groups, however again, there was a significant effect CDR plus FTLD NACC sum of boxes (p<0.01). There were no significant differences between genetic groups on the rigid subscale.

8.4.2.4. Correlation of BAPQ scores with measures of FTD symptom severity and proximity to onset

There was a positive correlation between CDR plus NACC FTLD global score and BAPQ total score (rho= 0.22, p=0.03), as well as pragmatic language score (rho= 0.23, p=0.02).

8.4.3. sO-LIFE

8.4.3.1. Comparisons to normative values in the literature

There were no significant differences between female mutation carriers and non-carriers, compared to mean scores reported in the general population for all subscales (UE p=0.64, CD p=0.77, IA p=0.94, IC p=0.75). There were also no significant differences between male mutation carriers and non-carriers, compared to mean scores reported in the general population for all subscales (UE p=0.36, CD p=0.77, IA p=1.00, IC p=0.47). When mutation carriers were compared only to normative means, there were also no significant differences for females (UE p=0.27, CD p=0.93, IA p=0.71, IC p=0.67) or males (UE p=0.20, CD p=0.67, IA p=0.77, IC p=0.78).

Table 45 - Mean and standard deviation scores for s-OLIFE subscales, including those reported in a normative data sample (Mason et al., 2005)

	Unusual experiences		**Cognitive disorganisation**		**Introvertive anhedonia**		**Impulsive non-conformity**	
	Females M (SD)	Males M (SD)	Females M (SD)	Males M (SD)	Females M (SD)	Males M (SD)	Females M (SD)	Males M (SD)
Values reported in a normative sample (Mason et al., 2005)	3.39 (2.92)	3.17 (2.92)	4.44 (2.88)	4.28 (3.00)	2.40 (1.98)	2.80 (2.16)	2.59 (1.99)	2.70 (2.59)
Non-carriers	1.94 (2.29)	1.22 (1.63)	2.94 (2.91)	2.94 (2.73)	2.50 (1.67)	2.72 (1.78)	2.06 (2.08)	2.06 (1.76)
All mutation carriers	1.79 (1.70)	1.38 (1.44)	3.42 (2.74)	3.58 (3.45)	2.5 (1.66)	2.96 (1.83)	2.05 (1.74)	2.63 (2.08)
C9orf72 mutation carriers	1.55 (1.61)	1.29 (1.38)	2.00(2.10)	3.43 (2.85)	2.15 (1.18)	3.14 (1.96)	1.55 (1.23)	2.21 (2.15)
GRN mutation carriers	1.38 (1.30)	1.60 (1.82)	5 (1.93)	4 (4.64)	2.50 (1.20)	2.2 (1.10)	1.75 (1.28)	3.2 (1.92)
MAPT mutation carriers	2.6 (2.01)	1.40 (1.52)	5 (3.02)	3.6 (4.51)	3.20 (2.53)	3.20 (2.17)	3.3 (2.36)	3.2 (2.17)

8.4.3.2. sO-LIFE score comparisons between mutation carriers and non-carrier controls

A Mann Whitney U test revealed no significant differences on sO-LIFE total score between mutation carriers and non-carriers (*p*=0.46). There were also no significant differences between mutation carriers and non-carriers across all subscales (UE *p*=0.50, CD *p*=0.45, IA *p*=1.00, IC *p*=0.42).

8.4.3.3. sO-LIFE scores between genetic groups

There were no significant differences in sO-LIFE total score for mutation groups compared to non-carriers. Exploratory pairwise comparisons between genetic groups also revealed no significant differences.

No significant differences were observed between mutation groups for the unusual experiences or introvertive anhedonia subscales. Although there were no significant differences in mutation groups compared to non-carriers for the cognitive disorganisation subscale, pairwise comparisons between genetic groups revealed a significant difference between *GRN* mutation carriers and *C9orf72* mutation carriers, with *GRN* mutation carriers scoring significantly higher (*p*=0.04, MD=1.82). There was also a significant difference between *MAPT* mutation carriers and non-carrier controls for the impulsive non-conformity subscale (*p*=0.05), with *MAPT* mutation carriers scoring higher than controls (MD=1.31). Pairwise comparisons between mutation groups also revealed significantly higher scores in *MAPT* mutation carriers compared to *C9orf72* mutation carriers (*p*=0.02, MD=1.50).

8.4.3.4. Correlation of sO-LIFE scores with measures of FTD symptom severity and proximity to onset

There was a significant positive correlation between cognitive disorganisation and CDR plus NACC FTLD global score (rho=0.20, *p*=0.05). Significant negative correlations were also found between age and sO-LIFE total score (rho= -0.33, *p*<0.01), unusual experience score (rho= -0.27, *p*=0.01) and cognitive disorganisation score (rho= -0.23, *p*=0.02). There was a further significant positive correlation between the unusual experiences subscale and years to parental age at onset (rho= 0.26, *p*=0.02).

8.5. Discussion

This chapter aimed to explore the presence of autistic traits relating to the broad autism phenotype, and schizotypal traits in presymptomatic FTD mutation carriers. Assessment against FTD symptom severity aimed to understand whether such traits are associated with progression towards the prodromal disease phase, with the wider goal of further understanding the interaction between neuropsychiatric and developmental symptoms and diagnoses in this population, and how this may affect psychological intervention.

8.5.1. Summary of main findings - BAPQ

Frequency of clinically significant BAPQ scores were not significantly different between mutation carriers and non-carriers, suggesting BAP caseness is not associated with mutation carriership. This is supported by the lack of significance found regarding BAPQ total scores, subscale scores and mutation carrier status. However, this may be due to the non-carrier group representing within-family controls. The limited literature in this area suggests that ASD diagnoses are more prevalent in relatives of mutation carriers (Devenney et al., 2018), therefore the lack of significant differences demonstrated here does not rule out the possibility of an association between BAP traits and growing up in a family affected by FTD. However, BAPQ and subscale scores were also not different between genetic groups, suggesting that the BAP did not capture those features observed in fFTD that are qualitatively similar to autism. In addition, based on the effect size reported here, a total of 214 participants were needed to detect a significant difference with a power of 80%, therefore the analysis was underpowered. This means that the sample size was not sufficient to detect true effects in the data. Therefore, this analysis should be replicated in future with a larger sample size.

There was, however, a significant association between BAPQ subscales and FTD symptom severity, supported by significant positive correlations for total and pragmatic language scores. This may be suggestive of an association with FTD symptom severity, rather than mutation status. The significant overlapping features of the BAP and FTD may therefore be captured by both measures. The significant association

between pragmatic language and FTD symptom severity may provide evidence to suggest that this is one overlapping feature between the BAP and FTD affected by development within an FTD family. Social cognitive impairment has been documented in FTD (Russell et al., 2020), therefore this finding may suggest that this impairment may also be reflected in the social elements of language and conversation. Language deficits in FTD syndromes may therefore disguise this social element to language, with impairment in social cognition also impacting fluidity and reciprocity of conversation and communication difficulties. FTD symptom scales may therefore also tap into these social cognitive elements when assessing language impairment. Further investigation amongst symptomatic individuals will be important in exploring this further.

8.5.2. Evaluation of the BAPQ in FTD

The BAPQ was selected for use in this study due to its intended application and validity for identifying subclinical traits of the BAP, rather than directly assessing autism symptomatology. The BAPQ has also been found to outperform these other more diagnostic tools when identifying BAP traits, with subscales found to have high internal consistency, and reflect the broad nature of the BAP (Ingersoll et al., 2011; Sasson et al., 2013). Another advantage of the use of the BAPQ within FTD, is the presence of well-validated self and informant report. The diminished insight observed in FTD may make self-report unreliable, therefore although not utilised in this study, the use of informant report may allow for more accurate measurement of such symptoms in those who lack insight. This also may provide the opportunity to study such traits within the symptomatic population, many of whom may no longer be able to complete self-report measures. The use of both self and informant report measures may also allow for a better understanding of insight and perception of neuropsychiatric symptoms, which could be particularly useful in the early disease stages. The BAPQ is short and simple to administer and does not require clinical expertise, unlike other measures of BAP such as the Broader Phenotype Autism Symptom Scale (BPASS), that are lengthy and require specialist training to deliver (Hurley et al., 2007; Sung et al., 2005). While the BAPQ may be a measure well-suited for use in this context, further work is needed to evaluate the presence of the BAP in FTD. Although the BAPQ subscales were designed to map onto core features of autism, it may be that they do not accurately

capture those traits that overlap with similar symptoms observed in FTD, that we qualitatively categorise as autism-like, aside from pragmatic language as discussed above.

8.5.3. Summary of main findings – sO-LIFE

No significant differences were observed in sO-LIFE subscale scores, in comparison to those found in normative data, suggesting that schizotypal traits were present at a comparable rate to that within the general population. This, alongside the lack of significant differences between mutation carrier groups, tentatively suggests that, as with the BAPQ, FTD mutation carriership is not associated with schizotypal traits, despite the many overlapping features observed in FTD.

Cognitive disorganisation was found to be elevated in *GRN* mutation carriers compared to *C9orf72* mutation carriers. Cognitive disorganisation also increased as FTD symptom severity increased. Cognitive disorganisation refers to attentional and concentration difficulties, as well as impairments in decision-making. Taken together, this may suggest that traits relating to cognitive disorganisation may be characteristic of early FTD symptom progression in *GRN* carriers, distinct to that in *C9orf72*.

Impulsive non-conformity was also raised in *MAPT* mutation carriers compared to both non-carriers and *C9orf72* mutation carriers. Impulsive non-conformity, as the name suggests, refers to impulsive and anti-social behaviour, features commonly indicative of FTD symptom onset. Therefore, this may be indicative of sub-clinical prodromal symptoms of FTD, specific to the *MAPT* mutation group.

As proximity to parental age at symptom onset increased, the occurrence of unusual perceptual experiences including hallucinations and delusions increased. As unusual experiences were not associated with mutation carriership or FTD symptom severity, this may be tapping into the symptom searching and anxiety regarding symptom onset in individuals at-risk. Many individuals in this study were not aware of their mutation status, and these individuals, along with known mutation carriers often report searching for signs of symptom onset. Symptom searching is likely to increase as individuals approach the age at which their parent became unwell, as this is often reported as a

benchmark in many people's minds (as reported in Chapter 4). As the search for symptoms and symptom related anxiety increases, these individuals may be more prone to noticing these odd perceptual experiences.

8.5.4. Clinical implications

The suggestion of subclinical autistic and schizotypal traits in presymptomatic FTD posed concern regarding its implication on psychological intervention in this group. For example, the social communication deficits and lack of affective expression seen in FTD, if experienced within the presymptomatic and prodromal phases, may pose challenges regarding engagement in an intervention, and utility of peer support. In turn this may increase feelings of 'uniqueness' and isolation as reported in Chapter 4. Similarly, traits relating to rigidity, as commonly observed in *MAPT*, could present challenges regarding certain psychological models focusing on psychological flexibility, such as ACT. These traits could also pose difficulties for engagement with alternative coping mechanisms and therapeutic techniques. Therefore, the lack of overwhelming significant findings, have positive clinical implications in terms of the suitability and accessibility of psychological intervention. As discussed throughout this thesis, psychological intervention in at-risk FTD is important in facilitating psychological adjustment to risk and genetic information, in improving wellbeing and to support throughout clinical trials. As such the minimisation of barriers regarding psychological intervention is an important factor in the development of such interventions. The lack of significant findings in this study therefore suggest that psychological intervention may be applied without adjustment for these traits. Although the presence of such traits at a frequency relative to the general population suggests that adjustment may be required on an individualised basis.

8.5.5. Limitations

As this was an exploratory study and the first study to explore such traits in fFTD, there are several limitations to note. Firstly, as discussed previously within this section, the lack of symptomatic data limits the conclusions that can be drawn from these findings, particularly regarding associations with FTD symptom severity. In order to determine whether these traits are different to those observed in presymptomatic FTD, or simply

not present, first it is necessary to ascertain whether these traits reflect those seen in symptomatic FTD. However, studying the symptomatic group is challenging due to lack of insight and capacity to participate in research, therefore although I initially hoped to analyse these traits in symptomatic individuals, the sample size was too small to be included. Secondly, sample sizes were small when stratified by genetic group, particularly for *GRN* and *MAPT*, meaning that findings regarding mutation specific features may not be reliable. Thirdly, there are issues to explore regarding the use of self-report measures in this study. Humans are often not accurate observers of their own behaviour and personal experience, this is supported within the validation of the BAPQ, with sensitivity and specificity of self-report scores consistently lower than informant ratings (Hurley et al., 2007). Hurley specifies that there were implications of self-report regarding the sensitivity for pragmatic language difficulties and specificity for rigidity and overall BAP score. In addition to this, the diminished insight observed in FTD may affect self-report measures. A reduction in insight may therefore lead to inaccuracy on self-report measures. As such the reliance on self-report is a limitation of this study. Finally, the use of family controls may obscure effects within the data. The limited literature in this area suggests that family members of mutation carriers and individuals with ASD and schizophrenia are at increased risk of BAP and schizotypy. Therefore, further comparison against non-family controls is required to draw conclusions regarding the effects of carriership and family membership.

8.5.6. Future work

As stated above, this work constitutes a small exploratory study investigating autistic and schizotypal traits. Therefore, significant future work is required to develop a comprehensive understanding of the neuropsychiatric and developmental features of presymptomatic FTD. Following Samra and colleague's recent work there are a number of additional neuropsychiatric features identified in this group that may warrant exploration, including impaired sleep, irritability and agitation, as well as visual hallucinations unrelated to schizotypal traits (Samra et al., 2023).

Further research involving larger sample sizes, symptomatic participants and non-family controls are needed to understand whether the traits measured by BAPQ and

sO-LIFE questionnaires reflect the neuropsychiatric and autism-like features observed in FTD. Future research may also evaluate the use of other similar measures within this group and may expand to include a range of other neuropsychiatric and developmental traits.

8.5.7. Conclusions

Overall, these findings, and lack thereof, suggest that the autism and schizotypy-like features observed in presymptomatic FTD, and overlapping features of BAP, schizotypy and overt FTD symptoms, are largely not captured by BAPQ and sO-LIFE measures. The lack of significant differences between mutation types and those subscales that bare resemblance to FTD mutation profiles, for example rigidity in *MAPT*, suggest that either these measures tap into different elements to those that are expressed in FTD, or that they simply are not experienced in the presymptomatic or prodromal stages. Similarly, the association between pragmatic language and FTD symptom severity may be indicative of social cognitive interactions with language and communication in FTD. Therefore, further investigation within a symptomatic population is required to determine the presence and relationships between these factors throughout the FTD disease course. Cognitive disorganisation and impulsive non-conformity traits may be indicative of early mutation-specific prodromal symptoms, although further exploration is needed with larger sample sizes when stratified by mutation type. The lack of significant BAP and schizotypy traits found within this study has implications for psychological intervention for individuals at-risk, as it allows for future psychological intervention without need for additional adjustment or barriers experienced on the basis of these features.

Chapter 9. Discussion

9.1. Chapter overview

This final chapter will summarise and discuss the overall findings reported in this thesis, implications of these findings both clinically and within the wider field, general limitations, and future directions for research concerning understanding the at-risk lived experience and further development of psychological interventions, as well as genetic testing.

9.2. Summary of findings

The overarching aim of this thesis was to further understand the lived experience of individuals at-risk of fFTD, and develop tailored psychological intervention, as well as more appropriate genetic testing procedures, in order to improve this lived experience. This was achieved through the use of a variety of qualitative, quantitative and consensus methods. Quantitative and qualitative data regarding the feelings and experiences associated with living at-risk, support needs, and predictive testing experience were used throughout the process of developing an online ACT based intervention, following MRC guidelines for intervention development, and integrated with expert consensus recommendations to create comprehensive expert and patient recommendations for diagnostic and predictive testing in FTD.

9.2.1. The lived experience of being at-risk of fFTD

Despite clear challenges faced by those living with 50% genetic risk, there has been remarkably little research to understand the psychological implications, as well as the more general feelings and experiences associated with this. This is the case across all hereditary neurodegenerative diseases, but particularly FTD, with much extrapolated from inconclusive and contradictory findings in HD. The existing research has often focused on the experience solely of those who have had predictive testing and therefore only represents the minority of the at-risk population. Chapter 3 describes the application of the GPRI*plus* questionnaire to individuals at-risk of fFTD, including both those who had predictive testing (mutation carriers and non-carriers), as well as those whose status was unknown. This questionnaire was designed to investigate the demographic characteristics of the at-risk population, such as the age at which people learnt of their risk, the percentage of those who had genetic counselling and/or predictive testing and reasoning for and against predictive testing. The inclusion of standardised measures of depression and anxiety within this questionnaire aimed to quantify the psychological challenges associated with living at-risk, as well as the need for psychosocial referral. Here I found elevated incidence of depression and anxiety caseness, as defined by threshold levels in the literature, within those at-risk compared

to normative data samples of the general population, suggesting an increased likelihood of developing clinically significant levels of depression and anxiety while living at-risk. By including both the individual's knowledge of their genetic status (i.e., mutation carrier, non-carrier and unknown) and their biological mutation status, I was able to investigate both the effect of status perception, as well as the biological impact of mutation status on depression, anxiety and psychosocial risk. There was also a significant effect of status knowledge on anxiety and depression, with those who had predictive testing (known mutation carriers and known non-carriers), demonstrating increased anxiety and depression symptoms compared to those with unknown status. Suggesting that there is an association between predictive testing and mood symptoms, with a possible explanation for this being that those who choose to have predictive testing are a self-selected sample of individuals who are more prone to or affected by anxiety and depression. I also found a significant effect of both status knowledge and biological status on anxiety and depression severity, when stratified by genetic group. *C9orf72* mutation carriers were consistently less anxious, while *MAPT* mutation were significantly more anxious compared to other mutation groups. The different effects observed across mutation groups suggest that this effect was driven by biological factors associated with the disease profile of each mutation group, with knowledge of status confounding this effect in terms of increased anxiety amongst those who had predictive testing. Finally, 38% met criteria for psychosocial referral. This is the first study to evaluate the demographic characteristics of the at-risk population, and to evaluate depression, anxiety and psychosocial risk using known and biological status across genetic groups. As mood symptoms have recently been found within prodromal FTD (Samra et al., 2023), the findings within this chapter therefore provide important insight into the interaction between status knowledge and the biological effects of mutation carriership. In addition, regardless of the mechanism by which these mood symptoms are experienced, the proportion of at-risk individuals experiencing clinically significant mood symptom severity, as well as a high proportion of those meeting criteria for psychosocial referral, speaks to a need for psychological intervention and improved psychosocial support for this group. These findings provide a rationale for the development of an intervention for this group, however more information was required to understand the particular emotions and FTD-specific

challenges that may provide a focus for such intervention, as well as identifying specific support needs, barriers and facilitators.

In Chapter 4, I investigated this lived experience further using semi-structured qualitative interview to provide more rich and detailed information to further understand the nuances of the at-risk experience, with the aim for later use in intervention development. As there have been no prior studies investigating the wholistic experience of living at-risk of fFTD in mutation carriers, non-carriers and those with unknown status, I felt that it was particularly important that no key elements of the experience were lost due to the large amount of data gathered. Important themes generated regarding the feelings and experiences of living at-risk related to the complex range of emotions experienced. These ranged from low mood, fear and anxiety to relief and hope, underpinned by the uncertainty and isolation that the unique circumstance brings. Interestingly, end of life plans were discussed, including assisted dying plans, despite acknowledgement of the illegality in the UK. I hope that this finding, alongside raised levels of suicidal ideation reported in Chapter 3, opens up conversations regarding end-of-life care and suicidality within at-risk individuals in future. Coping mechanisms discussed also highlighted high experiential avoidance, both by overt avoidance through 'burying your head in the sand' and also through extensive planning for the future, sometimes even based on a perceived mutation status rather than a confirmed one. A lack of support was generally noted, and participants requested psychological support from professionals with an understanding of FTD. A lack of knowledge of FTD amongst healthcare professionals was also identified as a barrier and source of frustration when accessing mental health support via more traditional routes. In addition, participants expressed a need for more accessible information with regards to FTD and their risk. Barriers to support included a lack of understanding of FTD among professionals and the public and limited accessibility of support, while online support was noted as a facilitator. Participants were emphatic regarding their experience of peer support and noted the positive impact this made.

In Chapter 8 I further investigated this lived experience by exploring the presence of BAP and schizotypy traits in individuals at-risk of fFTD. As with Chapters 3 and 4,

intervention implementation was in mind regarding this study, as the presence of such traits may have created barriers for such intervention, therefore it was important to identify this at an early stage. In addition to this, this chapter aimed to investigate whether such traits may be associated with mutation carriership, and also with early signs of disease progression. In this chapter I found that BAP traits and BAP caseness were not associated with mutation carriership. However, there was evidence to suggest that there may be an association between FTD symptom severity and BAP, suggesting that there may be a number of overlapping features captured by both BAPQ and FTD symptom severity measures. The pragmatic language subscale was associated with FTD symptom severity, suggesting a potential interaction between the social cognitive elements of language, with language symptoms in FTD. Similar to the BAP, schizotypal traits were present at rates comparable to that reported within the general population, and, like the BAPQ, were also not associated with mutation carriership. However sO-LIFE cognitive disorganisation and impulsive non-conformity subscales demonstrated some significant differences between genetic groups, suggesting that such features may be associated with mutation-specific subclinical symptoms. Therefore, I was able to conclude that BAP and schizotypal traits were unlikely to create additional barriers for intervention implementation, however further research is required to understand the link between autistic and schizotypal traits, and FTD.

9.2.2. Intervention development

In Chapter 5 the above findings were used in the application of the MRC framework for complex intervention development, along with a review of the literature regarding psychological interventions in hereditary neurodegenerative disease at-risk populations. On review of the literature, it was noted that there were no interventions approved for use in this context, nor had any RCTs taken place. There were, however, a small number of studies piloting and feasibility testing mindfulness-based therapies, narrative therapy and cognitive-behavioural techniques, largely in those at-risk of HD. The findings reported above provided a rationale for intervention development, with Chapter 3 identifying elevated symptoms of depression and anxiety, as well as a need for psychosocial referral in over a third of those at-risk. While qualitative findings

reported in Chapter 4 allowed me to define key topics for the intervention to focus around, forming an outline of potential modules, as well as identifying key problems to overcome in delivery of the intervention. This information also allowed the definition of key intervention objectives, features necessary to achieve these objectives, as well as a programme theory to articulate potential theoretical approaches to the intervention, and outlining mechanisms by which it might be efficacious. Due to the lack of literature within related fields, and the evidence to suggest relative success of mindfulness-based therapies, I looked to the chronic illness literature and chose to take a novel approach by using ACT as the theoretical basis for the intervention design. This approach incorporates elements of mindfulness found to be successful in the limited literature existing in HD and FTD, as well as aiding acceptance and adjustment within chronic illness literature. I also incorporated a person-centred approach to intervention development to ensure the resource developed was focused on the population it intended to serve, and to allow the voices of the at-risk community to be heard. This was achieved by incorporating expert by experience and stakeholder review of structure, procedures and materials developed. An outline of a final intervention prototype is reported in Chapter 5, in preparation for feasibility assessment with a view to future RCT and eventual implementation within NHS clinical services.

9.2.3. Patient perspectives and expert recommendations for genetic testing in FTD

Finally, qualitative data regarding patient perspectives of predictive testing, as well as a Delphi consensus of experts in the field, were analysed and incorporated to form comprehensive recommendations for genetic testing in FTD. This built upon existing gold-standard recommendations used in HD (Craufurd et al., 2015; MacLeod et al., 2013) to provide additional context and information to aid the counselling process in FTD. In addition, expert recommendations for diagnostic testing outlined to whom testing should be offered, as well as clarifying procedures regarding less common predictive testing scenarios. Patient perspectives were incorporated to create suggestions for improvement regarding predictive testing procedures, including management of expectations, individualisation, emotional preparation, sensitive result disclosure and the importance of psychological support and follow-up. This final point

was emphasised throughout the patient experience and is also highlighted in MacLeod's protocol, however, reports of patient experience identified this as lacking in FTD, demonstrating the need for clinical guidelines specific to FTD.

9.3. Clinical implications and wider relevance of this work within the field

This work was underpinned by a strong focus on future clinical application, therefore there are several clinical and wider academic implications to explore. The rationale behind this PhD thesis began based on anecdotal evidence from discussions during research visits, that living at-risk was extremely psychologically challenging and people wanted support to manage this but were not able to access it. Here I provide evidence to support the hypothesis had by myself and many colleagues who work with this population, that there is both demand and clinical justification for psychological intervention. In order to obtain approval for the application of a psychological intervention within the NHS, empirical evidence is required to demonstrate the necessity and rationale, as well as feasibility, acceptability and efficacy of the intervention itself. Therefore, the elevated levels of anxiety and depression found within Chapter 3, as well as the proportion of participants meeting psychosocial referral criteria, provides a basis upon which this argument may begin to be built. Similarly, the systematic application of MRC complex intervention guidelines ensured development of a robust intervention grounded in theoretical and empirical evidence. Although further work is required prior to clinical implementation, this provides a solid foundation for the intervention, increasing the likelihood of future approval for use in NHS contexts.

In addition, within this thesis I provide a basis upon which non-specialist clinicians may further their understanding of the at-risk experience to improve their clinical care experience. Due to the lack of familiarity amongst many healthcare professionals regarding FTD, both the qualitative and quantitative data reported here provide useful and comprehensive context within which clinicians may further understand their patient's symptoms or experience. Further to this, as the intervention described in Chapter 5 is grounded within ACT, components of the intervention maybe adapted and applied by those familiar with the model, therefore providing psychologists or

counsellors with evidence, a framework and materials to inform their own intervention and practice with an at-risk client on an individualised basis. Additionally, genetic testing recommendations build upon the gold-standard used in HD to provide guidelines for application in FTD based on both expert and patient recommendations and perspectives. This provides clear guidelines for best clinical practice to those clinicians who may not be experienced in working with individuals at-risk of fFTD, improving confidence when counselling these individuals. In turn, one would hope that this would lead to an improved genetic testing experience for families affected by fFTD, and fewer barriers to accessing this care.

For the at-risk individual, I provide evidence to validate their lived experience. The identification of mood symptoms, as well as the themes described relating to elements of the at-risk 'journey', and the complex range of emotions described, may resonate with those who share this experience. This is particularly important as, as previously discussed, fFTD is considered rare and those who do not engage with or cannot access peer support commonly have not met anyone outside their own family at-risk of fFTD, therefore validation of the shared elements of this experience can be integral in reducing the feelings of isolation and 'uniqueness'. This validation may also have positive impacts in terms of acceptance of the often-confusing range of emotions experienced, as well as encouraging self-advocacy and support seeking, and providing a basis for increased self-compassion. Most importantly, this work moves towards providing improved access to support for the at-risk community in two ways; via psychological intervention specifically focused around their needs, and through an improved genetic testing experience. It is important to see the at-risk period as part of the wider dementia experience. Often these individuals fall outside the scope of dementia services due to the unique nature of hereditary dementias; they are young and currently well, and the symptoms they expect to experience do not reflect those seen in more common memory-led dementias. Therefore, the needs of such individuals are often overlooked as they fall outside the scope of these services, yet are too specific for general mental health services. However, as stated above and as evidenced in this work, the psychological impact on the individual is great. While no treatments exist for fFTD, it is important to emphasise and facilitate living well during the at-risk period to maximise wellbeing and quality of life prior to potential symptom

onset. Similarly, as research in FTD moves towards clinical trial phases involving presymptomatic individuals, it is likely that this experience will become more complex, emotional and potentially turbulent. Furthermore, it is possible that clinical trial developments will lead to more people having predictive testing to meet eligibility criteria, however this information cannot be reversed and success at clinical trial is not guaranteed. Currently clinical trials underway in presymptomatic FTD do not provide psychological support to their participants. As this new era of research and clinical trials is on the horizon, this work is integral to build the foundation for providing evidence-based psychological support for this group, to aid management of the challenging paradoxical emotions that may arise.

There are also wider clinical implications for other hereditary rare dementias. The review of the literature reported in Chapter 5 demonstrated a lack of applied intervention for those at-risk of HD and fALS in addition to fFTD. Chapter 3 and 4 also identified common threads among those at-risk of HD and fALS such as coping mechanisms and the struggle with uncertainty. Therefore, although this thesis focuses on identifying those factors that are specific to fFTD, there may be evidence to support increased cross-collaboration towards a wider understanding of living at-risk of a hereditary neurodegenerative disease, as well as the potential use of a tailored psychological intervention that may be adapted and used across multiple of these hereditary disorders. More research will be necessary to highlight those factors that are shared across diseases and those that may be important to address specifically with a focus on a particular disease experience.

Finally, within the field of fFTD, there is a growing movement to investigating mood symptoms and neuropsychiatric symptoms, to identify how these may link to the prodromal phase of symptom onset to aid better understanding of the disease process, ensure better treatment leading up to diagnosis and assist diagnostic processes. This work demonstrates the biological influence on mood symptoms differentially across mutation types, providing evidence to suggest that they are not purely situational, although affected by factors such as status knowledge. In turn furthering our understanding of those changes prior to FTD symptom onset, within the presymptomatic or prodromal window.

9.4. Limitations

Beyond those limitations noted within each chapter, the work in this thesis has some additional relevant limitations to be discussed. The sample of participants represented throughout the work reported here are largely European and Caucasian individuals who are highly educated and often represent the middle class of society. Mental health in general is strongly tied to these socioeconomic factors, however this was not measured in this work therefore there are limitations in terms of the representation of the sample. When understanding the lived experience and developing a suitable intervention, adjustment strategies and support needs often focused around gathering information to further understand risk. This may be indicative of the more educated sample and the coping strategies they employed due to their needs and the resources at their disposal. Less well-educated families and those of a lower socioeconomic status may not have the resources to employ these same coping strategies, and may prioritise a different set of needs, e.g., financial planning. Therefore, although every effort was made to ensure the development of a person-centred intervention, the lack of diversity within the sample of participants as well as within experts by experience consulted, may limit its efficacy in practice. The findings discussed throughout the thesis, particularly those in Chapters 3 and 4, may not be generalisable to the wider FTD population as a result of the constraints of the sample studied. Due to the relative rarity of FTD, in comparison to a disease like AD, generalisability of findings and application to clinical practice is crucial to maximise limited NHS and research resources.

Further to this, these social factors may illuminate varied levels of mental health literacy within the population, that may not have been captured in this sample. Mental health literacy refers to *"knowledge and beliefs about mental disorders which aid their recognition, management or prevention"* (Jorm et al., 1997). Recognition of mental health problems in particular is fundamental to accessing help (Holman, 2015). Self-identification of factors addressed within this thesis such as emotional distress, depression and anxiety, may also pose a threat to self-identity of individuals for whom resilience is important e.g., working-class men. This was alluded to in terms of pride as a barrier to accessing support within Chapter 4. Mental health literature and stigma

are intrinsically linked to factors such as gender, socioeconomic status, education and social class, with women with higher socioeconomic status, education and social class demonstrating higher levels of mental health literacy and reduced stigma (Holman, 2015). As the participants sampled in this thesis were biased towards females and those with high levels of education, there may be an unrepresentatively high level of mental health literacy and low stigma displayed in participant responses. As responses relied on self-report measures and semi-structured interview these findings may be unrepresentative of the at-risk population as a whole, particularly those who fall outside these demographic parameters. This has implications regarding the lived experience characterised within this thesis, as this may be vastly different across more diverse subsets of the population, as well as for the support needs and barriers identified for support. Pride, which I identified as a barrier in this work, presents a challenge to overcome, as it is a quality engrained in British culture. Therefore, socioeconomic barriers, mental health literacy and stigma may present further challenges within this intervention development. In addition, as those with lower mental health literacy are less likely to recognise mental health problems and less likely to seek help and support, this may indicate a huge barrier in terms of application and efficacy of this intervention within the NHS. However, it is important that this is addressed in future to ensure fair and equal access to support across the at-risk population. For this reason, findings within this study may also be limited in terms of generalisability to other cultures, particularly those in less economically developed areas.

Another potential limitation of this work is the static time-point measurement of depression and anxiety. Symptoms of depression and anxiety are common, and often fluctuate due to a range of confounding variables relating to both internal and external experiences. Within the at-risk population, literature has also suggested that these individuals may be particularly prone to fluctuations in depression and anxiety symptoms (Samra et al., 2023), due to factors affecting the relevancy and salience of their genetic risk. It is possible that one such factor may be research participation, therefore measures of these symptoms may not be representative of mood across the at-risk period, but rather may indicate mood during highly relevant periods. Longitudinal research is required to elucidate the long-term mood changes experienced in this group.

Furthermore, statistical analyses reported in Chapter 3Chapter 8, multiple statistical analyses were run, without correction for multiple comparisons. This increases the likelihood of type I error, that is, finding a positive, or significant result that is not true. There are a number of ways in which corrections for multiple comparisons can be approached, most commonly this is done using the Bonferroni method, whereby the alpha level (0.05 throughout this thesis), is divided by the number of comparisons carried out. As this is an extremely conservative method of correction which increases the likelihood of type II error (not finding a significant result that exists in the data), there are other methods of correction that are less stringent such as using an alpha level of 0.01, or Benjamini-Hochberg method. However, due to the exploratory nature of the analyses reported within this thesis, it was decided that minimisation of type II error should be prioritised and therefore no corrections were made. Therefore, caution is necessary when interpreting results, particularly those with a significance level close to 0.05.

9.5. Directions for future work

Due to the limited existing literature and exploratory nature of these studies, there is much future research needed to develop on the findings highlighted here. Regarding the understanding of the at-risk fFTD lived experience, further exploration using the GPRI*plus* questionnaire within a larger and more diverse sample, incorporating measures of FTD symptom severity may allow for closer investigation of the biological and situation factors influencing mood symptoms in at-risk individuals. Similarly, further exploration using qualitative methods to understand in more depth, the nuances of the at-risk experience would be beneficial and allow for improved support across a variety of services e.g., further understanding of reproductive decision making in at-risk FTD may improve experience with assisted fertility services. As explored above as a limitation, qualitative exploration of different socio-cultural perspectives towards the at-risk experience may also be important in providing a more wholistic view, and in developing services that are suitable for application to a diverse population, but also in helping to reduce the barriers observed in research participation, and access to support services. Furthermore, as previously highlighted, clinical trials have begun recruiting at-risk participants which presents a more complex and challenging picture

in terms of psychological adjustment. Therefore, as this progresses, exploration of the clinical trial experience and evaluation of its impact on wellbeing may be important in building the foundations for application of future psychological intervention. The field may also benefit from improved cross-collaboration across hereditary neurodegenerative diseases, therefore future work may evaluate the similarities and differences in the at-risk lived experience across these multiple diseases. As all are considered rare and underserved, this may provide evidence for wider peer support, and for the adaptation and application of support interventions across this range of diseases. Additionally, this increased cross-collaboration may increase sample sizes needed for increased statistical power in observational research and future RCTs.

Finally, the intervention development outlined within this thesis will be continued over the coming 5 years under the supervision of JCS. Future work will include feasibility testing of the current content and framework, and further development prior to a full-scale RCT, scheduled to begin in 2024.

9.6. Wider implications

The implications of this work, explored throughout the thesis, outline a variety of academic and clinical implications which I believe will lead to an overall improvement in the wellbeing and lived experience of the at-risk population. In addition to the direct implications for the FTD community, there is an argument for extrapolation of some of these findings to other hereditary neurodegenerative disorders. There were a number of key similarities to lived experiences of fALS and young onset dementia in Chapter 4, suggesting that some of the themes identified, may be extrapolated. Additionally, in Chapter 7 minimal changes were made to the HD predictive genetic testing recommendations developed by (MacLeod et al., 2013), suggesting that with minor amendments to cater for specific issues within a particular disorder, this predictive testing protocol may be suitable for other autosomal dominant hereditary neurodegenerative diseases. Finally, the literature review carried out in Chapter 5 demonstrated minimal psychological interventions developed for individuals with genetic risk for any neurodegenerative diseases. The majority of studies focused on HD, however, to date no randomised control trials have been carried out, and this

thesis describes the first ACT-based intervention developed specifically for this population. Therefore, with minor amendments, again to cater for the specific needs of each population, as this was something identified as important in Chapter 4, this intervention may be appropriate for numerous hereditary neurodegenerative diseases including HD, fALS and fAD. This will form part of future work led by JCS.

9.7. Reflections

As addressed in the thesis acknowledgements and throughout this thesis, the journey to the completion of this work has not been straight-forward. Although the COVID-19 pandemic presented many problems and additional barriers, it did also lead to the development of the qualitative project outlined in Chapter 4 which I value as the most important findings within this thesis. I had previously held some scepticism towards qualitative research, due to the commonly heard criticism that it lacks objectivity. However, this work provided a voice for an unheard community and gathered data that can now be utilised in further work to better support individuals at-risk based on the needs that they themselves specified. This project was not planned at the initial conception of the thesis but rather came about as a way to remotely gather data for intervention development during the pandemic. Should I carry out this work again I would prioritise this qualitative work as it was foundational for all other elements presented within the thesis, and the process and findings were invaluable. Additionally, the scope of the work undertaken was ambitious, particularly with the additional time constraints following the pandemic, when carrying out research was slow and challenging, if not impossible, at times. Despite this, if I were to do it again, I would have enlisted help with the creation of the intervention materials, once the programme was outlined. It was very time consuming to film, animate and voice-over all video materials, and whilst enjoyable, that time could have been beneficial in facilitating the completion of the feasibility study.

9.8. Conclusions

Overall, this thesis aimed to better understand and improve psychological wellbeing in those with genetic risk of familial FTD. This was achieved by investigating mood symptoms of depression and anxiety, the qualitative lived experience, including

support needs while at-risk and broad autism and schizotypal traits. Improvements to psychological wellbeing were achieved by the development of a bespoke online ACT-based intervention, co-produced with stakeholders for implementation in fFTD, as well as the use of patient and expert perspectives in the development of an FTD-specific genetic protocol, to improve the genetic testing experience for families affected by fFTD.

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Appendices

Appendix 1: Genetic Psychosocial Risk Instrument *plus* questionnaire

Genetic Psychosocial Risk Instrument (GPRI) *plus*

[for presymptomatic participants only]

Section 0 – Demographics [not needed if included within main GENFI pack]

Name or GENFI code			
Gender (please circle)	Male/female	**Years in education** e.g. if left at 18 and started at 5 = 13	
Date of birth		GENFI site	
What genetic mutation are you at risk of? ☐ C9orf72 ☐ GRN (Progranulin) ☐ MAPT (Tau) ☐ Other (please specify):			

Section 1 – Living at-risk

1	At what age did you find out that you were at-risk of FTD or a related condition?	

Section 2 – Genetic counselling and presymptomatic genetic testing

1	Have you ever had genetic counselling?	Yes/No		
2	Have you had presymptomatic genetic testing?	Yes/No	If yes, when (number of years and months ago)?	_ _ years _ _ months
3	If Yes to Question 2, how long did you	☐ Less than 6 months		

	consider having genetic testing for before you had the test?	☐ 6 months to 1 year ☐ 1 year to 2 years ☐ 2 years to 3 years ☐ More than 3 years
4a	If Yes to Question 2, did presymptomatic genetic testing show that you were a carrier of the genetic mutation?	☐ Yes – mutation carrier ☐ No – not a mutation carrier ☐ Do not want to share
4b	If No to Question 2, on a scale of 0-100% (where 0 is no risk and 100 is a definite mutation carrier), what do you think your risk is of carrying a mutation? (place a X on the line)	0 _____50_____100 _____

Questions 5 and 6: If you have had presymptomatic testing or you have definitely decided you will have it, answer question 5. If you have decided not to have testing or are undecided on whether to have testing, answer question 6.

5	To what extent were the following reasons important in your decision to have presymptomatic testing?	Not at all	A little	Somewhat	Very	Extremely
	Relieving uncertainty	1	2	3	4	5
	General planning for the future	1	2	3	4	5
	Being able to inform my children about their risks	1	2	3	4	5
	Being able to make arrangements for my future care	1	2	3	4	5
	To relieve anxiety	1	2	3	4	5
	To alter the medical care I currently receive	1	2	3	4	5
	To confirm the feeling that I already	1	2	3	4	5

	have the disease					
	Planning a family	1	2	3	4	5
	Curiosity	1	2	3	4	5
	Other (please state):	1	2	3	4	5
6	To what extent were the following reasons important in your decision to not have presymptomatic testing?	Not at all	A little	Somew hat	Very	Extreme ly
	The results would be too difficult to handle	1	2	3	4	5
	The results would not alter my medical care	1	2	3	4	5
	The results would not affect my future planning	1	2	3	4	5
	There is nothing that can be done anyway	1	2	3	4	5
	It would make me worry about my children's risks of developing FTD	1	2	3	4	5
	I would not be able to continue enjoying life	1	2	3	4	5
	The results could change how people treat me	1	2	3	4	5
	I would just be preoccupied with the signs of onset of the disease	1	2	3	4	5
	Insurance companies can misuse my information	1	2	3	4	5
	Other (please state):	1	2	3	4	5

7	Do you have children?	Yes/No

Section 3 – Mental and physical health

1a	Have you had emotional problems in the past?		Yes No				
1b	Have you ever had any diagnosed mental health problems?		Yes – previous Yes – ongoing No				
1c	If the answer to Question 1b is yes, what diagnosis was made? Select all that apply (if more than one).		Depression Anxiety Other (please state):				
1d	Since finding out that you were at risk of FTD, have you had emotional problems that have led to you having thoughts about suicide?		Yes – currently Yes – more than 6 months ago Yes – more than 1 year ago No Prefer not to answer				
1e	In the past month:		Not at all	Hardly ever	Sometimes	Often	Almost all the time
		Have you felt generally sad	1	2	3	4	5
		Have you felt generally nervous and anxious	1	2	3	4	5
2	Has being aware of your at-risk status changed your mental health (please circle a number)?		Changed for the worse			Not changed	Changed for the better
			1	2	3	4	5	6	7

3	If you have had presymptomatic genetic testing, has that changed your mental health (please circle either N/A or a number)?		N/A (i.e. you have not had presymptomatic genetic testing)						
			Changed for the worse			Not changed	Changed for the better		
			1	2	3	4	5	6	7
4	To what extent do you currently agree with the following statements:		Not applicable	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	
	If I learn that I have a genetic mutation, I believe that:	I will have more problems in my life	0	1	2	3	4	5	
		I will change plans for my career/ profession	0	1	2	3	4	5	
		I will have difficulties in my family relationships	0	1	2	3	4	5	
	The disease for which I am at risk is *currently* causing a significant disruption in my family life		0	1	2	3	4	5	
	I am worried that my test result will impact on my relationship with my significant other (or future partner)		0	1	2	3	4	5	
	I am worried about talking to my children (young or adult) about the heritable nature of the disease		0	1	2	3	4	5	
	My worries about the disease affect my daily mood		0	1	2	3	4	5	

	I often find myself worrying or preoccupied with my risk of getting the disease	0	1	2	3	4	5
	I am concerned about my risk of getting the disease, however this concern interferes minimally with my everyday life	0	1	2	3	4	5
	I feel guilty that I might pass on the disease risk to my children	0	1	2	3	4	5
5	Have you taken care of a very ill parent or another close family member (e.g. sibling)	Yes/No	If yes, was the illness they suffered from FTD/related condition such as MND?			Yes/No	
6	Have you lost a close family member (e.g. parent/sibling) to FTD (or related disorders such as MND)?	Yes/No					
7	Have you had counselling with a counsellor and/or mental health professional in the past?	Yes/No					
8	Are you currently seeing a counsellor and/or mental health professional about any emotional concerns?	Yes/No					

Section 4 – Support during the at-risk period

1	Have you had any support during the at-risk period?	No Yes (please state what):
2	If you have accessed support (or attempted to), how easy was it to get?	1 (Extremely easy) – 2 – 3 – 4 – 5 – 6 – 7 (Extremely difficult)
3	If you have accessed support, how much have you benefited from it?	1 (Hugely) – 2 – 3 – 4 – 5 – 6 – 7 (Not at all)

GAD-7

Over the **last 2 weeks**, how often have you been bothered by the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Feeling nervous, anxious or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Worrying too much about different things	0	1	2	3
4	Trouble relaxing	0	1	2	3
5	Being so restless that it is hard to sit still	0	1	2	3
6	Becoming easily annoyed or irritable	0	1	2	3
7	Feeling afraid as if something awful might happen	0	1	2	3

PHQ-9

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself – or that you are a failure or have let yourself	0	1	2	3

	or your family down				
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

Appendix 2: Semi-structured interview schedule

Questions	Follow up/Prompts
1. How did you find out about being at-risk of FTD?	• E.g. Were you told by a family member or did you find out when someone became symptomatic • How old were you?
2. What was it like for you when you found out that you were at risk?	• How did you feel about it at the time? • (If say it was difficult) How did you adjust to the information? • How long did this take?
3. Has your experience changed since then?	• How?
4. How do you think your life has been affected by finding out about your risk?	• Have you done anything differently that you might not have done if you weren't at-risk?
5. Have you had any support?	• (if so) what support have you had? • How did you find this support? • Did you feel any different due to the support? • Did you do anything differently as a result of this support?
6. Is there any other support that you think would have made a difference?	• E.g. guidance around adjusting to your risk of FTD
7. What kinds of things, if any, may have got in the way of you receiving or accessing support?	• (If they don't bring up) do you have thoughts about how to overcome these? • (if so) please tell me them?
8. What kind of things, if any, helped you to get support?	• E.g. did you find support on the internet or via GP/research team etc?
9. Is there anything else that you think would have helped you?	• What might this look like? • How do you think this would have

	changed things for you?
(depending on whether had genetic testing) And lastly/finally… 10. What sort of support do you think other people in your situation would find most useful?	
If had genetic testing:	
11. What was going through the genetic testing process like?	• What sorts of feelings did you have along the way?
12. Did things change immediately after you found out your result?	• How so?
And lastly/finally… 13. How has this changed in the time since you found out your result?	
Debrief	
14. Is there anything you want to mention that we haven't covered?	
15. How was it having this interview?	
16. Any feedback for future interviews?	
17. Is there anything you weren't asked but thought you should have been?	

Appendix 3: Distribution of qualitative themes across participant groups

Table 46- A table to show distribution of themes and subthemes by genetic status for the feelings and experiences living at-risk of fFTD

Theme	P1	P2	P3	P4	P5	P6	P7	P8	P9	P 10	P 11	P 12	P 13	P 14	P 15	P 16
1. The reaction to learning about risk or status – *'it's like ups and downs all the time'*																
a) Attitude to 50% risk – 'it's 50-50 – I might have it, but I might not…'																
b) Dealing with a lot while also trying to process status																
c) Seeing symptoms in family causes concern for self – 'I was totally scared that it was something that could affect me'																
d) Strategies for adjustment																

2. The journey to finding out about your risk																
a) Finding out about risk was a gradually evolving process																
b) Finding out that you are at-risk - Predicting the future																
c) Found out when parent diagnosed																
d) Suspected a genetic cause																
3. The value of information - ‘I'm a bit more in control if I've got the knowledge’																
4. Coping																
a) Avoidance – burying the																

risk in the sand																
b) Planning																
c) Talking																
5. How risk influences life																
a) Effect on individual																
i) Having children																
ii) Importance of time																
iii) Risk factors into decisions																
iv) Risk is always in mind																
b) Effect on relationships – non-romantic																
c) Effect on relationships –																

romantic																
6. The *'whirlwind'* of emotions experienced throughout the at-risk journey																
a) negative																
i) Anger																
ii) Fear																
iii) Frustration																
v) General negative psychological response																
vi) Helplessness																
vii) Isolation – 'it's almost like you're left out at sea'																

viii)Low mood																
ix) Participant visibly emotional																
x) Shock																
xi) Survivor guilt																
xii) Uncertainty																
xiii)Worry & anxiety																
b) Positive																
i) Hope																
ii) Positivity																
iii) Relief																

Table 47 - A table to show distribution of themes and subthemes by mutation status for support needs while living at-risk of fFTD

Theme	P1	P2	P3	P4	P5	P6	P7	P8	P9	P 10	P 11	P 12	P 13	P 14	P 15	P 16
1. The presence or absence of support																
a) Lack of support																
2. The types of support received																
a) Psychological therapy																
3. Support is *'paramount'* - The impact of support																
4. 'I didn't know where to go to get proper support that actually understood' - Barriers to accessing support																
a) Accessibility																

b) ‘You don't want to bring people down about talking about it - it's quite miserable’																
c) Individual attitudes – ‘lots of people would rather saw their leg off than see a therapist’																
d) Lack of understanding																
e) Time																
5. Facilitators for support																
a) Utility of being online																
6. Support wanted																
a) Professional support																

b) Better coordination, timing and accessibility of support																
c) Peer support																
d) Knowledge and information																
e) Didn’t feel needed support																
f) Safe space to explore feelings																
7. The importance of understanding the specific difficulties – ‘I couldn't face talking to people that didn't know what I was talking																

about.’																	
a) Research support																	
b) Peer support groups																	
c) General peer support																	
d) Supportive partner																	
e) Supportive family																	

Appendix 4: Systematic review search terms

("psychological intervention" OR "psychological therapy" OR "mindfulness" OR "acceptance and commitment" OR "cognitive therapy") AND ("frontotemporal dementia" OR "huntington's disease" OR "motor neuron disease" OR "motor neurone disease" OR "amyotrophic lateral sclerosis")

Appendix 5: Distribution of articles across databases at each stage of review

Database:	Number of results	After duplicates removed	After reviewed for inclusion/exclusion criteria
Pubmed	59	59	4
PsycInfo	41	14	0
Web of science	40	8	0
EBSCO	37	18	1
CINAHL plus	35	1	0
Clinicaltrials.gov	0	0	0
Bibliography search	-	-	1
	212	100	6

Appendix 6: Number of articles excluded from full review across relevant exclusion criteria

Reason for exclusion	N
Review paper/meta-analysis/comment	18
Unrelated topic	22
Observational study of symptomatic individuals	14
Intervention for symptomatic individuals	22
Caregiver intervention	12
Caregiver observational study	6
Not autosomal dominant risk	1

Appendix 7: Intervention materials and questions provided to participants for review

Questions:

General

1. Would you like to leave any comments as a testimonial for use on the site?
2. Do you have any general comments about the content included?
3. Do you have any comments about the design of the website?
4. Do you have any comments about the structure of the intervention?
5. Any general feedback as to how we can improve this and make it tailored to the lived experience of being at-risk of FTD?
6. Is there anything barriers that would stop you from taking part in ther

Information materials

7. Is there anything you think needs adding here?

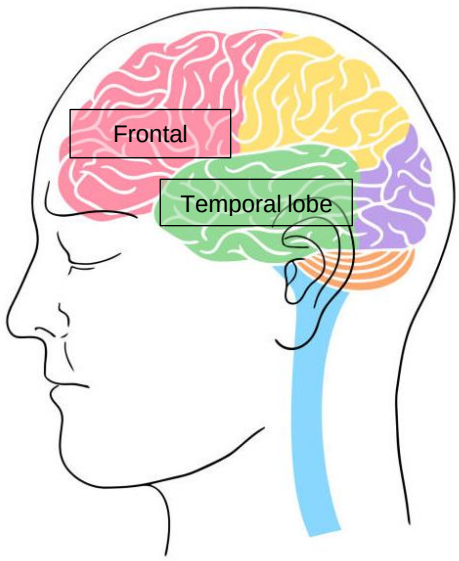
Introduction to managing your risk

8. Dissecting the problem: does this need to be related to FTD? How can we make it more specific?

1. **Information materials**

FTD (general)

- Dementia is a name we give to a set of symptoms that affect thinking and brain function that get worse over time.
- There are 4 main diseases under the umbrella of dementia: Alzheimer's disease, vascular dementia, dementia with lewy bodies and Frontotemporal dementia.
- Frontotemporal dementia, or FTD (previously called Pick's disease), is an illness that affects the frontal and temporal parts of the brain (i.e. the front and side bits)



- The frontal lobe is responsible for parts of our thinking such as: **memory, emotions, impulse control, problem solving, social interaction, judgement, language and motor function**.
- So damage to this area can lead to personality changes, difficulty concentrating or planning, and impulsivity.
- The temporal lobe is specifically involved in understanding language and speech production and memory.

- Around 30% of FTD is caused by a genetic problem in 1 of 3 genes called: MAPT, Progranulin and C9orf72. These genetic problems cause the proteins in our brain to go wrong and this progressively damages the brain over time – in particular the frontal and temporal areas.

- There are 2 main subtypes of FTD:
    - Behavioural variant (bvFTD) and
    - Primary progressive aphasia (PPA)
- In bvFTD the initial symptoms are usually a change in personality or behaviour. These may include:
    - Behaving inappropriately
    - Becoming less interested in things or in people
    - Becoming more obsessive or repetitive
    - Changes in the types of food eaten
    - Problems with planning or problem solving
    - Difficulty concentrating
- In PPA the initial symptoms are problems with language skills. There are 3 subtypes of PPA
- There is the Semantic variant: where we might see changes in someone's ability to find or understand words.

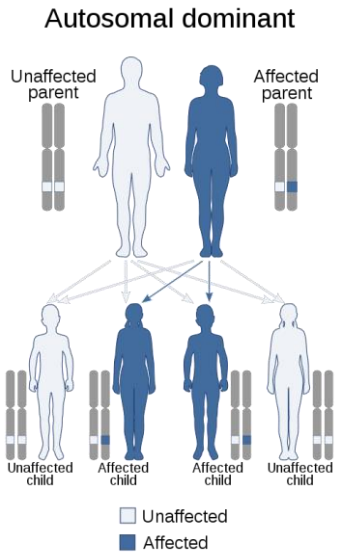
- Also there is the Nonfluent variant where the main problem is usually producing speech. Speech may become slow and hesitant, and words may be missed out or pronounced incorrectly.
- And also Logopenic variant where people may pause in the middle of sentences and have difficulties finding words.

- In some cases people with FTD will also develop problems with their movement.
- Some people may develop motor neurone disease which affects the body's nerves and muscles that control movement in their arms and legs and that allow people to speak and swallow
- Some people might develop parkinsonism which includes symptoms that are similar to Parkinson's disease. People may have greater difficulty moving or be slower in their movements. There may be stiffness in the arms and legs. People may also have too much movement such as a tremor where the hands shake.

Heritability

- For many people with FTD, the cause is not known. In around a third of people however it can be triggered by a genetic problem – we call this familial FTD.
- The main genes involved are called:
    - Tau or MAPT
    - Progranulin or GRN
    - C9orf72
- There are also some other rare genetic causes of FTD which are uncommon.
- Some families have a clear family history of FTD but no abnormal genes have been identified at present.

- For the majority of forms of genetic FTD, the disease is passed down in what is called an 'autosomal dominant' manner.
- In people with problems in these genes there is a 50 per cent chance that the abnormal version of the gene will be passed on to their children.
- Each child has a 50/50 chance of carrying the gene problem individually – some families might have 2 children who don't carry the gene, some might have two that carry the gene and some might have 1 child with the gene and one without



- We can't predict which children have inherited the gene problem and who hasn't.
- It is not linked who looks most like the affected parent and it is also not linked to whose personality is most like their parents.
- In order to find out whether someone carries the gene problem or not they must go through something called predictive testing. This can only happen once they have turned 18. Have a look at the predictive testing video for more information about this.

- If people do carry the mutation then they are very likely to develop symptoms of one of the FTD clinical syndromes at some point during life.

Gene specific videos

(C9/GRN/MAPT):

- Age related penetrance
- Age at onset
- Possible phenotypes by gene

Predictive testing including receiving predictive test results

- The content for this video will be written and delivered by a geneticist
- It will cover:
  - The process of predictive testing,
  - The things you might think about during the counselling procedure

    - Preparing for predictive testing
    - What to expect when receiving test results

Research

- This will explain GENFI for those who are not involved

Trials

Having children/PGD

- This will also be written by a geneticist to explain the options and procedure for having children including PGD
-

Signposting:

***This section will include documents, diagrams and links to other resources**

- Pathway to care diagram
    - This will cover things like:
        - How to get a referral for predictive testing
        - How to get a referral for PGD
        - What to do if concerned about symptoms
- Signpost genetic alliance
    - This is a specialist organisation who provide legal and insurance advice to people at-risk of genetic problems
- Reproductive options signposting
    - This document will include where you can get assistance with the different reproductive options mentioned above
    - E.g. a map of PGD centres (this can only be done in a small number of specialist centres around the country)
- Rare dementia support
    - This will signpost people to sign up to rare dementia support and allow them to look into the different support options that are available

FAQs

***This module is made up of a number of different pages as it is longer than the rest**

The idea of this module is to provide a basic understanding of the concepts that

we will revisit later on in the modules

2. Introduction to managing your risk

DISSECTING THE PROBLEM

This form is to help gather information about the nature of the main challenge, issue, or problem facing you. Please summarize, in one or two sentences, what the main issue or problem is:

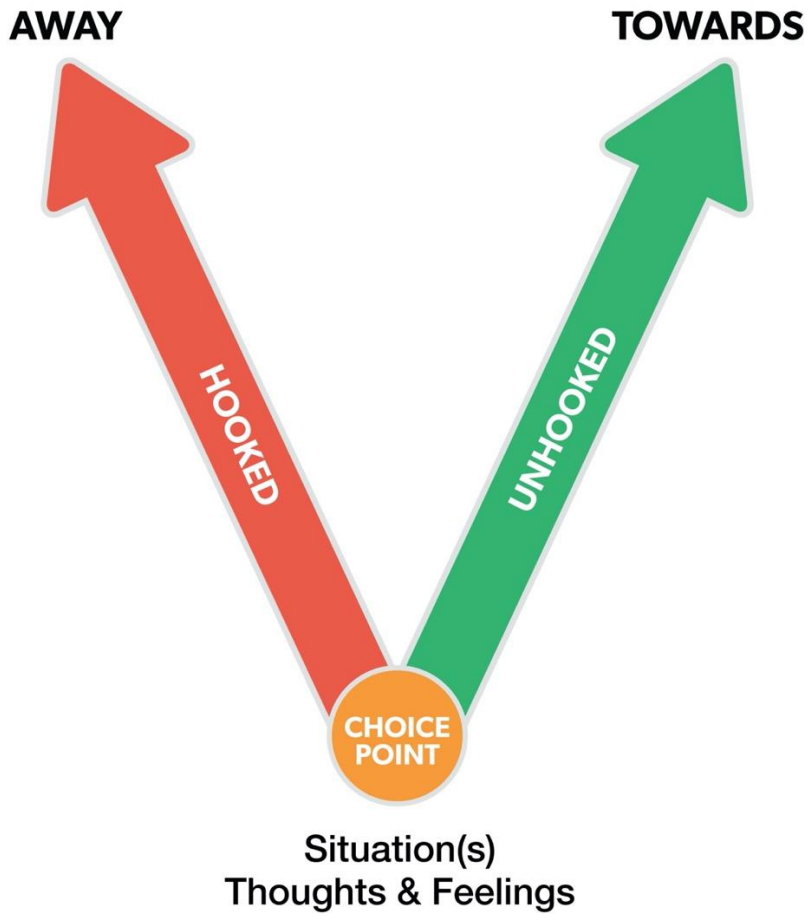
Please describe, in one or two sentences, how it affects your life, and what it stops you from doing or being:

Regardless of what your problem is—whether it is a physical illness, a difficult relationship, a work situation, a financial crisis, a performance issue, the loss of a loved one, a severe injury, or a clinical disorder such as depression—when we dissect the problem, we usually find four major elements that contribute significantly to the issue. These are represented in the boxes below. Please write as much as you can in each box about the thoughts, feelings, and actions that contribute to or worsen the challenge, problem, or issue facing you:

"Hooked" by Thoughts What memories, worries, fears, self-criticisms, or other unhelpful thoughts do you get "hooked" by or "caught up" in? What thoughts hold you back or jerk you around or bring you down?	**Life-draining Actions:** What are you currently doing that makes your life worse in the long run: keeps you stuck; wastes your time or money; drains your energy; restricts your life; impacts negatively on your health, work, or relationships; maintains or worsens the problems you are dealing with?
Struggle with Feelings What emotions, feelings, urges, impulses, or sensations do you tend to fight with, avoid, suppress, try to get rid of, or otherwise struggle with?	**Avoiding Challenging Situations:** What situations, activities, people, or places are you avoiding or staying away from? What have you quit, withdrawn from, dropped out of? What do you keep "putting off" until later?

>> Next page <<

The choice point



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Cognitive fusion and defusion techniques

EXPANSION PRACTICE SHEET

Expansion means opening up and making room for difficult feelings, urges and sensations – thereby allowing them to 'flow through' you without a struggle. You don't have to like or want these feelings – you just make room for them and allow them to be there even though they are unpleasant. Once this skill is learned, if these feelings should resurface, you can rapidly make room for them and let them 'flow on by' – so you can invest your time and energy in doing meaningful life-enhancing activities, instead of struggling. Aim to practice at least once a day breathing into and making room for difficult feelings and sensations

Expansion Practice Form			
Day/Date/Time Feelings/sensations	How long I practiced for (mins) Struggle switch rating, 0 -10 10 = switch on, 0 = switch off, 5 = halfway point (tolerance)	Used a CD or MP3 to assist? yes/ no	Benefits and/or difficulties

>> Next page <<

3. Dealing with uncertainty

Video

Content:

- There is considerable uncertainty associated with being at-risk of FTD whether you know that you carry the gene or not.
- There is uncertainty surrounding when symptoms might start, what symptoms you might have among lots of other things.
- The difficulty with these uncertainties is that it is really hard to stop worrying about them, or even just to stop thinking about them.
- These thoughts are rational, unlike like many of the usual things that might make us anxious or depressed in everyday life so it would be really difficult to make them go away.
- Instead, we can change how we respond to these thoughts.
- There are two ways that most people respond to this feeling of uncertainty: try to solve it, or bury their head in the sand.
- Trying to solve it might relieve some anxiety or worry, you might be able to make some plans for future hypothetical e.g. if I get symptoms I would like this care plan to be put in place. This is a good coping strategy to an extent and can help families to feel more clear on how to deal with some future scenarios. BUT you can't use this method for everything, some of these worries can't be solved because we just don't know enough about them yet.
- Besides, you want to live in the present and enjoy your life rather than looking forward all of the time and missing it.
- Burying your head in the sand can also be a helpful coping mechanism, as we have spoken about before, avoiding the worries is great in the short-term. The worry might pop into your mind and make your stomach drop for a moment, but you might be able to put it to the back of your mind and enjoy the rest of the day until it appears again. This could be minutes, hours, weeks or months but avoiding it won't make it go away forever.
- Instead, I am going to suggest that we take a different approach to these uncertainties, I would like to help you to stop struggling and live with them, without getting hooked.

What we are going to do about it

- Taking control of what you can and letting go of the rest
    - Connect with values and think of what is important for you to live a rich and meaningful life
    - What can be problem solved?
    - Because many of these are uncertain they're not problem solving issues but there may be elements where we can try this

    - When making big life decisions, it might be helpful to factor in thoughts about your risk/status. For example, some people may exercise caution over things such as mortgages as they approach the age range where symptoms may onset.
- Acceptance strategies for the things you can't control – framing is important
    - Observe, breathe, expand and allow exercise/ the compassionate hand
- Drop anchor/grounding – reminder to live in the present moment

Activity

- You will have noticed that many of these issues don't have solutions that fit within your values, because the uncertainty is too great.
- When these thoughts come in to your mind I would like you to practice the techniques we've used before:
    - Noticing and naming --> observing , breathe, expand and allow --> dropping anchor/grounding

Check in

- Come back to values and assess plan

4. **Rumination about risk/status**

Video

Content:

- It is understandable that, at times, you might worry about your own future, perhaps your family's future and this might be really difficult to deal with. Especially given all of the other things going on in your life.
- You might feel as though you are constantly thinking about these things, even if they're not at the forefront, they might live in the back of your mind, popping up every now and then.
- Being at-risk of FTD is complex and difficult and many of these worries will be about really complicated and difficult things, which makes it really hard to make them go away.
- Some of the things people at-risk of FTD commonly worry about at some point in the journey are:
    - Whether or not they carry the gene
    - When they might get symptoms
    - What symptoms they might get
    - Their family members, particularly people who are symptomatic or gene carriers, as well as partners or family members who might become a carer in future
    - Having children or the genetic status of children they already have
- Individually these worries are hard to deal with, all together on top of living everyday life, it is understandable that this might become overwhelming.
- As we have spoken about in previous modules, we can't make these worries go away, and avoiding them isn't helpful either - this can give it more power and make it even more difficult when it pops back up.
- By practicing some of the strategies we have talked about in the previous module(s) and

What we are going to do about it

- Defusion & acceptance exercise: Leaves, Streams, Clouds, and Sky exercise – audio
- Potentially also/instead:
    - Acceptance: Observe, breathe, expand and allow exercise
    - Defusion: Non-judgemental naming & noticing
    - Mindfulness: Contacting the present moment/dropping anchor

Activities

- Worry time

5. **Worry about symptoms - Including seeing symptomatic family member causes concern for own symptoms**

Video

Content:

- Developing symptoms is an understandable worry for anyone at-risk of FTD. Often this can be triggered by spending time with symptomatic family members.
- As a result of this you might;
    - Feel guilty for worrying about yourself when spending time with your family
    - Distance yourself from symptomatic family or family in general
    - Start noticing and worrying about potential symptoms in yourself
- This is a very common concern.
- Our instinct when these things are out of our hands is to control that which we can. We can't control what symptoms we may get or when they might happen but we can look for them and spot them as early as possible.
- But this might actually be counterproductive. Unlike breast cancer for example, where early diagnosis is crucial, there are few, if any, benefits to early diagnosis for FTD for those already at risk.
- By the time symptoms develop, it is likely that you will have lived with the knowledge of FTD for considerable time, you might have made financial and healthcare preparations and partners and family will be aware and experienced and better equipped to provide care.
- So the instinct to look for and identify these symptoms may actually be of little benefit to you and takes you away from that rich and meaningful life that we have talked about.
- It is also important to remember that we are not accurate observers of our own behaviour, famously 80% of people report that they are better than average drivers – statistically this is impossible, demonstrating how inaccurate our observations are of our behaviour.
- You want to enjoy your life rather than spending it looking for signs of FTD.
- It is important to remember that everyone forgets words sometimes, or might laugh inappropriately in an awkward situation. There are also lots of things that might affect your thinking temporarily including things like; a period of depression, lack of sleep, pregnancy and the menopause. While it is common to experience these symptoms occasionally throughout life, it is really hard to disentangle them from your worry about your risk of FTD. It is important to remember that in life these lapses in thinking or memory are likely short-lived or occasion. However when related to FTD you might notice prolonged change that has maintained and progressed over time.

What we are going to do about it

- You might want to consider the following stepped plan to manage concern about symptoms:

Step 1: Schedule a review

- Find a family member, partner or friend to schedule in a time at an interval that is suitable for you to review your health and discuss both of your perspectives and flag any issues. This does not need to be one sided, it can be reciprocal.
- Think about long-term changes, we all forget a word or may laugh inappropriately in an awkward situation. Try to think of things where you have noticed a change that has maintained or progressed over time. Click [here] to download a template listing things to look out for.

[Template]

  - Have you noticed changes in behaviour or personality?
    - Think about whether there has been a change in sense of humour, disinhibition (e.g. making inappropriate comments), impulsivity (e.g. making rash decisions or actions without thinking through the consequences or increased gambling).
  - Have you noticed changes in eating/drinking?
    - Has there been a change in preference for sweet foods?
    - Has there been a marked change in alcohol use?
  - Have you noticed changes in planning or problem solving?
  - Have you noticed changes in language?
    - Increased problems with reading or spelling
    - Has there been a change in their speech production? E.g. has their speech become progressively slow, hesitant and effortful, pronouncing words incorrectly e.g. aminal vs animal, missing connecting words in sentences like ‘the’ or ‘and’, saying the opposite of what they mean e.g. yes when they mean no, problems with grammar.
    - Have they had progressive difficulty finding the right word, has there been a change in their understanding of the meaning of words or what people are saying, have they begun to speak more vaguely?
  - Have you noticed changes in movement?
    - E.g. Wasting and weakness of muscles, twitching of muscles, unexplained stiffness of muscles (not following exercise), problems with articulation (production of speech) such that the speech may sound slurred, problems with swallowing

Step 2: Acceptance and self-compassion exercises

- Following a session to review on this topic, and routinely when these worries occur, it is important to remember to practice the following exercise(s);
    - Acceptance, self-compassion & mindfulness: Compassionate hand

Step 3: If symptoms are causing concern ask your GP to refer you for assessment from a neurologist.

Activity

- Think of how you might want to approach the plan above
    - make a list of who you might like to do this review exercise with
    - Think of what you are looking for from the exercise and how it can benefit both you, the person you have chosen. For example, you may ask your friend if they have noticed any changes in you, they might like your feedback on how they are approaching certain issues in their life. You may both want to reflect on your relationship, whether this is familial, romantic or platonic, and how you can improve.
    - Think of how frequently you feel you would want to have this discussion. Remember that checking too frequently might be counterproductive and that we are looking at long-term changes. If you feel you need this discussion frequently then plan to taper this down gradually as and when you feel comfortable.
- Practice the compassionate hand exercise so you are prepared to open up to these feelings, make room for them and stop yourself from being hooked in whenever they occur

6. **Survivor guilt & anger**

Video

Content:

- The aim of genetic counselling is to prepare people for these difficulties as well as the difficulties you may face as a gene carrier.
- But preparing for a negative result is challenging for a number of reasons:
    - Firstly, your reaction may depend on the result of other family members e.g. accepting a negative result is much easier if your siblings are negative too, it might be much more difficult if your sibling is a gene carrier or doesn't know their status
    - Secondly, although you may well have acknowledged the challenge posed by a negative result, it is hard to prepare with the same focus as you would a positive one.
    - Our minds like to help us to prepare for the worst-case scenario, which we would often deem to be carrying the mutation. In doing so we might become stuck on the idea of life as a gene carrier, preparing with this in mind and imagining future as a gene carrier. Imagining your future as a non-carrier might trigger hope which could feel dangerous in such a high stakes situation.
    - It is no surprise then when people are met with this overwhelming emotion at a negative result. The future is now vastly different than the future they may have imagined.
- The mixture of emotions following this result is likely really confusing. You might feel initial relief but also may feel guilt, anger and sadness as well.
- Another thing you may struggle with is support following your result, friends and family might not understand these conflicting emotions and expect you to be celebrating.
- You may now feel disconnected with services that supported you in your journey up until this point.
- I want to emphasise here that these emotions are valid and human. Emotions are designed to help us communicate well with people, motivate us to act in certain ways and illuminate what is important. By feeling these emotions your mind is communicating your empathy towards those who may carry the gene who are close to you, they might illuminate things like the importance of appreciating life and spending time with family. They may also motivate you to act positively or negatively.
- There are lots of ways to manage these feelings, and this is not limited to just guilt and anger, you can apply this to frustration, shame and many others
  What we are going to do about it

- **Assess values – choice point**

Ask yourself:

- How would you treat and/or what advice would you give to a loved one who had been through similar events and felt the same way as you do?
- What does this feeling tell you really matters to you that you need to address, face up to, take action on?
- What does this feeling remind you about the way you ideally want to treat yourself/others?
- What does this feeling tell you that you've lost/need to be careful about/you want to stand up for/you want to take a stand against/you deeply care about/you need to deal with?
- What does this feeling tell you about the way you'd like the world/yourself/others/life to be? What can you do to make that happen?

- What towards and away moves does survivor guilt create?
- Away moves – What happens when this feeling hooks you? What do you tend to do that takes you away from your values? Does it capture your attention and take it away from important things? Do you disengage/lose focus/get distracted?
- Towards moves – If this emotion could no longer hook you, what would you stop doing/start doing/do more/less of? How would you treat yourself/others/life/the world differently? What people, places, events, challenges would you face up to, deal with, handle better? What would you be better able to focus or engage in? Who would you be more present with, focused on or attentive to?

- Committed action: Values guided problem solving and Values guided goal setting and action planning
    - SMART goals?
    - 1000 mile journey/brief bullseye exercise

- **Acceptance strategies to help accept status and new role**
    - Defusion from self-judgement and self-blame e.g. noticing what the mind is telling you "it should have been me" "I'd have dealt with it better" "I am less worthy of living longer" (we are quick to assume that others are making these same judgements). Non-judgementally name the feeling e.g. I am noticing self-judgement , I am noticing a feeling of guilt/shame
    - Following this ideally should mindfully reconnect with values by practicing a mindfulness/self-compassion technique – e.g. dropping anchor
    - Acceptance/Self-compassion – can use the compassionate hand or:
        1. Notice/acknowledge the pain
        2. Be human – validate the pain
        3. Disarm the critic (defuse from harsh self criticism)
        4. Hold yourself kindly (in thoughts, words and actions)
        5. Make room for your pain (accept the pain)
        6. See yourself in others (common humanity)

- We can then reframe the guilt/shame/anger as a reminder to practice self compassion – “I’m noticing a feeling of X, that’s a reminder to practice self compassion”

Activity:

- Review your choice point again, think about the towards and away moves you might make when feeling this guilt/anger/frustration
    - Connect and reflect exercise
- Create SMART goal(s)
- Practice defusing from these thoughts, dropping anchor and self compassion when the thoughts arise

7. Isolation

Video

Content:

- Explanation of support group and buddying scheme including links
  SG:
    - Who usually attends (young people at-risk, including people who are negative), often attend with partner or sibling, children sometimes attend and young children and babies are welcome
    - Members are welcome to present anything important/relevant that they might like to share with the group e.g. Hannah's fundraiser

  Buddying scheme:
    - We try to buddy people based on certain criteria and what is important to them e.g. someone of a similar age and location so that they can meet up, similar stage in life e.g. thinking of having children etc.
    - This is peer support so the aim is that you both support each other as and when you can
- Walkthrough of how we run the familial FTD SG in person event:
    - Coffee and time to chat
    - A few presentations about trials and relevant research (things that are particularly relevant to the group that they can get involved in e.g. the development of this programme). This allows members to be involved in the design of projects and research that aims to benefit them in the future.
- Maybe walkthrough of how to get involved?
    - Screen recording of signing up
    - Picture of Nikki and the RDS team who they will hear from to notify them of events
    - Here we could maybe include some of the other benefits of being a member and connected with Nikki's team re support
- Testimonials from member(s) on their experience

8. Living well at-risk

Video

Content:

- So far this programme has focused on dealing with issues that may make life more difficult and complicated
- But it is important to also think about what you can do to make the most of life
- Although your risk of FTD poses lots of challenges, through working through these challenges it may be possible to create room for some positive aspects of the risk.
- TESTIMONIAL FROM PARTICIPANT

How might we help with this

- Firstly, it is always helpful to remember the pillars of good mental health when approaching anything in life: exercise, eating well, sleeping, and connecting socially with others.
- It is also important to remain connected to your values, what towards moves would you like to make more of?
    - Try to link this to the example given in the testimonial
    - Connect and reflect exercise
- Regularly practice grounding yourself in the present moment

Activity

- Guided meditation – leaves in the stream?

Summary

Action plan:

- Remember when difficult thoughts, feelings and situations arise:
    - Ground yourself in the present moment using some of the techniques we have practiced. E.g. dropping anchor
    - Unhook from the difficult thoughts/feelings/situation (naming the story/write thoughts on paper)
    - Practice making room for these thoughts (observe, breathe, expand, allow OR compassionate hand)
    - Act flexibly guided by your values
    - Self-compassion – hold yourself kindly

Check in session outlines:

Check in 1:

- Discuss areas of importance for participant
- Discuss experience of modules so far and 'homework' activities
- Draw choice point and discuss towards and away moves
- Discuss workability – if you let being at-risk dictate what you do and hook you, does it take you towards or away form the life that you want?
- Goal setting

Check in 2:

- Discuss experience of modules so far and 'homework' activities
- Review choice point and committed action
    - Include practical planning, problem solving and factoring risk into decision making

  Optional:

- Time to address additional issues identified in check in 1 – plan this in supervision with JCS for each individual
- Non-carriers: Using guilt/frustration as an ally
- Unknown/carriers: Worry about symptoms – go over plan for review

Using guilt/shame/anger as an ally

Emotions are designed to help us communicate well with people, motivate us to act in

certain ways and illuminate what is important. Instead of trying to ignore these emotions, instead we can try to make use of them and harness the energy they can give us. E.g. when professional actors or musicians prepare to perform, they often say they feel “buzzed” or “revved up” rather than anxious, but the emotion they’re feeling is the same, it has just been reframed to be useful and provide them with an “adrenaline rush” for their performance. We can apply this to guilt/anger by asking some of these reflective questions:

- *What does this emotion remind you to do in terms of caring for yourself or others?*
    - This could be things like spending more time with your family, spending quality time with siblings/parents/children, practice self-care
- *What does this emotion tell you…*
    - *That you care about?*
    - *About the sort of person you want to be?*
    - *About what you really want?*
    - *That you need to address?*
    - *That you need to do more/less of/differently?*
    - *That you need to do differently in the way you treat yourself or others?*

Check in 3:

- Discuss experience of modules so far and ‘homework’ activities
- Discuss plan for post-intervention
- Discuss referrals needed
- Time to address additional issues identified in check in 1 – plan this in supervision with JCS for each individual
- Revisit goals

Appendix 8: Intervention check-in draft agenda, script and worksheet

Check in 1 session script:

- Hello and agenda setting (5mins)
    - Thanks for joining / good to see you
    - Aims of these check ins generally are to: find out how you're getting on with the intervention and any problems with using it, to consolidate anything that you've found helpful so far and think about how you might implement that in your everyday life, to go deeper with anything that's really chimed that you'd like to explore further, and to revisit anything you didn't get or have questions about – does that all sound ok?
- Offer a 3 minute breathing space
    - We're aware people might be arriving to these sessions from a busy or stressful day and that it can be a bit of a gear-shift so there's no obligation but if you would like I can take us through a 3 minute breathing space exercise to ground us in the here and now and hopefully bring a bit of a sense of calm – would you like that or are you ok without?
- PART 1: Ok so the next about 15 minutes are for us to discuss your experience of the modules and homework so far (15 mins)
- Which modules have you mostly accessed so far (have a list handy to prompt)?
    - Prompts:
        - Anything that has really chimed/that you've really liked or found helpful?
        - Anything that needs clarifying, that you didn't understand?
        - Anything you think you might use again/going forward?
        - Anything you'd like to go through again with me here today?
- PART 2: Now we have about 15 minutes to go through an activity or exercise together: *[select together based on responses to above whether this is…]*
    - Prompts – this could be:
        - Us going through any homework activities you've done that you would be happy to/like to share

        - Us going through something that didn't chime or that you didn't get during the modules to see if we can problem solve
        - Me answering any questions for clarification
        - Us going through an activity you really liked to consolidate this and discuss what's helpful
        - Us exploring how you might use anything you really liked within your everyday life and any potential barriers to that which we can hopefully problem solve together
- Ok so now we have a few minutes and I would like to invite you to discuss and agree anything we are going to aim to do between now and next time:
    - You are going to (e.g. do modules XYZ, practice exercise ABC):
    - I am going to (e.g. have a look in to/follow up on/find out about XYZ:
- And now we have a brief worksheet we can complete together so you have a record of today's session and the main points we discussed to take away with you (10 mins)
-
- Would you like to close the session with a 3 minute breathing space exercise before you return to your day?
- Thank you very much for your time today, I will send a copy of that worksheet over and you have my email address if you want to get in touch about anything between now and our next check in session. Shall we schedule that now or would you prefer me to send some potential dates over by email?
- Thanks very much and look forward to seeing you next time, take care until then

Check in 1 worksheet:

The thing I found most helpful in the intervention was (e.g. an analogy, exercise):

_____

_____

I think this might be most helpful for (e.g. certain thoughts, feelings):

_____

_____

A good time for me to practice it would be:

_____

A good place for me to practice it would be:

_____

What has/might get in the way of me practicing it:

_____

Possible ways around that could be:

_____

_____

What has/might help me to practice this:

_____

_____

Who might help me/facilitate me in doing this?

Things to do before the next check in session:

Participant:_____

Facilitator:

_____

Check in 2 session script:

- Hello and agenda setting (5mins)
    - Thanks for joining / good to see you
    - Just a reminder that the aims of these check ins generally are to: find out how you're getting on with the intervention and any problems with using it, to consolidate anything that you've found helpful so far and think about how you might implement that in your everyday life, to go deeper with anything that's really chimed that you'd like to explore further, and to revisit anything you didn't get or have questions about – does that all sound ok?
- Offer a 3 minute breathing space
    - We're aware people might be arriving to these sessions from a busy or stressful day and that it can be a bit of a gear-shift so there's no obligation but if you would like I can take us through a 3 minute breathing space exercise to ground us in the here and now and hopefully bring a bit of a sense of calm – would you like that or are you ok without?
- Ok so first of all just to follow up on any action we agreed at our last check in... (10mins)
- PART 1: Ok so the next about 15 minutes are for us to discuss your experience of the modules and homework since our first check in (15 mins)
- Which modules have you mostly accessed since our last check in (have a list handy to prompt)?
    - Prompts:
        - Anything that has really chimed/that you've really liked or found helpful?
        - Anything that needs clarifying, that you didn't understand?
        - Anything you think you might use again/going forward?
        - Anything you'd like to go through again with me here today?
- PART 2: Now we have about 15 minutes to go through an activity or exercise together: *[select together based on responses to above whether this is…]*
    - Prompts – this could be:
        - Us going through any homework activities you've done that you

would be happy to/like to share
    - Us going through something that didn't chime or that you didn't get during the modules to see if we can problem solve
    - Me answering any questions for clarification
    - Us going through an activity you really liked to consolidate this and discuss what's helpful
    - Us exploring how you might use anything you really liked within you everyday life and any potential barriers to that which we can hopefully problem solve together
- Ok so now we have a few minutes to discuss and agree anything we are going to aim to do between now and next time:
    - You are going to (e.g. do modules XYZ, practice exercise ABC):
    - I am going to (e.g. have a look in to/follow up on/find out about XYZ:
- And now we have a brief worksheet we can complete together so you have a record of today's session and the main points we discussed to take away with you (10 mins)
- Would you like to close the session with a 3 minute breathing space exercise before you return to your day?
- Thank you very much for your time today, I will send a copy of that worksheet over and you have my email address if you want to get in touch about anything between now and our next check in session. Shall we schedule that now or would you prefer me to send some potential dates over by email?
- Thanks very much and look forward to seeing you next time, take care until then

Check in 2 worksheet:

The thing I found most helpful in the intervention was (e.g. an analogy, exercise):

_____

_____

I think this might be most helpful for (e.g. certain thoughts, feelings):

_____

_____

A good time for me to practice it would be:

_____

A good place for me to practice it would be:

_____

What has/might get in the way of me practicing it:

_____

Possible ways around that could be:

_____

_____

What has/might help me to practice this:

_____

_____

Things to do before the next check in session:

Participant:_____

Facilitator:

_____

Check in 3 session script:

- Hello and agenda setting (5mins)
    - Thanks for joining / good to see you
    - Just a reminder that the aims of these check ins generally are to: find out how you're getting on with the intervention and any problems with using it, to consolidate anything that you've found helpful so far and think about how you might implement that in your everyday life, to go deeper with anything that's really chimed that you'd like to explore further, and to revisit anything you didn't get or have questions about – does that all sound ok?
- Offer a 3 minute breathing space
    - We're aware people might be arriving to these sessions from a busy or stressful day and that it can be a bit of a gear-shift so there's no obligation but if you would like I can take us through a 3 minute breathing space exercise to ground us in the here and now and hopefully bring a bit of a sense of calm – would you like that or are you ok without?
- Ok so first of all just to follow up on any action we agreed at our last check in... (10mins)
- PART 1: Ok so the next about 15 minutes are for us to discuss your experience of the modules and homework since our last check in (15 mins)
- Which modules have you mostly accessed since our last check in (have a list handy to prompt)?
    - Prompts:
        - Anything that has really chimed/that you've really liked or found helpful?
        - Anything that needs clarifying, that you didn't understand?
        - Anything you think you might use again/going forward?
        - Anything you'd like to go through again with me here today?
- PART 2: Now we have about 15 minutes to go through an activity or exercise together: *[select together based on responses to above whether this is…]*
    - Prompts – this could be:
        - Us going through any homework activities you've done that you

would be happy to/like to share
    - Us going through something that didn't chime or that you didn't get during the modules to see if we can problem solve
    - Me answering any questions for clarification
    - Us going through an activity you really liked to consolidate this and discuss what's helpful
    - Us exploring how you might use anything you really liked within you everyday life and any potential barriers to that which we can hopefully problem solve together
- And now we have a final worksheet we can complete together so you have a record of today's session and some of the things we've covered but it will also help us to think about how you can keep implementing anything you've found helpful from the intervention now that these sessions and your participation in the intervention is coming to an end (10 mins)
- Would you like to close the session with a 3 minute breathing space exercise before you return to your day?
- Thank you very much for your time today and over the course of the intervention, I will send a copy of that worksheet over and you have my email address if you want to get in touch again in the future.
- Thanks very much and all the very best

Check in 3 worksheet:
Across the course of the intervention the analogies I have found most resonated with me are:

_____

_____

Across the course of the intervention the exercises I have found most helpful and that I plan to keep practicing are:

_____

_____

My plan for helping myself continue practicing (time and place) is

_____

What might get in the way of me continuing to practice these exercises?

_____

_____

Possible ways around that could be:

_____

_____

What has/might help me to practice these:

_____

_____

If I find myself struggling I will…

- Talk to/contact (e.g. friend, family, helpline):

_____

_____

_____

- Do (e.g. go for a walk, listen to a favourite song):

_____

_____

_____

Appendix 9: Intervention proposed outcome measure questionnaires

Acceptance and Action Questionnaire (AAQ-2)

AAQ-2

Below you will find a list of statements. Please rate how true each statement is for you by selecting a number next to it. Use the scale below to make your choice.

1	2	3	4	5	6	7
never true	very seldom true	seldom true	sometimes true	frequently true	almost always true	always true

1.	My painful experiences and memories make it difficult for me to live a life that I would value.	1 2 3 4 5 6 7
2.	I'm afraid of my feelings.	1 2 3 4 5 6 7
3.	I worry about not being able to control my worries and feelings.	1 2 3 4 5 6 7
4.	My painful memories prevent me from having a fulfilling life.	1 2 3 4 5 6 7
5.	Emotions cause problems in my life.	1 2 3 4 5 6 7
6.	It seems like most people are handling their lives better than I am.	1 2 3 4 5 6 7
7.	Worries get in the way of my success.	1 2 3 4 5 6 7

Generalised Anxiety Disorder -7 (GAD-7)

Over the **last 2 weeks**, how often have you been bothered by the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Feeling nervous, anxious or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Worrying too much about different things	0	1	2	3
4	Trouble relaxing	0	1	2	3

5	Being so restless that it is hard to sit still	0	1	2	3
6	Becoming easily annoyed or irritable	0	1	2	3
7	Feeling afraid as if something awful might happen	0	1	2	3

Patient Health Questionnaire – 9 item depression module (PHQ-9)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving	0	1	2	3

	around a lot more than usual				
9	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Impact of Event scale - Revised

Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to (the event). How much were you distressed or bothered by these difficulties?

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Any reminder brought back feelings about it	0	1	2	3	4
2. I had trouble staying asleep	0	1	2	3	4
3. Other things kept making me think about it	0	1	2	3	4
4. I felt irritable and angry	0	1	2	3	4
5. I avoided letting myself get upset when I thought about it or was reminded of it	0	1	2	3	4
6. I thought about it when I didn't mean to	0	1	2	3	4
7. I felt as if it hadn't happened or wasn't real	0	1	2	3	4
8. I stayed away from reminders about it	0	1	2	3	4
9. Pictures about it popped into my mind	0	1	2	3	4
10. I was jumpy and easily startled	0	1	2	3	4
11. I tried not to think about it	0	1	2	3	4
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them	0	1	2	3	4
13. My feelings about it were kind of numb	0	1	2	3	4
14. I found myself acting or feeling as though I was	0	1	2	3	4

back at that time					
15. I had trouble falling asleep	0	1	2	3	4
16. I had waves of strong feelings about it	0	1	2	3	4
17. I tried to remove it from my memory	0	1	2	3	4
18. I had trouble concentrating	0	1	2	3	4
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	0	1	2	3	4
20. I had dreams about it	0	1	2	3	4
21. I felt watchful or on-guard	0	1	2	3	4
22. I tried not to talk about it	0	1	2	3	4

Psychological Adaptation to Genetic Information Scale (PAGIS)

	Rate from 1-6 where 1= Strongly disagree 6 = Strongly agree
1. I can't seem to stop myself from thinking about having this gene.	
2. Knowing I have this gene is always on my mind.	
3. Other things in my life always seem to make me think about having this gene.	
4. I think about the fact that I have this gene when I don't mean to think about it.	
5. I rarely think about the fact that I have this gene.	
6. I have dreams about having this gene.	
7. It's hard for me to talk about having this gene with my relatives.	

8. It's hard for me to talk about having this gene with my friends.	
9. I feel satisfied with my communication with my family about what having this gene means to me.	
10. It makes me feel better to talk to my loved ones about having this gene.	
11. My relatives are supportive when I tell them about having this gene.	
12. My friends are supportive when I tell them about having this gene.	
13. Having this gene makes me feel inferior at times.	
14. Knowing that I have this gene sometimes makes me feel like a failure.	
15. Knowing that I have this gene decreases my feelings of self- worth.	
16. I would feel better about myself if I did not know that I had this gene.	
17. I understand how I came to have this gene.	
18. I understand the health risks my relatives face because of this gene.	
19. I feel certain that I understand the meaning of having this gene.	
20. I understand the chances I have of passing this gene along to my children.	
21. I feel that I can explain to other people what having this gene means.	
22. I feel confused because I have been given different explanations of what having this gene means.	
23. If a problem arises because of this gene I will be able to find a solution.	
24. I am confident that I can work out any problems	

having this gene might cause.	
25. I am confident that I can deal with any effects of this gene.	
26. I believe that there are things I can do to avoid the problems that may arise from having this gene.	

ICECAP-A

ABOUT YOUR OVERALL QUALITY OF LIFE

Please indicate which statements best describe your overall quality of life at the moment by placing a tick (✓) in **ONE** box for each of the five groups below.

1. Feeling settled and secure		
I am able to feel settled and secure in **all** areas of my life		4
I am able to feel settled and secure in **many** areas of my life		3
I am able to feel settled and secure in **a few** areas of my life		2
I am **unable** to feel settled and secure in **any** areas of my life		1

2. Love, friendship and support		
I can have **a lot** of love, friendship and support		4
I can have **quite a lot** of love, friendship and support		3
I can have **a little** love, friendship and support		2
I **cannot** have **any** love, friendship and support		1

3. Being independent		
I am able to be **completely** independent		4
I am able to be independent in **many** things		3
I am able to be independent in **a few** things		2
I am **unable** to be at all independent		1

4. Achievement and progress	
I can achieve and progress in all aspects of my life	4
I can achieve and progress in **many** aspects of my life	3
I can achieve and progress in **a few** aspects of my life	2
I **cannot** achieve and progress in **any** aspects of my life	1

5. Enjoyment and pleasure	
I can have **a lot** of enjoyment and pleasure	4
I can have **quite a lot** of enjoyment and pleasure	3
I can have **a little** enjoyment and pleasure	2
I **cannot** have **any** enjoyment and pleasure	1

Please ensure you have only ticked **ONE** box for each of the five groups.

DQ5

Distress Questionnaire-5 (DQ5)

This scale is designed to assess levels of general psychological distress.

Usage: No permission required - please cite reference

In the last 30 days:

	Never	Rarely	Sometimes	Often	Always
My worries overwhelmed me	☐	☐	☐	☐	☐
I felt hopeless	☐	☐	☐	☐	☐
I found social settings upsetting	☐	☐	☐	☐	☐
I had trouble staying focused on tasks	☐	☐	☐	☐	☐
Anxiety or fear interfered with my ability to do the things I needed to do at work or at home	☐	☐	☐	☐	☐

Scoring

The total score on the DQ5 is obtained by summing all of the responses, with “Never” scoring 1, “Rarely” 2, “Sometimes” 3, “Often” 4 and “Always” scoring 5. Total scores will range from 5-25. Scores of 11-14 indicate elevated distress and scores of 14 or higher indicate high psychological distress.

EUROQoL EQ 5D 5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.

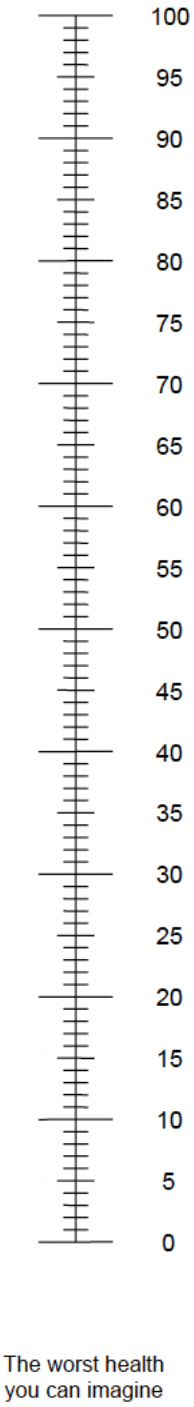
The best health you can imagine

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.

0 means the worst health you can imagine.

- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below

YOUR HEALTH TODAY = [ ]



Appendix 10: FTD genetic testing protocol Delphi consensus round 1 – Question 1 percentage of responses for each item

	All	All <50 years	All <60 years	All <x years (please include age in 2nd column)		Those with a strong family history (defined as modified Goldman 1 or 2)	Those with a family history (defined as modified Goldman score 1, 2 or 3)	Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5)
bvFTD	42%	25%	33%	17%	60/65	27%	27%	45%
FTD-ALS	67%	17%	33%	17%	any/65	27%	27%	36%
nfvPPA	25%	33%	33%	8%	any	27%	45%	55%
svPPA	8%	42%	25%	8%	60	45%	45%	45%
lvPPA (AD biomarkers unknown)	8%	50%	17%	8%	60	36%	45%	36%
lvPPA (AD biomarkers positive)	0%	33%	33%	8%	60	36%	18%	27%
lvPPA (AD biomarkers negative)	25%	33%	25%	17%	60/65	18%	27%	45%
PPA-NOS	17%	33%	33%	17%	60/65	27%	27%	36%
CBS	8%	50%	17%	8%	60	45%	45%	45%

PSP	0%	42%	17%	8%	60	64%	36%	36%
bvFTD/PPA overlap	42%	25%	33%	17%	60/65	27%	36%	36%
CBS/PPA overlap	17%	42%	25%	8%	60	36%	36%	55%
Late-onset psychosis (including schizophrenia)	17%	8%	17%	8%	60	55%	18%	0%

Appendix 11: FTD genetic testing protocol Delphi consensus round 2 – Question 1 percentage of responses for each item

Phenotype	**All**	**All <60 years**	**All <50 years**	**Those with a strong family history (defined as modified Goldman 1 or 2)**	**Those with a family history (defined as modified Goldman score 1, 2 or 3)**	**Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5)**
bvFTD	83%	0%	-	-	-	13%
FTD-ALS	92%	0%	-	-	-	4%
nfvPPA	42%	0%	0%	0%	13%	25%
svPPA	17%	0%	0%	9%	9%	39%
lvPPA (AD biomarkers unknown)	9%	4%	0%	4%	30%	22%
lvPPA (AD biomarkers positive)	0%	17%	0%	39%	4%	0%
lvPPA (AD biomarkers negative)	46%	4%	-	-	4%	25%
PPA-NOS	54%	4%	-	4%	0%	21%
CBS	18%	0%	0%	18%	9%	36%

PSP	9%	0%	0%	35%	4%	22%
bvFTD/PPA overlap	70%	0%	-	-	4%	9%
CBS/PPA overlap	26%	0%	0%	9%	9%	35%
Late-onset psychosis (including schizophrenia)	5%	-	-	73%	9%	14%

Appendix 12: FTD genetic testing protocol round 2 question 1 – percentage of responses for additional combined options

	Goldman score of 1-3.5 **AND** <60 yrs	Goldman score of 1-3.5 **OR** <60 yrs	Goldman score of 1-3.5 **AND** <50 yrs	Goldman score of 1-3.5 **OR** <50 yrs	Goldman score of 1-3 **AND** <60 yrs	Goldman score of 1-3 **AND** <50 yrs	Goldman score of 1-3 **OR** <60 yrs	Goldman score of 1-3 **OR** <50 yrs	Goldman score of 1-2 **AND** <60 yrs	Goldman score of 1-2 **OR** <60 yrs	Goldman score of 1-2 **AND** <50 yrs	Goldman score of 1-2 **OR** <50 yrs
bvFTD	0%	4%	-	-	-	-	-	-	-	-	-	-
FTD-ALS	0%	4%	-	-	-	-	-	-	-	-	-	-
nfvPPA	4%	8%	0%	0%	4%	0%	0%	4%	-	-	-	-
svPPA	0%	9%	0%	4%	4%	0%	4%	4%	-	-	-	-
lvPPA (AD biomarkers unknown)	-	-	-	-	9%	-	22%	-	-	-	-	-
lvPPA (AD biomarkers positive)	-	-	-	-	-	-	-	-	22%	17%	-	-
lvPPA (AD biomarkers	8%	8%	-	-	-	-	-	-	-	-	-	-

negative)												
PPA-NOS	13%	4%	-	-	-	-	-	-	-	-	-	-
CBS	-	-	0%	5%	-	-	-	-	-	-	0%	14%
PSP	0%	4%	0%	4%	-	-	-	-	4%	9%	0%	9%
bvFTD/PPA overlap	0%	4%	-	-	-	-	-	-	-	-	-	-
CBS/PPA overlap	9%	9%	0%	4%	-	-	-	-	-	-	-	-
Late-onset psychosis (including schizophrenia)	-	-	-	-	-	-	-	-	-	-	-	-

Appendix 13: FTD genetic testing protocol round 3 question 1 – percentage of responses for each item

	All	All <50 years	All <60 years	Those with a strong family history (defined as modified Goldman 1 or 2) at any age				Those with a family history (defined as modified Goldman score 1, 2 or 3) at any age	Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5) at any age		
				At any age	AND <60 yrs	OR <60 yrs	OR <50 yrs		At any age	AND <60 yrs	OR <60 yrs
bvFTD											
FTD-ALS											
nfvPPA	76%							4%	20%		
svPPA	16%			0%				8%	72%		4%
lvPPA (AD biomarkers unknown)								60%	20%		4%
lvPPA (AD biomarkers			12%	64%	12%	12%					

positive)											
lvPPA (AD biomarkers negative)	80%							8%		8%	4%
PPA-NOS	80%								20%	0%	
CBS	8%			16%					76%		
PSP	4%			64%		4%	4%		24%		
bvFTD/PPA overlap											
CBS/PPA overlap	20%			8%				0%	60%	4%	8%
Late-onset psychosis (including schizophrenia)											

Appendix 14: FTD genetic testing protocol results rounds 1-3 questions 2-4, percentage of responses for each item

2. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

	Round 1	Round 2	Round 3
No – they should have predictive testing instead of non-predictive testing	23%	8%	
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	25%	20%	12%
Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	37%	52%	64%
Other – please comment: - An individualised approach should be considered for each person according to their needs; on many occasions this will require predictive counselling	12% 4%	20%	24%

3. Should blood or CSF progranulin levels be used as a supplement to ACMG guidelines for determining pathogenicity of *GRN* mutations.

	Round 1	Round 2	Round 3
No – should use current guidelines – progranulin levels are not helpful	10%	5%	
Yes – a low blood or CSF level should be considered definitively pathogenic	19%	14%	
Yes – a low blood or CSF level should be considered supportive of pathogenicity but not definitive	62%	82%	
Yes – a low CSF (but not blood) level should be	5%		

considered definitively pathogenic			
Yes – a low CSF (but not blood) should be considered supportive of pathogenicity but not definitive	5%		
Other – please comment	0%		

4. Who should be offered predictive testing for genetic FTD?

Scenario 1: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is able and willing to consent to diagnostic testing.	Round 1	Round 2	Round 3
Do not offer predictive testing at all	4%		
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	0%		
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present and then offer predictive testing	70%	85%	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	22%	15%	
Other – please comment	4%		

Scenario 2: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is unable to consent to diagnostic testing	Round 1	Round 2	Round 3
Do not offer predictive testing at all	7%		
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	4%		
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	50%	81%	

Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	29%	15%	
Store a sample from the affected relative independent of their family history (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	11%	4%	
Store a sample from the affected only if the relative has a strong family history of FTD (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	0%		
Other – please comment	4%		

Scenario 3: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative but a sample of DNA or tissue is stored from an affected relative.	Round 1	Round 2	Round 3
Do not offer predictive testing at all	14%	4%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	0%		
Perform diagnostic testing on the affected relative's stored sample independent of their family history to ascertain whether a mutation is present and then offer predictive	43%	84%	

testing			
Perform diagnostic testing on the affected relative's stored sample only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	32%	12%	
Other – please comment	11%		

Scenario 4: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member	Round 1	Round 2	Round 3
Do not offer predictive testing at all	78%	88%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	11%	12%	
Other – please comment	11%		

Scenario 5: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD	Round 1	Round 2	Round 3
Do not offer predictive testing at all	18%	12%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	4%		
Perform targeted predictive testing based on the underlying characteristic pathology e.g. 1) presence of dipeptide repeats in the brain would lead to testing for	61%	88%	

C9orf72; e.g.2) presence of TDP-43 type D pathology would lead to testing for VCP			
Other – please comment	18%		

Appendix 15: FTD genetic testing protocol Delphi round 1 questionnaire

FTD genetics protocol Delphi consensus

1. What would you consider your specialist interest to be?

Neurologist with interest in FTD	
Neurologist with interest in neurogenetics	
Psychiatrist with interest in FTD	
Psychiatrist with interest in neurogenetics	
Clinical geneticist with interest in neurogenetics	
Other (please state):	

2. When would you recommend offering diagnostic testing for the following diagnoses? (Tick one or more boxes)

	All	All <50 years	All <60 years	All <x years (please include age in 2nd column)		Those with a strong family history (defined as modified Goldman 1 or 2)	Those with a family history (defined as modified Goldman score 1, 2 or 3)	Those with a family history (defined as modified Goldman score 1, 2, 3 or 3.5)
bvFTD								
FTD-ALS								
nfvPPA								

svPPA								
lvPPA (AD biomarkers unknown)								
lvPPA (AD biomarkers positive)								
lvPPA (AD biomarkers negative)								
PPA-NOS								
CBS								
PSP								
bvFTD/PPA overlap								
CBS/PPA overlap								
Late-onset psychosis (including schizophrenia)								

Please add any comments you have

Note:

Modified Goldman score =

1 - autosomal dominant family history

2 - familial aggregation of three of more family members with dementia (including FTD/PSP/CBS/ALS)

3/3.5 - one other first degree relative with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family i.e. <65, and 3.5 if onset above 65

4 - no or unknown family history.

3. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

No – they should have predictive testing instead of non-predictive testing	
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	
Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	
Other – please comment	

4. Should blood or CSF progranulin levels be used as a supplement to ACMG guidelines for determining pathogenicity of *GRN* mutations.

No – should use current guidelines – progranulin levels are not helpful	
Yes – a low blood or CSF level should be considered definitively pathogenic	

Yes – a low blood or CSF level should be considered supportive of pathogenicity but not definitive	
Yes – a low CSF (but not blood) level should be considered definitively pathogenic	
Yes – a low CSF (but not blood) should be considered supportive of pathogenicity but not definitive	
Other – please comment	

5. Who should be offered predictive testing for genetic FTD?

Scenario 1: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is able and willing to consent to diagnostic testing.	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present and then offer predictive testing	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	
Other – please comment	

Scenario 2: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is unable to consent to diagnostic testing	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	
Store a sample from the affected relative independent of their family history (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	
Store a sample from the affected only if the relative has a strong family history of FTD (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	
Other – please comment	

Scenario 3: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative but a sample of DNA or tissue is stored from an affected relative.	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform diagnostic testing on the affected relative's stored sample independent of their family history to ascertain whether a mutation is present and then offer predictive testing	
Perform diagnostic testing on the affected relative's stored sample only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	
Other – please comment	

Scenario 4: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Other – please comment	

Scenario 5: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD	
Do not offer predictive testing at all	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	
Perform targeted predictive testing based on the underlying characteristic pathology e.g. 1) presence of dipeptide repeats in the brain would lead to testing for C9orf72; e.g.2) presence of TDP-43 type D pathology would lead to testing for VCP	
Other – please comment	

Appendix 16: FTD genetic testing protocol Delphi round 2 questionnaire

FTD genetics protocol Delphi consensus

1. When would you recommend offering diagnostic testing for the following diagnoses? Tick only 1 box for each diagnosis. The percentage of respondents who selected each option is shown in brackets (%).

Note:

Modified Goldman score =

1 - autosomal dominant family history

2 - familial aggregation of three of more family members with dementia (including FTD/PSP/CBS/ALS)

3/3.5 - one other first degree relative with dementia (modified to give a score of 3 only if there is a history of young-onset dementia within the family i.e. <65, and 3.5 if onset above 65

4 - no or unknown family history.

bvFTD

☐ All (62%)
☐ Goldman score of 1-3.5 **(at any age) (**31%)
☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (19%)

FTD-ALS

☐ All (77%)

☐ Goldman score of 1-3.5 **(at any age)** (19%)
☐ All <60 yrs **(any family history)** (12%)

☐ Goldman score of 1-3.5 (19%) **AND** <60 yrs (12%)
☐ Goldman score of 1-3.5 (19%) **OR** <60 yrs (12%)

nfvPPA
☐All (38%)
☐ Goldman score of 1-3.5 **(at any age)** (27%)
☐ Goldman score of 1-3 **(at any age)** (23%)
☐ All <60 yrs **(any family history)** (19%)
☐ All <50 yrs **(any family history)** (12%)
☐ Goldman score of 1-2 **(at any age)** (12%)

☐ Goldman score of 1-3.5 (27%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (27%) **AND** <50 yrs (12%)
☐ Goldman score of 1-3.5 (27%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3.5 (27%) **OR** <50 yrs (12%)
☐ Goldman score of 1-3 (23%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3 (23%) **AND** <50 yrs (12%)
☐ Goldman score of 1-3 (23%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3 (23%) **OR** <50 yrs (12%)

svPPA
☐All (19%)
☐ Goldman score of 1-3.5 **(at any age)** (31%)
☐ Goldman score of 1-3 **(at any age)** (27%)
☐ All <50 yrs **(any family history)** (19%)
☐ Goldman score of 1-2 **(at any age)** (19%)
☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3 (27%) **AND** <50 yrs (19%)
☐ Goldman score of 1-3 (27%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3 (27%) **OR** <50 yrs (19%)
☐ Goldman score of 1-3 (27%) **OR** <60 yrs (19%)

lvPPA (AD biomarkers unknown)
☐ Goldman score of 1-3 **(at any age)** (31%)
☐ Goldman score of 1-3.5 **(at any age)** (23%)
☐ All <60 yrs **(any family history)** (23%)
☐ Goldman score of 1-2 (**at any age) (**19%)
☐ All (19%)
☐ All <50 yrs **(any family history)** (15%)

☐ Goldman score of 1-3 (31%) **AND** <60 yrs (23%)
☐ Goldman score of 1-3 (31%) **OR** <60 yrs (23%)

lvPPA (AD biomarkers positive)
☐ Goldman score of 1-2 **(at any age)** (31%)
☐ All <60 yrs **(any family history)** (27%)
☐ Goldman score of 1-3.5 **(at any age)** (23%)
☐ All <50 yrs **(any family history)** (15%)
☐ Goldman score of 1-3 **(at any age)** (12%)
☐ All (12%)

☐ Goldman score of 1-2 (31%) **AND** <60 yrs (27%)
☐ Goldman score of 1-2 (31%) **OR** <60 yrs (27%)

lvPPA (AD biomarkers negative)

☐ All (35%)

☐ Goldman score of 1-3.5 **(at any age)** (35%)

☐ Goldman score of 1-3 **(at any age)** (19%)

☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (35%) **AND** <60 yrs (19%)

☐ Goldman score of 1-3.5 (35%) **OR** <60 yrs (19%)

PPA-NOS

☐ All (31%)

☐ Goldman score of 1-3.5 **(at any age)** (27%)

☐ All <60 yrs **(any family history)** (27%)

☐ Goldman score of 1-3 **(at any age)** (19%)

☐ Goldman score of 1-2 **(at any age)** (15%)

☐ Goldman score of 1-3.5 (27%) **AND** <60 yrs (27%)

☐ Goldman score of 1-3.5 (27%) **OR** <60 yrs (27%)

CBS

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ Goldman score of 1-2 **(at any age)** (27%)

☐ All <50 yrs **(any family history)** (23%)

☐ Goldman score of 1-3 **(at any age)** (23%)

☐ All (23%)

☐ All <60 yrs **(any family history)** (19%)

☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (23%)

☐ Goldman score of 1-2 (27%) **AND** <50 yrs (23%)

☐ Goldman score of 1-2 (27%) **OR** <50 yrs (23%)

PSP

☐ Goldman score of 1-2 **(at any age)** (35%)

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ Goldman score of 1-3 **(at any age)** (27%)

☐ All <60 yrs **(any family history)** (23%)

☐ All <50 yrs **(any family history)** (23%)

☐ All (12%)

☐ Goldman score of 1-2 (35%) **AND** <60 yrs (23%)

☐ Goldman score of 1-2 (35%) **AND** <50 yrs (29%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (29%)

☐ Goldman score of 1-2 (35%) **OR** <60 yrs (23%)

☐ Goldman score of 1-2 (35%) **OR** <50 yrs (29%)

☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (29%)

bvFTD/PPA overlap

☐ All (54%)

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ Goldman score of 1-3 **(at any age)** (12%)

☐ All <60 yrs **(any family history)** (23%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (23%)

☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (23%)

CBS/PPA overlap

☐ Goldman score of 1-3.5 **(at any age)** (31%)

☐ All (23%)

☐ Goldman score of 1-3 **(at any age)** (23%)

☐ Goldman score of 1-2 **(at any age)** (19%)
☐ All <60 yrs **(any family history)** (19%)
☐ All <50 yrs **(any family history)** (15%)

☐ Goldman score of 1-3.5 (31%) **AND** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **OR** <60 yrs (19%)
☐ Goldman score of 1-3.5 (31%) **AND** <50 yrs (15%)
☐ Goldman score of 1-3.5 (31%) **OR** <50 yrs (15%)

Late-onset psychosis (including schizophrenia)
☐ Goldman score of 1-2 **(at any age)** (35%)
☐ Goldman score of 1-3.5 **(at any age)** (19%)
☐ Goldman score of 1-3 **(at any age) (**12%)
☐ All (12%)

For the following questions the percentage of respondents that selected each answer in the previous round is displayed. The answer you selected is highlighted in yellow (if still available – those options selected by less than 10% of respondents have been removed). Please re-answer these questions.

2. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

	Previous answers	Current answer
No – they should have predictive testing instead of non-predictive testing	28%	
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	28%	

Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	36%	
An individualised approach should be considered for each person according to their needs; on many occasions this will require predictive counselling	~16% (taken from 'other')	

3. Should blood or CSF progranulin levels be used as a supplement to ACMG guidelines for determining pathogenicity of *GRN* mutations.

	Previous answers	Current answer
No – should use current guidelines – progranulin levels are not helpful	10%	
Yes – a low blood or CSF level should be considered definitively pathogenic	19%	
Yes – a low blood or CSF level should be considered supportive of pathogenicity but not definitive	62%	

4. Who should be offered predictive testing for genetic FTD?

Scenario 1: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is able and willing to consent to diagnostic testing.		
	Previous answers	Current answer
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present and then offer predictive testing	70%	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to	22%	

ascertain whether a mutation is present and then offer predictive testing		

Scenario 2: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and a living, affected relative who is unable to consent to diagnostic testing		
	Previous answers	Current answer
Perform diagnostic testing on the affected relative independent of their family history to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	50%	
Perform diagnostic testing on the affected relative only if the relative has a strong family history of FTD to ascertain whether a mutation is present (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then offer predictive testing	29%	
Store a sample from the affected relative independent of their family history (if they are able to assent to having a blood or saliva sample taken and the family are all agreed on doing this) and then only test for a mutation after they have died i.e. only offer predictive testing after the relative's death	11%	

Scenario 3: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative but a sample of DNA or tissue is stored from a non-living affected relative. The family are in agreement with testing.

	Previous answers	Current answer
Do not offer predictive testing at all	14%	
Perform diagnostic testing on the affected relative's stored sample independent of their family history to ascertain whether a mutation is present and then offer predictive testing	43%	
Perform diagnostic testing on the affected relative's stored sample only if the relative has a strong family history of FTD to ascertain whether a mutation is present and then offer predictive testing	32%	

Scenario 4: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, and no knowledge of any pathology in an affected family member		
	Previous answers	Current answer
Do not offer predictive testing at all	78%	
Perform 'blind' predictive testing with a dementia panel/C9orf72 screening	11%	

Scenario 5: an asymptomatic person with a family history of FTD but no known genetic mutation in the family at present, and no living affected relative, and no DNA or tissue of an affected relative stored, but known pathology in an affected family member that is pathognomonic for a specific genetic form of FTD. E.g. only fixed tissue available, no DNA has been able to be extracted.		
	Previous answers	Current answer
Do not offer predictive testing at all	18%	

Perform targeted predictive testing based on the underlying characteristic pathology e.g. 1) presence of dipeptide repeats in the brain would lead to testing for C9orf72; e.g.2) presence of TDP-43 type D pathology would lead to testing for VCP	61%	

Appendix 17: FTD genetic testing protocol Delphi round 3 questionnaire

FTD genetics protocol Delphi consensus – round 3

Please re-answer these questions based on the new information provided, the percentage of respondents who selected each option in the previous round is shown and your previous answers are highlighted in yellow (if still available).

1. When would you recommend offering diagnostic testing for the following diagnoses? Tick only 1 box for each diagnosis.

nfvPPA		
	Consensus from previous round	Current answer
All	42%	
Goldman score of 1-3.5 (at any age)	25%	
Goldman score of 1-3 (at any age)	13%	
svPPA		
	Consensus from previous round	Current answer
All	17%	
Goldman score of 1-3.5 (at any age)	39%	
Goldman score of 1-3 (at any age)	9%	
Goldman score of 1-2 (at any age)	9%	
Goldman score of 1-3.5 OR <60 yrs	9%	
lvPPA (AD biomarkers unknown)		
	Consensus from previous round	Current answer
Goldman score of 1-3 (at any age)	30%	
Goldman score of 1-3.5 (at any age)	22%	
Goldman score of 1-3 OR <60 yrs	22%	

lvPPA (AD biomarkers positive)		
	Consensus from previous round	Current answer
Goldman score of 1-2 (at any age)	39%	
All <60 yrs (any family history)	17%	
Goldman score of 1-2 AND <60 yrs	22%	
Goldman score of 1-2 OR <60 yrs	17%	
lvPPA (AD biomarkers negative)		
	Consensus from previous round	Current answer
All	46%	
Goldman score of 1-3.5 (at any age)	25%	
Goldman score of 1-3.5 AND <60 yrs	8%	
Goldman score of 1-3.5 OR <60 yrs	8%	
PPA-NOS		
	Consensus from previous round	Current answer
All	54%	
Goldman score of 1-3.5 (at any age)	21%	
Goldman score of 1-3.5 AND <60 yrs	13%	
CBS		
	Consensus from previous round	Current answer
Goldman score of 1-3.5 (at any age)	36%	
Goldman score of 1-2 (at any age)	18%	
All	18%	
PSP		
	Consensus from previous round	Current answer

Goldman score of 1-2 (at any age)	35%	
Goldman score of 1-3.5 (at any age)	22%	
All	9%	
Goldman score of 1-2 OR <60 yrs	9%	
Goldman score of 1-2 OR <50 yrs	9%	
CBS/PPA overlap		
	Consensus from previous round	Current answer
Goldman score of 1-3.5 (at any age)	35%	
All	26%	
Goldman score of 1-3 (at any age)	9%	
Goldman score of 1-2 (at any age)	9%	
Goldman score of 1-3.5 AND <60 yrs	9%	
Goldman score of 1-3.5 OR <60 yrs	9%	

2. Should we consider a minimum criteria for 'symptomatic' (non-predictive) testing in those with prodromal symptoms from a known genetic FTD family [not currently meeting diagnostic criteria for bvFTD/FTD-ALS/PPA/CBS/PSP]?

	Consensus from previous round	Current answer
Yes – they should have at least mild cognitive and/or behavioural impairment, defined by meeting 2 of the Rascovsky criteria for bvFTD,	20%	
Yes – they should have at least minimal cognitive and/or behavioural impairment, defined by meeting 1 of the Rascovsky criteria for bvFTD,	52%	
An individualised approach should be considered for each person according to their needs; on many	20%	

occasions this will require predictive counselling		

Appendix 18: Amendments to MacLeod's HD predictive testing recommendations

	HD REC	HD COM	FTD REC	FTD COM	Change
1.	All persons who may wish to take the test should be given up to date, relevant information in order to make an informed voluntary decision.	The highest standards of counselling should be available in each country. It is recommended that informed consent for the test be documented with the signature of the person to be tested and the professional responsible for the counselling as a standard medical practice.			
2	Access to the test				
2	The decision to take the test is the sole choice of the person concerned. No requests from	The person must choose freely to be tested and not be coerced by family, friends, (potential)			

	third parties, be they family or otherwise, should be considered.	partners, physicians, insurance companies, employers, governments, etc.			
2.1	It is recommended that the minimum age of testing be 18 years. Minors at risk requesting the test should have access to genetic counselling, support and information including discussion of all their options for dealing with being at risk.	Testing for the purpose of adoption should not be permitted, since the child to be adopted cannot decide for him/herself whether he/she wants to be tested. It is essential, however, that the child should be informed about his/her at-risk status.			
2.2	Each participant should be able to take the test independently	Each national lay organization should use its influence with government			

	of his/her financial situation.	departments, public and private health insurers, etc, to reach this goal.			
2.3	Persons should not be discriminated against in any way as a result of genetic testing for Huntington's disease (see also REC 5.3.5).		Persons should not be discriminated against in any way as a result of genetic testing for **Frontotemporal dementia or related syndromes**		Changed wording – HD to FTD
2.4	Extreme care should be exercised when testing would provide information about another person who has not requested the test	This will arise when an individual(s) at 25% risk request(s) testing with full knowledge that his/her parent does not want to know his/her status. Every effort should be made by the			

		counsellors and the individuals concerned to come to a satisfactory solution of this conflict.			
2.5	For participants with evidence of a serious psychiatric condition, it may be advisable that testing is delayed and support services put into place.				
2.6	Testing for HD should not form part of a routine blood investigation without the specific permission of the subject.	Such a specific permission should in principle also be required for symptomatic persons.	Testing for **FTD** should not form part of a routine blood investigation without the specific permission of the subject.		Changed wording – HD to FTD

2.7	Ownership of the test results remains with the person who requested the test. Legal ownership of the stored DNA remains with the person from whom the blood was taken.	The consent form should address this issue. Local legal opinions may be helpful.			
2.8	All laboratories are expected to comply with the Organization for Economic Co-operation and Development (OECD) Guidelines for Quality Assurance in Molecular Testing by providing and practicing genetic testing under a quality assurance	At-risk individuals, family members and the lay organizations can enquire about the quality standards of the laboratory, including, for example, its certification and accreditation status. The lay organizations can also assist persons who want to be or have been tested with their enquiries and			

	framework, meet rigorous standards of accuracy, participating in external quality assessment (EQA) schemes and working towards certification and accreditation.	concerns.			
2.8.1	Laboratories should be cognizant of the limitations of the methodologies used (including, e.g. the possibility of missing a very large expansion, the risk of error that might lead to a non-carrier result if an affected relative has not been		Laboratories should be cognizant of the limitations of the methodologies used, and should indicate these clearly in reports issued, along with margins of error.		Minor amendment to the existing statement removing additional information.

	tested), and should indicate these clearly in reports issued, along with margins of error.				
2.9	The counsellors should be specifically trained in counselling methods and form part of a multidisciplinary team	Such a multidisciplinary team should consist, for example, of a clinical geneticist, genetic counsellor or social worker, neurologist, psychiatrist or psychologist.			
			There should be a minimisation of administrative issues wherever possible to make predictive testing more accessible to those living at-risk who may also be caregivers etc.		Added based on data from this study
3	Support during the test process				
3.	The participant should be encouraged to select a	This should be assessed on an individual basis and the presence			

	companion to accompany him/her throughout all the different stages: the pre-test, the taking of the test, the delivery of the results and the post-test stage.	of a companion may not be appropriate or required in all cases.			
3.1	The counselling unit should plan with the participant a follow up protocol which provides support during the pre- and post-test stages, whether or not a person chooses to be accompanied by a companion.	Wherever possible, support should be available close to the person's community, and on a remote basis, by phone or telehealth where necessary.			
			Access to counselling		

			and/or specialist psychological support should be available in tandem with predictive testing for FTD. There should be clarity regarding how to access this support and participants should be informed of this at the beginning of the predictive testing process.		
4	Recommendation on communication of information				
	Testing and counselling should be provided by genetic counselling units knowledgeable about molecular	Often the test will be conducted at a site different from the counselling centre. If no lay organization exists in the country, the centre should	Testing and counselling should be provided by genetic counselling units knowledgeable about molecular genetic issues in	If no lay organization exists in the country, contacts can be made with a lay organization of a neighbouring country or: - GENFI/ALLFTD - RDS	HD changed to FTD and information regarding lay organisations added

	genetic issues in Huntington's disease. These centres should work in close collaboration with the lay organization(s) of the country.	contact the IHA.	**FTD**. These centres should work in close collaboration with the lay organization(s) of the country.	- AFTD	
4.1	The laboratory performing the test should not communicate the final results to the counselling team until very close to the time the results are given to the participant.	The aim is to protect the participant from the possibility of counselling bias at any time (see also COM 5.2.6).			
4.2	As a rule, members of the counselling team or the technical staff should not communicate any information	Only in the most exceptional circumstances (e.g. prolonged coma or death) may information about the test result, if so			

	concerning the test and its results to third parties without the explicit permission of the person tested.	requested, be provided to family members whose risk is affected by the result.			
4.3	Neither the counselling centre nor the test laboratory should establish direct contact with a relative whose DNA may be needed for the purpose of the test without permission of the participant and of the relative. All precautions should be taken when approaching such a relative.				

4.4	Care should be taken regarding access to clinical reports of the test results.	Consent of the participant should be sought before sending a letter to any physician involved in their care (e.g. family doctor, neurologist, or hospital physician). The possible benefits and drawbacks of sending the result to such physicians should be discussed. These benefits include: post-test support, future clinical care including identification and support around the onset of symptoms, and their symptomatic treatment. The risks include: potential discrimination in			

		economic, social and medical domains, should their medical files be accessed by third parties. In general, it is good clinical practice for the counselling team to suggest that other physicians involved in the participant's care be kept informed about the test and the result. If the participant objects, his/her view should be respected except in the most exceptional of circumstances. If consent is given by the person tested for the test result to be communicated it should be			

		accompanied by a full explanation of the meaning of that result.			
5	Essential information - 'Essential information' means information which is absolutely vital to the whole test procedure. General information:				
5.1		This information should be both written and oral and be provided by the team responsible for the test service.			
5.1.1	On Huntington's disease, including the wide range of its clinical manifestations, the social and psychological implications, the genetic aspects, reproductive	It must be pointed out that at this time no proven prevention, treatment that slows disease progression, or cure is available.	On **FTD**, including the wide range of its clinical manifestations, the social and psychological implications, the genetic aspects, reproductive options, availability of treatment, etc.		HD changed to FTD

	options, availability of treatment, etc.				
5.1.2	On the implications of non-paternity (and nonmaternity).	Genetic testing may show, or suggest, that the putative parent is not the biological parent; this aspect should be drawn to the attention of the participant and discussed. With the presently available techniques of in vitro fertilization, etc., even occasional non-maternity may occur.	On the implications of non-paternity (and nonmaternity).	Genetic testing may show, or suggest, that the putative parent is not the biological parent; this aspect should be drawn to the attention of the participant and discussed.	Minor amendment removing additional information.
5.1.3	On lay organizations, including their documentation on HD, their addresses for help and social	If no lay organization exists in the country, contacts can be made with the IHA or lay organization of a neighbouring	On lay organizations, including their documentation on **FTD**, their addresses for help and social	If no lay organisation exists in the country, contacts can be made with a lay organisation of a neighbouring country or: - GENFI/ALLFTD	HD changed to FTD and information added regarding FTD lay organisations

	contacts, etc.	country.	contacts, etc.	- RDS - AFTD	
5.1.4.	Psychosocial support and counselling must be available before the test procedure commences.	Lay organizations should be mentioned as an additional source of support and information.			
			9. Predictive testing and genetic counselling should be tailored to the individual wherever possible: a. During the first genetic counselling session, a timeline for future appointments should be agreed with the patient, for some it may be appropriate to have fewer sessions or a shorter period between appointments due to other time-sensitive issues such as PGD. Therefore, it is important to assess on a case-by-case basis. b. As above, the length of the 'cooling off' period should be discussed and agreed with the patient, again to minimise		

			frustration. For some a shorter cooling off period may be appropriate if they have communicated certainty on their decision throughout the counselling process, while those who remain undecided may request a longer period to make their final decision. The content of genetic counselling should be tailored to the individual's knowledgebase. The counsellor should assess the patient's baseline knowledge and what they would like to understand through the counselling process. For some, it may be pertinent to cover the basic elements FTD psychoeducation and heritability, such as possible phenotypes and potential age at onset. Others may already be well-read on such information and prefer a higher-level of understanding, with the guidance of a professional who may be able to help them understand more complex issues		
5.2 – Information pertaining to the test					
5.2.1	How the test is done.				

5.2.2	Possible need for DNA from an affected family member and the possible problems arising from this.	Asking an affected person, who may be unaware of or unwilling to acknowledge his/her symptoms, to contribute a blood sample may be an invasion of privacy.			
5.2.3	The limitations of the test (error rate, uncertain predictive interpretation of some CAG repeat numbers, etc).		The limitations of the test (error rate, uncertain interpretation of some repeat numbers, variants of unknown significance etc).		HD testing limitations changed to include FTD testing limitations
5.2.4	The counsellor must explain that, although the genetic mutation has been found, at the present time only limited useful	The correlation between CAG repeat size and mean age of onset could be discussed, but it is important to point out the wide confidence	The counsellor must explain that, although the genetic mutation has been found, at the present time only limited useful	- Age at onset cannot be accurately predicted for GRN or C9orf72 however mean family age at onset is correlated with age at onset	Limits regarding usefulness of test included specifically for FTD

	information can be given about age at onset or about the kind of symptoms, their severity, or the rate of progression.	intervals. A specific repeat size is usually associated with a wide range of age at onset; current mathematical models of age of onset have not been validated for clinical practice.	information can be given about age at onset or about the kind of symptoms, their severity, or the rate of progression.	in MAPT - Age related penetrance can be seen in GRN (and to a lesser extent in C9orf72) see Moore et al. (2020) - Phenotype can't be predicted but common phenotypes seen for the relevant mutation should be explained e.g. C9orf72 and FTD-ALS	
5.2.5	Pre-test genetic counselling should mention all possible test outcomes, including intermediate and reduced penetrance results, which may be prone to repeat instability and	There is at present insufficient information regarding clinical implications of intermediate alleles for future generations.	Pre-test genetic counselling should mention all possible test outcomes, including intermediate repeat expansions and variants of unknown significance where	- The possibility of an intermediate repeat expansion should be discussed in relation to C9orf72, however care should be taken as to how this is interpreted. To date there is insufficient evidence to	Intermediate expansions and variants of unknown significance discussed in FTD

	may expand into higher repeat ranges upon transmission to future generations. However, there is insufficient information regarding the magnitude of the risk of expansion for future generations.		appropriate.	interpret intermediate expansions - Variants of unknown significance should be discussed where appropriate in GRN	
5.2.6	The predictive test indicates whether someone has or has not inherited the gene mutation, but it does not make a clinical diagnosis of HD if the gene expansion is present.	Particular care should be taken with participants who are believed by the clinician to be showing early symptoms of HD; however, persons with evident but unacknowledged symptoms should not automatically be excluded from the test. Rather,	The predictive test indicates whether someone has or has not inherited the gene mutation, but it does not make a clinical diagnosis of **FTD** if the gene expansion is present.	Particular care should be taken with participants who are believed by the clinician to be showing early symptoms of **FTD**; however, persons with evident but unacknowledged symptoms should not automatically be excluded from the test. Rather, they should be offered additional pre	HD changed to FTD

		they should be offered additional pre and post test support.		and post-test support.	
5.2.7	Pre-test counselling should also outline information on post-test counselling and options for future research participation and care.				
			10. Management of expectations a. Expected timelines and waiting times should be clearly communicated to patients wherever possible to minimise frustration. Patients should be fully informed regarding the purpose and procedures involved in genetic counselling. There should be transparency regarding the support available throughout the genetic counselling process.		

5.3 Information on consequences					
5.3.1	For the person him/herself.	Most participants will adjust to their predictive test result. Some individuals may, however, experience difficulty coping with any of the possible results in the short or long term (including a result in the normal range). Additional counselling should be offered to those at risk of having difficulties with coping (e.g. individuals with a history of psychiatric illness).			
5.3.2	For the spouse/partner and children.	If the participant is not accompanied by his/her spouse/partner			

		during the counselling sessions, there should be particular discussion about the potential impact of the test result on the spouse/partner. It is possible that the genetic test result and/or family history will impact the participants' current or future family members' eligibility for insurance, employment, legal care of and access to children, and adoption.			
5.3.3	For the affected parent and his/her spouse.	The feelings of the affected parent, who may well become aware of the results, must			

		be taken into account.			
5.3.4	For the other members of the participant's family.	Whatever information is obtained, it may influence the feelings of and the relationship with others, with a potential for discrimination in the family. This may include: disrupted patterns of behaviour and interaction, such as communication changes and feelings of altered sense of membership.			
5.3.5	Potential socioeconomic consequences, including employment, insurance, legal care of and access to				

	children, adoption eligibility, social security, data security and other problems which may occur as a consequence of disclosing the test result or family history.				
5.4 Information on alternatives the participant can adopt					
5.4.1	Not to take the test for the time being.				
5.4.2	To deposit DNA for research.				
5.4.3	To deposit DNA for possible future use by family and self.				
5.4.4	DNA deposited under 5.4 above would be made available to the donor's				

	family members at their request after the death of the donor if it is essential to obtain an informative result.				
5.4.5	In the case of DNA deposited under 5.4.2 and/or 5.4.3 above, the unit collecting the DNA must provide a written declaration that samples will not be used for purposes other than specified in the said declaration with the exception of the provisions of 5.4.4.				
6 - Important preliminary investigations					

6.1	It is important to verify that the diagnosis of HD in the person's family is correct.		It is important to verify that the diagnosis of **FTD** in the person's family is correct.	However, many family histories may be complex with varied presentations or misdiagnoses. Relevant diagnoses should be used in support of the family history, rather than creating a barrier to predictive testing. e.g. late-onset psychiatric diagnoses, broad diagnoses of 'dementia'	Changed HD to FTD and added information regarding ambiguous family history in fFTD.
6.2	Neurological examinations (if possible) and psychological appraisal are considered important to establish a baseline evaluation of each person. This however is not a requirement for participation in predictive	Refusal to undergo these and other additional examinations will not justify the withholding of the test from participants.			

	testing.				
7 Reproductive options					
7.0.1	Preconception counselling should be available to couples where one partner is at risk of HD or is a carrier of the HD gene expansion.	The importance of preconception counselling is stressed, because of the timeframe in making a decision about testing during an ongoing pregnancy. Moreover, such preparation may help to decrease the simultaneous requests for presymptomatic and prenatal diagnosis; a very stressful situation due to the limited time available and the potential for consecutive adverse outcomes.	Preconception counselling should be available to couples where one partner is at risk of **FTD** or is a carrier of the **FTD** gene expansion.	The importance of preconception counselling is stressed, because of the timeframe in making a decision about testing during an ongoing pregnancy. Moreover, such preparation may help to decrease the simultaneous requests for presymptomatic and prenatal diagnosis; a very stressful situation due to the limited time available and the potential for consecutive adverse outcomes.	HD changed to FTD
7.0.2	Preconception				

	counselling should include discussion around the range of reproductive options available. These options may include proceeding with a pregnancy without testing, prenatal diagnosis (PND) preimplantation genetic diagnosis (PGD), donor insemination and adoption.				
7.1					
7.1.1	Couples should be made aware of all the options available to them in	Careful pre-test counselling by an informed professional is necessary in order to ensure	Couples should be made aware of all the options available to them in pregnancy,	Careful pre-test counselling by an informed professional is necessary in order to ensure that the (future) pregnant woman and her	Removal of irrelevant HD-specific information.

	pregnancy, including the possibility of prenatal testing.	that the (future) pregnant woman and her partner are fully aware of the consequences of prenatal testing. All possible test outcomes (full expansion, reduced penetrance, intermediate and normal alleles) should be made clear to the couple. It is preferable for the counselling to take place in a specialized (prenatal or genetics) centre.	including the possibility of prenatal testing.	partner are fully aware of the consequences of prenatal testing. All possible test outcomes should be made clear to the couple. It is preferable for the counselling to take place in a specialized (prenatal or genetics) centre.	
7.1.2	Direct prenatal testing for the HD mutation is usually only performed if the parent at risk has already		Direct prenatal testing for **FTD mutations are** usually only performed if the parent at risk has already		HD mutation changed to FTD mutations

	been tested. For a possible exception see 7.1.6.		been tested. For a possible exception see 7.1.6.		
7.1.3	PND for an individual with a reduced penetrance allele of the HD gene is justified.				
7.1.4	PND for an individual with an intermediate allele of the HD gene is justified.	There is insufficient information regarding the magnitude of the risk of CAG repeat expansion of intermediate alleles in the transmission to offspring. The risk of expansion into the full penetrance range is small, but may vary with the CAG size of the intermediate allele and the ethnicity			

		of the individual.			
7.1.5	Exclusion PND should be available as an option for couples where the at-risk parent does not want to know his/her genetic status. The pros and cons of this procedure, however, should be discussed in detail during counselling.	The major advantage of exclusion PND is that it allows the possibility of a prenatal test where the at-risk parent does not wish to have a predictive test but where the couple is clear they do not wish to have a child at risk of HD. The disadvantage is that the couple may end up terminating an unaffected pregnancy where the at-risk parent is not a mutation carrier.	Exclusion PND should be available as an option for couples where the at-risk parent does not want to know his/her genetic status. The pros and cons of this procedure, however, should be discussed in detail during counselling.	The major advantage of exclusion PND is that it allows the possibility of a prenatal test where the at-risk parent does not wish to have a predictive test but where the couple is clear they do not wish to have a child at risk of **FTD**. The disadvantage is that the couple may end up terminating an unaffected pregnancy where the at-risk parent is not a mutation carrier.	HD changed to FTD
7.1.6	Direct prenatal testing of the fetus where one of the parents is at risk but	The only advantage of this approach is that, in the case of a normal result in			

	prefers not to know his/her carrier status should be considered where the couple requests this in pregnancy.	the fetus, the parent at risk still does not know his/her carrier status, preserving his/her wish not to know. However, in the case of identifying the gene mutation in the fetus, the carrier status of the parent at risk will be disclosed. The possibility of this adverse outcome should be clearly outlined and the couple adequately prepared for such an eventuality, before agreeing with this test proposal.			
7.1.7	The couple requesting prenatal testing must be clearly informed that if	This is in line with the recommendation not to test minors. The child's	The couple requesting prenatal testing must be clearly informed that if	This is in line with the recommendation not to test minors. The child's autonomy regarding his/her future right to	Gene expansion changed to gene mutation to

	they intend to complete the pregnancy whether the fetus is a carrier of the gene expansion or not, there is no valid reason for performing the test.	autonomy regarding his/her future right to decide whether or not to undergo a pre-symptomatic test is violated if pregnancy is continued in the case of an abnormal prenatal test result. The limiting of the couple's autonomy and their right to freely decide on the action taken on the basis of the prenatal test result should be explained and clarified with respect. Also, there is a small, but not negligible risk of spontaneous abortion related to the procedure.	they intend to complete the pregnancy whether the foetus is a carrier of the **gene mutation or expansion** or not, there is no valid reason for performing the test.	decide whether or not to undergo a pre-symptomatic test is violated if pregnancy is continued in the case of an abnormal prenatal test result. The limiting of the couple's autonomy and their right to freely decide on the action taken on the basis of the prenatal test result should be explained and clarified with respect. Also, there is a small, but not negligible risk of spontaneous abortion related to the procedure.	expansion

7.1.8	It is not recommended to terminate the pregnancy of a fetus on the basis of an intermediate allele result.	An allele in the intermediate range is not associated with HD symptoms. Although an intermediate allele can expand into a reduced penetrant or full penetrant allele in future generations, this fact per se is not a reason for a pregnancy termination.			
7.2 Preimplantation genetic diagnosis					
		Preimplantation Genetic Diagnosis (PGD) in association with IVF is a reproductive option for people at risk of passing on a genetic condition. The different types of PGD for HD and		Preimplantation Genetic Diagnosis (PGD) in association with IVF is a reproductive option for people at risk of passing on a genetic condition. The different types of PGD for **FTD** and the different situations where PGD may be an option will be outlined in the following specific	HD changed to FTD

		the different situations where PGD may be an option will be outlined in the following specific recommendations regarding PGD for HD.		recommendations regarding PGD for **FTD**.	
7.2.1	It is recommended to offer PGD to an asymptomatic carrier of the HD gene expansion (36 or more repeats) and his/her partner if there is access to this technology in the country where genetic counselling is being provided.	In general, PGD is offered to people at risk of passing on a serious genetic condition. The risk of expansion of an intermediate allele to a reduced penetrant or full penetrant allele is not exactly known, but is low. Participants with an intermediate allele requesting PGD should be offered genetic counselling.	It is recommended to offer PGD to those with an asymptomatic carrier of an **FTD gene mutation or expansion** and his/her partner if there is access to this technology in the country where genetic counselling is being provided.	In general, PGD is offered to people at risk of passing on a serious genetic condition.	HD gene expansion changed to FTD gene mutation or expansion and irrelevant HD-specific information has been removed.

7.2.2	Exclusion PGD should be available for couples at high risk for offspring with HD.	The major advantage of exclusion PGD is that it enables prospective parents to avoid the transmission of the HD mutation, while at the same time respecting the atrisk person's wish not to know. The counselling should explicitly address the impact of the parent's remaining uncertainty about his/her own genetic status upon the welfare of the future child(ren).	Exclusion PGD should be available for couples at 50% risk of inheriting an FTD mutation or expansion.	The major advantage of exclusion PGD is that it enables prospective parents to avoid the transmission of the **FTD mutation/expansion**, while at the same time respecting the at-risk person's wish not to know. The counselling should explicitly address the impact of the parent's remaining uncertainty about his/her own genetic status upon the welfare of the future child(ren).	HD risk changed to statistic for FTD and HD mutation changed to FTD mutation/ expansion
7.2.3	Non-disclosure PGD should be discouraged.	Non-disclosure PGD raises troubling practical and ethical issues. First, in			

		practice it will be extremely difficult to preserve the participant's wish not to know. Second, the procedure creates difficult situations where reproductive physicians would be obliged both to offer more IVF/PGD cycles and to perform a sham transfer while the risk of having a child with HD will be (practically) zero.			
7.2.4	Couples where one partner is already symptomatic should have access to counselling for PGD. Psychosocial counselling on	Being symptomatic is not a priori an exclusion criterion for PGD. Special attention should be given to the effects of the symptoms of HD upon the future	Couples where one partner is already symptomatic should have access to counselling for PGD. Psychosocial counselling on	Being symptomatic is not a priori an exclusion criterion for PGD. Special attention should be given to the effects of the symptoms of **FTD** upon the future child's welfare. The condition and coping skills of the partner are crucially	HD changed to FTD

	the impact upon a child of growing up with a parent with HD in general and exploration of the potential effects in the specific case is an important aspect of the PGD procedure.	child's welfare. The condition and coping skills of the partner are crucially important in this regard. A case-by-case approach does optimal justice to couples where one partner faces the personal burden of HD in her/himself, while being aware of the ramifications for future children.	the impact upon a child of growing up with a parent with **FTD** in general and exploration of the potential effects in the specific case is an important aspect of the PGD procedure.	important in this regard. A case-by-case approach does optimal justice to couples where one partner faces the personal burden of **FTD** in her/himself, while being aware of the ramifications for future children.	
7.2.5	Only embryos with two normal HD alleles should be transferred.		Only embryos with two normal alleles should be transferred.		HD removed
8 The test and delivery of results					
8.1	Excluding exceptional circumstances there should be a minimum	Such an interval is necessary to give the person sufficient time to assimilate the pre-	A conversation should be had with the participant regarding their		Added information regarding individualising the 'cooling

	interval of one month between the giving of the pre-test information and the decision whether or not to take the test. The counsellor should ascertain that the pre-test information has been properly understood and should take the initiative to be assured of this. However, contact will only be maintained at the participant's request.	test information in order to make an informed decision. During this interval, specialists from the test centre must be available. Prenatal testing may represent an exception, as it is important to complete testing procedures as early as possible during the pregnancy.	preferred 'cooling off period'. Other circumstances may be at play which the counsellor should pay mind to. Should the participant request a shorter waiting period than recommended (<1 month), the counsellor should explain the reasoning behind this and help the participant to understand how this can be beneficial to them, while accounting for their personal circumstances. Excluding exceptional		off' period

			circumstances (**e.g. where other care depends on this information – like PGD)** there should be a minimum interval of one month between the giving of the pre-test information and the decision whether or not to take the test. The counsellor should ascertain that the pre-test information has been properly understood and should take the initiative to be assured of this. However, contact will only be maintained at the participant's		

			request.		
8.2	The result of the predictive test should be delivered as soon as reasonably possible after completion of the test, on a date agreed upon in advance between the centre, the counsellor, and the person.				
8.3	The manner in which results will be delivered should be discussed between the counselling team and the person.		The manner in which results will be delivered should be discussed between the counselling team and the person.	Delivery of results: a. A rapport should be built during the counselling process so that genetic counsellors can	Added comment based on data from this study.

				understand how best to approach result disclosure for the individual they are working with. They should consider their body language and maintain their 'routine' behaviour where possible as patients may be analysing this non-verbal behaviour to attempt to predict the result	

				they may receive. b. Regardless of outcome, patients should be reminded of the range of emotions they may experience and a plan should be made for follow up and additional support if needed. If not already in progress, patients should be offered psychological support.	
8.4	The participant has the right to decide at any time that the				

	result shall not be given to him/her.				
8.5	The results of the test should be given personally by the counsellor to the person and his/her companion. In geographically remote areas the result session may be arranged by prior agreement with a clinician known locally to the participant No result should ever be given by telephone or by mail. The counsellor must have sufficient time to discuss any questions				

	with the person.				
8.6	All post-test provisions (see Section 9) must be available from the time the test results are given.				
			Delivery of results: a. A rapport should be built during the counselling process so that genetic counsellors can understand how best to approach result disclosure for the individual they are working with. They should consider their body language and maintain their 'routine' behaviour where possible as patients may be analysing this non-verbal behaviour to attempt to predict the result they may receive. b. Regardless of outcome, patients should be reminded of the range of emotions they may experience and a plan should be made for follow up		Added based on data from this study

			and additional support if needed. c. If not already in progress, patients should be offered psychological support.		
9 Post test counselling					
9.1	The frequency and the form of the post-test counselling should be discussed between the team and the participant before the performance of the test, but the participant has the right to modify the planned programme. Although the intensity and frequency will vary from person to person, post-				

	test counselling must be available at all times.				
9.2	The counsellor should have contact with the person within the first week after delivery of the results, regardless of the test result.				
9.3	If there has been no further contact within one month of the delivery of the test result, the counsellor should initiate the follow up.				
9.4	It is essential that post-test counselling is made available regardless of the person's				

	financial situation.				
9.5	During post-test contact specific information on followup options, including (if applicable) participation in clinical research studies, can be provided. The nature of emerging prodromal signs of pre-motor manifest mutation carriers and their management possibilities (if available) could be discussed.	Information should be provided on: • specialist centres providing clinical care for HD • provision for regular follow up after the test • option of participation in observational studies (e.g. REGISTRY, Enrol-HD) • option of participating in future clinical trials • there is a pre-motor stage of HD that results in symptoms and signs likely reflecting HD-induced brain changes ('prodromal' signs) • prodromal signs and	During post-test contact specific information on follow-up options, including (if applicable) participation in clinical research studies, can be provided. Referral to a cognitive neurologist may be discussed should there be concerns regarding symptom onset.	Information should be provided on: - specialist centres providing clinical care for **FTD** - provision for regular follow up after the test - option of participation in observational studies **(e.g. GENFI/ALLFTD)** - option of participating in future clinical trials - Participation in research is entirely voluntary and the standard of follow up care provided will be unaffected by whether or not the individual chooses to take	Changed HD to FTD and added GENFI and ALLFTD study information

		symptoms might respond to symptomatic pharmacotherapy, even if no reliable data on this point are available at present. Participation in research is entirely voluntary and the standard of follow up care provided will be unaffected by whether or not the individual chooses to take part.		part.	
9.6	Ideally, information in Section 9.5 should be raised during the pre-test counselling.				
9.7	The lay organization has an				

	important role to play in the post-test period. The information and support that it can provide should always be offered to the participant regardless of whether he or she belongs to that organization.				
			Follow-up should be considered a priority At least one follow-up appointment should be scheduled during the final genetic counselling session or following the delivery of the genetic result. Follow appointments should be in-person wherever possible, however video or phone appointments may also be suitable. If a patient does not attend their follow up appointment, contact should be made via email or letter to provide contact details for follow up support.		Added based on data from this study

			Connect to support and research Regardless of test outcome, patients should be connected to available research studies e.g. GENFI (UK, Europe and Canada) and ALLFTD (US), genetic counsellors or geneticists may refer patients directly to the study, or provide contact details for the patient to self-refer. Regardless of test outcome, patients should be linked to appropriate support services e.g. Rare Dementia Support (UK) and AFTD (US). Regardless of test outcome, patients should be provided information on how to access further psychological support if necessary.	Added based on data from this study