The experience of ‘at-risk’ status for genetic variant frontotemporal dementia (GvFTD) and its impact on reproductive decision-making: A qualitative study

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Thesis declaration form

I 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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Date: 17th of June, 2022

Overview

Genetic variant FTD (GvFTD) is genetically heritable, autosomal dominant neurodegenerative disorder. Though heritability of GvFTD is well understood, there is little research exploring the experience of those at risk for GvFTD. This thesis aims to explore the relationship between GvFTD risk and reproductive decision-making, and its connection with earlier experiences with FTD-symptomatic relatives. Part 1 details a systematic review of literature concerning reproductive decision-making in Huntington's Disease (HD), a similar neurodegenerative disorder. 25 studies were included in the review. Findings outline reproductive intentions in HD-risk population, views on assistive technologies, and reproductive outcomes. Findings suggest reproductive decision-making in the context of genetic risk is a complex, challenging process, involving multiple decisions and emotional difficulties, with at-risk individuals employ several strategies to navigate. Further research is required on outcomes of the total HD-risk population, and to develop a psychological model of reproductive decision-making. Part 2 presents a qualitative study exploring reproductive decision-making among those at risk for GvFTD, including parents and non-parents. Thematic analysis of 13 interviews was conducted, identifying six main themes, covering fears of participants about repetition of their own earlier experiences and strategies to avoid this, responses to genetic risk in reproductive decision-making, discussing risk with children, timing and other influencing factors. Findings emphasise future caring burden as a major concern for at-risk individuals. Part 3 involves discussion of the reflexive process of research, including the positionality of the researcher, its effect on research, and outline of decision-making in response to methodological questions and issues.

Impact Statement

Despite increasing research on GvFTD's heritability, pathology and prognosis, there is little research about the impact of living at risk for GvFTD, and apparently no research regarding impact of genetic risk knowledge on reproductive decision-making. This thesis explores the relationship between reproductive decision-making and at-risk status for GvFTD, as well as the role played by earlier experiences with FTD-symptomatic relatives in influencing this relationship. By providing insight into this area for those living at risk, it has potential to inform appropriate application of genetic counselling, the broader approach of clinicians, researchers, and policymakers.

A systematic review of literature exploring reproductive decision-making in HD was conducted. As a novel systematic review topic, the results represent a useful summarisation of available research in this area and provide a useful starting point for future research. Findings suggest genetic risk plays a major, though not totalising, role in reproductive decision-making. It suggests there is a gap between the positive view of assistive testing options and actual uptake, suggesting possible contributory factors to this. It outlines clear emotional and practical complexity of reproductive decision-making in the context of genetic risk, and the diverging approaches at-risk individuals take to navigating risk to pursue reproductive intentions. This review offers insight into this topic in the context of HD, and also suggests relevant points for GvFTD, given comparable symptomatology and heritability. It highlights several areas in which available data and theory-making in reproductive decision-making are lacking, offering useful guidance to future researchers on areas to pursue to widen the knowledge base.

The qualitative study offers insight into the relationship between GvFTD risk and reproductive decision-making. It highlights both the relationship to earlier experience, and various approaches to management of genetic risk to facilitate pursuit of previously held reproductive intentions. It outlines both challenges of navigating reproductive decision-making under time pressure, and of disclosure of genetic risk to children. Its findings offer useful insight on how application of genetic counselling to this area might be improved, by

making it reflexively available at key points such as considering reproduction, and by focusing on helping at-risk individuals to explore likely outcomes of various reproductive outcomes as well as providing information about them. It further suggests the value of signposting within genetic testing procedures to appropriate organisations for management of legal and financial arrangements ahead of future symptomatology. It suggests avenues for future research, exploring both the joint process of reproductive decision-making within couples, as well as a direct comparison of processes in HD and GvFTD to identify areas of similarity and difference.

The findings of this thesis will be summarised and shared in written form with participants and the GENFI study team. Findings will aim to inform future approach to genetic testing and support in GvFTD as much as is possible. Finally, both papers will be prepared for academic publication to ensure they contribute to the available knowledge base in this area and can be built upon, both by future research and in informing future policy.

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Part 1: Literature Review

Reproductive decision-making and genetic risk for Huntington's Disease (HD): A systematic review

Abstract

Introduction: Huntington's Disease (HD) is an autosomal dominant single gene neurodegenerative disorder with typical onset in mid-life, characterised by motor difficulties, cognitive impairment, and behavioural and personality changes. It is associated with quality-of-life impact for both symptomatic individuals and carers, and currently without cure. A long history of genetic and related reproductive testing means that affected and at-risk individuals must make reproductive decisions with genetic risk in mind.

Methods: Two searches conducted and combined over five databases, combining terms for 'reproductive decision-making' and synonyms with 'Huntington's Disease' and synonyms. Findings were synthesised using Framework analysis to identify common factors across results of quantitative and qualitative studies. The review aimed summarise available research on reproductive decision-making in the context of HD risk in terms of outcomes and subjective experience of at-risk individuals.

Results: A total of 1846 studies were identified. They were screened, appraised and quality rated, leading to the inclusion of 25 studies. The following key areas of research findings were found: 'The relationship between reproductive intentions and HD genetic risk', 'Views on assistive options', 'Complexity and challenges in reproductive decision-making', 'Actual reproductive outcomes', and 'Other factors influencing reproductive decision-making'.

Conclusions: The quality of included studies, especially in reporting of actual reproductive outcomes, is variable. Findings from synthesis relevant to HD, and potentially relevant to similar diseases, are highlighted. Further research is required into reproductive decision-making and outcomes among those not utilising assistive options, and in developing a model of reproductive decision-making in HD.

Introduction

Huntington's Disease (HD) is a rare (worldwide prevalence of 2.71 per 100,000 (Pringsheim et al., 2012).) neurodegenerative disorder characterised by motor impairment, behavioural disturbance and psychiatric symptoms, and cognitive impairment (Roos, 2010). Its disease trajectory is progressive and fatal (Novak & Tabrizi, 2011), with gradually increasing care and support needs for symptomatic individuals as behavioural, motor and dementia-like symptoms progress (McColgan, & Tabrizi, 2018). Average age of onset is between 30-40 years (McColgan, & Tabrizi, 2018; Novak & Tabrizi, 2011), and the mean duration of the disease is 17-20 years (Roos, 2010). HD demonstrates a well-documented pattern of autosomal dominant genetic inheritance (Mahalingam & Levy, 2014; Reiner, Dragatsis & Dietrich, 2011), with biological children of a HD-diagnosed parent having a 50% chance of developing the disease themselves. Due to a combination of its strong genetic heritability, its progressive and debilitating disease trajectory, its average onset in mid-life, and its characteristic disturbance of mood, cognition and behaviour, a diagnosis of HD has profound effect not just on the diagnosed individual, but their immediate family, and prospective future. Furthermore, it raises questions regarding genetic heritability to current and potential future children.

Clinical characteristics of HD

The core identifying symptoms of HD are characteristic motor impairment, behavioural and psychiatric changes, and cognitive impairment (Roos, 2010). Motor symptoms include a characteristic addition of involuntary movements, initially in facial muscles and extremities but gradually spreading to all muscles (McColgan, & Tabrizi, 2018). Later motor symptoms are characterised by impairment and loss of voluntary motor movements, impaired fine and later gross motor skills, characteristic unsteady gait, and later dysphagia and muscle rigidity (Roos, 2010).

Behavioural and psychiatric changes occur independently of motor disturbance (Goh, Wimbawa & Loi, 2018), and can often appear years in advance of motor and cognitive

indicators (Goh, Wimbawa & Loi, 2018; Paulsen et al., 2001). These changes are characterised by novel or increased dysphoria, agitation, irritability, apathy and anxiety (Paulsen et al., 2001), with low mood (Rosenblatt, 2007) with disinhibited or impulsive behaviour (Anderson & Marshall, 2005; Paoli et al., 2017) also common. Personality changes are also noted, though less comprehensively understood, and can take the form of increased propensity towards aggressive behaviour or criminal misdemeanours such as indecent exposure or disturbing the peace (Anderson & Marshall, 2005; Rosenblatt, 2007). These symptoms, particularly apathy and aggression, are associated with increased carer burden and distress (Paoli et al., 2017), and overall psychiatric and behavioural disturbance contributes to disease burden and impaired quality of life for the symptomatic individual and carers (Goh, Wimbawa & Loi, 2018). Low mood in the prodromal phase of HD is associated with an increased risk of death by suicide (Fiedorowicz et al., 2011).

Similar to psychiatric and behavioural symptoms, cognitive impairment in HD can precede the onset of motor disturbance (McColgan, & Tabrizi, 2018; Roos, 2010). These changes are progressive, initially observable in visuomotor integration and psychomotor speed impairments, decline in executive functioning and reduced emotional recognition abilities, with attentional deficits and reduced episodic and working memory emerging later (Papoutsi et al., 2014). Semantic memory and cognitive language abilities tend to remain relatively intact (Stout et al., 2012), though communication difficulties as a result of motor disorder can emerge in the later stages of disease (Novak & Tabrizi, 2011).

In addition to these core areas of symptomatology, secondary characteristic symptoms included disordered sleep, unintended weight loss (Roos, 2010) and sexual pre-occupation or disinhibition (Anderson & Marshall, 2005) are commonly observed.

Prognosis, treatment and management

There are currently no treatments or interventions available that prevent, modify or delay the underlying disease processes implicated in HD (Bonelli & Hofmann, 2007; Mason & Barker, 2016). Treatment options for HD therefore currently focus on management of

symptoms and support for symptomatic individuals and their carers in maintaining their quality of life as much as possible. These include pharmacological treatments to manage (Novak & Tabrizi, 2011) and anti-depressant or anti-psychotic medication to manage psychiatric symptoms (Mason & Barker, 2016). There are no drug options suggested to manage cognitive symptoms, with best practice consisting of effective non-pharmacological therapeutic support and MDT management (Novak & Tabrizi, 2011). It is important to note that evidence for the above treatments is relatively sparse, and therefore treatment plans are largely individualised and based on professional experience of involved clinicians (Bonelli & Hoffman, 2007; Roos, 2010).

Practically, most day to day support for people with HD is provided by family carers. The caregiver role in HD is particularly challenging, both due to the significant practical challenges of managing disinhibition, aggressive and emotional lability, as well as the emotional challenges of navigating the emotional and relationship changes brought on by personality changes in HD (Domaradzki, 2015). Carers report experiencing dissatisfaction with the demands of the caregiver role, emotional distress at changes in the symptomatic individual (Aubeeluck, Buchanan & Stupple, 2012). Quality of life for both symptomatic individuals and their carers are negatively associated with increased cognitive and functional impairment (Ready et al., 2008).

Genetic heritability in HD

HD is a single-gene disease following an autosomal dominant pattern of inheritance with complete penetrance, meaning that anyone inheriting the implicated gene will develop the disease, and any child of a parent with HD has 50% chance of inheritance, thus considered genetically at-risk of HD (Mahalingam & Levy, 2014)

The implicated *huntingtin* or *HD* gene is located on chromosome 4p16.3 (Reiner, Dragatsis, & Dietrich, 2011), and was first fully located in 1993 (HDCRG, 1993). The gene controls production of the *huntingtin* protein, with the HD-associated mutant version of the gene associated with expansion of the cytosine-adenine-guanine (CAG) repeat within the

gene (Mahalingam & Levy, 2014). Normal versions of the gene express less than 27 CAG repeats and are not associated with developing HD, and mutant versions of the gene with great than 36 CAG repeats leading to definite development of HD, with CAG repeats of 27-35, known as intermediate alleles, not associated with development of HD but leading to increased CAG repeats and thus possible development in offspring (Myers, 2004). CAG repeats increase per inheriting generation, and increasing CAG length is associated with earlier age of onset, as is inheritance from a male parent (Myers, 2004).

Presymptomatic genetic tests (PGT) to confirm a diagnosis of HD have been available in the form of linkage tests since 1986, and as a direct genetic test since isolation of the gene in 1993 (Myers, 2004). HD was the first genetic disorder to be mapped to a specific chromosome location (Mahalingam & Levy, 2014), and the first for which confirmatory PGT was widely available (Myers, 2004). This long history of genetic testing has led to the development of robust guidelines for the approach to PGT within the disorder, pre-test genetic counselling and post-test support for those receiving a positive PGT result (McLeod et al., 2013). For these reasons, it has become the model on which the approach to testing and support within other genetically heritable conditions has been based. Testing takes the form of confirmatory genetic testing of individuals presenting with characteristic symptoms. In addition, those with first-degree relative with a diagnosis of HD are considered genetically at-risk for HD, and can pursue PGT to establish whether they have inherited the gene and are therefore pre-symptomatic.

Reproduction and HD

Given HD's high heritability, its age of onset in mid-life, and its characteristic impairment of personality and functioning, HD genetic risk knowledge has profound implications for multiple aspects of the lives both of symptomatic individuals, and those genetically at-risk. As well as being aware of their potential symptom trajectory, and in the case of at-risk individuals often having witnessed the disease progression in their symptomatic parent (Novak & Tabrizi, 2011), they are also aware of the risk of heritability to

their children.

De Die-Smulders et al. (2013) outline the reproductive options available to those at genetic risk of HD: 1) pursuing natural conception without medical intervention, accepting the heritability risk; 2) use of prenatal diagnosis (PND) – natural conception, followed by in utero genetic testing, with the option to terminate or continue affected pregnancy; 3) use of pre-implantation genetic diagnosis (PGD) – genetic testing of in vitro fertilised (IVF) embryos, followed by implantation of gene-negative results; 4) non-biological routes to parenthood, in the form of fostering or adoption; and 5) abstinence from having children. Each presents with challenges – PND is associated with greater risk of miscarriage, as well as the emotional toll of potential termination; PGD is expensive, emotionally taxing and has a low success rate; HD genetic risk can act as a barrier to being considered for adoption or fostering; and both choosing to have at risk children and abstaining from children can be challenging for couples on an emotional level.

Clinical reviews acknowledge the challenges that reproductive decision-making can have for symptomatic and at risk individuals, involving multiple choices both about reproductive intentions, use of assistive technologies and knowledge regarding their own risk status (Novak & Tabrizi, 2011), and there is clear guidance within the PGT protocol for HD (McLeod et al., 2013) for the support that should be offered to both presymptomatic and at-risk individuals, focused on providing clear and useful information on reproductive options and all potential outcomes. The ethical complexity of reproductive decision-making in the context of HD risk has also been noted to highlight a process that is likely to play out across other genetically heritable conditions as genetic testing becomes more widespread following the model of HD (de Die-Smulders et al., 2013).

Summary of existing literature and limitations

Since the development of PGT for HD, and later development of reproductive assistive options such as PND and PGD, there has a small but developing body of research exploring both the reproductive intentions and outcomes of those at genetic risk of HD,

including both those who are at 50% risk and those who are pre-symptomatic, as well as their attitudes and uptake of technological options such as PND and PGD. These range from straightforward reports on reproduction in this cohort over time to studies exploring the impact of PGT on reproductive intentions. In addition, there is a smaller body of qualitative studies exploring the subjective experience of reproductive decision-making in the context of genetic risk within the same cohort. This includes a small number of studies in which reproductive decision-making and outcomes are the main focus of the study, and a larger body of research in which information on reproductive decision-making and outcomes are one among a wider range of reported outcomes within studies.

However, though this body of research is available, there has not to date been a review that attempts to gather, appraise and synthesise the findings of these studies to allow for identification of themes and patterns regarding the impact of HD genetic risk on reproductive decision-making. Given the long-standing availability of genetic testing for HD in comparison with other disorders, and given its position as among the first genetic disorders for which PND was available (Mahalingam & Levy, 2014), in some ways the experience of reproductive decision-making in the context of HD risk, and the impact of new testing technologies on both decision-making and outcomes represents a bellwether as to how these topics might be navigated in other genetically heritable conditions. For this reason, a comprehensive summary of reproductive decision-making and outcomes in the context of HD following genetic testing development is important, both in informing understanding of and approach to HD, and also to other comparable genetically heritable conditions

Rationale and aims

The current review will attempt to provide a synthesis of qualitative and quantitative literature regarding reproductive decision-making and outcomes in the context of HD. It will attempt to account for both available research on reproductive intentions and outcomes, as well as attitudes towards and uptake of assistive technologies. It will further attempt to

synthesise qualitative findings of the subjective experience of reproductive decision-making among those at genetic risk for HD, the challenges and barriers involved, and the additional factors influencing reproductive decision-making in this cohort. This will provide relevant information for future directions in research and clinical practice, both for HD and potentially for other genetically heritable conditions. comparable genetically heritable neurodegenerative diseases.

This review will therefore aim to cover the following objectives: 1) to integrate research findings regarding reproductive intentions, decision-making and outcomes among those at genetic risk for HD; 2) to report relevant findings on attitudes towards and uptake of developing assistive technologies available to aid reproduction in HD; and 3) to meaningfully summarise the available research on the subjective experience and challenges of reproductive decision-making in the context of HD genetic risk.

Methods

Search strategy

The following databases were used for systematic search to identify relevant research: Medline, EMBASE, EMCARE, PsycINFO, AMED, Maternity and Infant Care. Search strategy involved combining terms related to a) reproductive decision-making, with reference to a previous systematic review regarding reproductive decision-making (Leyva-Moral et al., 2021), and b) Huntington's disease, with reference to a previous systematic reviewing covering HD (Bonelli and Hoffman, 2007).

The following search terms were used: 1) Reproductive health *or* Reproductive decision making *or* Reproduction *or* Reproductive behav* *or* Family Planning *or* Fertility *or* Childbearing Decision *or* Fertility Intention *or* Child desire *or* Child Wish *or* Reproductive choice *or* Having a child *or* Having Children *or* Parent*; 2) Huntington's Disease *or* Huntington's Chorea *or* Huntington*; 3) Combination of Search 1 and Search 2 Searches were standardised across all databases, and were combined using Boolean commands to

identify relevant results (See *Appendix A* for step-by-step breakdown of search strategy employed).

An additional hand search of reference lists from identified relevant studies, as well as through review of studies that had referenced identified relevant studies, as well as a Google Scholar search. Where these additional searches identified potentially relevant 'grey literature' in the form of dissertations and theses, their inclusion was only considered where all inclusion criteria were met, and where results were clearly identifiable and available in full. These sources were included as they can be helpful in guarding against publication bias (Paez, 2017), and as it has been noted that these results can impact reviews where there is a relatively small body of published research (Hartling et al., 2017).

Study Selection

In line with PRISMA guidance (Page et al., 2021), study selection progressed iteratively. Search results from above strategy were imported to EndNote. Duplicate study records were identified and removed, initially automatically using EndNote functionality, followed by additional duplicate removal by main author. Studies were then reviewed for inclusion in three stages, first by title, then abstract, then full text using eligibility criteria below. To enhance reliability of study selection, 10% of studies at each level of eligibility review (title, abstract, full-text), were reviewed against criteria by a second reviewer. Overall agreement between main author and second reviewer outcomes was 95%. The full study selection process with numbers at each stage is outlined in the PRISMA flow diagram (see Fig. 1)

Eligibility criteria

Inclusion criteria were as follows:

a) Studies involving individuals at genetic risk of developing Huntington's Disease, where being 'at genetic risk' is defined as: individuals with a known Huntington's Disease diagnosed first degree relative, including at-risk individuals who have not

pursued confirmatory genetic testing at the time of their involvement in research, pre-symptomatic gene carriers identified by confirmatory genetic testing, and symptomatic individuals.

b) Studies where *at least one aim* is related to reproductive decision making among the above identified population, with reproductive decision making understood to include decisions and views on having or not having biological children, pursuing prenatal diagnostic testing as part of pregnancy, pursuing preimplantation genetic testing to avoid at-risk pregnancy, and pursuing adoption, as well as reproductive outcome rates associated with these options.

c) Studies published on or before 1983. The date when initial genetic markers facilitating confirmatory genetic testing for Huntington's Disease were first isolated (Gusella et al., 1983),

d) All peer-reviewed studies reporting novel quantitative and qualitative research were included in addition to relevant publicly accessible Masters and Doctoral theses identified through above-outlined hand search.

e) Studies accessible in full text form in the English language,

Exclusion criteria were as follows:

a) Studies concerning other heritable genetic conditions, or studies where multiple genetic conditions were considered without subgroup analyses that would allow for distinguishing of Huntington's Disease related results independently

b) Studies focusing on medical or technical elements of confirmatory genetic testing, prenatal diagnostic testing or preimplantation genetic testing without reference to the reproductive decision making of affected individuals,

c) Research published before 1983,

a) Published materials not reporting novel research, including editorial introductions, clinical overviews, reviews and responses to published research were not included. Studies where abstract was available in English but remainder of the text was not were not included. Abstracts reporting on conference or poster presentations where full scale report of the research was not available were not included.

Data Extraction and Quality Appraisal

Each identified paper was reviewed in full, with the key characteristics of the study (main author and publication year; research aims; study design; setting; participant characteristics and numbers (and comparison group where present); methods of analysis, and main findings) extracted to an excel form.

Study quality was assessed using the QualSyst tool (Kmet, Lee and Cook, 2004). This tool was chosen due to its clear and replicable guidance for assessing quality, as well as providing separate systems for assessing quality for both quantitative (including cross-sectional and observational designs) and qualitative research. The QualSyst tool assigns each paper a numerical value between 0.0 and 1.0 based on the study meeting a number of criteria related to quality (e.g. appropriate analysis in quantitative research, use of verification procedures in qualitative research; see *Appendix B* for full outline of QualSyst criteria). The tool's original authors offer no cut off points for unacceptable study quality. For the purposes of this review, following initial quality rating for several studies, the following quality cut-off ranges were arrived at by the main author: studies which achieved a score of between 1.0 and 0.8 are considered of 'High' quality, studies achieving a score of between 0.8 and 0.7 are considered of 'Good' quality, studies achieving a score of between 0.7 and 0.6 are considered of 'Medium' quality, and studies achieving a score of below 0.6 are considered of 'Low' quality and excluded from synthesis.

All included studies were assessed for quality in this way. Each study was evaluated separately with reference to the above-extracted data. Where studies reported on several

aims with one being reproductive decision-making in the target population, only those portions relevant to the aims of this review were evaluated, and only data relevant to the aims of this review were extracted. Data analysis proceeded following quality assessment, both to allow for the removal of low quality studies, and to allow for quality differences to inform interpretation of differing or contradictory findings between studies.

Data Synthesis

Gathered characteristics and results for included studies were reviewed in their totality. Given the heterogeneity of study designs, outcomes measured and reported, and given the need to account for both the quantitative outcomes of reproductive decision making in this population along with their qualitative experience of genetic risk and reproductive decision making, a narrative synthesis was identified as an appropriate method of data synthesis.

Ritchie and Spencer's 'Framework Analysis' approach to data synthesis (Ritchie & Spencer, 1994) was utilised, as it provides a flexible approach to accounting for both quantitative and qualitative data within synthesis, as well as a robust iterative process of stepped analysis to ensure that relevant data is accounted for both within and between studies. The development of the framework analysis consisted of five stages: 1) familiarisation with both the full texts of included studies and the relevant extracted data and characteristics; 2) development of a thematic framework, based on previous research and patterns identified during familiarisation, and later reflexively adapted as analysis proceeded; 3) Indexing of extracted data to identified framework, using textual codes to connect specific data to different themes; 4) Charting of data across all studies to headings from developed thematic framework; and 5) mapping of patterns and associations between the data across studies, and interpretation of the dataset as a whole into themes.

This thematic framework was used in, and reflexively adapted in response to, broad areas of reported data within the studies, covering both attitudes towards reproductive

decision-making and assistive technologies among the target population, as well as actual reproductive outcomes and uptake of assistive technologies. The subjective challenges and complexities of reproductive decision-making in the context of genetic risk, both practical and emotional was also synthesised from across included studies. Where possible, themes attempted to synthesise qualitative and quantitative results with equal weight in the development of overarching themes, though certain sub-themes emerge as containing only qualitative or quantitative data. On completion of the initial five-stage analysis process, a second pass analysis was undertaken to ensure the representativeness of the developed synthesis in accounting for the whole dataset.

Results

Search Findings

Initial searches produced an initial set of 1849 prospective studies. Following removal of duplicate records and studies not meeting inclusion criteria by date, 1075 studies were screened at title level. 660 records were removed at title screening. Following abstract screening, 64 papers were screened at full text level, leading to the inclusion of 27 relevant studies in this review. A PRISMA chart detailing of the study selection process can be seen in Figure 1.

Quality of included studies

Of the 27 studies included from search, the application of the QualSyst tool rendered the following outcomes – 9 (33%) studies were found to be of 'High' quality (Decruyenaere et al., 2007; Ever-Kieboom et al., 2002; Gong et al., 2016; Klitzman et al., 2007; Markel et al., 1987; Quaid et al., 2010; Tibben et al., 1990; Tsang, 2019; Van Rij et al., 2014b); 10 (37%) studies were found to be of 'Good' quality (Fowler et al., 1999; Kessler et al., 1987; McCormack et al., 1983; Richards et al., 2005; Simpson et al., 2002; Schoenfeld et al., 1984; Schoenfeld et al., 1984b; Van Rij et al., 2012; Van Rij et al., 2013; Van Rij et al., 2014); 6 (22%) of studies were found to be of 'Medium' quality (Decruyenaere et al., 1996; Holloway

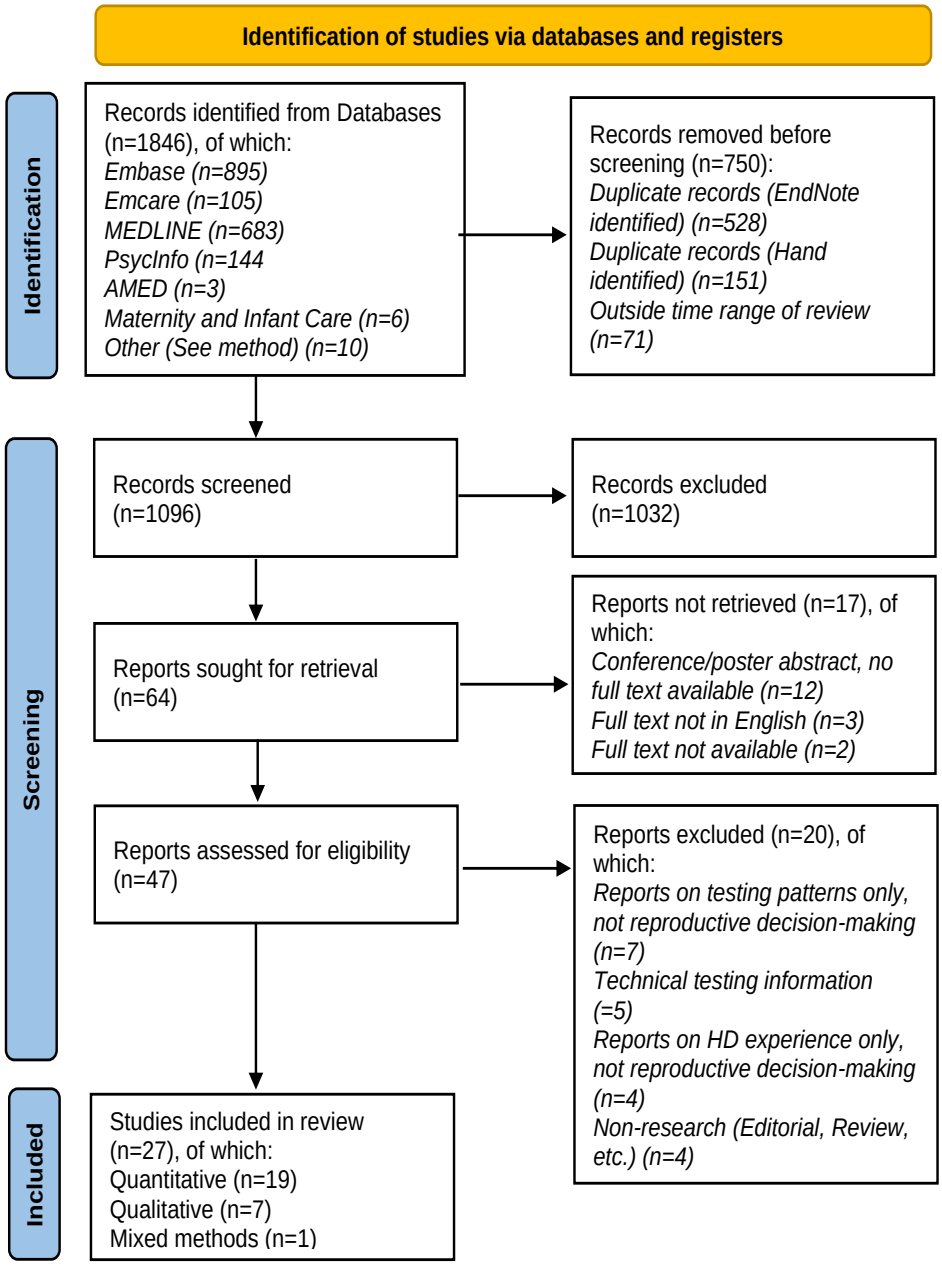


Figure 1. PRISMA Flowchart (Page et al., 2021)

et al., 1994; Downing et al., 2005; Maat-Kievet et al., 1999; Tassicker et al., 2006; Wedderburn et al., 2013); 2 (7%) of studies were found to be of 'Low' quality (Krukenberg et al., 2012; Leontini, 2010), and for this reason were excluded from further analysis.

In the case of Leontini (2010), a qualitative study exploring the conceptualisation of 'risk' in reproductive decision making among those at genetic risk of Huntington's Disease, a number of methodological shortcomings led to this study receiving a 'Low' score for quality. The overall aims of the study were only partially described, as were context of the research and sampling method. The approach to interview was only vaguely outlined. A key shortcoming was the failure to clearly outline the method of qualitative analysis used – the paper describes each interview transcript being 'analysed as a narrative', but does not further specify the approach used to do so. Finally, there was a lack of reported verification procedures to establish the credibility of analysis, such as second-rater reliability checks.

In the case of Krukenberg et al. (2012), a quantitative study including a subgroup analysis reporting the association of certain demographic characteristics and various reproductive outcomes among those at risk of Huntington's Disease, a number of methodological flaws led to its low quality score. The key shortcoming is the insufficient sample sized (n=16) and consequent lack of power used for the basis of this subgroup analysis. Though the study acknowledges this insufficiency, it goes on to report the results and draw conclusions from them. Thus, 25 studies were included in the review.

Study characteristics

Of the included studies, 72% (18/25) were quantitative with 24% (6/25) being qualitative, and the remaining study using a mixed methods design. Among those studies with a quantitative element, 37% (7/19) included a comparison group. Included studies were located in the USA, (40%; 10/25); Continental Europe (37%; 10/25); Australia (12%; 3/25); and UK (4%; 1/25), with the remaining study leaving the location of research unspecified. Included studies covered the following broad areas, with some studies covering more than one: factors influencing reproductive decision making among those at risk of developing

Huntington's Disease (HD) (28%; 7/25), uptake and outcome of prenatal diagnosis (PND) (32%; 8/25), reproductive decision making following presymptomatic genetic testing (PGT) (24%; 6/25), uptake and outcome of preimplantation genetic testing (PGD) (20%; 5/25), views of individuals at genetic risk of HD on genetic testing and influence on reproductive decision making, 24% (6/25) (See Table 1 for a full summary of all studies).

Narrative Synthesis

Framework analysis of the relevant extracted data from included studies, including reported outcomes in quantitative studies and analysis in qualitative studies led to the development of five key areas within the narrative synthesis. These are: 1) The relationship between reproductive intentions and HD genetic risk, 2) Views on assistive options, 3) Complexity and challenges in reproductive decision-making in the context of HD genetic risk, 4) Actual reproductive outcomes, and 5) Other factors influencing reproductive decision-making.

1: The relationship between reproductive intentions and HD genetic risk

1.1 Child desire and future reproductive intentions

Five quantitative studies of high and good quality reported on participant's future reproductive intentions (Decruyenaere et al., 2007; McCormack et al., 1983; Schoenfeld et al., 1984a; Schoenfeld et al., 1984b; Tsang, 2019). Earlier studies reported higher proportions of participants with future reproductive intention – Schoenfeld et al. (1984a) reported that 82% of participants at genetic risk for HD intended to have at least one child, and 78% two or more, Schoenfeld et al. (1984b) reported that in a similar sample, 80% of participants intended to have a child, whether their first or in addition to current children, at time of survey. In comparison, Decruyenaere et al. (2007) found that 51.69% of participants had future reproductive intention, and Tsang (2019) reported that 38% of participants intended to have children in future. McCormack et al. (1983) identified that males at genetic risk for HD were more likely to express intention to have children in future than comparable

TABLE 1
Summary of included studies

Main author, Study Year, Location	Study Aim	Design, Participants, Comparison (if applicable)	Main outcomes	Quality Rating
McCormack (1983), USA 1	Comparison of reproductive intention and decision-making, and attitudes towards artificial insemination between HD-risk individuals and comparable controls	Cross-sectional comparative survey, chi-square analysis Participants: individuals at genetic risk of HD (n=91) Comparison: demographically comparable individuals not at risk (n=63)	At risk males less likely to have and more likely to want children than controls. Younger at risk females less likely to have children than controls. At risk females less likely to want children than controls. Younger at risk males and females less likely to intend to have children post HD risk knowledge than older at risk males and females. No reported statistical significance of differences.	0.77
Schoenfeld (1984a), USA 2	Reporting attitudes of HD-risk individuals towards having children	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals at genetic risk for HD (n=45) Comparison: none	At time of study, more than half had a child; significant negative correlation with college education. 82% desire to have at least one child. Response to HD-gene positive pregnancy: 60% continue, 16% terminate, 34% unsure; significant negative correlation between having a child and termination, significant positive correlation between college education and termination.	0.72
Schoenfeld (1984b), USA 3	Reporting impact of availability of presymptomatic genetic testing (PGT) for HD on reproductive decision making	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals at genetic risk for HD (n=55) Comparison: none	73% willing to pursue PGT when available 80% intend to have (more) children at time of study Among those willing to take test, impact of hypothetical positive result on reproductive decision making: 2.5x increase in those reporting would not have further children. No significant between-group differences identified.	0.72
Kessler (1987), USA 4	Reporting impact of availability of PGT for HD on reproductive decision making	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals at genetic risk for HD (n=69) Comparison: none	67.2% indicate HD has major influence on family planning. 78.8% willing to pursue PGT when available; significant negative correlations between length of marriage, PGT willingness 65% willing to pursue PND when available. Anticipated response to positive PGT result: no (further) children, 70.9%, fewer children 13.9%, adoption 6.5%, unsure 6.5%	0.70

Markel (1987), USA 5	Reporting attitudes of HD-risk individuals towards PGT and PND	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals at genetic risk for HD (n=155) Comparison: none	63.2% willing to pursue PGT when no treatment available; significant predictors of increased likelihood, earlier age of onset for affected parent, more affected relatives. 86.5% willing to pursue PGT if treatment available. 66.67% would want children to pursue PGT; older respondent age significant predictor of increased likelihood. Anticipated effect of positive PGT result: 42.6% deterred from having children (significantly associated with college education, more affected relatives); those who already have children less likely to be deterred Response to pregnancy post positive PGT result: 41.1% complete, 13.5% terminate (significant positive correlation between Catholic faith and continuing) Attitude to PND: would use when available, 49.0%, 33.5% would continued affected pregnancy (all participants significantly more likely to terminate pregnancy post positive PND vs post positive PGT)	0.89
Tibben (1993), The Netherlands 6	Reporting attitudes towards PGT and reproductive decision making six months post-test	Cross-sectional comparative survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals receiving positive PGT result (n=24) and partners (n=17) Comparison: individuals receiving negative PGT result (n=27) and partners (n=44)	All groups less likely to endorse statement 'test result has allowed me to plan for the future of my family' post-test vs. pre-test, with largest drop in individuals receiving positive PGT result. However, no significant changes or between-group comparisons. 20.83% decrease in intention to have children among those receiving positive PGT result. No change in willingness to terminate pregnancy to avoid gene transmission. Actual outcomes 18 months post-test: one completed pregnancy without PND, one terminated pregnancy following positive PND, one completed pregnancy following positive PND.	0.90
Holloway (1994), UK 7	Reporting characteristics of those seeking PGT between 1984-1994 in UK, comparison of reproductive decision making between positive and negative result groups	Cross-sectional comparative survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals receiving positive PGT result (n=22)	80 individuals applied for testing – 22 positive results, 27 negative results, 6 inconclusive results, 25 withdrawals Post-test reproductive decision making: 5 negative results intending to have children where didn't before, 4 positive results intending not to have children where previously did; 7 sterilised or out of reproductive age.	0.60

		Comparison: individuals receiving negative PGT result (n=27)		
Decruyenaere (1996), Belgium 8	Comparison of impact of PGT on reproductive decision making twelve months post-test, positive result vs. negative result.	Cross-sectional comparative survey, descriptive statistics, statistically significant between group differences highlighted. Participants: individuals receiving positive PGT result (n=22) Comparison: individuals receiving negative PGT result (n=31)	Of 13 individuals intending to have children pre-test who received positive PGT result: 30.76% no longer intend, had/having child pos-test, 30.76%, undecided 38.46% Of 17 individuals intending to have children pre-test who received negative PGT result: had/having child post-test, 47.06%; intending to have child in future, 29.41%. No reporting of statistical significance of any differences.	0.67
Fowler (1999), USA 9	Exploration of impact of positive PGT result number of factors including on reproductive decision making	Qualitative case study series, grounded theory analysis, only relevant subthemes to reproductive decision making included in this review Participants: interviews with couples where one partner received positive PGT result (n=3)	All couples report impact of test result on family planning, but no unity of themes due to idiosyncrasies of each situation. Couple 1: no pre-test children; female partner continues to want, male partner does not; consideration of adoption. Couple 2: both desire no further children post result, regret pre-test child due to risk, used adoption to expand family. Couple 3: complex picture where dynamics of relationship played main role in having child post test without PND.	0.70
Maat-Kievet (1999), The Netherlands 10	Reporting uptake and outcomes of PND among HD-risk individuals in The Netherlands, 1987-1997	Retrospective cohort study, statistically significant between group differences highlighted. Participants: individuals at genetic risk of HD seeking PND (n=43) Comparison: individuals at genetic risk of HD seeking PGT (n=582)	2% estimated uptake among HD-risk population under 50; those seeking PND statistically younger, less likely to have children vs. those seeking PGT. Total tests: 72, negative result 44, positive 17, indeterminate 11 60% seeking PND following PGT 35% using PND across more than one pregnancy. No statistically significant differences reported.	0.60
Ever-Kieboom (2002), Several European Countries	Reporting pre-test reproductive history and post-test reproductive decision making, uptake of PND, impact of PGT result on later reproductive decision making	Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted.	Approximately 50% of both participants and controls have had a pregnancy pre-test. Post test, no pregnancy: 85% of carriers and 72% of non-carriers Post-test, one or more pregnancies: 15% of carriers and 28% of non-carriers.	0.91

11	across several European genetic testing centres, 1992-1999.	Participants: individuals under 45 receiving positive PGT result in study period (n=181) Comparison: individuals under 45 receiving negative PGT result in study period (n=271)	'Family Planning' subgroup: carriers significantly less likely than non-carriers to have post-test pregnancy. Test result significant predictor of subsequent reproductive decision making, especially in 'family planning' subgroup.	
Simpson (2002), Several European Countries 12	Reporting characteristics of HD-risk individuals seeking PND in several European and PND outcomes	Retrospective cohort study, descriptive statistics. Participants: individuals at genetic risk of HD seeking PND (n=305)	Characteristics: mean age of 31, 53.9% female, 48% in ongoing relationship, positive PGT result 51% untested 42%. 57% of PND produced negative results, 43% produced positive result, with 8 positive pregnancies being carried to completion	0.79
Downing (2005), USA 13	Exploring how responsibility is understood and constructed among HD-risk individuals with regard to reproductive decision making	Qualitative case study series, grounded theory analysis, only relevant subthemes to reproductive decision making included in this review Participants: interviews with individuals/families where one partner received positive PGT result (n=3)	Forming expectations of responsibility: gendered expectation of caring responsibility towards female children, with some hierarchical age effect also. Growing awareness of responsibility: across all cases, lack of knowledge regarding HD, heritability and impact allowing reproductive outcomes that would otherwise be viewed as less responsible, and for this reason sometimes choosing to maintain ignorance to allow for conception without considering testing. Changing responsibility perceptions: as affected parent deteriorates, role as parent develops, changes in relationship – difficulty of maintaining consistency of decisions across time re genetic testing etc., feeling need to demonstrate responsibility of decision through contrast with other 'irresponsible' actions.	0.60
Richards (2005), Australia 14	Reporting and comparison of pre and post PGT reproductive decision making	Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted. All testees at involved centre, between 18-45 at time of test result, between 1990-2002 Total pre-test N=281 (carriers, N=118; Non-carriers, N=163)	Pre-test, 132 subject with at least one child; 53% with knowledge of potential HD risk; 2.2% used PND previously. 1.2% used aided methods (adoption, fostering, donation). Post-test, 28% of carriers and 32% of non-carriers became pregnant; no significant differences. 6 PNDs undertaken by carriers – 4 terminated positive results, 2 negative results carried to term. No other statistically significant differences found.	0.76

		Total post-test N=231 (carriers, N=109; Non-carriers, 122)		
Tassicker (2006), Australia 15	Reporting uptake and outcome of PGT, PND, PGD in Australia, 1994-2003.	Mixed methods. Quantitative section, retrospective cohort study, descriptive statistics. Qualitative, considers clinician experience, beyond scope of this review. Participants: individuals seeking PGT, PND, PGD during study period (n=unspecified)	776 positive PGT results during study period 63 PND tests undertaken, of which 52% negative, 48% positive 18 PGD cycles undertaken, resulting in 13 unaffected live births.	0.62
Decruyenaere (2007), Belgium 16	Reporting on reproductive decision making among HD gene carriers five years post-test, and exploration of factors influencing these decisions	Mixed methods. Qualitative: retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted. Participants: consenting individuals receiving positive PGT result in study period (n=89) Qualitative: grounded theory analysis of interview transcripts with consenting individuals receiving positive PGT result in study period (n=32)	Quantitative: 46 with reproductive intention, significantly younger and more likely to be childless vs. no reproductive intention group. 23 participants with at least one pregnancy in the study period; 51 individual pregnancies, 46 utilising PND leading to 23 live births and 23 terminations, 3 utilising PGD resulting in no live births. 25 children born to 20 participants – none unaided. No other statistically significant results found. Qualitative: balancing pros of PND/PGD vs distress and discomfort; emotional challenges of approaches (e.g. avoiding attachment); decision complex, multifacted, leading to ambivalence, difficulty balancing responsibility with desire for child. Sense of pressure to utilise new technologies. Eventual choice not to have child as way to stop disease, avoid suffering.	0.82
Klitzman (2007), Country Unclear 17	Exploring the factors influencing reproductive decision making among HD-risk individuals, tested and not.	Qualitative: grounded theory analysis of interview transcripts. Participants: n=21 (8 gene carriers, 4 non-carriers, 9 untested)	Having children: push-pull between responsibility to others (stop disease, care for child) count against having children, at other going with desire for children - even ignorance of HD; pregnacny sometimes divorced from HD, viewed as 'taking a gamble' Role of others: often decision between people, but conflict between lots of sources (eg. spouce, family, HCWs, societal pressures) - power in relationships affecting this decision; role of HCWs, especially in optimism re potential cure, or source of judgement	0.85

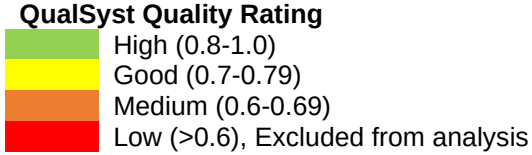
			Other options: adoption - mixed, helping someone but also burdening them; PGD - generally positive, though not resolving question of what happens when HD appears; CVS/Abortion - tension of responsibility to look after potential child but not engender suffering, also ambivalence to idea of abortion because of HD, need for things to 'sit right'. Guilt and shame: pouring over current and past reproductive decisions, concerns about future views of e.g. not testing or having children from self and others, responsibility to children complicated Abstience: sometimes considered, from children and relationships, as way out - also leaving it 'up to God' as relief from complex and heavy decisions.	
Leontini (2010) Country Unclear 18	Explore how people at risk of Huntington's Disease discuss their reproductive decision making in terms of risk, and how their conceptualisation agrees or disagrees with broader social narratives about how people with genetic risk of disease should approach reproductive decision making	Qualitative case study series: method of analysis unclear beyond interview transcripts being analysed ‘as narratives’. Participants: individuals currently or previously at genetic risk for HD (n=3)	First case: relatively low uptake of testing among at risk individuals despite potential benefits. Two children post knowledge of risk, without testing - sense of testing 'setting them apart' rather than helping. Change of POV following death of HD affected parent, and seeking own test with positve result - challenge of how to share 50% risk status with children. Retrospective guilt regarding choice not to be tested, concerns about 'selfishness', passive contribution to children's suffering. Second case: had test pre-marriage following death of affected parent, received negative result. Ambivelence as to whether positive result would or should have prevented having children - shared story of discussed sterilisation when he was child to 'stop spread'. Draws attention to eugenic/oppresive nature of this view, and emphasises the legitimacy of any individual choice counter to broader narratives. Third case: changing medical technological landscape attempts to shift issue from moral to techincal one - participant stressed choosing not to have children despite options for avoiding risk, as burden of caring for affected parent as challenging as passing on risk.	0.38

			Stresses idea of 'good parent' as healthy, not placing child at risk.	
Quaid (2010), USA 19	Explore reproductive decision making among three groups: those having children while known carriers, those having children and choosing not to test, and those choosing not to have children due to known carrying.	Qualitative: thematic analysis of interview transcripts. Participants: N=51 (Knew risk, had children = 26, Had children without risk knowledge = 15, No children because of risk = 10)	**Group 1 Themes:** Hoping for cure: optimism regarding treatment and improvement, trusting that it will be worked out ahead of it affecting children; Magical thinking: mix of denial, optimism - theme of 'decision I don't have it', or focusing on other aspects like suitability for parenthood; 'Just another something': acknowledgement of HD as a risk among many **Group 2 themes:** Too little too late: knowledge of HD coming too late, going back over things to look for clues,; Getting it wrong: incorrect info being shared, either through familes or professionals, or previously thought correct info being updated too late to resolve situations. **Group 3 themes:** Vigilant witness: deterioration of loved one with HD leaving a lasting impression of not wanting to put others through this; Stopping HD: advice from others or own conviction; Being alone: isolation from others to protect them and you - saving a child from looking after you, or partner, but feeling lonelier as a result	0.85
Van Rij (2012), Several European Countries 20	Reporting characteristics of HD-risk individuals seeking PGD, uptake and outcome of PGD, 1995-2008	Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted. Participants: individuals at genetic risk for HD seeking PGD during study period (n=174) Comparison: none	174 individuals undertook 331 PGD cycles (68% direct). Previous reproductive history: at least one previous pregnancy, 39%; at least one at least one previous termination following PND, 21% (significant correlation with seeking direct rather than exclusion testing), at least one living child, 18% (45% of whom born using PND/PGD). Percentage couples having unaffected live birth: 37.4%. Rate PGD uptake vs eligible at-risk population per country: Belgium, 8.5%; Netherlands, 5,8%, France, 3.7%	0.70
Krukenberg (2012), USA	Brief reporting of comparative demographics associated with likelihood to change reproductive	Retrospective cohort study, descriptive statistics and between-group	Factors significantly associated with increased likelihood to reevaluate reproductive decision making in light of HD risk knowledge: not attending church	0.58

21	decisions in light of HD risk knowledge	comparisons with statistically significant results hightughted. Participants: N=16, carriers identified at Centre who had at least one child, and had not been aware of risk status when having child	regularly, having less than three children pre-test, and having one's father as HD-affected parent.	
Van Rij (2013), The Netherlands 22	Explore motivations for at-risk couples pursuing exclusion prenatal diagnosis (ePND) or preimplantation genetic diagnosis (ePGD)	Qualitative: IPA analysis of interview transcripts. Participants: individuals with HD-diagnosed parent, and sometimes partner, who have used ePND/ePGD (N=17)	Reasons for exclusion methods: desire not to know own status balanced with desire to avoid having a carrier child - to avoid that child experiencing HD, to avoid a 'double loss' for partner, or to attempt to 'break chain' of HD inheritance. Choice of method: previous unawareness of unavailability of ePGD; issue of natural conception vs. IVF; difficulties with idea of termination; non biological methods also considered. Changes in decision: ePND discontinued due to distress at terminations, either to stop or to ePGD; delicate balancing of rights of child, partner and need to avoid suffering; ePGD as 'least bad' option. Desire for outside moral judgement to be removed. Impact of HD: desire to 'live in moment', 'I could be hit by a car tomorrow'; balanced with concerns about future and child's wellbeing. Change of method: majority stick, some change – general sentiment of 'making right choice at the time'.	0.70
Wedderburn (2013), Australia 23	Reporting uptake, outcomes of PND, PGD among HD at risk individuals in Australia during study period.	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participant: HD-risk individuals referred for genetic testing (n=466) Comparison: none	38 people sought out: 34 PND, 4 PGD. PND: 12 negative pregnancies carried to term, 11 positive pregnancies terminated, 3 positive pregnancies carried to term. 8 withdrew in counselling phase. PGD: no pregnancies occurred.	0.65
Van Rij (2014a), The Netherlands 24	Reporting uptake, outcomes of PND over ten years among those at HD risk	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participant: HD-risk individuals seeking PND (n=126)	126 seeking PND – 216 tests undertaken, 214 pregnancies. 74% had PGT prior to or during PND process (significantly more females than males). Of 216 PND, 53% produced negative result, 4% intermediate allele, 2% withdrew prior to result.	0.75

		Comparison: none	Of 91 positive test, 76 terminations, 12 carried to term, 2 miscarriages. 126 children born, 86% without HD inheritance. Uptake of PND vs. HD-positive population 22%, with young people significantly more likely to opt in.	
Van Rij (2014b), The Netherlands 25	Report uptake and outcomes of PND and PGD for HD risk individuals over ten year course, looking for statistically significant differences between and within groups	Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted. Participant: HD-risk individuals seeking PND and PGD (n=162) Comparison: none	162 individuals at least one attempt of one method – 108 PND only, 20 PGD only, 25 both. Total attempts – 458. PND – 47% had at least one termination, 76.5% at least one non-carrier child, 9.1% continued affected pregnancy. PGD – 53.5% at least one unaffected child, 48.8% at least one miscarriage, 7% at least one termination. Total children born – 183, 92.3% non HD inheritance. Uptake as proportion of HD-positive population, 32%.	0.90
Gong (2016), USA 26	Explore impact of positive HD genetic test on young adult's attitude towards life milestones, challenges faced - including reproductive decision making	Qualitative: Thematic and Grounded Theory analysis of interview transcripts Participants: young people who have received a positive PGT result (n=14)	'Get started early' on romantic relationships, family planning post test result (n=8) Worries about disclosure and potential rejection by partners in romantic relationships (n=8) Greater selectivity of potential romantic partners around HD acceptance and understanding of reproductive challenges (n=10) Family planning (female participants): desire to have unaffected child via aided conception (n=10), though concerns about cost of PGD (n=5). Family planning (male participants): unsure, dependent on desire of future female partners, context at time (n=2)	0.90
Tsang (2019), USA 27	Explore impact of HD risk on romantic relationships and reproductive decision making	Cross-sectional comparative survey design: descriptive statistics, statistically significant between group differences highlighted. Participants: individuals at genetic risk for HD and their partners (n=202)	Family planning subsection: Current reproductive intent: 36% currently have children; 38% had no children but intended to; 26% neither had nor want children. Factors influencing reproductive decision making: HD inheritance as very important 79%; Those with children significantly less likely to report this as very influential factor. Awareness of PGD: 88%; willingness to use, 55%. Common reasons: cost 44%, lack of info 29%, time 26%, negative experience, 24%	0.9

Key:


QualSyst Quality Rating
High (0.8-1.0)
Good (0.7-0.79)
Medium (0.6-0.69)
Low (>0.6), Excluded from analysis

controls, while females at genetic risk were less likely than controls to express future intention to have children.

Gong et al.'s (2016) qualitative study outlined the inter-relation between genetic HD risk and reproductive intentions among young people at genetic risk. The majority desired to have children in future, often considering utilisation of PGD to achieve this without the risk of inheritance. A smaller minority expressed changes to reproductive intentions explicitly because of genetic risk of HD, either in the form of a choice not to have children, or a subjective decreased emphasis on becoming a parent in future planning, though with a willingness to consider in the context of an appropriately supportive romantic relationship. Of note is a tendency among male participants to defer future reproductive intentions to their female partners.

1.2 Major role of HD knowledge in reproductive decision making

Three high quality studies, one qualitative (Quaid et al., 2010), one mixed-methods (Decruyenaere et al., 2007) and one quantitative (Tsang, 2019) comment on the major role that HD knowledge plays in reproductive decision-making for individuals at risk. In Quaid et al. (2010), among those who either had children prior to their knowledge of their HD risk status, and those who chose to refrain from having children as a result of their HD risk status, the knowledge of HD risk heritability is identified as a major if not predominant consideration in reproductive decision making, overshadowing other issues such as parenting suitability and life circumstances. Similarly, in Decruyenaere et al. (2007), in the qualitative portion of the study, the overriding reproductive considerations are highlighted as those related to HD inheritance, especially among those who ultimately chose not to have children. Tsang (2019) 79% (n=155) of at-risk individuals rated HD inheritance as a 'very important' factor in reproductive decision-making. An additional good quality quantitative study (Kessler et al., 1987) reported that 67.2% (n=43) of participants reporting HD inheritance having a 'significant' or 'enormous' impact on areas of life related to having children. A final relevant medium quality qualitative study (Downing, 2005) suggested that

ignorance of HD risk is approximated with less responsibility for reproductive outcomes among participants, and the point of gaining knowledge regarding one's own HD risk status is characterised as a 'turning point' in terms of responsibility to respond to HD genetic risk in reproductive decision-making going forward.

1.3 Impact of genetic testing on reproductive intentions

Seven quantitative studies of various quality reported on the anticipated and actual impact of a positive genetic test result on reproductive intentions among the at-risk population (Decruyenaere et al., 1996; Ever-Kieboom et al., 2002; Holloway et al., 1994; Markel et al., 1987; Schoenfeld et al., 1984a; Schoenfeld et al., 1984b; Tibben et al., 1993). Two commented on the anticipated response to a positive PND result during pregnancy – between 33.5% (Markel et al., 1987) and 60% (Schoenfeld et al., 1984a) reported that they would carry an affected pregnancy to term, between 16% (Schoenfeld et al., 1984a) and 22.6% (Markel et al., 1987) would pursue termination, and between 27% (Schoenfeld et al., 1984a) and 29.7% (Markel et al., 1987) unsure of their response. Schoenfeld et al. (1984a) identified demographic factors associated with response to positive PND result, with current parents at the time of survey significantly less likely to report intention to pursue termination of an affected pregnancy, and pursuit of termination significantly more likely among those with higher levels of educational attainment. Holloway et al. (1994) reported an 40% decrease in individuals reporting definite future reproductive intention post positive PGT result. Anticipated impact of a positive PGT result were also reported on – Markel et al. (1987) reported that a high proportion of those intending to have children would be deterred (42.6%), with a smaller proportion (16.1%) undeterred and 30.3% unsure of their response; both higher educational attainment and higher numbers of HD-symptomatic relatives were significantly associated with being deterred by a positive PGT result. Schoenfeld et al. (1984) reported a 22% reduction in the proportion of participants intending to have children in the context of an anticipated positive PGT result.

While the above studies deal mainly with the anticipated responses of at-risk individuals to testing outcomes, Tibben et al. (1993) reported on the changes in reproductive intention after PGT occurred, with a 20.83% reduction in the proportion of participants expressing future reproductive intention 18-months post receipt of a positive PGT result. Similarly, Decruyenaere et al. (1996) found at 12-month follow up post positve PGT result, among those previously expressing reproductive intent, approximately a third no longer intended to have children due to result, approximately a third intended to pursue PND, and a third remained undecided. Ever-Kieboom et al. (2002) found a small but significant association between receipt of a positive PGT result and decreased likelihood of pregnancy 12-months post-test, more pronounced among those who identified 'family planning' as a motivator for pursing PGT.

2: Views on assistive options

2.1 Views on PGT, PND and PGD

Seven studies of high and good quality (Fowler, 1999; Gong et al., 2019; Kessler et al., 1987; Klitzman et al., 2007; Markel et al., 1987; Schoenfeld et al., 1984b; Tsang, 2019) report on views about PGT, PND and PGD within the target population. In studies conducted during the period in which PGT was fist becoming available, between 63.2% (Markel et al., 1987), 73% (Schoenfeld et al., 1984b) and 78% (Kessler et al., 1987) reported willingness to pursue PGT when available regardless of treatment options available, rising to 86.5% in the event of treatment options becoming available (Markel et al., 1987). As reported later however, actual uptake rates of PGT once widely available emerge as much lower than the above intentions would indicate. Prospective willingness to utilise PND was reported as between 48% (Markel et al., 1987) and 65% (Kessler et al., 1987), with qualitative results highlighting the perceived emotional challenges of PND associated with potential termination of an affected pregnancy (Klitzman et al., 2007). Similarly, the case studies outlined in Fowler (1999) highlight the interpersonal challenges raised by the possibility of pregnancy termination in PND, with its potential negative impact on the relationship a major reason it

was not pursued as an option. Views of PGD were generally positive in included studies – with participants in qualitative literature characterising it as the preferred option for pursuing biological children while avoiding genetic risk (Gong et al., 2016), and the 'least bad option' for having children, specifically contrasted with PND which was characterised as emotionally taxing (Klitzman et al., 2007). Tsang (2019) reported that 88% of participants were aware of PGD, and 58% considered it's use in future. Common negative aspects of PGD were identified as its prohibitive cost (Gong et al., 2016; Tsang, 2019), and previous negative experiences of the process (Tsang, 2019).

2.2 Views and use of other assistive options (adoption, donation)

Three studies of high and good quality reported on participant's views and use of non-medical assistive options, specifically adoption (Fowler, 1999; Klitzman et al., 2007; Richards & Rea, 2005). Adoption is viewed in mixed terms – in Klitzman et al. (2007) it is characterised as avoiding genetic inheritance and potentially 'helping someone in need', but also potentially burdening a disadvantaged child with later caring responsibilities, and therefore morally ambiguous. Two case studies in Fowler (1999) engage with the issue of adoption – in one case it is considered as a response to a positive PGT result, in another engaged with through the adoption of two children. Both case studies stress the emotional complexity associated with adoption – strong connection with the adopted child existing alongside a sense of loss and sadness regarding the loss of potential biological parenthood. There is limited studies exploring the uptake of adoption among at risk individuals, with only Ricards and Rea (2005) explicitly reporting on this – in the 12 year follow up post-PGT in this Australian sample, no individuals receiving a positive PGT result had pursued adoption, while 1.2% of those receiving a negative result had.

2.3 Response to changing technological options

During the period of time covered by this review, there have been significant changes to the technological options available to people living with genetic risk related to

reproduction, from initial tests by linkage analysis, to direct testing, and later PND and PGD. Five studies of varying quality (Decruyenaere et al., 2007; Maat-Kievet et al., 1999; Simpson et al., 2002; Van Rij et al., 2012; Van Rij et al., 2013) report on participants' responses to these changes in available technological options. Decruyenaere et al. (2007) highlighted that, while new assistive options are generally viewed as positive developments, participants experienced a implicit pressure to engage with new options as they emerge, sometimes facilitated by information and encouragement from healthcare professionals, such as attempting PGD where previously PND had been unsuccessful, which could be emotionally taxing. Conversely, Maat-Kievet et al. (1999) found that actual changes in assistive option used were uncommon in their sample, with the vast majority of participants (84%) continuing with PND or PGD where previously used.

A second area of concern regarding which assistive options to pursue was direct PND/PGD, whereby the parent must themselves know their genetic status, or exclusion PND/PGD, whereby the parent can pursue these options without having to know their own risk status. In studies reporting on the breakdown of direct versus exclusion methods, between 32% (Van Rij et al., 2012) and 35% (Simpson et al., 2002) of those seeking PND or PGD opted for exclusion testing. Qualitative results exploring the reasons for pursuing exclusion methods highlighted the choice as an attempt to balance the strong desire to avoid genetic risk to the child with a desire to avoid knowing own genetic status, to avoid hopelessness, stigma or a sense of life being overshadowed by HD risk knowledge. As above, the emotionally distressing nature of the terminations potentially involved in ePND was highlighted, with ePGD again characterised as a less distressing and morally challenging, but more medicalised 'least bad option'.

3: Complexity and challenges in reproductive decision-making

3.1 Balancing desire for a child with responsibility

Five studies of varying quality (Decruyenaere et al., 2007; Downing, 2005; Fowler, 1999; Klitzman et al., 2007; Van Rij et al., 2013) explore participant experiences of struggling

to balance desire for a biological child with concerns about the potential impact of HD genetic risk on that child's life. Decruyenaere et al. (2007) reported that, five years post-PGT, participants experienced difficulty in reconciling their child desire with a sense of responsibility to the child, both in avoiding risk inheritance as well as in avoiding future caring burden. Klitzman et al. (2007) describe a similar 'push-pull' dynamic between desire for children and responsibility. This process is characterised by rumination and uncertainty in ultimate decisions (Decruyenaere et al., 2007; Klitzman et al., 2007). At-risk individuals occasionally express a wish to return to a state of pre risk knowledge 'ignorance', where they do not have to contend with this feeling of responsibility (Downing, 2005; Klitzman et al., 2007). This sense of need to achieve a balance of responsibility or 'fairness' is also highlighted in Downing (2005), where each of the case studies outlines challenges faced in establishing what constitutes a 'responsible' reproductive choice, the need to maintain consistency of approach across pregnancies to avoid unfairness to already-living children, and attempts to establish responsibility in other areas by demonstrating aptitude for parenthood. This complex dynamic is highlighted in Fowler (1999) where a couple outline the difficult balance of accepting responsibility to avoid inheritance by abstaining from having biological children with a deep sense of sadness at the loss of this opportunity. Where individuals have opted for exclusion methods, this balance becomes a three way process – desire for children balanced against responsibility to avoid inheritance for the good of children and partners, coupled with the individual's strong desire not to know their own status (Van Rij et al., 2013).

3.2 Risk acceptance and optimism

Five studies explore themes of acceptance of HD genetic risk in aid of pursuing strongly held reproductive intentions (Downing, 2005; Fowler, 1999; Klitzman et al., 2007; Quaid et al., 2010; Van Rij et al., 2013). Across several studies, a theme emerged whereby participants accepted the risk of their children inheriting HD by acknowledging HD risk as one risk among many, contrasting with potential but unavoidable disasters (“could be hit by a

bus tomorrow"; "could get cancer"), suggesting that risk minimisation may not be possible, and placing an emphasis on pursuing valued options in the here and now. (Klitzman et al., 2007; Quaid et al., 2010; Van Rij et al., 2013). In this theme, longer-term future planning is characterised as of limited utility due to the possibility of unforeseen circumstances (Van Rij et al., 2013). Some participants describe engaging in a process of 'positive denial' whereby they will decide their children have not inherited HD, or that a cure or treatment will be available, thereby lessening their concerns (Quaid et al., 2010; Fowler, 1999). Others emphasise aspects of parenting beyond genetic risk, and de-emphasise genetic risk, characterising 'good parenting' holistically (Downing, 2005).

3.3 Guilt, regret and rumination on past decisions

Four studies report on participant's struggles with feelings of guilt or regret for, and rumination on, past reproductive decisions (Downing, 2005; Fowler, 1999; Klitzman et al., 2007; Quaid et al., 2010). Guilt and rumination regarding the outcome of reproductive decision-making emerges as a common experience (Fowler, 1999; Klitzman et al., 2007; Quaid et al., 2010). It can include worries about the acceptability of reproductive decisions to other people, to their future selves, and most commonly to their children as they grow and become aware of the role of HD genetic risk in their lives (Klitzman et al., 2007). This can be particularly pronounced among those who had children prior to risk knowledge, who experience a process of looking for 'signs' they might have missed in the past (Quaid et al., 2010) or a desire to 'start over and make different decisions' (Fowler, 1999). Thre can be an experience whereby participants, previously accepting of their reproductive decisions, as a result of changes such as emergence of HD symptoms in a relative, go through a stressful process of re-evaluation in the light of this new experience, sometimes regretting previous decisions (Downing, 2005).

3.4 Role in relationships with others

Four studies comment on the role played by relationships with other people and reproductive decision-making in the context of HD genetic risk (Fowler, 1999; Gong et al., 2016; Klitzman et al., 2007; Quaid et al., 2010). The experience of HD risk knowledge and resultant reproductive decision-making is mediated through relationships with healthcare professionals who are depended upon to share pertinent and accurate information (Klitzman et al. 2007; Quaid et al., 2010), with situations where this does not occur viewed as particualrly harmful (Quaid et al., 2010). Interactions with healthcare professionals can prove to be an importance source of information and optimism about treatment, while also acted as one avenue of implicit judgement on reproductive decisions made (Klitzman et al., 2007). Further to this, reproductive decision-making is characterised as inherently interpersonal, as it requires negotiation with partners (Fowler, 1999; Gong et al., 2016; Klitzman et al., 2007), and in some instances reproductive intentions are understood as entirely contextual to the correct romantic relationship to an extent where they are not actively considered outside of this (Gong et al., 2016). The challenge caused by conflicts of opinion, either with a partner (Fowler, 1999) or due to multiple strong, differing opinions being shared by multiple family members (Klitzman et al., 2007; Quaid et al., 2010) can be difficult to navigate, and a source of doubt and distress in reproductive decisions. In addition, the complexity of relational dynamics can sometimes overshadow management of HD genetic risk in reproductive decision-making, leading to utilisation or non-utilisation of options that might otherwise have been taken (Fowler, 1999).

4. Actual Reproductive Outcomes

Ten studies report on actual reproductive outcomes among the population of people at genetic risk for HD across various countries (Decruyenaere et al., 2007; Maat-Kievet et al., 1999; Richards & Rea, 2005; Simpson et al., 2002; Tassicker et al., 2006; Tibbens et al., 1993; Van Rij et al., 2012; Van Rij et al., 2014a; Van Rij et al., 2014b; Wedderburn et al., 2013). In a very early study exploring reproductive outcomes six months post PGT in the first cohort of people receiving a HD genetic testing in the Netherlands in 1989-91, Tibbens et al.

(1993) reported one pregnancy without intervention, one termination post positive PND result, and one HD-inheriting pregnancy carried to term following a positive PND result. Between 1998 and 2008 in the Netherlands, among those at risk individuals seeking PND or PD, 183 children were born, with HD inheritance precluded in 92.3% of these births (Van Rij et al., 2014a; Van Rij et al., 2014b). Across multiple European test centres, between 1993 and 1998, 184 pregnancies, 8 of which inheriting HD, and 123 occurred among those utilising PND, while between 1995 and 2008, 37.4% of individuals pursuing PGD gave birth to at least one unaffected child. Among the cohort of 46 at-risk individuals with reproductive intent reported on by Decruyenaere et al. (2007), 25 unaffected births occurred during the study period, 23 using PND and 2 using PD.

Several studies commented on the amount of PND tests and PD cycles undertaken. In Australia, a total of 63 PND tests and 18 PGD cycles were undertaken between 1994 and 2010 across (Tassicker et al., 2006; Richards & Rea, 2005; Wedderburn et al., 2013), with at least 776 positive PGT results received over the same period (Tassicker et al., 2006). In the Netherlands, 43 individuals sought PND during the period 1987 to 1997, 60% of which did so following a positive PGT result, and 35% of which utilised PND across more than one pregnancy (Maat-Kievet et al., 1999). During the period 1998-2008 in the same country, 126 individuals sought PND, leading to 216 tests (Van Rij et al., 2012), while 162 at-risk individuals used PND (66.67%), PGD (17.90%) or a combination (15.43%) (Van Rij et al., 2014b). Among this sample, 47% of those using PND experienced at least one termination and 76.5% gave birth to at least one child without HD inheritance, while among those using GD 77.8% experienced at least one unsuccessful cycle, and 44.4% gave birth to at least one child without HD inheritance (Van Rij et al., 2014b). Across European testing centres as a whole, between 1993 and 1998, 305 individuals sought PND, 53.9% female with a mean age of 30.8 years, 51% following a positive PGT result (Simpson et al., 2002), while in the period 1995 to 2008 across three testing centres in the Netherlands, Belgium and France, 174 individuals started at least one PGD cycle (Van Rij et al., 2012).

Several studies attempted to estimate the uptake of PND and PGD as a proportion of the reproductive-age population at genetic risk of HD in their respective countries. An early study by Maat-Kievet et al. (1999), estimated a 2% uptake of PND versus the eligible population of the Netherlands during the study period. Later estimates of uptake in this population in the Netherlands increased to 22% for PND alone (Van Rij et al., 2014a), 5.8% for PGD alone (Van Rij et al., 2012) and 32% for both PND and PGD in total (Van Rij et al., 2014b). Uptake of PGD in other European countries is estimated at 8.5% of eligible population in Belgium and 3.7% in France. Outside of continental Europe, two studies comment on levels of uptake in Australia – Tassicker et al. (2006) reported 776 positive PGT results during the study period led to 63 PND tests and 18 PGD cycles, but does not specify how many individuals these tests occurred across or what proportion of the eligible population they represent; Wedderburn et al. (2013) estimated a rate of uptake of 8.15% for both PND and PGD considered together at a single Australian genetic testing centre.

5: Other factors influencing reproductive decision-making

Eight studies reported on other factors associated with differences in reproductive decision-making beyond genetic risk for HD (Decruyenaere et al., 2007; Gong et al., 2016; Kessler et al., 1987; Maat-Kievet et al., 1999; Markel et al., 1987; McCormack et al., 1987; Schoenfeld et al., 1984a; Tsang, 2019).

Age was reported as associated with response to PGT results – being younger was significantly associated with increased likelihood to maintain reproductive intentions post positive PGT result (Decruyenaere et al., 2007); this however is contracted by McCormack et al. (1983) who reported that males and females under 45 were less likely than older counterparts to maintain reproductive intention post positive PGT result. Additionally, younger age was significantly associated with being more likely to seek PND than PGD (Maat-Kievet et al., 1999).

Being a parent at the time of study was found to be significantly associated with a number of factors – decreased likelihood of being deterred from having more children as a result of a positive PGT result (Markel et al., 1987), a decreased likelihood to consider HD inheritance or symptoms an important factor in reproductive decision-making (Tsang, 2019), and a decreased likelihood to pursue PND (Markel et al., 1987). Decruyenaere et al. (2007) reported a contradictory finding, whereby those without children were significantly less likely to change reproductive intentions as a result of a positive PGT result.

Gender was identified as having contradictory influences in different studies – in McCormack et al. (1983), males were more likely than females, regardless of age or HD risk, to report future reproductive intention, however Gong et al. (2016) found that female participants expressed clear reproductive intentions whereas male participants reported uncertainty of future reproductive intentions, viewing this as reflexive to the potential desire of future female partners.

Several other demographic factors emerged as influential on reproductive decision making. Higher educational attainment (characterised as having attended college or university for any length of time) was significantly associated with a higher likelihood of being deterred from having children by a positive PGT result (Markel et al., 1987). It was also significantly associated with decreased likelihood to currently have children at the time of survey (Schoenfeld et al., 1984a) and increased likelihood to terminate an affected pregnancy identified via PND (Schoenfeld et al., 1984a). Familial experience with HD was also influential with both those with more HD-symptomatic relatives and those whose symptomatic relatives experienced an earlier age of symptom onset significantly more likely to pursue PGT (Markel et al., 1987). Religious affiliation affected views on termination of pregnancy, with Catholic participants significantly less likely to consider termination of pregnancy following positive parental PGT result or positive PND result (Markel et al., 1987). Finally, length of marriage was negatively associated with intention to pursue PGT (Kessler et a., 1987).

Discussion

This review was to our knowledge the first to integrate available research findings regarding reproductive decision-making in the context of genetic risk for HD, considering both uptake and outcomes of assistive options such as PGT, PND and PGD, as well as to outline the more subjective aspects of reproductive decision-making in terms of attitudes towards available support, approaches to and influences on the decision process, and emotional responses to the challenges of reproduction in this context.

The first key area in this study, '*The relationship between reproductive intentions and HD genetic risk*' highlights the important interplay between existing child desire and HD risk knowledge. Earlier studies report a high level of future reproductive intentions, reducing over time in later studies. This follows general population trends within Western countries where stated reproductive intention as a proportion of the population has decreased over past decades as a result of changing social norms regarding parenthood, education and childcare costs (Beaujouan, & Berghammer, 2019). HD risk knowledge emerges as playing a major role in reproductive decision-making across multiple studies. Given HD's high level of heritability, and its significant quality of life impact on those affected and their immediate families (Ready et al., 2008) this is an understandable finding, and mirrors the major role played by genetic risk knowledge in reproductive decision-making across multiple genetically heritable conditions (Gietel-Habets et al., 2017; Severijns et al., 2021). Positive PGT results, both anticipated and actual, appear to reduce future reproductive intentions, though the proportion of people deterred following an actual test is lower than those who anticipated they would be, perhaps suggesting other factors at play such as strength of reproductive intention or contextual factors at the time of PGT, such as relationship or life stage. Anticipated termination of a HD-inheriting pregnancy as a result of PND proved to be challenging to commit to across a number of studies, understandable given the emotional difficulty of termination (De Die-Smulders et al., 2013), and may go some way to explaining

the relatively low uptake of this assistive option among the population of those at genetic risk for HD.

The second area, '*Views on assistive options*' outlines trends in attitudes towards options available to at-risk individuals to understand and mitigate genetic risk inheritance in reproduction. Generally positive attitudes towards PGT and high anticipated uptake in earlier studies are interesting, given the widely reported low actual uptake of PGT as it has become widely available (Baig et al., 2016). Though logistical barriers to accessing testing, and desire to avoid stigma or hopelessness following a positive result have been posited as reasons for low uptake (Baig et al., 2016), review findings suggest that lack of available treatment options (Markel et al., 1987) is also a relevant modifier of uptake. As above, mixed views on PND among those at-risk for HD are mainly associated with the potential need to terminate an otherwise viable pregnancy, with PGD generally characterised favourably by comparison, though with noted cost barriers to use. This appears to lead to PGD being identified as the 'least-lose option' within the reproductive decision (Lippman-Hand, & Fraser, 1979). Given this, it will be important to address practical barriers to its availability to HD-risk individuals, especially cost. Adoption emerges as a morally complex response to the dilemma of HD interitance – viewed as possible, but with both moral issues regarding future caring burden and emotional desire for a biological child making it less appealing. This mirrors findings in other genetically heritable conditions, where adoption is often viewed as final reproductive option where other avenues have been unsuccessful (Severijns et al., 2021). It is interesting to note the complex relationship outlined with changing reproductive technologies, with both positive elements such as the emergence of preferred options such as PGD, as well as more complex or negative elements such as a perceived 'pressure', internal and external, to consider and use newly available options. This appears to contribute to the sense of reproductive decisions in HD as never fully 'made', but rather fluid and reflexive to changing context.

The third key area, '*Complexity and challenges in reproductive decision-making'*,

outlines the subjective difficulties in reproductive decision-making, as well as in the acceptance of these decisions after the fact. Several studies outline the subjective experience of attempting to balance a desire for children with a sense of responsibility related to genetic inheritance, which appears to be responded to in multiple ways. Some people respond by accepting the possibility of genetic inheritance as aggregate with other potential risks, a potential 'simplifying heuristic' (Lippman & Hand, 1979) allowing for the reduction of complexity in reproductive decision-making to allow them to move forward. Conversely, for others, reproductive decision-making is characterised by feelings of guilt and repeated rumination on past and current decisions. As with new technological options above, this may indicate that for some individuals, reproductive decisions are not necessarily discretely made, but rather regularly returned to in a process of re-evaluation over time and in response to changes in context. The challenge and distress associated with risk knowledge is contrasted with a sense of eased responsibility prior to risk knowledge across multiple studies, and occasionally a wish to be able to return to this state of 'ignorance' to resolve the challenges faced in reproductive decision-making. Reproductive decision-making in the context of HD genetic risk is also highlighted as an inherently interpersonal process, involving not just partners, but often input from various healthcare professionals and the wider family, leading to ample but often contradictory information and opinions. This interpersonal element is mirrored in other genetically heritable conditions (Severijns et al., 2021) and in medical decision-making more generally (Gray et al., 2019), and is important to acknowledge as a major influence on reproductive decision-making, at times overshadowing the impact of genetic risk knowledge in the process

The fourth area, '*Actual reproductive outcomes*' summarises available information about reproductive outcomes among those at genetic risk for HD, both in terms of births, and utilisation of PND and PGD. There are a number of notable limitations to the quantitative research related in this theme, which will be discussed in a later section. A general trend emerges across studies whereby, among those utilising PND or PGD, HD inheritance is avoided in the vast majority of cases, though some HD-inheriting pregnancies are continued

out of choice, though it is important to note that as these studies report only on reproductive outcomes among those already seeking to utilise PND or PGD, those included represent a relatively self-selecting sample with high concern regarding potential HD inheritance to children, and therefore these patterns are not necessarily applicable across the entirety of the at-risk population. Uptake of PGD, and to a lesser extent PND, appears to be increasing over time, with more recent studies reporting greater uptake than older studies, but the combined uptake of both remains low as a percentage of the eligible at-risk population, mirroring patterns in PGT (Baig et al., 2016). Though some research findings indicate that awareness of PGD may not be total among the at-risk population, and there are issues such as cost that limit utilisation, the above-outlined findings that reduced risk knowledge can be associated with reduced responsibility to respond to risk may be relevant. It may suggest that some individuals may avoid acquisition of additional genetic risk knowledge, such as via PGT, PND or PGD, as a strategy to avoid its outsized influence on decision-making, especially in the context of lack of available treatments. However, this topic would require additional dedicated research exploring it for any more definitive statements to be made.

The fifth and final area, '*Other factors influencing reproductive decision-making*', outlines the impact of other significant factors, largely demographic and experiential, on reproductive decision-making among the at-risk population. These are important indicators that reproductive decision-making does not occur in a vacuum where risk status is the only influential factor, but rather is modified and influenced by many demographic and social characteristics. Gender is reported as having contradictory influence, with females being more likely to express reproductive intention in Gong et al. (2016) and males being more likely in Markel et al. (1987), however given the lack of significance reporting in this result by Markel et al. (1987), and given its lower quality assessment than Gong et al. (2016), this finding should be considered critically. A similar pattern plays out with age, with one study reporting that younger people are more likely to maintain a reproductive intention after positive PGT result (Decruyenaere et al., 2007), while the opposite is reported by

McCormack et al. (1983); given Decruyenaere et al.'s (2007) higher quality and being conducted significantly more recently, it may be safe to assume that it is more representative of the current cultural influence of age on reproductive intention. Being a parent previously appears to have a major impact, with current parents less likely to consider inheritance as important, and less likely to pursue assistive options. We might consider that, having successfully navigated parenthood already, current parents are more likely to consider themselves capable of doing so again, and have a broader experiential category for what has been and therefore will be important in parenting. Perhaps unsurprisingly, increased experience with HD-symptomatic relatives leads to increased hesitance regarding inheritance, (De Die-Smulders et al., 2013), and we might consider the association of Catholic faith and hesitancy (Markel et al., 1987) to pursue termination equally explicable. Educational levels are associated with a range of views related to forgoing or terminating affected pregnancies, mirroring a general trend towards greater acceptance of termination as an option generally associated with greater educational attainment (Dutta et al., 2021).

Critique of the literature

Several limitations of the published research available on this topic are evident. Firstly, there are a number of studies which appear to replicate data used in other studies with minor changes, such as covering PND (Van Rij et al., 2014a) and PND and PGD (Van Rij et al., 2014b) in the same area in the same period, or where it is less clear if data covers the same test centres (Van Rij et al., 2012). Though use of the same data across multiple studies is not an issue in and of itself, where this is not explicitly identified and confirmed by study authors, there is a risk that outcomes may be pooled without consideration for duplication of results, thus leading to trends or patterns being exaggerated in terms of size or significance. Further to this, barring studies which attempt to estimate the uptake of PND and PGD as percentage of the eligible at-risk population (Maat-Kievet et al., 1999; Van Rij et al., 2012; Van Rij et al., 2014a; Van Rij et al., 2014b; Wedderburn et al., 2013), the majority of studies which reported on actual reproductive outcomes do so by reporting simply on the

numbers of births or tests undertaken in a given period, without any attempt at clarifying statistical analysis to identify trends, or indeed providing contextualising information such as comparing the birth-rate in this cohort with comparable controls in the general population. The simple presentation of these rates in numbers is of limited utility in identifying whether, for example, the introduction of new reproductive options over the past decades has led to a decrease in HD inheritance. Relatedly, where a number of qualitative studies provide us with insight into the reproductive decision-making of those who do *not* pursue PND/PGD (e.g. Decruyenaere et al., 2007; Klitzman et al., 2007; Quinn et al., 2010), the quantitative studies which comment on reproductive outcomes exclusively do so with reference to the self-selecting sample of those who pursue these options, which via estimated uptake we know to represent only a minority of the at-risk population – no studies identified were able to comment on trends in reproductive decision-making or outcomes in the at-risk population as a whole. Finally, there is a lack of development or consideration of an overarching psychological model outlining mechanisms of reproductive decision-making in HD, despite a relatively rich body of qualitative research exploring its complexities. Models of reproductive decision-making in genetically heritable conditions such as the 'Shock-Adjust-Decide' model in cystic fibrosis (Myring et al., 2011) or in *BRCA* inheritance (Reumkens et al., 2019) do exist, however generally focus on the process within heritable physical health conditions, and may not account for the relational and interpersonal challenges related to personality change in HD. Given HD's status as among the longest tested for and most researched genetically heritable neurodegenerative disorder, and one on which the approach to others if often based, the lack of explanatory model of this key issue for those at genetic risk for HD is an area for development.

Limitations and strengths

There are a number of limitations and strengths to this review. As an initial review seeking to synthesise all available data on the topic, the inclusion criteria were deliberately wide. Though this elicited a broad range of results, this led to a situation where included

studies were disparate in methodology, reported upon outcomes and time frame, limiting the scope of analysis to broad descriptive thematic categories, rather than allowing for more detailed analysis of a smaller number of more similar studies to allow accounting for complexities and contradictions between findings in more depth (Butler et al., 2016; Dixon-Wood et al., 2006). Though attempts were made to ensure the search methodology was as robust, transparent and replicable as possible, the use of hand-search to identify potentially relevant research may introduce bias otherwise avoided if a purely systematic search approach had been used. The framework analysis, especially at the stage of indexing of studies and pattern mapping, was conducted solely by the main author, and though the resultant key areas were reviewed by the research supervisor and modified based on feedback, the lack of a second reviewer confirming the theme development process means that potential bias may enter the process at this point, though efforts were made to ensure that each stage of the synthesis was clearly documented in a transparent and replicable manner to minimise this.

Despite these limitations, this review has a number of strengths. As a novel review covering the area of reproductive decision-making in HD for the first time, it provides an important comprehensive summary of the available research on this topic to date. Though the broad scope of the studies included in this review may have influenced the depth of analysis, it nevertheless has a number of benefits: it provides a summary of multiple areas relevant to the topic at once, the time frame of included studies allows for trends and changes in reproductive decision-making over time to begin to be identified, and it attempts to account for both the quantitative trends in reproductive outcomes as well as the subjective complexities of the decision-making process. Furthermore, by focusing on HD specifically rather than genetically heritable conditions in general, it provides us with meaningful insight into characteristics of the process that may be relevant to both HD specifically, and genetically heritable neurodegenerative disorders more generally.

Recommendations and Conclusions

Overall, this study highlights that reproductive decision-making in the context of HD genetic risk as complex, challenging process characterised by a number of practical and emotional responses to risk. A changing technological picture over past decades have introduced new options for at-risk individuals to gain knowledge on and response to HD genetic risk, however their uptake has been limited. It further highlights key areas of knowledge within the topic which currently available research fails to meaningfully address, such as our knowledge of overall reproductive trends in the complete at-risk population.

Future research should attempt to focus on establishing conclusively the reasons for the lack of uptake of available assistive options among the at-risk population, so as to establish what measures might be taken to facilitate access, as well as attempting to meaningfully report on the issue of reproductive decision-making and outcomes among those who do not engage with available assistive options. Furthermore, the need for a theoretical model of reproductive decision-making suggests that this may be an area of fruitful further research, both for individuals at-risk for HD, as well as suggesting directions for other genetically heritable neurodegenerative disorders. Clinically, the finding that reproductive decision-making is experiencing as an on-going process where decisions are returned to and re-evaluated as context changes suggests that it will be important to facilitate access to genetic counselling reflexively to need across the lifespan for at-risk individuals, rather than discretely only during the genetic testing process and engagement with reproductive technologies. Further to this, the emotional complexity of these processes outlined in qualitative findings suggests that genetic counselling may need to provide space for emotional processing and time given to consider the medium- and longer-term implications of various approaches, rather than solely taking providing necessary clinical information for reproductive decision-making.

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Part 2: Empirical Paper

The experience of ‘at-risk’ status for genetic variant frontotemporal dementia (GvFTD) and its impact on reproductive decision-making: A qualitative study

Abstract

Introduction: Genetic variant frontotemporal (GvFTD) is an autosomal dominant heritable form of FTD with onset in mid-life and characterised by loss of empathy, behavioural and personality changes. Genetic testing means there is a growing group of people at 50% risk for GvFTD, who often experienced their parent developing symptoms. Given both experience and potential heritability, it has implications for reproduction. This study aims to explore attitudes and approaches to reproductive decision-making among those at risk for GvFTD.

Method: Thirteen qualitative interviews were conducted with people at risk for GvFTD, including parents and non-parents, and analysed using Thematic Analysis to explore experiences with FTD-symptomatic relatives, attitudes towards reproductive decision-making in context of genetic risk, and, among parents, influences of genetic risk status on parenting.

Results: Six main themes were identified from analysis: 1) Fear of repetition of own experience with symptomatic relatives; 2) Approaches to mitigating repetition; 3) Responses to genetic risk in reproductive decision-making; 4) Accounting for timing in at-risk reproductive decision-making; 5) The challenges of disclosing genetic risk to children; 6) Other mitigating factors in reproductive decision-making.

Conclusions: Findings highlight the key role of previous experiences with symptomatic relatives in shaping attitude toward genetic risk status and approach to managing it in reproductive decision-making. Findings highlight a need for responsive genetic counselling focused on exploring options as well as providing information, and signposting to practical support with legal and financial preparations. Future research should specifically compare experiences in GvFTD with experiences in HD, and explore reproductive decision-making between partners in at-risk couples.

Introduction

Frontotemporal dementia (FTD) is a form of progressive neurological degenerative disease characterised by atrophy of the frontal and temporal lobes (Sivasathiaseelan et al., 2019). Clinically, FTD manifests as a progressive decline in certain complex behaviours, with three main variants demonstrating differing characteristic impairments. Behavioural-variant FTD (BvFTD), the most common variant, emerges primarily as a deterioration in emotional control, executive function and interpersonal abilities, characterised by impulsivity and disinhibition, apathy, reduced empathy, and the emergence of unusual behaviours with obsessional and ritualistic elements. Semantic Dementia variant FTD (SdvFTD) emerges as impairment of semantic memory in the form of impaired knowledge of word meaning, difficulty in name retrieval, and characterised by fluent but pleonastic speech. Progressive Non-fluent Aphasia (PNFA) variant is also characterised by a deterioration in language production, in the form of effortful, non-fluent speech (Warren, Rohrer & Rossor, 2013). Though these presentations initially emerge as relatively distinct, there is a tendency for them to overlap as underlying neuropathology progresses (Sivasathiaseelan et al., 2019). Age of onset is typically between 50 and 60, but can occur earlier in the 30s and 40s, and more rarely later in life (Warren, Rohrer & Rossor, 2013).

Though FTD is a relatively rare form of dementia, with a prevalence rate of 4-15 per 100,000 in Europe and North America (Warren, Rohrer & Rossor, 2013), it is the second most common form of dementia associated with onset before the age of 65 (Fadil et al., 2009; Rossness et al., 2016). Additionally, there is a significant element of genetic heritability within FTD – it has been suggested that 30-50% of cases are familial (Onyike & Diehl-Schmid, 2013), with 26-31% of cases of diagnosed FTD demonstrating a strong family history (Greaves & Rohrer, 2019). For a subset of approximately 10% of overall cases, and 48.8% of BvFTD cases, there is a clear autosomal dominant inheritance pattern (Rohrer et al., 2009), whereby a child of the FTD-symptomatic individual has a 50% chance of inheriting the implicated genetic mutation and going on to develop symptoms of FTD themselves.

Genetic variant FTD (GvFTD) is any case of FTD which demonstrates both a family

history of FTD symptomatology and inherited mutation of one implicated gene, which are, in decreasing order of estimated frequency, C9orf72, GRN and MAPT (Greaves & Rohrer, 2019). GvFTD can occur across all varianits, with BvFTD being most commonly genetically inherited (Hogan et al., 2016; Rohrer et al., 2009). Considering the autosomal dominant inheritance pattern of the implicated genes within GvFTD, biological children of GvFTD-diagnosed individuals are at genetic risk for GvFTD themselves.

Challenges in diagnosis, treatment and support of FTD

Diagnostic criteria for BvFTD have been identified through cross-comparison of symptoms across confirmed cases (Rascovsky et al., 2011), and are: 1) behavioural inhibition, 2) apathy or inertia, 3) loss of sympathy or empathy, 4) perseverative, stereotyped or compulsive and ritualistic behaviour, 5) hyperorality or dietary changes, 6) neurologically confirmed impairment of executive functioning with relative sparing of episodic memory and visuospatial skills.

However, due to the gradual and subtle onset of symptoms (Johannsen et al., 2017), with initial personality and behavioural changes often hard to categorise (Tookey et al., 2022; Van Vliet et al., 2011), initial misdiagnosis as psychiatric issues is common (Manoochehri & Huey, 2012; Rosness et al., 2008), and general clinicians often lack knowledge to correctly identify FTD in its early stages (Rosness et al., 2016). This, coupled with the lack of insight characteristic of FTD (Van Vliet et al., 2011; Van Vliet et al., 2013) mean that accurate diagnosis can take from 5 (Rosness et al., 2016) to 6.5 (Van Vliet et al., 2013) years from onset. Within first degree relatives of diagnosed individuals, the presence or absence of the gene mutations associated with GvFTD can be determined via blood test. However, uptake of testing is low, with 70-80% of those at risk for GvFTD choosing not to pursue testing (Greaves & Rohrer, 2019).

There are currently no disease-modifying treatments available (Manoochehri & Huey, 2012; Rosness et al., 2016; Sivasathiaseelan et al., 2019; Warren, Rohrer & Rossor, 2013), though research is ongoing (Young et al., 2018). Management focuses on control of behavioural symptom and practical support for symptomatic individuals and carers in coping

with the significant stress resulting for the impact of FTD symptoms. Prescription of SSRIs and anti-psychotic medications to manage agitation, disinhibition and unusual behaviours is relatively common (Sivasathiaseelan et al., 2019; Warren, Rohrer & Rossor, 2013), though the evidence base for the effectiveness of these treatments is limited (Young et al., 2018). Other interventions focus on practical adaptions to minimise the impact of behavioural symptoms, such as simplification of daily routines, and avoidance of environmental and social risks (Warren, Rohrer & Rossor, 2013).

Practically, most responsibility for managing the symptoms of FTD falls to the carers of symptomatic individuals. Given the idiosyncratic rate of functional decline and the interpersonal challenges of characteristic symptom, carers face a significant and unique burden, including manage unpredictable and socially disruptive behaviours (Massimo, Evans & Benner, 2013), and tolerating the loss of previous emotional relationship due to empathy and personality changes (Caceres et al., 2016). Caring in FTD is associated with greater stress than Alzheimer's Disease (Kaiser & Panegyres, 2006; Riedijk et al., 2006), and increased rates of mental and physical health issues (Caceres et al., 2016; Wong & Wallhagen, 2014). Qualitative findings highlight the emotional impact on carers of the perceived 'loss of the person' and 'loss of the relationship' that emerges from both the emotional and empathic changes in the affected person, and the change in dynamics affected by the need to take on a caring role (Massimo, Evans & Benner, 2013; Oyebode, Bradley & Allen, 2013), along with the frustration and distress associated with attempting access appropriate support for a rare and complex disease (Bruinsma et al., 2022). Caring in FTD emerges as a complex and demanding experience at many levels – in seeking an explanatory diagnosis, in managing ongoing changes in the symptomatic individual, and in effectively engaging support through considerable personal effort (Tookey et al., 2022; Van Vliet et al., 2011).

Reproductive decision-making in the context of genetic risk

In GvFTD, as in other genetically heritable conditions, there is an implicit question of inheritance to biological children of symptomatic and genetically at-risk individuals. This is

often a key concern of these individuals and their partners across a range of conditions (Hershberger et al., 2012; Severijns et al., 2021). In addition, the provision of accurate information about genetic inheritance and its impact on reproductive decision-making in at-risk individuals has long been a central focus of genetic counselling (Frets et al., 1990; Kessler, 1989; Lippman-Hand & Fraser, 1979). There is currently little specific research examining the relationship between being at genetic risk for FTD and reproductive decision-making; however, there is research regarding the impact of genetic risk on reproductive decision-making both generally and in regard to specific genetically heritable conditions which is illustrative of the complexity of the issue at hand.

For genetically at-risk individuals, there are several reproductive options, the first three of which can lead to the birth of a biological child. The first option is to pursue natural conception without intervention, accepting the risk of heritability to the child. The second is prenatal diagnosis (PND) – natural conception following by diagnostic genetic screening of the foetus, with the option to either terminate or continue an affected pregnancy. The third is pre-implantation genetic diagnosis (PGD) – genetic testing of in vitro fertilised (IVF) embryos, with only gene-negative embryos going on to be implanted. The fourth option is to pursue non-biological routes to talk on a parental role, such as adoption, fostering or use of donors, and the fifth and final option is to abstain from having children (de Die-Smulders et al., 2012).

Each of these options carries their own benefits and challenges. PND allows for a relatively quicker process and the establishment of a natural pregnancy, but decisions about termination can be physically and emotionally difficult (Severijns et al., 2021). PGD can be seen as an option to avoid termination, but the process is financially, physically and emotionally demanding, and has a relatively low success rate (de Die-Smulders et al., 2012). Choice to abstain from parenthood where there was a persistent child desire prior to risk knowledge precludes the risk of genetic transmission, is associated with ongoing difficulty in and rumination on the reproductive decision-making process (Frets et al., 1991). The choice to have a potentially at-risk child by natural, untested pregnancy can lead to challenges in

managing the worry about the current and future ramifications of disease for the self, children and in the relationship between the two (Hershberger et al., 2012). Non-biological options are often considered, but are rarely taken up in practice (de Die-Smulders et al., 2012), with concerns about the non-biological relationship to the child and uncertainty about their potential physical and mental health being common concerns (Severijns et al., 2021).

General research into reproductive decision-making across multiple genetically heritable conditions suggests a number of processes utilised by at-risk couples to navigate reproductive decision-making. Lippman-Hand and Fraser (1979) highlight the utilisation of 'simplifying heuristics' to condense and simplify options to allow for a decision to be made – these include binarisation of risk through reduction of outcomes to negatives occurring or not, and scenario-based thinking, where individuals and couples attempt to project forward the likely outcome of several options to arrive at the most acceptable outcome. Others (Gray, Nolan & Wenzel, 2019; Severijns et al, 2021) emphasise the role which joint discussion and decision-making within the parental couple as a key process by which various options are effectively considered, as well as by which the burden of responsibility for outcome can be shared. Gray, Nolan & Wenzel (2019) develop the characteristics of useful 'decision partners' as including a trusting prior relationship, willingness to be involved in decision-making and offer support with outcomes, and informational and emotional understanding of the decision being made. Beeson and Golbus (1985) in their study of factors associated with reproductive decision-making across X-linked conditions highlighted the role that previous experience with a symptomatic relative played in these choices, with significant previous experience 'concretising' the potential implications of disease trajectory and decreasing likelihood to accept genetic risk. Similarly, Brouwer-Dudokdewit et al. (2002) discuss the disruption of the 'usual' family life-cycle caused by the emergence of hereditary diseases, and how earlier experiences of this by at-risk individuals with symptomatic parents can influence later attitudes towards becoming symptomatic and risk inheritance.

In addition to this general research into the interplay of genetic risk and reproductive decision-making, there is a body of condition-specific research which highlights the impact of

differing disease characteristics such as heritability patterns, specific symptomatology, age of onset and perceived impact on others on reproductive decision-making.

In both Cystic Fibrosis (CF) and *BRCA* gene inheritance, potential genetic inheritance to children plays a significant subjective role in the reproductive decision-making of affected individuals, often struggling to balance own reproductive desires with feelings of responsibility towards potential children (Kazmerski et al., 2017; Quinn et al., 2010). It is common for affected individuals to express a desire for ‘normalcy’ in reproductive decision-making which they experience their genetic risk status as precluding (Kazmerski et al., 2017), as is a sense of time pressure to make reproductive decisions based on estimated age of onset (Quinn et al., 2010). In addition, in both conditions at-risk individuals expressed a sense of implicit judgement from healthcare professionals and wider societal attitudes towards certain reproductive outcomes, which was experienced as unhelpful and leading to feelings of guilt (Kazmerski et al., 2017; Quinn et al., 2010). Views toward PGD are generally positive, especially among those who have experienced negative health outcomes in relatives (Gietel-Habets et al., 2017). Online tools developed to aid reproductive decision-making in *BRCA* inheritance have been associated with greater knowledge and less partner conflict in decision-making, though not necessarily on certainty and acceptance of decision made (Reumkens et al., 2019a; Reumkens et al., 2019b). Myring et al. (2011) outline a useful psychological model of reproductive decision-making in CF, the 'Shock-Adjust-Decide' model, whereby the initial shock of CF heritability is followed by a period of grief-like adjustment, finally leading to a mutual but female partner led decision-making process regarding reproduction. Previous experiences with CF-symptomatic relatives influence the couple's attitude to risk, and having had a CF-carrier pregnancy makes couples more likely to consider more children in future.

There are a number of key differences between these genetically heritable physical health condition and GvFTD which may make direction comparison difficult. Firstly, their status physical health conditions that, though challenging and debilitating, leave the personality and emotional functioning of affected individuals relatively intact differentiates

them from FTD. Secondly, they demonstrate different patterns of heritability and risk conferred by inheritance, along with variability in age of onset.

The genetic condition most directly comparable to GvFTD both in symptomatology and inheritance is Huntington's Disease (HD), a neurodegenerative disease demonstrating an autosomal dominant inheritance pattern and characterised by psychiatric symptoms, personality changes and motor issues, with an average age of onset of between 30-50 (Roos, 2010). The available research in reproductive decision-making in HD is outlined extensively in Part 1 of this Thesis, and therefore will be presented here in summary. Among those at-risk for HD, desire to have children is relatively common. Potential for HD inheritance is commonly reported as a major influence on reproductive decision-making, with a strong desire to avoid inheritance. Views of assistive options are generally favourable, especially of PGD due to the lack of implied need to consider termination, though uptake of all testing options remains relatively low. At-risk individuals outlined a challenging task of balancing a sense of responsibility to avoid further HD inheritance with strong, longstanding desire for parenthood. Some responded to the topic of risk inheritance by expressing an acceptance of this risk as one potential risk for their child among many, and maintaining optimism for the development of future treatments. Guilt, rumination and uncertainty over past reproductive decisions were also common, often influenced by explicit or implicit judgement of reproductive choices by family, healthcare professionals, or wider social narratives.

Genetic testing for HD has been long established and represents a gold standard approach to testing and management of genetically heritable symptoms (MacLeod et al., 2013), and this had led to its application to GvFTD due to their relative similarity (Greaves & Rohrer, 2019). However, given differences in age of onset, both in timing and variability, as well as the relative heterogeneity of symptoms within GvFTD presentations, it is perhaps best to assume that, while research about reproductive decision-making in the context of HD risk is illuminating of what might occur for those at genetic risk of FTD, independent research will be beneficial in establishing more clearly where the similarities and differences lie.

Reproductive decision-making and GvFTD

So, in the case of GvFTD there is a highly genetically heritable disease, characterised by a prognosis of erratic but progressive decline, and for which there are currently no effective treatments. Its symptom profile of disinhibition, personality changes, loss of empathy and behavioural changes have profound implications for the quality of life of both symptomatic individuals and their family network. Symptoms impair an individual's ability to effectively engage with complex tasks, which parenting can reasonably considered. Due to the average age of onset in the fifth to sixth decade, it is not uncommon for a symptomatic person to be fully engaged with parenting when the disease emerges. In the case of those at risk for GvFTD, they are therefore likely to have had significant contact with a symptomatic parent or close relative, with whom they experienced the profound changes in personality, everyday functioning and interpersonal relationships brought on by this disease. They are also likely to be acutely aware of their own risk profile for later developing GvFTD, whether they have chosen to pursue their own genetic testing or not.

We might reasonably hypothesise that these experiences will have meaningful impact on at risk individuals view of their own risk status, attitudes towards the experience of caring for an FTD-symptomatic individual, and furthermore their attitudes towards reproductive decision-making in the context of their ability to care for their (potential) children, the future impact on their children of having to care for them, as well as the potential for their children to inherit the implicated genetic mutation. However, there is currently a lack of research exploring these topics among those at risk for GvFTD.

Study aims

The overarching aim is to broadly explore the views and attitudes towards reproductive decision-making among those at risk for GvFTD. This study will further aim to explore the connections at risk individuals draw between their own earlier experiences with FTD symptomatic relatives and their own current views and intentions with regards to reproductive decision-making. Further, for those who are currently parents, it will aim to explore both how risk status has influenced their reproductive decisions, and whether there

are ongoing links between their risk status and their approach to parenting. Among those without children at the time of interview, future reproductive intentions will be explored, along with influence of risk on reproductive decision-making. Given the lack of previous research, the exploratory nature of this research, and the inherently subjective and experiential nature of these experiences, this study will employ a qualitative approach in which participants own experiences and views are discussed and analysed to develop relevant themes.

Method

Participants and Setting

Participants were 13 individuals at risk for Genetic variant Frontotemporal Dementia (GvFTD). For the purposes of this study, at risk status was characterised as having a parent with a confirmed diagnosis of GvFTD (Greaves & Rohrer, 2019). Additionally, to meet criteria for participation, individuals needed to be able to understand and communicate fluently in English, and those currently experiencing FTD preventing their providing informed consent to participation were excluded.

The majority of participants (n=8) were female. Age of participants ranged from 27 to 61 (M = 41, SD = 9.34). All participants identified as White British. Six participants had children at the time of interview, and seven were currently childless. Regarding current GvFTD genetic knowledge, six participants had received a confirmatory genetic test, while the remainder chose not to pursue a test to date (n=3), had undertaken a test as part of participation in research but chose not to know the result at time of interview (n=2), were awaiting appointment for genetic testing (n=1) or had receiving a disconfirmatory genetic test (n=1). Among those who had received a genetic test result, the range of time since testing was between 1 and 15 years (M = 5, SD = 4.8) (see Table 1 for summary of participant characteristics).

Table 1

Participant Demographics

Code	Age	Sex	Ethnicity	Genetic Test Status	No. of children	Children before or after Risk Knowledge?	No. of affected relatives	Years in education
P1	41	M	White British	Positive	0	N/A	1	15
P2	34	M	White British	Not yet tested	0	N/A	2	16
P3	38	M	White British	Chose not to know result	2	After	1	16
P4	35	F	White British	Positive	2	One before, one after	1	16
P5	38	F	White British	Positive	0	N/A	3	17
P6	61	F	White British	Not yet tested	1	Before	2	14
P7	28	F	White British	Not yet tested	0	N/A	1	16
P8	45	F	White British	Positive	3	Before	1	17
P9	58	F	White British	Positive	3	Before	3	12
P10	39	M	White British	Positive	0	N/A	1	13
P11	39	F	White British	Negative	0	N/A	1	16
P12	39	F	White British	Chose not to know result	0	N/A	1	17
P13	42	M	White British	Not yet tested	3	After	1	14

Recruitment and Data Collection

Potential participants were identified and recruited from the existing cohort of the Genetic Frontotemporal Dementia Initiative (GENFI), an ongoing cohort study monitoring outcomes for those at risk of GvFTD. (See *Appendix C* for GENFI consent and information forms). Initially, a purposive approach to sampling was adopted to pursue a balance of parents and non-parents, as well as representing a diversity of positions with regards to knowledge of genetic risk status. As research progressed, to achieve saturation of data, it was necessary to utilise a more opportunistic sampling approach. Ultimately, 13 participants were recruited over the course of 8 months between 28/04/2021 and 24/01/2022.

Recruitment initially involved an identification by GENFI staff of GENFI participants meeting inclusion criteria for this study. These potential participants were then contacted by GENFI administrative staff via email, with information regarding the focus of the research, and an outline of the structure and topics to be covered in interviews. Interested participants were then able to contact GENFI administrative staff to arrange a convenient time for interview, which was then confirmed with the main author and interviewer. Due to ongoing restrictions on face-to-face contact related to COVID-19 during the time that interviews were conducted, participants were given the choice of several remote options for conducting interviews – via Zoom video-conferencing software (n=10), via Microsoft Teams video-conferencing software (n=1) or via telephone (n=2). Participants were encouraged to ensure that, where possible, they had access to a quiet, private space to conduct their remote interview session.

As part of the interview process, the following demographics were gathered verbally from clients: age, gender, ethnicity, current number of children (if any), current knowledge of genetic status (if willing to disclose). In addition, the following demographics were gathered from GENFI's existing participant data: local authority of residence (used to establish relative deprivation index), years in education, number of relatives affected by FTD.

Semi-Structured Interview

Each participant took part in a semi-structured interview exploring their views on

reproductive decision-making and parenting in the context of their at risk status, as well as their experiences with FTD-affected relatives and how these might have influenced their views on reproduction and parenting. The initial interview schedule was developed with reference to relevant literature, both related to GvFTD broadly and reproductive decision-making in the context of other single gene autosomal dominant neurodegenerative diseases, especially Huntington's Disease (see Systematic Review in Part 1) and developed in collaboration with members of the GENFI research team. This initial interview schedule draft was reviewed by three experts by experience, GENFI participants at risk for GvFTD but not participating in the current study, who offered feedback on the appropriateness and sensitivity of the wording of questions, as well as highlighting interview items which may have implied judgement on certain reproductive outcomes. The interview schedule was modified in line with this feedback.

Prior to interview, participants were offered a brief synopsis of the focus of research and the topics to be covered in interview, an explanation of processes for pausing or ending interview, and how data would be managed post-interview, as well as an opportunity to ask any additional questions. The interview began with an invitation to the participant to briefly summarise their experience thus far with their at risk status, from becoming aware of changes in their FTD affected relative, to diagnosis, to awareness of the possibility of heritability. Interviews then explored experiences with FTD affected relative, their presymptomatic relationship and changes as symptomatology progressed, as well as changes in behaviour and personality that were of particular note to participants. The interviews then moved on to discussing reproductive decision-making – for those who were parents at time of interview, it explored decision-making about having children, approach to conversations with partners, and the role of at risk status in decisions about childbearing and childrearing; for those without children, current stance of reproduction was explored, along with the role played by at risk status in those stances. Finally, connections between experiences and views of FTD affected relatives and reproductive decision-making were explored explicitly. Finally, participants were offered an opportunity to share any views,

thoughts or information which they deemed relevant to the topic not covered by previous interview items (see *Appendix D* for full interview schedule). All interviews were audio recorded using a Dictaphone and transcribed verbatim, followed by a removal of all identifying information (e.g. names, place names, etc.). The length of interviews ranged between 40 and 75 minutes.

Analysis

Interview transcripts were analysed using Braun and Clarke's (2006; 2013) Thematic Analysis framework. This approach to qualitative analysis involves exploration of the data at level of individual codes, which are then developed into themes based on patterns of similarity and difference across the data set. A systematic, six stage approach to analysis (Braun & Clarke, 2006) was followed using the NVivo software package for Windows PC. The stages of analysis were as follows.

1) immersion and familiarisation with the data set, through a combination of transcription and repeated reading, accompanied by initial memoing.
2) Initial coding of the data set, achieved by assigning a code to each portion of the data according to content,
3) Developing initial themes through comparison and grouping of individual codes according to relevance and significance to research questions,
4) Review of identified themes against both included codes as well as the data set more broadly,
5) Definition of the reviewed themes, seeking to both clearly outline the concepts included in each themes, as well as their relationship to each other, and
6) Reporting the results of the analysis, illustrating themes and sub-themes with relevant quotations from interview transcripts and offering a summative response to the study's research questions.

Thematic analysis has several characteristics which make it an appropriate analytic tool for use in this study. It is a relatively a-theoretical approach which supports many epistemological frameworks. Given this study’s focus on the experience of those at-risk for

GvFTD, and the meaning-making process they undertake in regards to reproductive decision-making in light of this experience, a descriptive phenomenological (Sundler et al., 2019). Phenomenology is an epistemological stance which prioritises the subjective experience of a phenomenon as the basis of our understanding of it, prioritising lived experience as a primary organiser of understanding and knowledge (Dowling, 2007). Thus, it assumes that it is through elicitation of individual's experience of a phenomenon that we can begin to develop our knowledge of it. Descriptive phenomenology is characterised by a focus on understanding and reporting the experience of individuals as they report and understand it, as opposed to interpretation of this experience on the part of the researcher as in interpretative phenomenological research (Sundler et al., 2019). Given the exploratory nature of this research, seeking to elicit novel information about at-risk individuals experiences and meaning-making, this approach seemed appropriate. Finally, Thematic Analysis supports both inductive and deductive approaches to code generation. Given the relatively novel focus of this research, this study aims to utilise a hybrid approach in which deductive generation of broad categories of code from both the research questions and consideration of the findings of Part 1's systematic review on reproductive decision-making in a comparable genetic illness are complemented with novel codes identified in the process of analysis. Thematic Analysis's flexibility allows for such an approach (Fereday & Muir-Cochrane, 2006) and has additionally been effectively utilised in qualitative research exploring reproductive decision-making in other genetically heritable conditions (Gong et al., 2016; Kazmerski et al., 2017; Quaid et al., 2010).

Ethics

This project was conducted in line and as part of GENFI's NHS ethical approval (Reference Number: GENFI 14/0377). All transcripts were pseudonymised for the purpose of participant confidentiality.

Results

Six core themes related to reproductive decision-making and parenting in the context of genetic risk for FTD were identified. These themes were: 1) Fear of repetition of own experience with symptomatic relatives; 2) Approaches to mitigating repetition; 3) Responses to genetic risk in reproductive decision-making; 4) Accounting for timing in at-risk reproductive decision-making; 5) The challenges of disclosing genetic risk to children; and 6) Other mitigating factors in reproductive decision-making (See Table 2 for breakdown of themes across participants).

Theme 1: Fear of repetition of own experience with symptomatic relatives

This first theme outlines the connection between participants experiences with their FTD-symptomatic relatives, and the concerns and anxieties about the potential for aspects of these experiences being replicated for themselves and their loved ones. Most participants, and all participants who reported consistent contact with an symptomatic relative identified the process as practically challenging and emotionally taxing, with different participants emphasising different aspects as most impactful on their own concerns about the future

1.1. Process of becoming symptomatic

Many participants described the process of change in their symptomatic relatives as symptoms developed, with the range of presentations highlighting the diversity of FTD presentations. These changes ranged from the relatively benign in the form of eccentric but harmless and undisruptive behaviours, to the interpersonally challenging in the form of loss of inhibition and loss of empathy, to the dangerous in the form of wandering and vulnerability to exploitation, to the emotionally distressing in the form of loss of communication abilities and ultimately loss of independence. In the below excerpt, P8 outlines the challenges their non-symptomatic parent faces in caring for their FTD-symptomatic parent, emphasising the regression of the symptomatic parent to an almost child-like state:

Table 2

Representation of participants by theme

Themes		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13
1	**Fear of repetition of own experience with symptomatic relatives**	X	X	X	X	X	X	X	X	X	X	X	X	X
1.1	*Process of becoming symptomatic*	X	X	X	X	X	X	X	X		X	X		X
1.2	*Caring burden*	X	X	X	X	X		X	X	X	X	X	X	X
2	**Approaches to avoiding repetition**	X		X	X	X	X	X	X	X	X	X	X	X
2.1	*Practical planning to mitigate worst aspects*	X		X	X	X	X							X
2.2	*Emphasis on parenting 'in the here and now' (Parents only)*			X	X		X		X	X				X
2.3	*Research Involvement*	X		X	X	X	X	X			X	X	X	X
2.4	*Suicide as a potential response to future FTD emergence*				X		X				X			
3	**Responses to risk in reproductive decision-making**	X	X	X	X	X	X	X	X	X	X	X	X	X
3.1	*'I want to be part of the reason the gene disappears': Risk minimisation*	X	X			X		X			X	X	X	
3.2	*It sucks, but I can't rule everything out': Risk acceptance*			X	X		X		X	X				X
4	**Accounting for timing in at-risk reproductive decision-making**	X				X		X			X	X	X	X
5	**The challenges of disclosing genetic risk to children**	X	X	X	X		X	X	X	X	X	X		X
6	**Other mitigating factors in reproductive decision-making**	X	X			X	X	X			X	X	X	

Key: Main themes in **bold**, subthemes in *italic*

P8: *He's said it's like having a 20 stone toddler, right? If she doesn't want to do something, she won't do it [...] She won't walk, you can't get her to walk. She doesn't want to eat her food, whatever. You can't, he's finding it very hard. He knows she needs exercise, but she's resisting and saying I don't want to.*

In this quote, P8 highlights both the pervasive, global changes noted in the personality and functioning of the symptomatic parent, and the resultant sense of the symptomatic individual as they were pre-symptomatically being effectively lost. This highlighting of the loss of the symptomatic person prior to their death due to changes in personality is a common pattern, with several participants raising similar experiences. Below, P2 outlines the sense of loss of the symptomatic relative as they were, emphasising a subjective sense of their loss of an ability to meaningfully engage with their surroundings and others:

P2: *It was basically like very little human left of him because he... just didn't seem to understand anything that was going on, and you know, if someone spoke he'd just turn to look at them because he's heard a noise, but not understanding anything.*

This sense of FTD as leading to a whole loss of self as symptoms progress was a particular area of distress for several participants, and highlighted as a fear for their own future should or when FTD symptoms began to appear. Some participants also highlighted their symptomatic relatives experiencing brief moments of lucidity and returning to something approximating their pre-symptomatic personality at times during the course of their illness, experiences which were both valued and difficult as they highlighted the marked change that had occurred. This gulf in pre-symptomatic and symptomatic personality are highlighted in the below extract from P11, where they discuss the changes they observed in their symptomatic parent, and draw explicit connection to fear that they may experience similar changes in the case of developing FTD:

P11: *The thing that was upsetting me the most when I thought -you know, when I,*

before, I before I got my result - that I could behave in a completely different way and lose my identity and start treating people with no empathy and and all of that. It's just an odd thing.

This highlights a recurrent pattern across several participant's accounts – an understandable distress when witnessing the changes in their symptomatic relatives brought about by FTD symptomatology, and a concern about experiencing a similar trajectory. Some participants, as in P11's quote above, highlighted their concerns about the impact of future symptoms on their partners and children, voicing concerns that the process of watching a partner or parent become symptomatic would be distressing, and in the case of children, that the process of becoming symptomatic would impair their ability to effectively engage with the process of parenting, thereby negatively impacting their child. P1, in the below quote, highlights this aspect of distress at a potential child witnessing their future FTD symptoms, independent of the issue of heritability:

P1: *Not only would I be passing it on, I'd be dying early and they'd have to see that, it'd be terrible. So even if I didn't pass it on, it'd be awful*

1.2. Caring burden

Many participants identified the practical and emotional toll of care for those around their FTD-symptomatic relative as a demanding and challenging experience, and one which they explicitly worried about conferring to their children and families in the case of their own symptom development. Aspects of caring that were identified as particularly arduous included navigating the complexities of services and legal issues, and the need to respond to unexpected challenging behaviours as they emerged. Similarly, the loss of the relationship as it previously was with the symptomatic relative due to changes in empathy, personality and communication were distressing. Caring responsibilities were associated with the loss of previous plans for the future, both for the participants and other members of their family, and this could be associated with frustration and resentment towards the symptomatic relative, an experience that was associated with feelings of guilt. Many participants highlighted the

negative impact of caring on their non-symptomatic parent. Below, an excerpt from P4 highlights the challenges of this caring role, both in the practical difficulties of personal care, and in the emotional challenge associated with the complete reversal of the caring dynamic within the parent-child relationship:

> ***P4:*** *Basically he soiled it himself and was wandering around the house [...] I then have to clear up. I had to shower him, which I had never done. Of course, you know, until that happens, it's not the relationship you have with your parents, of course. So that was huge in terms of when I thought, 'oh my God, I'm showering my dad'.*

The caring burden was understood as challenging, distressing and demanding. Some participants compared the experience of carers and the symptomatic relative, contrasting the relative obliviousness of the symptomatic relative to the change with their hyper-awareness and distress of familiar carers. The below quote exemplifies this, highlighting the caring role as potentially more challenging to bear than that of the symptomatic person:

> ***P4:*** *I think that with FTD, the suffering is more on the carers than the person. Because you lose everything that makes it hard for you, you know, you lose the emotions kind of any sense of that. So you're not in the hard part having being symptomatic, so everyone around you has to manage that.*

These challenging experiences of caring symptomatic participant's views on how it might be experienced by those around them in the instance of their own illness. Several participants explicitly highlighted a desire to avoid to as great an extent as possible the experience of a similar caring burden by their own children specifically, and families more generally. This desire to avoiding replication of their own experience of caring is highlighted in the below quote:

> ***P5:*** *But I wouldn't really want them to have to experience what I experienced at a younger - and it would definitely happen younger, because mum had me when she was 28. So I, once I go, I don't really want a 12 year old to have that, was more what*

I was worried about.

Theme 2: Approaches to avoiding repetition

This theme relates to the above identified fears and anxieties about the repetition of participant's own challenging FTD-related experiences, and the various approaches participants took to mitigating these feared outcomes. Different participants opted for different approaches, often based on personal circumstances, with some participants using more than one.

2.1. Practical planning to mitigate worst aspects

Many participants described the difficulties encountered as a result of FTD's unexpected emergence in their symptomatic relative's lives. Issues related to lasting power of attorney necessary for caring decisions, as well as legal matters related to caring costs, home ownership and inheritance were repeatedly highlighted – for those whose symptomatic relatives had these in place it was experienced as a relief, but for those who faced protracted legal processes as a result of these not being in place, it was experienced as a source of significant stress. Among these participants, it was regularly highlighted that as a result of their experiences, they were more conscientious about ensuring they had effectively prepared for such eventualities far in advance of their being needed. This is highlighted in the below quote from P5:

> ***P5:*** *Soon as I have anything to leave, the will is getting done. I think, I think I want to have all that in place. Hopefully I'll have a lovely life and hopefully won't need if for quite a long time time yet (laughs). But yeah I think, I just think everyone should get sorted – you never know what might happen […] I think if there's one moral of my mother's story, I think it's that.*

Similarly, some participant's had given great consideration to safeguarding their children and partners financially against their potential early illness and death. This took the

form of comprehensive life insurance policies, legal methods of insulating their children against responsibility for care costs, as well as making career decisions to maximise their current capacity to earn and save ahead of later need. P3, in the below quote, discusses this planning process, while also highlighting the way in which this approach allows them to feel secure in thinking about FTD risk less in their day-to-day life:

> ***P3:*** *I have critical illness life cover, you know any insurance we can have because... ehm that would weigh, they have a certain way of life, I have a good job with a good wage, they have a good life, and so if I'm not able to carry on with that I wouldn't want them to be... affected. [...] I guess- I guess I... you build a structure around it that means you don't have to think about it, that's really the plan.*

2.2. Emphasis on parenting 'in the here and now' (Parents only)

Among participants who were parents at the time of interview, or intended to have children in future, many reported an influence of both their experience with symptomatic relatives and their knowledge of their potential genetic risk on their approach to parenting. Several participants reported an increased desire to ensure they made life decisions to maximise their time spent with their children day-to-day, such as structuring work to facilitate involvement in their children's lives, and a conscious effort to 'make memories' with their children now, rather than assuming that they will have the opportunity to do so in the future. The below excerpt from P4 exemplifies this approach to parenting in the context of genetic risk:

> ***P4:*** *I definitely have a different approach of live now, like if I can spend longer at home with my kids, so I work flexibly. I, you know, I could work and earn a bit more. And I choose not to. I choose to be able to pick them up from school, not today, but normally I do all of that side of things. Then I've definitely put more of an emphasis and a focus on that. And my husband has done the same. I think that's kind of more of our approach is don't. Don't lose out on the now stuff.*

In considering the above, it is important to note that, of those participants who did identify a similar approach to parenting, some were explicit that, while the context of FTD risk was influential, other factors such as witnessing and appreciating a similar tendency in their own parents, and their own personality, were also involved.

Related to this, some participants reported a concerted effort to communicate 'life lessons' to their children actively in their day-to-day parenting, so as to prepare them for later challenges and stressors, and safeguard against potentially not having the opportunity to do so later in their children's lives. P13 speaks about this in the below excerpt, having previously spoken about their sense of loss of opportunity to similarly seek out life advice from their own symptomatic parent due to FTD:

> ***P13:*** *But I feel as though when, you know, when I'm with our children, I do, I do feel as though, when – I can feel myself doing that – I'm trying to convey life lessons onto them, earlier than they probably care about. But I feel as though it's made me a very much calmer head, and obviously like, you know, I'm very lucky in that I do get to spend a lot of time with them. So yeah, I mean, I feel a wee bit more thorough as a parent.*

2.3. Research Involvement

Uniformly, all participants emphasised the personal importance to them of taking part in FTD-related research. For many of the participants, research involvement was viewed as a productive, positive action that could be taken in response to genetic risk knowledge that felt threatening or oppressive. Several participants viewed research participation in terms of moving towards effective treatment options for FTD, so as to minimise or remove the impact of FTD on the lives of others relative to their own earlier experiences. P6 outlines this attitude in the below quote:

> ***P6:*** *I've opted to be part of the GENFI research. Because, you know, obviously, you know. The sooner we can find treatments for this gene mutation, then, you know, you*

know FTD would be something that could be treated.

Related to this, several participants with children explained their view of their participation in research as something undertaken for their children's benefit, in the hope that it will lead to treatments that minimise the role of FTD in their children's lives. Some also identified research participation as a way of putting FTD risk knowledge to one side in the rest of their lives, leaving them more free to enjoy their time with their children, as P3 outlines below:

> ***P3:*** *You know, it's selfish, it could benefit me, and I think it will absolutely benefit [my children] if it needs to, so that's really what I do to... I guess it evens the scales in your mind without you... thinking about it frankly.*

2.4. Suicide as a potential response to future FTD emergence

A subset of participants explicitly referred to their plans to pursue ending their lives in future as a way to avoid the impact of FTD symptoms on their loved ones. For some participants, they had reflexive plans, in the sense of intending to pursue this route in the case of the emergence of symptoms. For one of these participants, the plans were tied to a specific age milestone estimated from the age of onset of FTD symptoms in their symptomatic parents. All participants expressing these plans had discussed them within the context of close relationships with partners, adult children or parents who were understanding and agreed to offer practical support should it become necessary. For some, the primary reason for considering this option was to avoid a repetition of the decline in functioning and autonomy witnessed in their symptomatic relative, such as for P10 in the below quote, explaining their thought process in considering ending their life as a response to becoming symptomatic:

> ***P10:*** *Because I don't really want to get ill. So, I said if, if that was the case - because after seeing my mother like that, the - you're not there anymore, not, this is not the same person. So I personally wouldn't see the point in being around if I'm honest.*

For other participant's, the main motivator was to avoid placing a caring burden on their

children in future, should they become symptomatic, such as for P4:

> ***P4:*** *And I would do anything I could to alleviate that [caring burden] for them. So I do, I do - oh god this has gone so deep! But I am I sort of have a bit of a back up plan in my mind that I would aim to do something along the lines of Dignitas or some sort of end before the end. That's my almost like - I feel better if I think that that's my plan. And then they don't have to take that.*

It is important to note that for all participants who discussed this topic, there was an explicit emphasis that these plans were potential options that they were considering in the relatively far future in response to their FTD status, and all denied any thoughts, plans or intent related to harm to self in the present or in the near future. Participants viewed consideration of the option of assisted dying in future as a form of reassurance that potential future suffering for them and their loved ones might be averted, with P4 expressing the view that having considered the plan felt akin to having an *'escape hatch (P4)'* from potential future risk.

Theme 3: Responses to risk in reproductive decision-making

All participants identified their knowledge of their genetic risk for FTD as major information that could be challenging to integrate at times. Most participants identified that there was a process through which they needed to decide the extent to which they would re-orientate their life plans and approach in response to this knowledge. As expressed by P7:

> ***P7:*** *Obviously, the whole FTD thing comes into it because it's - you either make a kind of conscious choice to address it, or it's a conscious choice to not.*

In the context of reproductive decision-making, this process emerged in the form of divergent responses to the knowledge of potential FTD inheritance to biological children. These responses are discussed below. Prior to discussing these, it is important to note the emphasis placed by many participants on the highly personal nature of these decisions.

They stressed an aversion to placing judgement on the reproductive decisions of others, and the negative impact of outside judgement from other parties in general on this complex, challenging decision-making process. This theme is offered with these points in mind.

3.1. 'I want to be part of the reason the gene disappears': Risk minimisation

For many participants, the idea of further inheritance of genetic risk for FTD was personally unacceptable, and as a result they categorically rejected reproductive outcomes that could lead to such. It was common for these participants to also identify a long-standing ambivalence towards having children even before they became aware of their risk status. There were several motivators behind this view: a desire to contribute to the overall cessation of genetic FTD inheritance in the wider population, a desire to avoid children and dependants experiencing caring burden and the distress of witnessing parental deterioration, or anticipated feelings of guilt towards potential children for their future difficulties in relation to their own genetic risk. P1, in the following excerpt, expresses this idea, couched in the language of perceived responsibility:

> ***P1:*** *I don't want to spread the gene at all, I want to... be part of the reason that the gene... disappears or... stops, or you know, I want to do everything I can make sure no one else gets that gene, the worst thing I could do is to... create more lives with that gene...*

For those participants who ascribed to the idea of minimisation of genetic risk, there are degrees to which they considered this responsibility to extend. Some viewed PGD as an acceptable approach to having biological children while avoiding genetic risk, such as P10:

> ***P10:*** *If I was going to have children, that's the woman I would like to have children with, but as well because you had the PGD, there was an option there. Yeah. You know, grabbed it with both hands, you know.*

However, others identified difficulties with PGD, such as prohibitive cost and the emotional toll of unsuccessful cycles which made it less appealing. One participant

described their difficult experience in ceasing PGD without achieving a successful pregnancy. Other participants considered the options of adoption or fostering children as a way to take on a parental role while minimising risk of genetic risk inheritance, identifying this as a dual opportunity to take on parental role if desired while providing support to a needful child. However, some participants considered these options, but ultimately decided against them, as they did not resolve the question of how the child might manage the eventual burden of caring for an symptomatic parent.

A subset of participants who ascribed to a responsibility for risk minimisation took a more absolute stance of taking as many steps as necessary to minimise the impact of potential illness on others by precluding the idea of any dependant relationships whatsoever, including avoidance of romantic relationships, to limit the effect of their potential FTD experience in future. P2 expresses this view in the following extract:

> ***P2:*** *Well (Pause) I'm in a situation now where I have zero dependents, and... I guess if I was already in a relationship with someone who wanted kids, then you know we'd... have that conversation but... since I'm in a position where I've got no dependants, if I'm at risk why would I want to introduce those?*

3.2 'It sucks, but I can't rule everything out': Risk acceptance

In a differing approach to the issue of genetic risk inheritance, many participants expressed a view that, though challenging, risk of genetic inheritance of FTD represented one risk among many potential challenges that children might face, and that it in itself did not represent a disqualifying reason from pursuing biological parenthood. This view was common among participants who were parents at the time of interview, or who reported a long-standing concrete desire for children prior to becoming aware of FTD genetic risk. Some participants expressed a need to avoid allowing FTD risk knowledge to control their lives or derail important valued actions, such as P12, here describing their perception of the impact of allowing risk knowledge to control important life decisions:

P3: *You wouldn't want to do anything if you let it consume you in that way and kind of let it prevent you from doing. What's the point in living then, anyway, if you're not going to do the things that you want to do?*

Other participants who accepted the fact of potential genetic risk inheritance in reproductive decision-making explicitly considered the risk in the context of other potential risks in their future child's life, including those that were unpredictable or unavoidable, making the decision that total risk avoidance was not possible as a result, and emphasised the reality of challenges in any child's life, without FTD risk representing an outsized influence. This view is eloquently expressed by P4 in the following excerpt:

P4: *The other thing that was quite big for both of us, which I know is really uncommon in the FTD world is, yes, I could get it. Yes, my child could get out, but we could also get a million other things. We could also get hit by a bus. We could also get cancer. We could also have heart disease. Like it's not the only thing. It's not that, oh, I got the FTD, therefore I don't get anything else. You know, it doesn't make you immune to any other death, illness or disease. So we kind of went with. Yeah, it sucks, but I can't rule everything out.*

This view of risk was also endorsed by some participants who found out about their potential genetic risk later in life, when they already had adult children, and therefore were not in a position to make reproductive decisions with risk knowledge in mind. For these participants, there was an expressed need to make peace with previous decisions made in the context of knowledge held at the time, and accepting that this risk was ultimately simply a factor which their adult children would navigate in their own manner. P9 describes this viewpoint in the below quote:

P9: *I was very philosophical about it because I said to deny the fact that I might get Huntington's disease, not knowing about the Pick's bit, is to deny my family. And how can you deny your family? That's my genes. That's my. That's me.*

This process of acclimatising to previous reproductive decisions in the context of new

genetic risk was more challenging for some participants than others. One participant who had children prior to becoming aware of their genetic risk described an immediate process of acceptance. Another described it as a gradual, partial process whereby they accepted what had occurred, but would consider different options such as PGD were they aware of risk prior to becoming a parent. A third participant described the process of risk acceptance for children born prior to risk knowledge as an ongoing, intensely emotionally difficult process, characterised by periods of partial acceptance and periods of ruminative guilt and frustration.

Theme 4: Accounting for timing in at-risk reproductive decision-making

Many participants, both parents and non-parents, and both those who had chosen to know their genetic status and not, outlined the major role that the perceived limited time they have before potential symptom onset as playing a significant role in their thinking about reproductive decision-making. Though the unpredictability of onset and symptom trajectory within FTD was commonly acknowledged, many described using the age of onset of symptoms for their symptomatic relative as a estimated 'time limit' related to questions of childbearing and parenting, as this represented a potential point in time at which their ability to effectively engage in parental responsibilities might be impaired.

For some participants, this awareness of a potential 'time limit' on reproductive decision-making acted as a dis-incentivising factor regarding having children. They described a process of estimating back the necessary age from the potential age of onset to calculate when they might have a child so as to allow it to be an adult by this time. For these participants, when reaching this age without children, they described a sense of acceptance that biological parenthood would not occur. PX outlines this process below:

> ***P10:*** *Now, like I say, I'm 39 now. So I'm I'm at that age now where even that well, even if I even if we were successful on the third cycle for myself I think that's the limit really and we've we've got closure on it now, it is a little bit harder for*

my wife to take but you know we said that's it, that's closure on it yeah.

Conversely, for other participants, this awareness? of a 'time limit' acted as a motivating factor. They described performing a similar age calculation to that described above, and then setting out to proactively prioritise pursuing relationships, marriage and parenthood within this time-frame to maximise their time available for definite active parenting and involvement in their children's lives. P3, in the below quote, describes the process by which estimated age of onset acted as motivator to 'get going earlier':

> ***P3:*** *So my father was 40 when I was born, and I'm the eldest. I think I mentioned when we last spoke, he didn't meet any of his grandchildren because he started having kids a lot later. I didn't want to do that.*

Finally, there was a smaller subgroup of participants who described a process by which the perceived time-limit on their reproductive decision-making, rather than changing their view in either direction, simply led to a clarifying or solidifying of a long-held disinterest in parenthood. For these participants, this time-limit led to a more active process of consideration of their view earlier than would otherwise have been the case, but ultimately led to a re-affirmation of their already held reproductive decisions. This is expressed in the below quote from P5:

> ***P5:*** *Obviously it has, it has... It has an importance in so far as emphasis of the timing, when I made some of the decisions made around it. But I do not think at all that it has any definitive part to play in any of the decisions I've made around it.*

Theme 5: The challenges of disclosing genetic risk to children

The majority of participants, both those with children and without, identified the prospect of outlining the reality of FTD risk inheritance to their children as challenging. For some participants without children, the anticipated difficulty of such a disclosure formed part of the reasoning behind the decision for not having children. Common patterns of concern

regarding disclosing risk status to children were uncertainty in the child's ability to cope with such challenging knowledge, as well as potential permanent damage to the quality and strength of the relationship should the child fundamentally disagree with their parents' decisions. P8 describes this second concern in the below quote, along with the intense emotional distress they experience when considering? disclosure as a result:

> ***P8:*** *In retrospect, now my daughter's 18 and I should really tell her what I found out. And I don't know how the hell to do that. The reality of it is that I don't actually know how to tell them. I just can't face it.*

One participant, with an adult child at the time, though acknowledging the distressing nature of this potential conversation, opted to immediately share their risk knowledge with their child once they became aware themselves, explaining this in the context of both fairness and an inclination to keep their child updating to important health information, in the context of multiple heritable diseases within their family. P6 describes this below:

> ***P6:*** *I found out that, you know, that my uncle had it as well, I told my daughter, you know, and I told my daughter that it's obviously in the family. Yeah, I told her, but she would have worked it out. But you know, it was just the I found out first that my my uncle was diagnosed a month after my mom. So, you know, that was I told my daughter that that's what happened.*

Some participants described a subjective sense of being trapped in a challenging situation with regards to disclosure to their children – feeling that disclosure was important and necessary in providing their children with relevant information to navigate their life's and own decision-making with regards to testing and reproduction, but distressed by the potential reaction of their children to the disclosure to the point of inaction. This led to situations where disclosures of risk heritability were made under pressurised circumstances related to important events in their children's lives, leading to distress for both parties. P9 outlines such an experience in the below quote:

P9: *But in the end what happened was he met a girl and they bloody got pregnant, didn't they? So then he come round to tell us we're expecting and I basically told him, Well, I've got this and you might have to terminate your baby and, test your baby, and duh duh duh, and he basically lost the plot and left the room.*

Several participants, especially those with younger children, described their sense that their children would at some point approach them with questions regarding FTD, either through curiosity regarding grandparents or from noting their parent's involvement in research, and that it would be at this point which they would navigate the disclosure of risk. For these participants, the decision to wait for their children to ask was viewed both in terms of enabling their autonomy, while avoiding over-burdening their children with complex, distressing information prior to an age where they could fully understand its implications. Some participants held a provisional idea in mind that, had their children not broached such a discussion by their late teens, it may be necessary to take a more proactive stance towards disclosure. P3 outlines their thought process in adhering? to this approach here:

P3: *I think at the moment, they don't understand you know, they ask where my father is but they wouldn't understand if I told them what was wrong with him or what that is, they just wouldn't be able to understand it, so... you know I think, as I just said to you that in their teens might be a time, but if one of them's ten years old and specifically asks you the question then you'd probably answer it*

Theme 6: Other mitigating factors in reproductive decision-making

Several participants, both with and without children, were careful to ensure that the role of FTD risk within their reproductive decision-making was not over-emphasised, and that it did not come to be viewed as the single definitive factor in pursuing their decided-upon reproductive path. They emphasised that FTD risk, though important, existed within a complex network of assumptions and personal prerequisites related to reproductive

decision-making, all of which played a role in their ultimate decisions.

Among those who chose not to have children, or were undecided, there was an expressed view of their desire for children as related to a number of factors, including relationship with a secure and supportive partner with a strong desire for children, the ensuring of material circumstances in terms of housing and income necessary to support a child, and a desire for maintenance of their own desired lifestyle. These factors were identified as playing an equal or even greater role than FTD risk in their reproductive decision-making at times. For example, here P4 describes the process by which their own child desire is mostly a reflection of their partners:

> ***P10:*** *Yeah. Know for me like so I'm, I'm happy in my relationship with my wife. So we for me is something that she wanted, you she wanted to have a child and so did I, you know, but if for me, if I couldn't, um, I've got very strong relationship anyway and I'm happy, so, you know, it would enhance our life. But if we couldn't, in my view, it wouldn't, it'd be okay either way.*

Among those with children, while acknowledging the role played in their own lives by FTD risk and the likely role it may play in their children's, several nonetheless identified other factors that played as great if not greater a role in their reproductive decision-making. These include perceived suitability as parent, pre-existing child desire, and a personal value placed on family and family life. Some participants, even without children, stressed that their reproductive decision-making was made before risk knowledge was in the picture, and that the emergence of risk knowledge ultimately did not change their decision, as P4 explains below, discussing their decision to have a child while awaiting the results of their own genetic test:

> ***P4:*** *I mean, not necessarily quick right before you find out, but while I was going through that process, we decided this is the right time for us and that isn't going to be a contributing factor. Okay, let's just go with that. So we did.*

Discussion

This is the first study to my knowledge on how those at risk of GvFTD conceptualise and respond to their risk status in relation to reproductive decision-making and parenting, as well as exploring what explicit and implicit connections these at-risk individuals draw to their own experiences with FTD-symptomatic relatives, both as witnesses to the progression of the disease and in a caring capacity. Its findings provide us with the opportunity to explore the similarities in the interplay between genetic risk status and reproductive decision-making with other genetically heritable conditions, as well as differences unique to the experience of those living at genetic risk for FTD.

The results of this study emphasise the participant's complex relationship and attitude towards their genetic risk status, as well as the multi-faceted ways in which risk knowledge is engaged with and responded to in the context of reproductive decision-making. Additionally, it highlights the major role played by experience with FTD-symptomatic relatives in shaping and informing participant's views, both of what it would mean to develop FTD for themselves and those around them, and their approaches to management of that risk in total or partial ways. Genetic risk in reproductive decision-making emerged as a major, though not totalising, factor in reproductive decision-making for participants, and one which was responded to in various ways, often in the context of attempting to act in line with pre-existing child desire. Genetic risk was characterised as introducing an additional layer of complexity to reproductive decision-making, both in placing reproductive decisions on a shorter implicit timeline than might otherwise be the case and thus encouraging definitive decisions made earlier in life, as well as introducing the emotionally and logistically complex issue of discussions of genetic risk with children, a process which participants viewed as requiring delicate balancing of providing important life-altering information to their children with a desire to effectively manage the perceived distress and challenges to the relationship that this information might cause. Participants also drew attention to genetic risk as representing but a single, though influential, factor influencing reproductive decision-making which occurred in a complex web of pre-existing child desire, pursuit of correct material and

relational conditions to facilitate parenthood, as well as a range of other social, cultural and material influences.

This study's findings that experiences of caring for an FTD-affected relative are characterised as practically demanding, emotionally difficult and lead to significant impacts on the wellbeing of the carer are in line with previous research suggesting that FTD cares experience significant carer burden (Caceres et al., 2016; Kaiser & Panegyres, 2006; Riedijk et al., 2006; Wong & Wallhagen, 2014). Participants regularly highlighted the emotional distress associated with changes in the personality and interpersonal approach of symptomatic relatives, and the sense of the loss of the relationship as it existed pre-symptomalogically as the most challenging element of FTD progression to experience. This echoes the findings of qualitative research with FTD carers, which routinely identifies the extreme emotional toll associated with the 'loss of person' caused by FTD symptoms (Caceres et al., 2016; Massimo, Evans & Benner, 2013; Oyebode, Bradley & Allen, 2013). In qualitative research regarding reproductive decision-making generally in genetically heritable conditions (Breeson & Golbus, 1985; Hershberger et al., 2012; Severijns et al., 2021), as well as specifically in HD (Klitzman et al., 2007; Quaid et al., 2010), CF (Kazmerski et al., 2017) and *BRCA* inheritance (Quinn et al., 2010), it is common for participants to report, as some participants in this study do, that concerns about potential inheritance of the disorder by children has a great impact on reproductive decision-making. However, the majority of participants in this study emphasised the deleterious impact of caring burden in their own lives related to FTD, and the desire to avoid this for children, irrespective of actual disease inheritance, as a major factor in reproductive decision-making and orientation to managing genetic risk in addition to concerns about the direct impact of witnessing a parent becoming symptomatic on their children, a perspective that is relatively uncommon in other disorders, though is occasionally expressed in relation to HD (Klitzman et al., 2007). Given the above-identified unique interpersonal and emotional challenges imposed in caring in FTD as a result of its symptom profile, it appears that these caring experiences have a lasting impact on participant's views of a potential future in which FTD symptoms are present and a

resultant desire to lessen the impact on others in ways that may be similar to HD, but differ from conditions more characterised by physical health symptoms.

The findings also highlight the role of FTD genetic risk as a factor within a range of factors influencing reproductive decision-making, acknowledged as important but not in and of itself exclusively influencing reproductive decision-making. Participants did not characteristically drastically change their reproductive intentions as a result of genetic risk knowledge – those who had previously strongly wished to have children continued to pursue this course, and those who had no wish for children intensified in their certainty of this decision. Genetic risk knowledge perhaps is more likely to lead to change of reproductive intent among those who had less strongly formed intentions prior to risk knowledge. However, though genetic risk knowledge does not appear to overly influence participants' *overall intentions* to reproduction, it is reported as influential on participants' *strategic approach* to mitigating genetic risk, with participants considering use of options such as PGD and adoption, and practical planning in the form of legal and financial safeguards against future difficultly where they might not have otherwise. This mirrors findings in HD (Klitzman et al., 2007) where strong reproductive intentions prior to risk knowledge remained relatively stable post knowledge introduction, but specific approaches to childbearing may change over time, and in *BRCA* inheritance (Quinn et al., 2010) where affected women reported stable intent to pursue reproduction, but an increased subjective willingness and perceived social pressure to consider assistive options such as PGD as a result of risk knowledge. These findings concur with Severijns et al. (2021) in their finding that, among those at genetic risk for a number of conditions, reproductive decision-making is a complex process in which multiple options must be considered by couples, with a general preference for biologically-related children remaining prioritised among those who expressed pre-existing reproductive intent. Our findings would suggest that those at genetic risk for FTD experience a similar pattern in which pre-existing reproductive intent remains the prime motivator of reproductive decision-making on the broad level of overall intent, but meaningfully influenced by genetic risk knowledge in the realm of strategic actions towards

desired reproductive and parenting outcomes.

This study's findings also provide insight into how genetic risk is conceptualised and responded to in the context of reproductive decision-making in GvFTD. Among participants, risk responses were expressed as existing on a spectrum – at one end characterised by total risk minimisation in the form of abstinence from reproduction and even romantic relationships in an attempt to limit the impact of potential symptoms on others, and on the other a complete acceptance of the possibility of inheritance as part of pursuing strongly held reproductive and parenting plans. Many participants placed themselves somewhere on this spectrum between these two extremes, attempting to mitigate inheritance risk if not caring burden through the consideration of PGD or adoption, or partial acceptance of previous reproductive decisions made prior to risk knowledge. Quaid et al. (2010) in their study of reproductive decision-making in HD found a similar range of risk responses, between what they classified as 'vigilant witnesses' who wish to end transmission of HD through abstinence from reproduction as a result of their experiences with HD-symptomatic relatives, to those who view HD risk as 'just another something' to be accepted in the pursuit of parenthood. This commonality suggests that the process of coming to terms with risk knowledge may follow a pattern in terms of how risk is categorised.

In consideration of reproductive decision-making, participants appeared to engage in some of the 'simplifying heuristics' outlined by Lippmann and Hand (1979) as commonly engaged by individuals contending with genetic risk knowledge in reproductive decisions – in accepting genetic risk, some participants expressed 'risk binarisation' ideas, whereby genetic risk was presented as part of a larger risk of any negative health or social outcome for children, contrasted against an unachievable state of total risk avoidance, to highlight the necessity of accepting risk in pursing reproductive intentions. This is similar to reported findings in qualitative research in HD (Klitzman et al., 2007; Quaid et al., 2010), whereby acceptance of genetic risk in reproduction is sometimes characterised as one aspect of a broader category of risk that cannot be wholly avoided. Participants also demonstrated 'scenario-based thinking' (Lippman & Hand, 1979), whereby they attempted to think through

the various potential outcomes of various reproductive options, often in ongoing discussions with partners, as a way of preparing for and affirming reproductive decisions as representing the “least-lose option” (Lippman & Hand, 1979) available to them. This process of scenario-based thinking is common in reproductive decision-making in the context of genetic risk (Kazmerski et al., 2017; Severijns et al., 2021; Quinn et al., 2010).

It is of note that, in addition to decisions and behaviours that might readily be identified as responsive to risk knowledge, such as having children or not, and utilising available technologies to mitigate risk, there is a category of behaviours which participants identified as specifically risk responsive in the context of reproduction. These included their intentions to make practical, legal and financial preparations in advance of their potential development of symptoms to minimise the impact of same. It also encompassed an approach to parenting that might be characterised as involving prioritisation of time spent with children and active instilling of values and lessons deemed important, though parents were clear to emphasise that this was both attributable to genetic risk knowledge, and their own personality and experience of parenting. Research involvement was also often seen as a response to risk, attempting to contribute to the process by which treatment options might become available, and therefore negate the risk to children. Finally, some participants considered taking actions towards suicide in the far future as a potential response to future decline, again framed and understood in terms of risk mitigation and an attempt to avoid repetition of their own experiences with FTD-symptomatic relatives. These responses highlight the complex nature of responses to genetic risk in reproductive decision-making in this cohort, where risk has implications for decisions across the lifespan, and far beyond the direct choice to pursue parenthood or not.

In attempting to draw together these findings, consideration of the 'Shock-Adjust-Decide' Model of reproductive decision-making in CF developed by Myring et al. (2011) may be appropriate. In this model, genetic risk knowledge awareness is experienced as an intense emotional shock, which requires a period of emotionally difficult and grief-like adjustment which must be tolerated before moving to a point of decision-making with risk

knowledge in mind. It also emphasises both the role of personal experience with the genetic condition in easier or more difficult movement through the stages, and the role of unexpected knowledge such as genetic risk knowledge coming to awareness during or after pregnancy as 'forcing' individuals through stages at a quicker, more challenging rate. It furthermore emphasises the dynamic nature of the process, in which decisions are not final, but rather regularly re-made in the context of ongoing scenario-based thinking and conversations with partners. This model appears to broadly apply to the experience of participants of this study, with some modifications. Firstly, whereas in CF genetic risk knowledge may more regularly occur through personal diagnosis, in GvFTD this knowledge often arrives primarily through the deterioration and diagnostic process of an affected relative, and so the 'Shock' portion of the model may occur earlier in the life of affected individuals. Secondly, the 'Adjustment' period of the model may be characterised by greater emotional difficulty or distress, as in GvFTD it involves contending with the interpersonal challenges of consideration of changing personality, and as a result may be more challenging to navigate. Thirdly, the 'Decide' stage of the original model is characterised as fluid and ongoing. Though this is of course also the case in participants of this study, it is important to consider the 'time limit' element that many participants expressed with regards to reproductive decision-making related to the estimated age of onset for symptoms, and for this reason it may be reasonable to assume that the decision process in GvFTD, though fluid and dynamic, may be perceived as having a more fixed end-point. Finally, it is important to consider the experience of those who had children prior to risk knowledge – in their case, the experience of shock and adjustment might be thought to co-occur, as they deal with both the emotional distress of new knowledge and the attempt to reconcile previous reproductive decisions to this new knowledge, a process which may not be easily navigable. In addition, the characteristics of the decision phase change, from being about primary decisions about reproduction, to secondary decisions about disclosure to children and approach to parenting and planning in the context of this new and challenging knowledge.

Limitations

The current study is subject to a number of limitations, both in sampling and methodology, that bear consideration. This study examines reproductive decision-making and outcomes among this population, however only gives indirect consideration to the input and views of the partners of at-risk individuals through second-hand report. Reproductive decision-making has been identified in other research as often occurring in the context of relational discussions between partners, and other qualitative studies have highlighted the inherently dynamic, interpersonal nature of these decisions within this context (Myring et al., 2011; Reumkens et al., 2019a; Reumkens et al., 2019b; Severijns et al., 2021), and often includes input from partners in the interview process. It is therefore likely that the exclusion of partners from the current study means that information about the process of the reproductive decision-making process may have been missed. Similarly, in terms of sampling, it is important to note that all participants were White British, and a majority were female. This follows a broad trend in research participation where ethnically White participants are overrepresented, leading to research that is unrepresentative of and therefore less sensitive to differences of experience informed by broader societal racial, ethnic and sexual diversity (Henreich, Heine & Norenzayan, 2010; Wendler et al., 2006). In the context of this study, a more balanced distribution of ethnicity may have been helpful in exploring any gender differences in reproductive decision-making as have been highlighted in similar research in other genetically heritable conditions (Myring et al., 2011; Severijns et al., 2021). In regards to ethnic and sexual diversity, greater consideration would have been preferable in providing the opportunity to consider differing social and cultural influences, norms and expectations related to reproductive decision-making that might influence the process. Finally, there is a broader methodological consideration of the heterogeneity of the participants involved in relation to reproductive decision-making and genetic status. Though demographically comparable, there is a range of genetic statuses present – those who know of their positive genetic status, those who know of their negative genetic status, those who chose not to know their status, and those who have not yet been tested. Similarly, there are

a range of reproductive experiences – some not yet considering children actively, some who had children knowing their risk status, some who had children prior to this, and some who chose to abstain following risk knowledge. Though it is of course advisable in exploratory research such as this to broadly account for a large range of experience so as to begin to identify themes and patterns, it is possible that a more purposive approach to sampling, such as exclusively engaging with participants who had children post risk knowledge, or exclusively with those who were not parents, may have facilitated a greater level of specificity or granularity of data and therefore findings (Palinkas et al., 2015).

Future research directions

With the above limitations of research generally in relation to diversity of participation in mind, it would be beneficial to pursue similar research exploring the experiences of other demographic groups in regards to reproductive decision-making in this regard, to establish to what extent the findings here maintain relevancy across changing cultural and socio-economic conditions. Similarly, research exploring the involvement from the partners of at-risk individuals may provide us with the opportunity to understand in greater detail the mechanisms by which reproductive decisions are discussed, arrived at and affirmed in the discursive process between involved partners. Finally, it is important to consider the direct comparability of the experience of genetic risk for GvFTD with genetic risk for HD. Often approaches to genetic counselling and information provision for HD, considered the 'gold standard' due to its relatively long history of provision (Greaves & Roher, 2019; MacLeod et al., 2013). However, as this study demonstrates, though there are similarities in the research regarding reproductive decision-making in HD and the results found here, it is by no means a matter of direct 1:1 reproduction. Therefore, there would be benefit in future research explicitly comparing the experience of genetic risk within HD and GvFTD, so as to identify what areas are similar enough for direct transposition, and what differences emerge as potentially highlighting areas for modification.

Clinical Implications

The findings identified in this study, though exploratory, indicate a number of potential clinical adaptions that might be made to support at-risk individuals navigate reproductive decision-making. The first is the expansion of access to and scope of genetic counselling for those at genetic risk of GvFTD. Typically those pursuing a genetic test for GvFTD will receive three sessions of genetic counselling prior to testing. It has been noted that the provision of genetic counselling for GvFTD generally falls behind that available for other genetically heritable conditions (Greaves and Rohrer, 2019), and that the quality of received genetic counselling is variable (Paneque, Sequeiros, & Skirton, 2015), and goals may vary from non-judgemental support in accepting genetic risk to actively preventing genetic risk spread (Biesecker, 2001). This study's findings suggest that at-risk individuals would benefit from access to genetic counselling, not just related to testing, but at important and challenging decisional intervals such as when considering reproduction to weigh options and reach decisions in a supportive, non-judgemental environment. Thus, a broadening of the accessibility of genetic counselling to this cohort would be beneficial, as would ability to re-refer in the context of later life decisions. Similarly, though provision of accurate risk information is a necessary step in supporting at risk individuals to make informed reproductive decisions, these findings highlight that information in and of itself is not sufficient to navigate the process. A counselling approach that supports and encourages at-risk individuals in navigating 'scenario-based thinking' (Lippman & Hand, 1979) of available options to arrive at the most personally acceptable may be beneficial, possibly informed by the 'Shock-Adjust-Decide' Model (Myring et al., 2011). Similarly, it is interesting to note that many participants stressed the benefits of proactive practical planning related to legal issue such as power of attorney, wills and financial management in managing distress at their risk status, often counterpointing this to their symptomatic relatives' lack of opportunity to do so. They similarly highlighted the benefit, both personal and for potential children, of research involvement. It may therefore be beneficial to consider, in the diagnostic pathway for GvFTD, explicit and active provision of information and signposting to resources to pursue such

practical planning, and active provision of information regarding research participation, so as to allow individuals living at genetic risk to access the potential benefits of engaging with these options.

Conclusions

GvFTD is a condition with profound implications for those who are diagnosed with it, their loved ones and children. For those at genetic risk, the process of witnessing the decline in their symptomatic relative can be emotionally challenging, and in addition they often have experience of the intensely demanding and distressing role of a carer. They must also contend with the question of if or when they might experience a similar decline, and often are faced with concerns of how this may affect their family, both in terms of their own potential symptomatology and the question of heritability to their children. This study provides us with useful insights into how people living with genetic risk for FTD engage with this genetic risk knowledge, and how they navigate the process of reproductive decision-making in light of it. It highlights how risk is understood by this cohort, often through the lens of their own prior experience with symptomatic relatives, as well as the multi-faceted approaches and behaviours they undertake to mitigate the role this risk plays in their own lives, and that of their children and families. It provides us with useful clinical implications of how they might best be supported in navigating these complex decisions, both in terms of information-provision and support. It also offers an interesting insight into the commonalities and differences in reproductive decision-making in the context of GvFTD in comparison to other genetically heritable conditions, and highlights a need for research directly examining the direct comparability of the GvFTD experience with that of HD, to establish how the approaches developed for HD may need to be modified to ensure their effectiveness in the context of GvFTD.

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Part 3: Critical Appraisal

In this critical appraisal, I will outline a response to the process of conducting this research. I will discuss the methodological and epistemological decisions made, and reflect on the factors influencing these. I will outline personal factors that emerged as relevant to the research and attempt to account for how these factors are related, how they may have influenced my positionality in relation to research topics and interview process, and the ways in which I attempted to acknowledged these and account for them. Thus, I will outline my attempts to 'bracket' my own experience and presuppositions and therefore identify and minimise their impact on the research. Finally, as a relative novice in the field of qualitative research, I will reflect on the process of research as a whole, both in terms of areas which my lack of expertise may have adversely impact, and the skill and experience gained from this process.

Concepts in the reflective process

This process of reflection is undertaken in the spirit of reflexivity. Reflexivity can be understood as a process of acknowledging and accounting for the relation between the researcher and the research being undertaken (Ahern, 1999). It is closely tied to the idea that researcher's suppositions, background and internal processes are inherently influential in qualitative research (Sutton & Austin, 2015). Indeed, this inter-relation between the researcher and research topic and process, and the subjectivity and bias that accompany it, is not viewed as necessarily negative, but is necessarily unavoidable (Porter, 1993; Sutton & Austin, 2015). Reflexivity is therefore the concept that this relationship is best approach by actively and explicitly considering and elaborating on its elements and potential impacts, both to attempt to account for these impact (Ahern, 1999), and as a facilitator of maintaining the "persistent curiosity" (LeVasseur, 2003, p. 419) necessary for good qualitative research. Bracketing is the process of applying this concept of reflexivity to the research at hand in an operationalised manner (LeVasseur, 2003; Fischer, 2009). Bracketing involves the explicit accounting by the researcher of presuppositions, ideas and values which may influence the research (Fischer, 2009), and ideally proceeds alongside and integrated into the process of

developing the research question, data collection and analysis (Ahern, 1999). There are many approaches to bracketing emphasising different types of suppositions and ideas (Gearing, 2004), and additionally many techniques that can be employed for the purposes of undertaking the bracketing process (Tufford & Newman, 2010). For the purposes of this critical appraisal, I feel it is best to be explicit both about the overall bracketing approach being employed and the techniques used as a part of it.

Reflexive bracketing, as outlined by Gearing (2004), focuses providing a transparent accounting of the researcher's personal background and experiences, as well as their cultural context and values, in an attempt to account for and minimise their impact as much as is possible. It involves preparatory bracketing of these elements ahead of data collection through careful consideration and reflection on the part of the researcher. During data collection, attempts are made to limit their influence, though acknowledging that total objectively is neither possible nor necessarily desirable (Ahern, 1999). Finally, these bracketed values and ideas can be explicitly considered at the analysis stage and later, such as in the process of this critical appraisal. Given its pragmatism and flexibility to be used in many qualitative approaches, this appeared to be an appropriate approach to me and therefore was selected. In terms of techniques used, there were two key elements: the first was the maintenance of a research journal, maintained through the process of research from developing the initial research question, to development of the interview schedule, to participant interviews, and through data analysis. I maintained this as a record of subjectively noteworthy experiences and reflections on these throughout the process – for example, where review of literature led to reflection on my own experiences of relatives with dementia, or where I noted a particularly strong emotional reaction after a participant interview. This provided a useful longitudinal tool for thinking about the relationship between my own characteristics and experiences and the ongoing research. The second was the use of a bracketing interview (Tufford & Newman, 2010) after the development of the research question but prior to any other steps, to elucidate through discussion with peers my own

views and presuppositions about dementia and reproduction explicitly and thoroughly, and relating these to my own cultural background, identity and experiences. I audio-recorded and later transcribed this interview, and found it to be invaluable to highlighting to myself previously implicit views and ideas which may have influenced the research process.

With these ideas in mind, I will below provide an accounting of decisions made with relation to methodology and epistemology, and where I may have influenced that process.

Epistemology

As a novice qualitative researcher, this study represented a new experience in explicitly considering and appropriately identifying epistemology underpinning qualitative analysis. This topic was highlighted early in the research process by my supervisor, who encouraged me to take time in considering what approach was both appropriate for the topic under study, and fit with my own attitudes towards qualitative research in general. As the broad area of research emerged via discussion with both my supervisor and GENFI project staff, along with my own consideration of the literature and gaps in the knowledge base, this was a topic that warranted further consideration. In aid of this, I started by first considering the two major concepts within the study, the first of which was genetic risk status for frontotemporal dementia (FTD). As outlined in the introduction of part one of this study, children of parents with genetic variant FTD (GvFTD) have a 50% chance of inheriting the implicated gene and developing GvFTD themselves. Though this process of inheritance can broadly be characterised as biological, the experience of being at genetic risk for this or any genetically heritable condition is marked by uncertainty, and the response to and understanding of this status by at-risk individuals is inherently subjective, in that it is informed by the biological possibility of inheritance but cannot be wholly predicted or determined by it. Two people receiving the same genetic testing result may experience wholly different emotional responses, and make sense of this knowledge in wholly different ways, none of which can be pre-determined based simply on this genetic information, but necessarily influenced by broader categories of previous experience and personality. Thus it

seemed to me that in considering the impact of risk for GvTD on at-risk individuals, I was to be exploring an inherently *subjective* phenomenon. Similarly, reproductive decision-making emerged as a similar subjective category likely to be influenced by, but not wholly determined by, the biological process of potential inheritance. Individuals make reproductive decisions in the context of myriad competing influential factors, internal and external, and the exact influence and weighting of each of these factors in decision-making is again likely best understood through the individual experience of the person making them. Again, I felt that the processes of reproductive decision making were inherently *subjective*, likely influenced but not determined by genetic risk information. Thus, it seemed clear that the interplay between these two factors would be best understood through an accounting of how the phenomenon of risk for GvFTD was subjectively understood, interpreted, and responded to in the lived experience of affected individuals. For this reason, it appeared that a phenomenological epistemological stance would be most appropriate. Phenomenology can be understood as both a philosophical orientation that emphasises humans as embodied, conscious being that use the processes of consciousness to categorise, interpret and define discrete phenomena (Connelly, 2010), and as an approach to research developing from this philosophical underpinning (Balls, 2009). It prioritises the subjective understanding developed by individuals in attempting to understand phenomena they encounter as providing as essential in developing a full understanding of that phenomena, and attempts to elicit and explore this subjective understanding (Balls, 2009). Within phenomenology, there is a broad delineation between 'descriptive phenomenology', focused on the uncovering and elaboration of the 'essences of phenomena' as described by participants (Lopez & Willis, 2004), and 'interpretative phenomenology', which attempts to build additional interpretative understanding from the basis outlined in participant data (Lopez & Willis, 2004). It has been identified that descriptive phenomenology is of most use in providing initial insight and illumination of poorly defined or understood phenomena or experiences (Lopez & Willis, 2004; Matua & Van Der Wall, 2015). Given that this study sought to explore the subjective experience of participants in relation to both included concept, that it represented the first

attempt to do so in the absence of previous robust exploration of this topic, a descriptive phenomenological orientation seemed appropriate. Given my lack of previous in-depth knowledge of the topic, and a strong personal desire to allow as much as possible for participant's own understanding and meaning-making to take precedence over my own interpretations, I felt that this orientation additionally presented a good 'fit' for my own values.

Methodology

Though all aspects of research methodology were given due consideration, there are two major aspects which required significant reflection. The first was the choosing of a method of qualitative analysis. Given review of the available literature, and consultation with my supervisor, thematic analysis appeared to be appropriate. There were a number of reasons for this. Firstly, the novel and exploratory nature of the research meant that I felt it was important to primarily focus on the elicitation of the experience of reproductive decision-making in the context of risk for GvFTD in as great a level of detail as possible, outlining as much as possible the resultant level of complexity and diverging experience among participants. This seemed important to provide initial insight and outline areas of complexity which might provide direction for further exploration. For this reason, the relatively open, adaptable, data-driven process of thematic analysis (Fereday & Muir-Cochrane, 2006) seemed appropriate. Secondly, given my status as a relatively novice qualitative researcher, it seemed to me important to realistically account of my current skill level in selecting an approach which I might effectively utilise to derive meaningful findings which were respectful of the effort undertaken by participants to share their experience, while also providing me with the opportunity to begin to develop the basic skills of qualitative analysis using a pragmatic, relatively flexible approach. Thematic analysis has often been characterised as a-theoretical (Braun & Clarke, 2006), supportive of many epistemological stances and varying levels of scope of analysis, and for both an exploratory study of a relatively novel area, and a relatively 'fresh' researcher attempting to reckon with the processes of qualitative research for the first time, this seemed useful.

The second area was that of data collection, beginning with the development of the interview schedule (see *Appendix D*). I was acutely aware of my lack of knowledge in the area of GvFTD approaching this project, and therefore prioritised utilising multiple sources of information to inform this schedule. After initial idea generation independently, I reviewed available interview schedules for qualitative research regarding reproductive decision-making in other genetically heritable conditions and updated accordingly. I then reviewed this second draft with available expert opinion, both within the GENFI project team and from my supervisor, with guidance on weighting of various topics and relevance of questions taken on board. I was highly aware of the potential sensitivity of the topic for at-risk individuals, and was concerned to ensure both that the tone and wording of questions was respectful of their experience, and avoided implicit judgement of any reproductive choices as much as was possible. The opportunity to have the interview schedule reviewed by three experts by experience, at-risk individuals not participating in this study, was an invaluable opportunity to check this aspect, and the illuminating response received allowed me to further ensure that the schedule was relevant, respectful, and subject to views other than my own. The interview process was initially designed to provide maximum flexibility to participants, to reduce participation burden and to facilitate recruitment and engagement, and I had given due consideration to conducting interviews in-person as well as remotely vi video or telephone call, with a preference for in-person interview to maximise my ability to effectively respond to emotional distress from participants and ensure a confidential, quiet interview space. However, the context of the then-occurring COVID-19 pandemic rendered these preparations and considerations relatively pointless, as travel and social distancing restrictions meant that in-person interviews were not a safe and practical option during the data collection period, with all interviews being conducted remotely. In retrospect, I think this had both positives and negatives – it certainly facilitated participation from people who would not otherwise have been able to due to geographical distance or work arrangements, and therefore led to a broad spread of participants across multiple countries within the UK which might not otherwise have been the case; however, I noted a difficulty in responding to

participant emotional distress as effectively in the moment when working remotely, and had less ability to ensure privacy and confidentiality of interview time on their end, as interviews were often conducted via phone or video in quiet corners of busy family homes. Though I think I adapted to the sudden changes to plans instigated by COVID-19 as well as possible, as we all did, I am left wondering whether other findings might have occurred outside of this context.

Researcher's positionality in the research

As described above, it is important in reflexive bracketing for the author to provide an account of themselves, and how their characteristics, experiences and views may impact the research. In aid of this, I am a heterosexual White Irish man in my early 30s. I was born in the south of Ireland, and lived there until moving to the UK ten years ago. I have worked in a number of settings related to mental health, including learning disability services, mental health crisis services, and services for those experiencing severe and enduring mental illness. I am currently completing my final year of doctoral training in Clinical Psychology at University College London, and considered myself far more experienced in and aligned with the clinical elements of training and work than with the research elements. A number of my relatives have developed dementia, although not FTD, and I and my immediate family have acted as carers for relatives experiencing dementia at periods in the past. I do not have children, and do not currently intend to have children. There are a number of elements of the above which I think have been relevant to the process of research and my role as the researcher during this study, both identified during bracketing and later, which I will outline below.

The first is my familial experience of dementia. A number of relatives, now deceased, have experienced dementia, though none have experienced FTD. At times during their illness, both I and my immediate family took on caring responsibilities for them. Though happening earlier in life, I have found that these experiences have had a lasting impact on me. I found the process of witnessing their struggles with memory and communication

difficult, and struggled emotionally at times with a similar feeling of ‘loss of relationship as it was’ as their decline progressed as outlined by many participants in this study. As a result of this, dementia has been an active topic of conversation in my family, and I have had conversations with relatives where they outlined what they would like to happen to them in the case that they develop dementia, as well as queries about the heritability of these experiences. I am fully aware that these experiences have instilled in me an interest in the experiential and interpersonal ramifications of dementia in general, which led to my pursuit of this topic. During bracketing interviews, I became aware through conversation that I held a negative and somewhat fatalistic view of dementia in general, viewing it as leading to steady decline, loss of dignity and independence, and causing stress and distress around the affected person. I became aware that I was not considering any neutral or positive aspects of dementia that might be experienced by individuals, and by not considering this I was unlikely to ask and therefore unlikely to elicit information about experiences of different emotional valences. Becoming aware of this, I endeavoured to consciously work to ensure that I maintained as much as possible a curious and open attitude towards the impact of dementia in the lives of participants in my questioning and documenting, rather than pre-supposing this as an inherently negative experience. Though the majority of experiences were challenging, in attempting to consciously hold this more neutral stance I think I was more able to identify exceptions to negativity and appropriately explore these in interview. I think this process of reflection on my own experience with dementia was also beneficial in preparing me for the potential emotional impact of the stories shared by participants, both because of their difficult nature, but also in overlapping to certain extents with my own past experiences.

The second is my position as a man without children, and without a desire to have children. As the process of interviewing progressed, I noticed three relevant details to this fact. The first was that I found myself easily understanding the decisions and views of participants who expressed little desire for or interest in parenthood; as it aligned closely with

my own views, I was able to more readily ‘fill in the blanks’ between their points, possibly interpreting their own experience as my own. Interestingly, I wondered whether this led to a lessening of my curiosity in the form of follow-up questions about this topic in them, as I felt I already ‘understood’ this from my own position. Having noted this, I attempted again to aim for greater neutrality and curiosity regarding this stance when it emerged in later interviews, ensuring that I have ample time and follow up, and attempting to elicit explicit discussion rather than assuming I understood. Ultimately I believe this was fruitful in developing a richer discourse on this topic. The second detail was my lack of knowledge of the intricacies of parenting. With no experience of it myself, I found that I was often surprised by the aspects of parenting that participants with children identified as most challenging, most important and most rewarding, and the (often smaller than I would have expected) role played by risk knowledge in the process. Having little experience of this area of life myself, I reflected that, following initial interview, I may be guilty of a relatively flattened view of what constitutes parenting and the concerns of parents. I again sought to resolve this by widening my curiosity, and using my lack of knowledge as a basis to open a longer, more detailed discussion with parent participants going forward. Finally, in speaking to some of the female participants, both parents and non-parents, I became cognisant through what they shared regarding the differing levels of social pressure and messaging regarding reproduction that occur on gender lines. The decision to or not to have children for woman can be subject to greater outside pressure and influence than for me, with more people freely expressing normative opinions on what should or should not be done, something that I had not as a man experienced personally. In recognising this, I going forward attempted to be ‘live’ to this aspect, at times explicitly asking about it in later interviews.

A final relevant element is my work and experience as a clinician, most often working in a therapeutic framework of conversation which holds some superficial similarities to that of the research interview. Both involve a conversation between two individuals, both about topics of significance that can be distressing, and which involve discussion of meaningful

past experiences. In addition, an interviewer, like a clinician, attempts as much as is possible to take a facilitating role in the interaction, encouraging and eliciting information, without engaging too much in a responsive dialogue of sharing. However, there are key differences, the most pertinent of which is that, as an interviewer unlike a therapist, there is not an expectation of attempts to arrive at solutions to dilemmas or difficulties outlined in interview, and there is no expectation of a process of moving towards a resolution in the discussion. Though this was highlighted to me by my supervisor at the very beginning of the research project, at times I found the process of 'changing speeds' between clinical work and research interviews to take some mental effort at times. There were some positive aspects to my clinical background in interviewing that I noticed. My skills in engagement, eliciting further information, asking open ended questions and building rapport were all useful in facilitating productive interviews. In addition, a clinical background meant that when participants shared information about far-future plans to consider assisted dying, I was able to respond to this information in what I felt was a calm, non-judgemental manner, allowing space for participants to discuss this topic openly, and appropriately following up in debrief to confirm, as it was in all cases, that there was no current or near-future risk of any kind. However, there were elements of my clinical background that were less helpful. I noted in listening to interview recordings that I was regularly engaging in detailed summarisation of information shared by participants as a rapport building technique. Though helpful in this regard, I noted that not-insignificant time periods of our limited interview time were used up in this way. Also of note was the difficulty I experienced in holding back from engaging in problem-solving discussions with participants, particularly those who expressed emotional distress at their dilemmas. In a clinical setting this would be appropriate, and I was surprised at the strength of the draw to respond as I would in such a setting. Overall, this outlined to me the overlapping roles of clinician and qualitative interviewer, which can sometimes aid us and sometimes work against us, and a need to be actively and consciously aware of what 'role' I was in, and what 'role' I was feeling drawn to be in.

Conclusion

In the outlining of the above reflexive account of the research process, I have endeavoured to account both for decisions made as the research progressed, and position myself as researcher within the research. I have attempted to provide the transparent account necessary for effective and useful reflexive bracketing, and more generally offer my insights gleaned from the process of conducting this study. As a novice qualitative research I have found the process of research to be at turns interesting, tedious, enervating and humbling. I have been deeply grateful for the opportunity to hear the stories of my participants and to attempt to account for the depth and complexity of their experience and thoughts in this research. It is my firm hope that I have done them justice.

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Appendices

Appendix A

Search strategy and order used in database search

SEARCH NO.	SEARCH TERMS
1	"Reproductive health" OR "Reproductive decision making" OR "Reproductive decision-making" OR "Reproduction" OR Reproductive behav* OR "Family Planning" OR "Family Planning Services" OR "Fertility" OR "Childbearing Decision" OR "Fertility Intention" OR "Child desire" OR "Child Wish" OR "Reproductive choice" OR "Having a child" OR "Having Children" OR Parent*
2	"Reproductive health" AND Decision*
3	Reproductive AND Decision*
4	Reproductive behav* AND Decision*
5	Fertility AND Intention
6	Childbearing AND Decision*
7	Reproductive AND Choice
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9	"Huntington's Disease" OR "Huntington's Chorea" OR Huntington*
10	8 AND 9

Appendix B

QualSyst Study Quality Assessment Tool, Criteria for Qualitative and Quantitative research

1. Manual for Quality Scoring of Quantitative Studies

Definitions and instructions for quality assessment

Scoring: How to calculate summary scores

Total Sum= (number of 'yes'*2) + (number of 'partial'*1)

Total Sum Possible= 28 – (number of 'N/A'*2)

Summary Score= Total Sum/Total Sum Possible

Quality assessment items

1. Question or objective sufficiently described?

Yes: Is easily identified in the introductory section (or first paragraph of methods section). Specifies (where applicable, depending on study design) all of the following: purpose, subjects/target population, and the specific intervention(s) /association(s)/descriptive parameter(s) under investigation. A study purpose that only becomes apparent after studying other parts of the paper is not considered sufficiently described.

Partial: Vaguely/incompletely reported (e.g. “describe the effect of” or “examine the role of” or “assess opinion on many issues” or “explore the general attitudes”...); or some information has to be gathered from parts of the paper other than the introduction/background/objective section.

No: Question or objective is not reported, or is incomprehensible.

N/A: Should not be checked for this question.

2. Design evident and appropriate to answer study question? (If the study question is not given, infer from the conclusions).

Yes: Design is easily identified and is appropriate to address the study question / objective.

Partial: Design and /or study question not clearly identified, but gross inappropriateness is not evident; or design is easily identified but only partially addresses the study question.

No: Design used does not answer study question (e.g., a comparison group is required to answer the study question, but none was used); or design cannot be identified.

N/A: Should not be checked for this question.

3. Method of subject selection (and comparison group selection, if applicable) or source of information/input variables (e.g., for decision analysis) is described and appropriate.

Yes: Described and appropriate. Selection strategy designed (i.e., consider sampling frame and strategy) to obtain an unbiased sample of the relevant target population or the entire target population of interest (e.g., consecutive patients for clinical trials, population-based random sample for case-control studies or surveys). Where applicable, inclusion/exclusion criteria are described and defined (e.g., “cancer” -- ICD code or equivalent should be provided). Studies of volunteers: methods and setting of recruitment reported. Surveys: sampling frame/ strategy clearly described and appropriate.

Partial: Selection methods (and inclusion/exclusion criteria, where applicable) are not completely described, but no obvious inappropriateness. Or selection strategy is not ideal (i.e., likely introduced bias) but did not likely seriously distort the results (e.g., telephone survey sampled from listed phone numbers only; hospital based case-control study identified all cases admitted during the study period, but recruited controls admitted during the day/evening only). Any study describing participants only as “volunteers” or “healthy volunteers”. Surveys: target population mentioned but sampling strategy unclear.

No: No information provided. Or obviously inappropriate selection procedures (e.g., inappropriate comparison group if intervention in women is compared to intervention in men). Or presence of selection bias which likely seriously distorted the results (e.g., obvious selection on “exposure” in a case-control study).

N/A: Descriptive case series/reports.

4. Subject (and comparison group, if applicable) characteristics or input variables/information (e.g., for decision analyses) sufficiently described?

Yes: Sufficient relevant baseline/demographic information clearly characterizing the participants is provided (or reference to previously published baseline data is provided). Where applicable, reproducible criteria used to describe/categorize the participants are clearly defined (e.g., ever-smokers, depression scores, systolic blood pressure > 140). If “healthy volunteers” are used, age and sex must be reported (at minimum). Decision analyses: baseline estimates for input variables are clearly specified.

Partial: Poorly defined criteria (e.g. “hypertension”, “healthy volunteers”, “smoking”). Or incomplete relevant baseline / demographic information (e.g., information on likely confounders not reported). Decision analyses: incomplete reporting of baseline estimates for input variables.

No: No baseline / demographic information provided. Decision analyses: baseline estimates of input variables not given.

N/A: Should not be checked for this question.

5. If random allocation to treatment group was possible, is it described?

Yes: True randomization done - requires a description of the method used (e.g., use of random numbers).
Partial: Randomization mentioned, but method is not (i.e. it may have been possible that randomization was not true).
No: Random allocation not mentioned although it would have been feasible and appropriate (and was possibly done).
N/A: Observational analytic studies. Uncontrolled experimental studies. Surveys. Descriptive case series / reports. Decision analyses.

6. If interventional and blinding of investigators to intervention was possible, is it reported?
Yes: Blinding reported.
Partial: Blinding reported but it is not clear who was blinded.
No: Blinding would have been possible (and was possibly done) but is not reported.
N/A: Observational analytic studies. Uncontrolled experimental studies. Surveys. Descriptive case series / reports. Decision analyses.

7. If interventional and blinding of subjects to intervention was possible, is it reported?
Yes: Blinding reported.
Partial: Blinding reported but it is not clear who was blinded.
No: Blinding would have been possible (and was possibly done) but is not reported.
N/A: Observational studies. Uncontrolled experimental studies. Surveys. Descriptive case series / reports.

8. Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?
Yes: Defined (or reference to complete definitions is provided) and measured according to reproducible, “objective” criteria (e.g., death, test completion – yes/no, clinical scores). Little or minimal potential for measurement / misclassification errors. Surveys: clear description (or reference to clear description) of questionnaire/interview content and response options. Decision analyses: sources of uncertainty are defi ned for all input variables.
Partial: Definition of measures leaves room for subjectivity, or not sure (i.e., not reported in detail, but probably acceptable). Or precise definition(s) are missing, but no evidence or problems in the paper that would lead one to assume major problems. Or instrument/mode of assessment(s) not reported. Or misclassification errors may have occurred, but they did not likely seriously distort the results (e.g., slight difficulty with recall of long-ago events; exposure is measured only at baseline in a long cohort study). Surveys: description of questionnaire/interview content incomplete; response options unclear. Decision analyses:

sources of uncertainty are defined only for some input variables.

No: Measures not defined, or are inconsistent throughout the paper. Or measures employ only ill-defined, subjective assessments, e.g. “anxiety” or “pain.” Or obvious misclassification errors/measurement bias likely seriously distorted the results (e.g., a prospective cohort relies on self-reported outcomes among the “unexposed” but requires clinical assessment of the “exposed”). Surveys: no description of questionnaire/interview content or response options. Decision analyses: sources of uncertainty are not defined for input variables.

N/A: Descriptive case series / reports.

9. Sample size appropriate?

Yes: Seems reasonable with respect to the outcome under study and the study design. When statistically significant results are achieved for major outcomes, appropriate sample size can usually be assumed, unless large standard errors (SE > ½ effect size) and/or problems with multiple testing are evident. Decision analyses: size of modeled cohort / number of iterations specified and justified.

Partial: Insufficient data to assess sample size (e.g., sample seems “small” and there is no mention of power/sample size/effect size of interest and/or variance estimates aren’t provided). Or some statistically significant results with standard errors > ½ effect size (i.e., imprecise results). Or some statistically significant results in the absence of variance estimates. Decision analyses: incomplete description or justification of size of modeled cohort / number of iterations.

No: Obviously inadequate (e.g., statistically non-significant results and standard errors > ½ effect size; or standard deviations > _ of effect size; or statistically non-significant results with no variance estimates and obviously inadequate sample size). Decision analyses: size of modeled cohort / number of iterations not specified.

N/A: Most surveys (except surveys comparing responses between groups or change over time). Descriptive case series / reports.

10. Analysis described and appropriate?

Yes: Analytic methods are described (e.g. “chi square”/ “t-tests”/“Kaplan-Meier with log rank tests”, etc.) and appropriate.

Partial: Analytic methods are not reported and have to be guessed at, but are probably appropriate. Or minor flaws or some tests appropriate, some not (e.g., parametric tests used, but unsure whether appropriate; control group exists but is not used for statistical analysis). Or multiple testing problems not addressed.

No: Analysis methods not described and cannot be determined. Or obviously inappropriate analysis methods (e.g., chi-square tests for continuous data, SE given where normality is

highly unlikely, etc.). Or a study with a descriptive goal / objective is over-analyzed.
N/A: Descriptive case series / reports.

11. Some estimate of variance (e.g., confi dence intervals, standard errors) is reported for the main results/outcomes (i.e., those directly addressing the study question/ objective upon which the conclusions are based)?
Yes: Appropriate variances estimate(s) is/are provided (e.g., range, distribution, confidence intervals, etc.). Decision analyses: sensitivity analysis includes all variables in the model.
Partial: Undefined "+/-" expressions. Or no specific data given, but insufficient power acknowledged as a problem. Or variance estimates not provided for all main results/outcomes. Or inappropriate variance estimates (e.g., a study examining change over time provides a variance around the parameter of interest at "time 1" or "time 2", but does not provide an estimate of the variance around the difference). Decision analyses: sensitivity analysis is limited, including only some variables in the model.
No: No information regarding uncertainty of the estimates. Decision analyses: No sensitivity analysis.
N/A: Descriptive case series / reports. Descriptive surveys collecting information using open-ended questions.

12. Controlled for confounding?
Yes: Randomized study, with comparability of baseline characteristics reported (or non-comparability controlled for in the analysis). Or appropriate control at the design or analysis stage (e.g., matching, subgroup analysis, multivariate models, etc). Decision analyses: dependencies between variables fully accounted for (e.g., joint variables are considered).
Partial: Incomplete control of confounding. Or control of confounding reportedly done but not completely described. Or randomized study without report of comparability of baseline characteristics. Or confounding not considered, but not likely to have seriously distorted the results. Decision analyses: incomplete consideration of dependencies between variables.
No: Confounding not considered, and may have seriously distorted the results. Decision analyses: dependencies between variables not considered.
N/A: Cross-sectional surveys of a single group (i.e., surveys examining change over time or surveys comparing different groups should address the potential for confounding). Descriptive studies. Studies explicitly stating the analysis is strictly descriptive/exploratory in nature.

13. Results reported in sufficient detail?
Yes: Results include major outcomes and all mentioned secondary outcomes.
Partial: Quantitative results reported only for some outcomes. Or difficult to assess as study

question/objective not fully described (and is not made clear in the methods section), but results seem appropriate.

No: Quantitative results are reported for a subsample only, or “n” changes continually across the denominator (e.g., reported proportions do not account for the entire study sample, but are reported only for those with complete data -- i.e., the category of “unknown” is not used where needed). Or results for some major or mentioned secondary outcomes are only qualitatively reported when quantitative reporting would have been possible (e.g., results include vague comments such as “more likely” without quantitative report of actual numbers).

N/A: Should not be checked for this question.

14. Do the results support the conclusions?

Yes: All the conclusions are supported by the data (even if analysis was inappropriate). Conclusions are based on all results relevant to the study question, negative as well as positive ones (e.g., they aren’t based on the sole significant finding while ignoring the negative results). Part of the conclusions may expand beyond the results, if made in addition to rather than instead of those strictly supported by data, and if including indicators of their interpretative nature (e.g., “suggesting,” “possibly”).

Partial: Some of the major conclusions are supported by the data, some are not. Or speculative interpretations are not indicated as such. Or low (or unreported) response rates call into question the validity of generalizing the results to the target population of interest (i.e., the population defined by the sampling frame/strategy).

No: None or a very small minority of the major conclusions are supported by the data. Or negative findings clearly due to low power are reported as definitive evidence against the alternate hypothesis. Or conclusions are missing. Or extremely low response rates invalidate generalizing the results to the target population of interest (i.e., the population defined by the sampling frame/ strategy).

N/A: Should not be checked for this question.

2. Manual for Quality Scoring of Qualitative Studies

Definitions and Instructions for Quality Assessment

Scoring

Total Sum = (number of “yes” * 2) + (number of “partials” * 1)

Total Possible Sum = 20

Summary score: Total Sum / Total Possible Sum

Quality assessment items

1. Question / objective clearly described?

Yes: Research question or objective is clear by the end of the research process (if not at the outset).

Partial: Research question or objective is vaguely/incompletely reported.

No: Question or objective is not reported, or is incomprehensible.

2. Design evident and appropriate to answer study question? (If the study question is not clearly identified, infer appropriateness from results/conclusions.)

Yes: Design is easily identified and is appropriate to address the study question.

Partial: Design is not clearly identified, but gross inappropriateness is not evident; or design is easily identified but a different method would have been more appropriate.

No: Design used is not appropriate to the study question (e.g. a causal hypothesis is tested using qualitative methods); or design cannot be identified.

3. Context for the study is clear?

Yes: The context/setting is adequately described, permitting the reader to relate the findings to other settings.

Partial: The context/setting is partially described.

No: The context/setting is not described.

4. Connection to a theoretical framework / wider body of knowledge?

Yes: The theoretical framework/wider body of knowledge informing the study and the methods used is sufficiently described and justified.

Partial: The theoretical framework/wider body of knowledge is not well described or justified; link to the study methods is not clear.

No: Theoretical framework/wider body of knowledge is not discussed.

5. Sampling strategy described, relevant and justified?

Yes: The sampling strategy is clearly described and justified. The sample includes the full range of relevant, possible cases/settings (i.e., more than simple convenience sampling), permitting conceptual (rather than statistical) generalizations.

Partial: The sampling strategy is not completely described, or is not fully justified. Or the sample does not include the full range of relevant, possible cases/settings (i.e., includes a convenience sample only).

No: Sampling strategy is not described. 6. Data collection methods clearly described and systematic? Yes: The data collection procedures are systematic, and clearly described, permitting an “audit trail” such that the procedures could be replicated. Partial: Data collection

procedures are not clearly described; difficult to determine if systematic or replicable. No: Data collection procedures are not described.

7. Data analysis clearly described, complete and systematic?

Yes: Systematic analytic methods are clearly described, permitting an "audit trail" such that the procedures could be replicated. The iteration between the data and the explanations for the data (i.e., the theory) is clear – it is apparent how early, simple classifications evolved into more sophisticated coding structures which then evolved into clearly defined concepts/explanations for the data). Sufficient data is provided to allow the reader to judge whether the interpretation offered is adequately supported by the data.

Partial: Analytic methods are not fully described. Or the iterative link between data and theory is not clear.

No: The analytic methods are not described. Or it is not apparent that a link to theory informs the analysis.

8. Use of verification procedure(s) to establish credibility of the study?

Yes: One or more verification procedures were used to help establish credibility/ trustworthiness of the study (e.g., prolonged engagement in the field, triangulation, peer review or debriefing, negative case analysis, member checks, external audits/inter-rater reliability, "batch" analysis).

No: Verification procedure(s) not evident.

9. Conclusions supported by the results?

Yes: Sufficient original evidence supports the conclusions. A link to theory informs any claims of generalizability.

Partial: The conclusions are only partly supported by the data. Or claims of generalizability are not supported.

No: The conclusions are not supported by the data. Or conclusions are absent.

10. Reflexivity of the account?

Yes: The researcher explicitly assessed the likely impact of their own personal characteristics (such as age, sex and professional status) and the methods used on the data obtained.

Partial: Possible sources of influence on the data obtained were mentioned, but the likely impact of the influence or influences was not discussed.

No: There is no evidence of reflexivity in the study report.

Copied from: Kmet, L. M., Lee, R. C., & Cook, L. S. (2004). *Standard quality assessment criteria for evaluating primary research papers from a variety of fields.* Edmonton, Canada: Alberta Heritage Foundation for Medical Research https://era.library.ualberta.ca/items/48b9b989-c221-4df6-9e35-af782082280e

Appendix C

GENFI Information Sheet and Consent form

University College London Hospitals NHS Foundation Trust

CONFIDENTIAL

Subject Information Sheet
Version 10.0: 13 August 2019

Study Title: Genetic Frontotemporal dementia Initiative (GENFI)

Chief Investigator: Dr Jonathan Rohrer

You are invited to take part in a research study at the Dementia Research Centre (DRC). Before you decide whether to take part it is important for you to understand why we are doing the research and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?
The study purposes are to improve our understanding about frontotemporal dementia (FTD) and help measure effectiveness of future treatments. The specific aims are to identify the earliest features of genetic FTD and to understand how it progresses over a period of several years.

Why have I been asked to participate in the study?
We are inviting people who have received a diagnosis of genetic FTD as well as people who have informed us of a family history of genetic FTD.

Do I have to take part in the study?
No, your involvement in this study is voluntary. Having read this information sheet you should take time to consider your involvement and to discuss this with your family and friends. If you have any questions about the study and what participation will mean for you please ask to speak to the study team. If you decide not to participate in the study this will not affect your clinical care in any way. You may decide to leave the study at any time without giving a reason.

What will I have to do if I take part in the study?
We will ask you to identify somebody who knows you very well to act as your informant during the course of the study. This person will be asked to provide information (in person, via postal questionnaires or on the telephone) on your general health and medical care as well as information about their own wellbeing. We will ask you and your informant to sign a consent form before entering the study.

We will ask you to come to the DRC with your informant for detailed assessments of your memory and thinking. These visits will take place for three years unless:

1. the study ends prematurely
2. you or your informant decide not to continue in the study
3. you develop severe impairment of your thinking such that you are unable to comply with the study
4. you develop severe impairment of your thinking and someone representing your wishes decides that you should not continue in the study,
5. the research team decide to withdraw you from the study

Each annual visit will usually take place over two days and we can arrange accommodation for you if needed. We may also ask you to consider participating in optional sub-studies. You will be given separate information sheets for these studies. The timetable for the study is shown below:

PROCEDURE	Day 1		Day 2	
	AM	PM	AM	PM
Taking of consent	✓			
Medical history and examination	✓			
Blood and urine sample	✓			
Urine pregnancy test (if applicable)	✓			
MRI scan	✓			
Lumbar puncture		✓		
Informant interview		✓		
Neuropsychology			✓	
Retinal imaging (if applicable)				✓
Digital biomarker study (if applicable)				✓
Actigraphy (if applicable)				✓

You do not have to agree to undergo all of the study procedures and you should discuss any concerns or questions you have about each of the procedures with the study doctor before deciding to take part.

Medical assessment and neuropsychological tests
At each visit you will have a medical assessment and an interview with a doctor who will ask questions about how you have been feeling, and about any symptoms you may have been experiencing. The doctor will also ask you and your informant for information about your previous health and that of your family and for details of any medications you are taking. The doctor will perform a physical and neurological examination. You will also see a psychologist who will carry out a detailed assessment of your memory and thinking. The assessments with the doctor and the psychologist will last one to three hours. You will be offered breaks and refreshments during the assessments..

Blood and urine sampling
We would like to collect a blood sample which will be used in biochemical research into dementia and for genetic analysis. We will take about 60ml of blood (about 4 tablespoons full) from a vein in your arm. If you participate in the lumbar puncture study (described later in the information sheet) the blood sample will be drawn from your arm before the lumbar puncture. Taking blood is a safe procedure; there is minimal discomfort when the needle is inserted, and there are small risks of bruising. We will also ask you if you would be willing to provide a urine sample (up to 25ml) which will be used for biochemical research into dementia.

The department which is doing the genetic analysis will code your blood sample, and a number rather than your name is kept. The link between the code and your name will remain confidential and secure and will only be known by the department undertaking the genetic analysis. Our research team will receive anonymised information only, which means all data will be without a link to individual participants.

Lumbar puncture
We will also ask you if we can collect spinal fluid by performing a lumbar puncture. This is a procedure in which a small amount of spinal fluid that surrounds the brain and spinal cord is removed by inserting a needle in the lower back. You do not have to agree to have a lumbar puncture in order to enter the study. We will provide you with a separate information sheet about having a lumbar puncture.
Anonymised (without your name) blood and spinal fluid samples may be shared with other research groups for analyses; this is a common scientific practice. All samples will be managed in accordance with the requirements of the Human Tissue Act (2004).

Magnetic Resonance Imaging (MRI) scan
You will also have a MRI brain scan. MRI generates an electronic picture of your brain using a strong magnet instead of an X-ray. Before each MRI scan you will be asked questions to make sure you are happy with having the MRI and that it is safe for you to have the MRI. The scan takes about 45 to 60 minutes. During the MRI, you will lie on your back on a table which will enter the MR machine and you will be asked to remain very still. If you wish, you will be able to communicate with the study team during the MRI.

Computerised testing
During or shortly after your initial visit you will be asked to complete a short computer-based set of tasks using an iPad, designed to assess your memory and thinking. The tasks will take around 30 minutes to complete. You will be asked to complete this task every 3 months over the next year at home via an iPad that will be sent to you via the post.

No individual results of any tests undertaken as part of the research study will be available. Furthermore, in order to keep your personal information secure, the individual results of genetic analyses of blood samples you provide will not be available to you or to the research team.

Audio and Video Recording
We may ask you to consider giving your consent for us to video or audio record some of the study assessments. The recordings will be reviewed by the study team to look at any symptoms you may be experiencing in more detail and help to improve understanding of FTD. If you agree to video or audio recording you will be able to request that the recording be stopped at any point. We will also ask you if you would be willing to give your consent for the video and audio recordings to be used for teaching purposes and/or for use in scientific publications and presentations. It is important that you understand that some people may be able to recognise or identify you from video or audio recordings posted on educational websites and that once any recordings have been published online this information is in the public domain and cannot be retrieved.

Use of previously acquired clinical/research information
If you have had neuropsychological assessments and/or MRI scans performed as part of your clinical care or participation in other research studies conducted by the Dementia Research Centre, it may be helpful for us to include results from these investigations in this study. We will ask you if you consent for us to use this information. If you chose not to give consent this will not affect your involvement in the study.

If you choose not to have a lumbar puncture as part of the study but you have had or are due to have a lumbar puncture as part of your clinical care we may ask for your consent to collect some additional CSF or to have access to samples held in the laboratory for use in this research study.

Registering as a brain donor
We would like to discuss with you whether you would like information about the Queen Square Brain Bank and if you would wish to consider donating your brain for the purposes of scientific research after your death. This would provide the scientific community with invaluable information about the disease processes that cause dementia. If you would prefer not to discuss becoming a brain donor, please tell us. If you prefer not to discuss or you decide not to register as a brain donor this will not affect your participation in the study in any way.

Will I receive any payment for participating in this study?
We will refund any travel, accommodation or other reasonable expenses you incur in order to attend the research visits. Reimbursement will be according to Dementia Research Centre research expenses guidelines. You will receive a copy of the guidelines if you enter the study.

What will happen to the results of the study?
Results of the study will be available at a group level once the study is completed. We then plan to publish the results of the study in scientific journals. Information that would identify you or any other participant will not be included in any publication. It will not be possible for you to know your own test results.

What are the possible disadvantages and risks of taking part in the study?

Medical assessment and neuropsychological tests
These assessments and tests may involve you answering questions that are of a personal nature and the testing may be tiring. You do not need to answer any questions you do not wish to, and you may ask for a break during the testing if you need one.

Blood sampling
Taking blood can result in a minimal discomfort when the needle is inserted and there may be a small risk of bruising or a local skin reaction.

Lumbar puncture
We will give you a separate information sheet about having a lumbar puncture which will explain the possible disadvantages and risks associated with the procedure.

Magnetic Resonance Imaging (MRI) scan
You may feel claustrophobic or uncomfortable lying in the MRI scanner. You will hear loud knocking noises but we will provide you with earplugs to wear during the MRI. You can ask to stop the MRI at any time if it becomes uncomfortable.

What are the possible benefits of taking part in the study?
Participation in this study will not benefit you personally. However, we hope to gain new insights into the diagnosis and progress of frontotemporal dementia and hopefully this will contribute to helping others in the future.

How will personal information about me and my involvement in the study be kept confidential?
Any information collected during the study will be kept confidential. Assessment and test results will be stored on a secure, confidential, computer network on the University College London (UCL) system, accessible only to members of the DRC and the study sponsor, and in a form where you will not be identifiable, to other research groups who we work with on the GENFI study. When this study is completed we would like to continue to hold the data on the computer network and any blood and spinal fluid samples as it may be helpful to look again at the data and samples in the light of discoveries that may be made in the future. We will protect your personal information in accordance with UCL's Information Governance policy; the handling, processing, storage and destruction of data will be conducted in accordance with current UK Data Protection laws to ensure that confidential information is safeguarded. If you chose not to remain in the study or it is decided that you should not continue in the study, data and samples already collected will be retained and included in the analysis of results from the study.

Involvement of your general practitioner
With your consent we will inform your General Practitioner (GP) of your involvement in the study. Your GP will not routinely receive any information or results from your assessments or investigations, but we will advise your GP of any information relevant to your health. For example, a radiologist will look at your MRI scan. If the MRI shows something which requires medical attention, the study team will let you know and will inform your GP. We will also ask for your consent to contact your GP in the future should we lose contact with you and your informant.

You should be aware that being in a research study does not take the place of routine physical examinations or other appointments with your doctor and should not be relied upon to diagnose or treat medical problems.

Who is organising and funding this research?
This study is organised by the DRC, a research department linked to UCL and UCLH NHS Foundation Trust. The study is sponsored by UCL and is funded by a research grant awarded to the DRC by the Medical Research Council.

What if there is a problem?
If you, your relatives or your informant have any concerns about the research study you can speak to a member of the research team who will do their best to answer any questions. Contact details are at the end of this information sheet.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this. You, your relatives or your informant can also contact the UCLH Patient Advice and Liaison Service at the following address; PALS, Box 25, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG

In the unlikely event that you are harmed by taking part in this study, compensation may be available. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Dr Jonathan Rohrer who is the Chief Investigator for the research and is based at The Dementia Research Centre, Box 16, The National Hospital for Neurology and Neurosurgery, London WC1N 3BG. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Who has reviewed the study?
This research project has been reviewed by the London Queen Square Research Ethics Committee, and has been subject to comprehensive review as part of a competitive funding application process.

Further information and contact details

If you would like any further information or have any questions about this research study please contact Dr Jonathan Rohrer at the Dementia Research Centre

Dementia Research Centre
The National Hospital for Neurology and Neurosurgery
8-11 Queen Square
London, WC1N 3BG **Telephone: 020 3448 3193** **Fax: 020 3448 3104**

Research at UCL and your data

UCL is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will keep identifiable information about you for 20 years after the study has finished.
Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information by contacting data-protection@ucl.ac.uk or Data Protection Officer, UCL Gower Street, London WC1E 6BT. Further information is provided in UCL's health and care research privacy notice: https://www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice.

The Dementia Research Centre (DRC) will use your name, contact details, date of birth and hospital number to contact you about the research study and make sure that relevant information about the study is recorded for your care and to oversee the quality of the study. Individuals from UCL (the sponsor) and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The DRC will pass these details to UCL along with the information collected from you and/or your medical records. The only people in UCL who will have access to information that identifies you will be people who need to contact you to fulfill safety and regulatory requirements e.g. to talk to you about a concern, complaint or unexpected or adverse event related to the research study or audit the data collection process. The Dementia Research Centre will keep identifiable information about you from this study for 20 years after the study has finished.

UCL will collect information about you for research from your health records and other UCL databases. This information will include your name, address, date of birth, hospital number, and health information, which is regarded as a special category of information. We will use this information to verify and interpret the results of the research tests.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified, your data will only be used in research that has been independently reviewed by an ethics committee.

University College London Hospitals NHS
NHS Foundation Trust

DRC DEMENTIA RESEARCH CENTRE

UCL

SUBJECT CONSENT FORM **CONFIDENTIAL**

Genetic Frontotemporal dementia Initiative (GENFI)
Version 12: 13 August 2019

Chief Investigator: Dr Jonathan Rohrer

PLEASE INITIAL BOX

1. I confirm that I have read and understood the information sheet dated 13 August 2019 (version 10.0) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I understand that if I withdraw from the study, all data and samples already collected will be retained for further use in the research. ☐

3. I understand that sections of any of my medical notes may be looked at by the research team or by representatives of regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I give my consent for data from my UCLH clinical record and/or other research participation to be included in this study. ☐

5. I agree for my data to be shared in a non-identifiable form with other research groups that are collaborators with UCL. ☐

6. I agree to my GP being informed of my participation in the study and consent for the study team to contact my GP for an update on my health in the event of them being unable to contact my informant or me. ☐

7. I nominate the person named below as my informant and understand that they will share information about my medical details with the research team. ☐

   Name of Informant _____

8. I agree to take part in the above study. I understand that I will not receive any individual results from the tests undertaken as part of the research. ☐

Optional Procedures

You do not have to agree to all study procedures and we ask you to indicate if you do or do not give your consent to some study procedures here. Please initial one box in each line.

Do you agree to give a blood sample for research?	No	☐	Yes	☐
Do you agree to give a urine sample for research?	No	☐	Yes	☐
I give my consent for spinal fluid collected from me as part of my UCLH clinical care or research participation to be used in this study.	No	☐	Yes	☐
I give my consent for samples collected for this research study to be used for further research where appropriate ethics approval has been obtained.	No	☐	Yes	☐

I consent to having a video/audio recording made of me, I understand that the recordings will be used for:

- Research
- Teaching
- Educational presentations to professionals and members of the public
- Educational websites

No ☐ Yes ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

Appendix D

Interview schedule

1. General information

First it would be good to learn a bit more about you.

- What age are you?

- Do you have any children at the moment?

- Tell me a little bit about who is in your 'network' – partners, family, close friends?

- When they find out about their potential genetic risk of FTD, some people choose to find out what their test results are, and some people choose not to find out. Could I ask which is the case for you?

- Some people talk about their experience with their at-risk status being like a bit of a journey, from not knowing to finding out and then living with it. Could you tell me a bit about your journey with your at-risk status so far?

2. Experiences with relatives with FTD

Sometimes people who are at-risk of frontotemporal dementia will have had some experiences with a relative with frontotemporal dementia. Is that the case for you? (If Yes, continue; if No, proceed to next section). What have your experiences with them been like?

- What sort of changes did you notice in your relative?
- What was your relationship like with your affected relative? Did it change as things progressed?
- Are there any specific events that come to mind?

3. Parenting and Family Planning

<u>For participants who have children:</u>

You mentioned that you have children. What impacts has being at-risk had on your relationship with your children?

- Have you discussed your at-risk status with your partner?
- Have you discussed your at-risk status with your children? If so, tell me a bit about how you decided, and how it went?
- If you haven't discussed it with them, do you think you might in the future?
- What sort of things do you think are different about being a parent when at-risk of FTD?
- Has your relationship with your children changed at all as a result of your at-risk status?
- How does your at-risk status influence decisions you make about how you raise your children?
- Does it impact how you make plans for the future about/with your children?

- Do your experiences with relatives with FTD earlier in life impact how you make decisions about your parenting? How you approach your relationship with your children?

<u>For participants who do not have children:</u>

You mentioned that you don't currently have children. What are your current thoughts about having children in the future?

- Does your at-risk status contribute your thinking about having children or not in the future? In what ways?
- Have you discussed your at-risk status with partners? How was it to do this?
- Do you think your at-risk status might impact what it is like to be a parent? In what ways?
- What sort of things do you think might be different about being a parent when at-risk of FTD?
- Do you think your decision about having/not having children might change?
- Do your experiences with relatives with FTD earlier in life impact your thinking about having children in the future?

4. **Finally, are there any thoughts that you have about any of the topics we have discussed that you would like to share, but haven't had the opportunity to during our interview so far?**