Primary care blood tests: Understanding how we can support GP decision-making for patients presenting with new symptoms of possible cancer.

PhD dissertation

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Declaration

I, Ben Cranfield, 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.

Abstract:

Background:

Appropriately suspecting the diagnosis of cancer is often challenging. Half of all patients subsequently diagnosed with cancer present with non-specific symptoms, and for those patients diagnostic strategies to aid GP decision-making are limited. Recent evidence indicates that common blood tests may have diagnostic utility for predicting cancer, where their diagnostic utility relies on their effective use.

Aim:

The purpose of this PhD is to generate evidence that identifies the correlates of the use of common blood tests for suspected cancer in primary care as a first step in identifying the potential for their optimal use. To facilitate this, the research objectives are to better understand:

- How often common blood tests are used in patients subsequently diagnosed with cancer and how patient characteristics and symptom types predict greater or lower use
- The key factors (other than the clinical presentation per se) that influence blood test use in patients presenting with possible cancer symptoms.

Method:

1. Using a quantitative approach and using data from the National Cancer Diagnosis Audit, I explored variation in common blood test use in English general practice for patients subsequently diagnosed with cancer and examined different patient and clinical factors associated with the diagnostic process. I further explored variation in blood test use by presenting symptoms in a subsequent quantitative analysis of nine primary care blood tests.

2. Using a qualitative approach I explored non-clinical presentation influences on GP's use of blood tests for suspected cancer. Social cognitive theory using the Situativity Perspective Framework guided the development of semi-structured interview schedules to elicit GP perceptions about contextual elements of blood testing. Thematic analysis allowed for an in-depth assessment of the blood testing process, illuminating external barriers to testing that previously have received relatively less attention than those arising during patient and GP interactions.

Results:

Certain patient groups and cancer sites are associated with greater or lower use of blood tests. Symptom categories, and individual presenting symptoms are associated with large variability in general use of blood testing, and that of individual blood tests. The findings indicate both the possible higher than expected use of blood tests in patients with alarm symptoms, and their possible under-use in those presenting with symptoms of lower specificity. A range of contextual barriers other than GPs knowledge in response to specific clinical presentations have been identified as influencing decisions about the use of blood tests, including the organisation of the phlebotomy service and patient expectations for blood tests. There is scepticism among GPs about the usefulness of point-of-care blood tests that are analogues to those currently commonly used.

Implications:

This PhD generated evidence to help translate the promising evidence supporting the diagnostic utility of common blood test use for early cancer diagnosis. The research identifies patient groups in whom blood tests may be underused (and others where over-testing may be occurring); it highlights the importance of optimising the total testing process for blood testing and identifies the need for further research into mitigating barriers to blood test use. Through addressing logistical and practical barriers to blood testing, GPs may be better supported in making greater use of blood tests as a diagnostic strategy for patients who present with non-specific symptoms.

Impact Statement:

The findings contribute to the growing evidence base about the use of blood tests in patients subsequently diagnosed with cancer and our understanding of factors that influence GPs' use of blood tests in cancer populations and related variability in such decisions.

The PhD project has led me to collaborate with experts in early cancer diagnosis research, covering epidemiological, statistical, psychological and implementation science disciplines. Many of these experts were affiliated with the international CanTest Collaboration, connecting researchers in early cancer diagnosis from across three continents. Outside academia, I have benefited from valuable input from researcher-active scientist in government agencies or charity sectors, namely the National Disease Registration Service (currently part of NHS Digital) and Cancer Research UK. These networks may provide future opportunities for information sharing and collaboration.

Publications arising from this Thesis may influence policy (Appendix 1). I presented preliminary findings from Chapter 4 at an international cancer and primary care (Ca-PRI) conference in 2021, prior to publication of a paper relating to this study in the British Journal of General Practice in 2022.

A version of Chapter 5 is being prepared for submission to Cancer Epidemiology. Extending the findings of Chapter 4, this evidence will help provide more symptom-specific and blood test-specific evidence on use. That evidence may influence recommendations within the clinical guidelines for suspected cancer. Preliminary results have been presented during seminars within the Department of Behavioural Science and Health (UCL).

Findings from Chapter 6 are being prepared for submission to the British Journal of General Practice. Preliminary results have been presented during internal department seminars and at the CanTest international school in Cambridge in 2019, online (2021) and Oxford in 2022. The evidence from this research is intended to contribute towards health system level interventions and policy aimed at optimising blood testing in patients presenting with possible cancer symptoms.

Together, the cumulative impact of my research projects advocates for the inclusion of recommendations within clinical guidelines for using common blood tests to support decision-making for suspected cancer (particularly in patients presenting with non-specific symptoms) and highlights the need for future research to explore system-wide barriers to testing. Thompson and Gentile in a recently published accompanying editorial to the paper arising from chapter 4 also make similar helpful points (1)

As alluded at the end of the above paragraph, efforts to amplify the findings have been strengthened the BJGP's Editor commissioning an independent accompanying editorial to the paper arising from Chapter 4 (Cranfield et al, 2020 - *British Journal of General Practice*: https://pubmed.ncbi.nlm.nih.gov/36253112/). This paper is now also cited.

Outside the publication and policy impacts, I have attended many courses/events to advance my professional development (Appendix 2).

Outline

1. Introduction

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5. Frequency of blood test use by symptom presentation

6. Factors influencing GPs decisions to use blood tests

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Abbreviations

National Institute of Health and Care Excellence (NICE)
Point of care test (POCT)
General Practitioner (GP)
National Health Service (NHS)
Long Term Plan (LTP)
Primary care interval (PCI)
Diagnostic interval (DI)
Positive Predictive Value (PPV)
Negative Predictive Value (NPV)
C-Reactive Protein (CRP)
Erythrocyte Sedimentation Rate (ESR)
Plasma Viscosity (PV)
Odds Ratio (OR)
Full Blood Count (FBC)
Urea & Electrolytes (U&E)
Liver Function Test (LFT)
National Audit of Cancer Diagnosis in Primary Care (NACDPC)
National Cancer Diagnosis Audit (NCDA)
Electronic Health Records (EHR)
Interquartile Range (IQR)
Prostate Specific Antigen (PSA)
Carcinoembryonic Antigen (CEA)
Cancer Antigen 125 (CA-125)
Cancer Antigen 19-9 (CA19-9)
Theoretical Domains Framework (TDF)
Wheel of Behavioural Change (WBC)
Total Testing Process (TTP)
Situativity Perspective Framework (SPF)

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Outside my immediate supervisory team, I am thankful for the social and academic support I have received from other CanTest members (particularly Gary Abel), ECHO members (particularly Meena Rafiq) and fellow PhD students. During Covid-19, I was lucky to have such a caring and helpful network whose influence should not be understated.

Finally, thank you to my parents, who may not have fully understood the ins and outs of this PhD, but have always been supportive (in everything I do). Other family and friends have also provided much needed respite during the write up of this Thesis, for which I am very grateful.

Chapter 1: Introduction

1.1 Achieving early cancer diagnosis – How important is it?

In the United Kingdom (UK), half of the population are expected to be affected by cancer in their lifetime (2). Around 1000 new cancer patients are diagnosed with cancer daily, representing a cancer incidence that is ranked higher than 90% of countries of the world (3). Projections suggest an increasing number of cancer cases and deaths as a consequence of both population growth and ageing (4).

Earlier diagnosis is now an important aspect of modern day cancer prevention strategies, yet the notion is nearly a century old. Dr George N. Papanicolaou first discovered correlations between cervical smear cytology with abnormal cells from women with endocrine and genitourinary disease (1923/1924; (5,6), later presenting the findings as an opportunity for earlier cervical cancer screening (1928; (7). Although the finding was met with scepticism, the concept of early detection of cancer began to ripple throughout academic literature. In MEDLINE, one of the earliest editions featured an article published in the Canadian Medical Association Journal describing early diagnosis as chief to treatment and radiotherapy:

"…We must still, perforce, rely upon already existing clinical knowledge – diagnosis, operation, irradiation – the indispensable triad. Of these three the greatest is, "diagnosis"; but this is only fully effective when it is early."

– AG Nicholls, editor of the Canadian Medical Association Journal, writing in the November issue of the journal in 1933

The growing awareness of earlier diagnosis as a solution for preventing cancer mortality is embedded into the conception of primary care cancer initiatives today. The National Health Service (NHS) published their Long-Term Plan (LTP) in January 2019, which outlines their ambitions for improving cancer outcomes and services in England over the following 10 year period (8). Earlier diagnosis underpins the LTPs desire for improving survival rates, aiming to have three in four cancers diagnosed at an early stage by 2028. Shortly after the LTP publication, European guidelines were published that highlighted the need for more evidence pertaining to primary care-led cancer care (9).

Earlier detection is assumed to benefit patient prognosis, as research indicates an association between prolonged times to diagnosis and worse clinical outcomes (10–12). Furthermore,

timely diagnosis of cancer is cost-saving for the health sector as delayed diagnosis contributes considerably to NHS cancer treatment costs (13). For the public and policymakers, timely diagnosis is a priority with primary care being the preferred setting for this to take place given that before their diagnosis the majority of cancer patients present to a general practitioner with symptoms caused by their cancer (14).

1.2 What is the evidence for achieving timely diagnosis of cancer?

1.2.1 Theoretical Frameworks

Early diagnosis of symptomatic cancer is vital for achieving better outcomes (15). Our recognition of the benefits of earlier detection is well founded, yet only more recent theoretical concepts helped researchers to better appreciate diagnostic timeliness. Previous literature has described the events and processes of the diagnostic pathway for symptomatic patients (16), leading to the development of subsequent guidelines about the design and reporting of research studies in this field (the Aarhus Statement). The Aarhus Statement was conceptualised by Weller and Colleagues in 2012 to provide guidance for early cancer diagnosis researchers (17). This marked a significant step in aiding the reporting and conduct of research in this field, as consensus was reached for a standardised list of definitions and methodologies to improve the interpretation of early cancer diagnosis research. The Aarhus Statement was originally supported by primary research in Denmark categorising delay throughout the clinical pathway and illustrating key time intervals from first symptom presentation to the start of treatment (See Figure 1; (16,18).

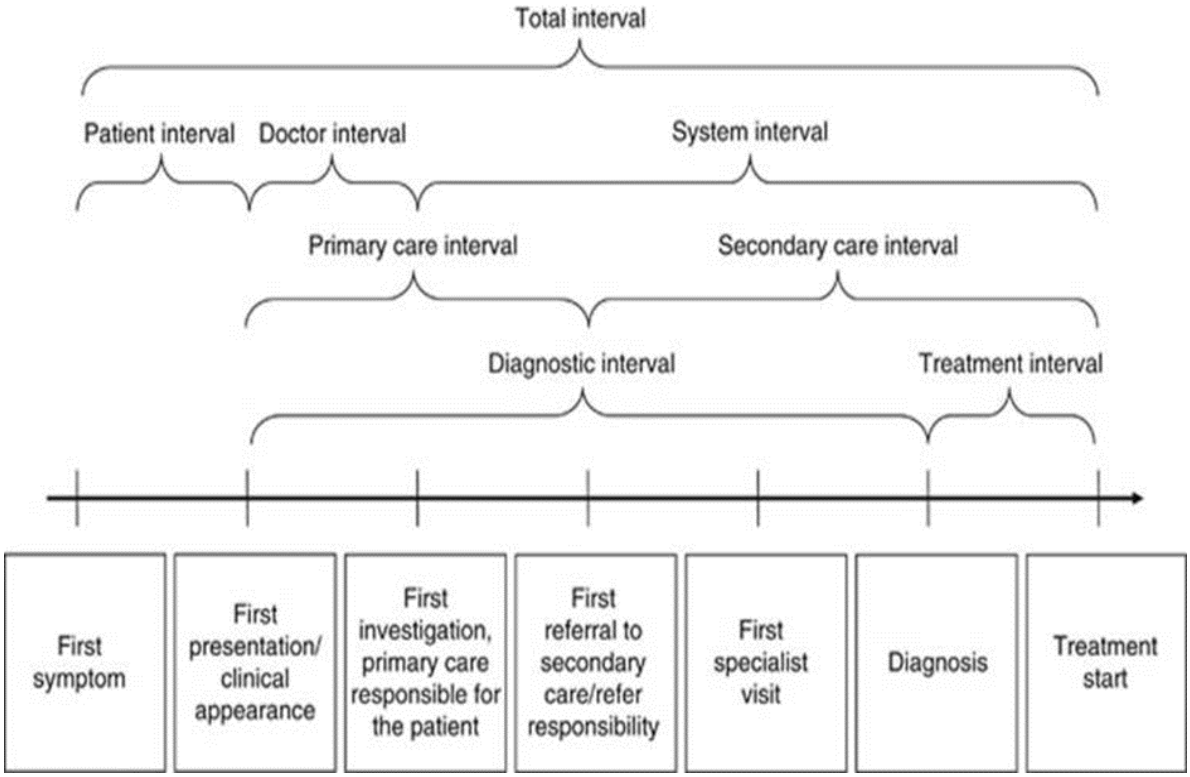


Figure 1: Time intervals from first symptom presentation to the start of treatment (The Aarhus Statement) (17).

Key events on the pathway comprise the first presentation of a patient with symptoms to a healthcare professional, the first investigations and the first possibility to refer occur during the primary care interval (PCI). The PCI is considered a key interval by the Aarhus Statement and is the focal aspect of the diagnostic process that this Thesis is concerned with.

Early cancer diagnosis frameworks can benefit from theory across other disciplines describing diagnostic process delays. A landmark report published in the National Academies of Sciences (2015) highlights opportunities for reducing diagnostic error (19). Importantly, the repercussions of diagnostic errors were considered to lead to inaccurate and untimely explanation of health problems to patients. The below conceptual model (see figure 2) was developed to better understand the complexity of the diagnostic process within the working healthcare system, and to identify opportunities for reducing diagnostic error (improving the diagnostic process). While this framework is not cancer-specific, diagnostic error is not isolated to any disease and therefore the model usefully translates into the early cancer diagnosis arena.

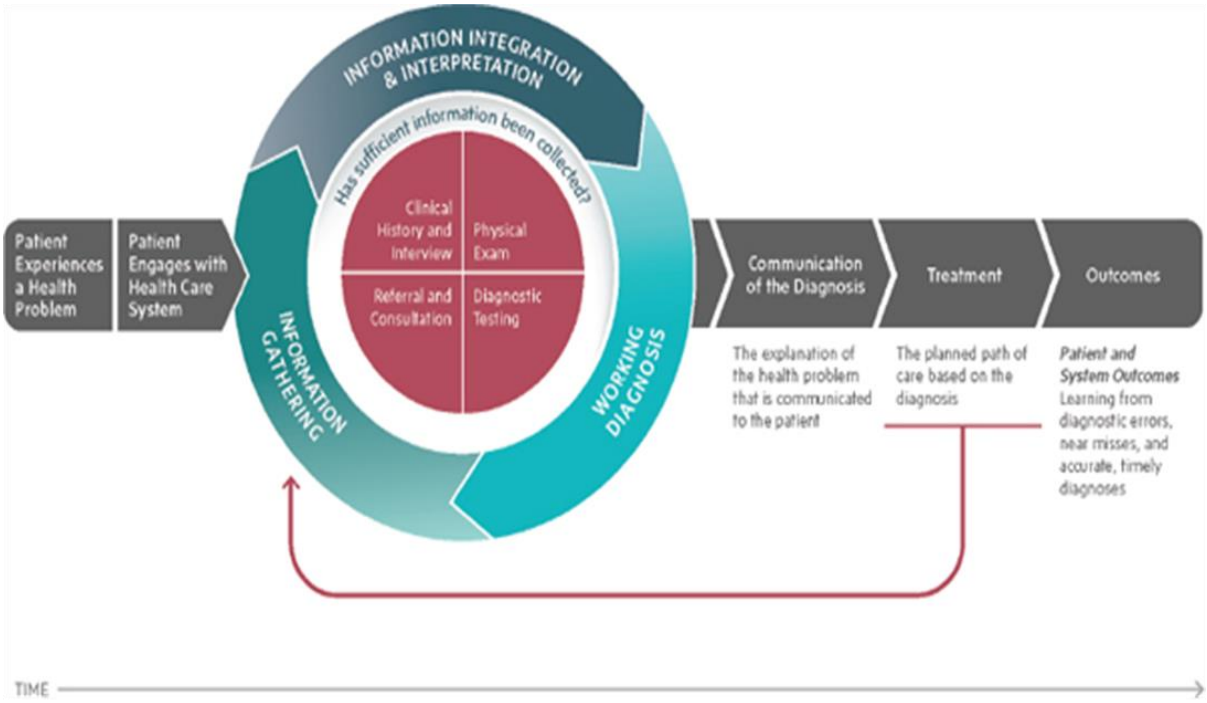
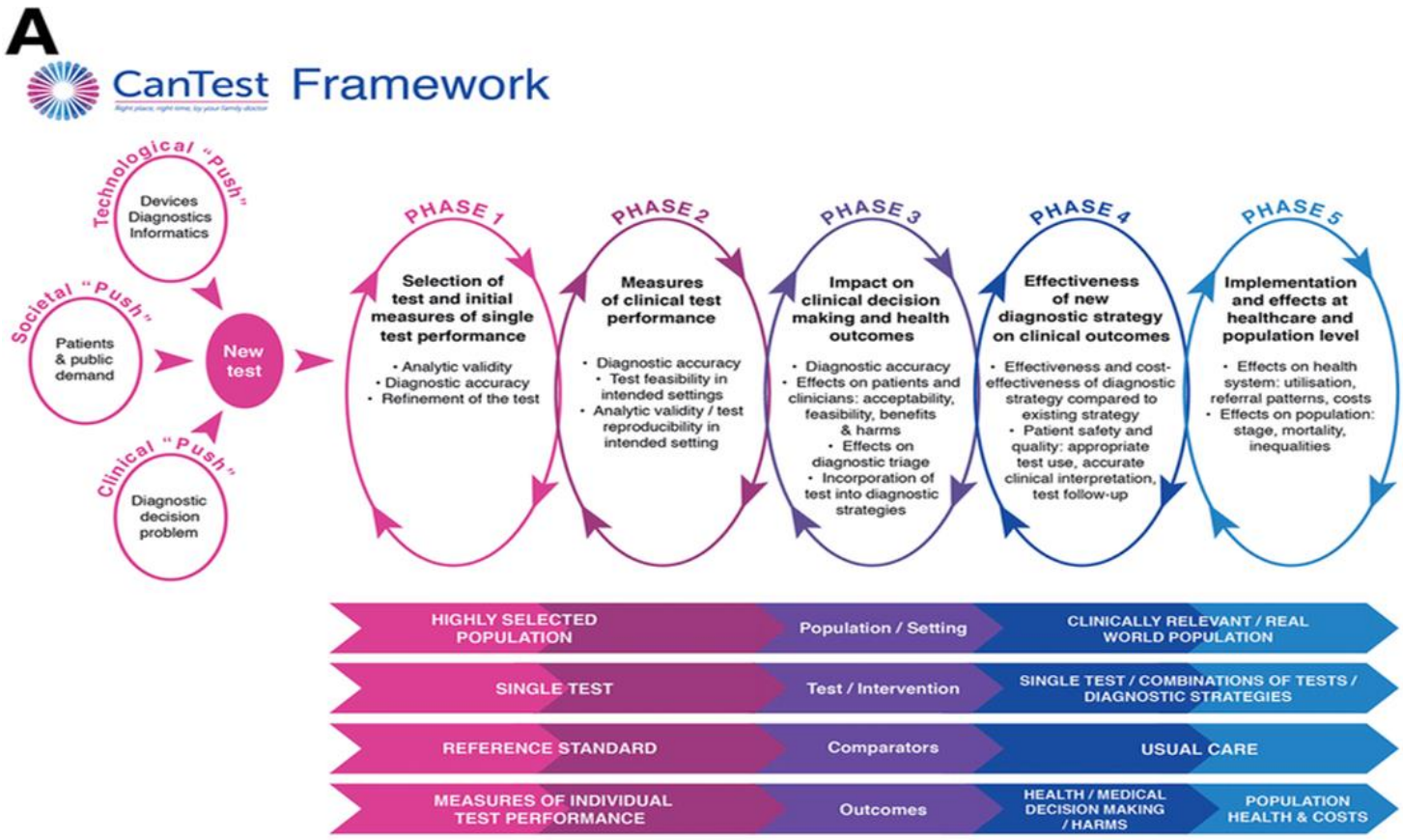


Figure 2: Conceptual model of diagnosis process (opportunities for reducing diagnostic errors) (19)

A consequence of diagnostic error is overdiagnosis. In the context of cancer, some diagnoses may be considered serendipitous to the presenting symptoms (20,21), leading to possible overdiagnosis in seemingly asymptomatic cancers with protracted lead-times (22,23). Overdiagnosis may also be contributing to growing cancer incidence rates in the UK, partly as a result of early cancer diagnosis initiatives advancing the detection of progressive cancers (increasing the likelihood of death from other causes; (14,24). Acknowledging overdiagnosis, the CanTest Framework provides an important conceptualisation for how to evaluate diagnostic tests for early cancer diagnosis in primary care (see figure below; (25).



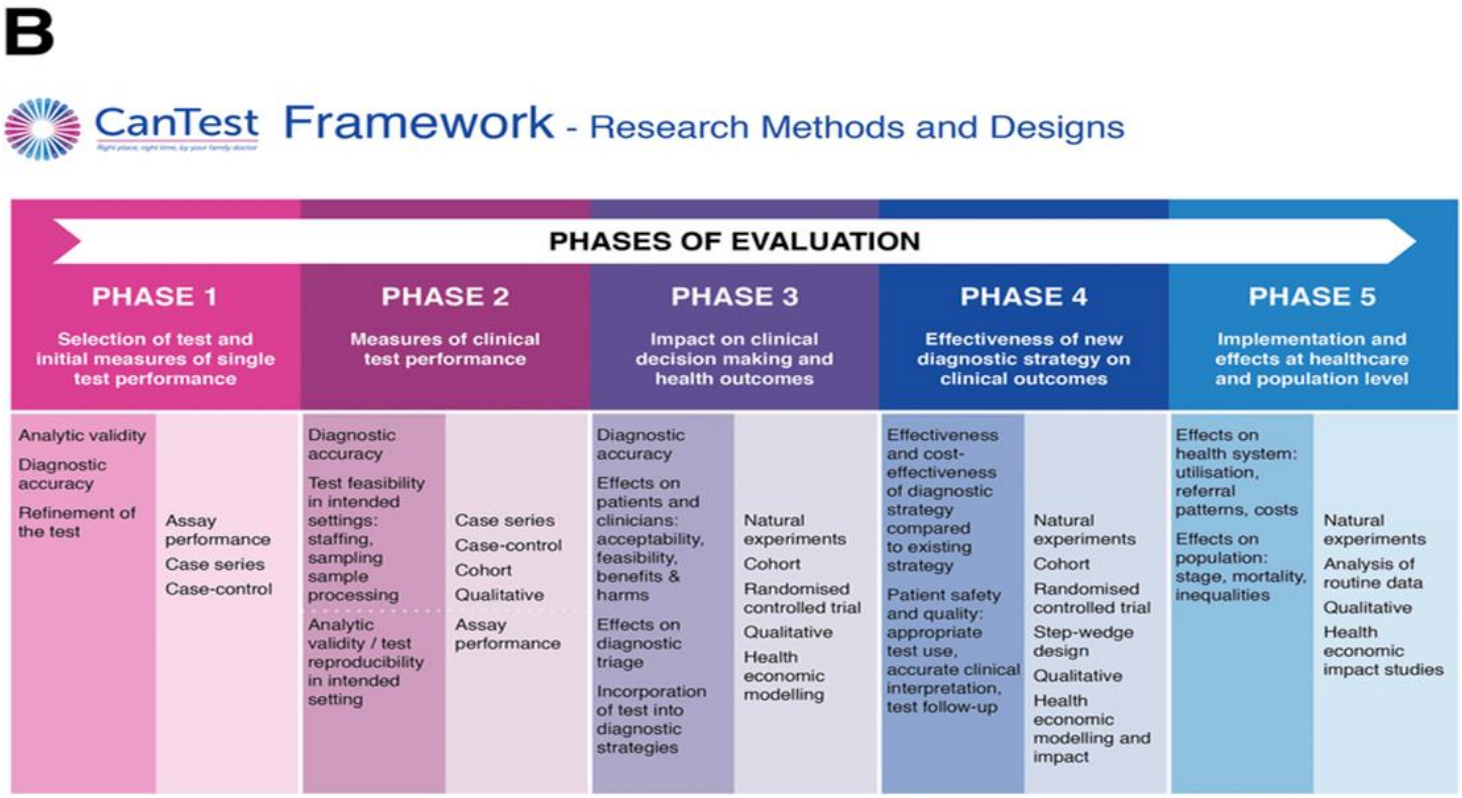


Figure 3: CanTest Framework comprising A). CanTest Framework, B). Research Methods and Design (25).

Collating evidence from 16 frameworks, the CanTest framework illustrates a translational pathway for new tests that progress from single test evaluations (in selected populations with high cancer incidence) to comparative assessments of implementation in the real-world (in clinically relevant populations with lower cancer incidence). The implications of this framework for cancer diagnostic tests are yet to be demonstrated, although it would have obvious utility for potentially relevant innovating cancer screening tests where the potential impact on the population is not fully understood (such as multicancer screening blood tests including the CancerSEEK assay (26), the Galleri test (27) and the PanSeer assay (28). Quantitative frameworks have already been proposed for assessing the harms and benefits of these novel diagnostics (29), although important behavioural factors that influence testing decisions are omitted (which phase 3 of the CanTest Framework would be more likely to address).

1.3 Current evidence for achieving timely diagnosis

Reported cancer survival rates in England compare poorly to other European countries, advocating a need for more timely diagnosis (30). After taking into account that some patients with poor prognosis will have short diagnostic intervals, an association can be observed between the length of interval from first symptomatic presentation to a health care professional to when they receive a diagnosis (the diagnostic interval - DI) and decreasing survival due to tumour growth over time (12). Given that nine in ten patients first present their symptoms to a GP, it is likely that the PCI contributes to the length of the DI. The median PCI for patients diagnosed with cancer during 2014 in England was 5 days, indicating prompt referral for the average patient (31). However, an important minority had a PCI longer than 90 days (8%). The relative length of the PCI varies by cancer site, as different cancers have different proportions of patients presenting with symptoms of low predictive value that make diagnostic suspicion harder and can prolong the interval (32,33). Further research is warranted to explore potential solutions to reduce intervals to diagnosis particularly in patients with non-specific symptoms and for cancers whose symptom signature is dominated by such symptoms.

1.4 Suspecting Cancer in Primary Care

Appropriately suspecting cancer in primary care is challenging. The implementation of national cancer strategies designed to tackle this issue have helped encourage earlier diagnosis for patients who present symptomatically to their GP (34). However, half of patients subsequently diagnosed with cancer present with symptoms of low specificity (35). The implementation of NICE NG12 recommendations is successful in facilitating "fast-track" referrals (shortening the DI for patients presenting with more predictable symptoms; (36,37), but do not support the triaging process for the many patients presenting with symptoms of low predictive value. Instead, cancer patients who present with non-specific symptoms experience prolonged diagnostic intervals arising from increased pre-referral activity (37). Despite the advent of multidisciplinary diagnostic centres (MDC) to aid the investigation of patients who present with non-specific symptoms, these services are not extensively available in England (with evaluations ongoing and population wide delivery of MDCs expected in 2024; (38). Findings from early pilot studies suggest MDCs offer GPs a pathway to streamline diagnosis in patients presenting with non-specific cancer symptoms in the UK (39). Evidence from MDCs in Denmark suggest that 60% of referred patients present with at least one focal symptom, including some alarm symptoms (40). MDC referred patients therefore appear to include a population at relatively high risk of cancer that is unlikely to be reflected by clinical intuition alone (41,42), but also well-utilised pre-referral investigations.

Decision-support tools have been introduced into primary care health record systems to help GPs to risk stratify patients with suspected cancer, including those presenting with vague symptoms (43–46) Although decision-support tools are an important part of the triaging function, they are limited to providing clinical recommendations and cannot provide confirmation of potential illness.

A potentially useful, yet under-utilised diagnostic test for early cancer investigation are blood tests. Blood tests are frequently used in primary care to aid the diagnosis of multiple conditions and evidence indicates their predictive value can extend to several cancers (47); although they are associated with later referrals for specialist assessments and prolonged PCIs due to additional consultations (48,49). The objective of this Thesis is to determine the value of blood tests as an early diagnostic strategy for aiding GP decision-making in patients

presenting with vague symptoms of possible cancer and explore opportunities to optimise their use for cancer investigations in primary care.

1.5 Summary

The perceived importance of early cancer diagnosis is widely understood. Most patients first present symptoms to their GP, signifying the first possible opportunity for diagnostic intervention. Current diagnostic pathways support decision-making for half of patients who present symptomatically to their GP, yet the other half of patients who present with non-specific symptoms do not benefit from these pathways. Some blood tests have predictive value for several cancers if appropriately used. Therefore, interventions designed to optimise the use of blood tests might facilitate earlier diagnosis for patients who are subsequently diagnosed with cancer.

Chapter 2: Common Blood Tests and Cancer: Current perspectives, evidence and frameworks determining their use.

In this Chapter, I overview subjects that provide a motivating conceptual framework for my empirical enquiry of use of blood tests in patients with symptoms of possible cancer. This includes the balance between over- and under-testing, the recently evolved evidence-base about the diagnostic utility of common blood tests for assessing the risk of underlying cancer, current clinical guideline recommendations with regard to blood test use, the Situativity Perspective Framework, and Point-of-Care-Tests and their potential role.

2.1 The use of Blood tests in Primary Care.

Up to 80% of health care decisions affecting diagnosis or treatment are influenced by blood test results (50). Blood tests can be very clinically informative, and their use in UK primary care is increasing (51,52). Most GPs in England have direct access to commonly ordered blood tests (53). However, reports of substantial geographical variation in pathology testing may contradict such findings and indicate that some tests may be either over- or under-used in at least some parts of the country (54,55). The difference in test use represents a financial concern (reported NHS expenditure on laboratory tests between 2015 to 2016 of £1.8 billion reflected a large economic deficit; (52,56,57).

2.1.1 Campaigns and events influencing primary care blood test use

Previously recognised potential for overuse of diagnostic tests has prompted interventions over the past 20 years to minimise the risks of overdiagnosis (see figure 4 & 5). Since the NICE guidelines was established in 1999, more than 800 recommendations for divestment of healthcare interventions have been published to help tackle overuse (58). Initiatives including the "Too Much Medicine" movement increased awareness of overdiagnosis arising from uncritical testing (2002; (59,60). A quality improvement framework (quality of outcomes: QOF) was embedded into primary care in 2004 as a payment scheme, which in part supported GPs' use of blood tests for monitoring chronic conditions (61). A year later, NICE updated their guidelines on suspected cancer recommendations (2005). A decade later (2015), the Choosing Wisely campaign was endorsed by the NHS with the aim of addressing the overuse of medical interventions by prompting organisations to question the necessity of commonly used procedures; (62,63).

Potential harms of overdiagnosis associated with labelling of benign conditions as in-situ cancer and the overuse and underuse of diagnostic tests in primary care continued to be

reported in the following years (64,65). The NHS further recognised unwarranted variation in testing rates as a potential source of morally inappropriate healthcare (66), giving rise to the NHS "RightCare" initiative to improve outcomes for patients (67). The RightCare approach has been integrated into NHS England to maximise value and minimise waste, generating diagnostic testing models including the Clean Framework (conceived 2019; (68) - an initiative for reducing inappropriate pathology testing. The Clean Framework was embedded into a national NHS report for improving pathology services in England (69) and published within the "Getting it right first time" (GIRFT) program.

Furthermore, the outbreak of covid-19 in the UK (2020) and associated restrictions on social distancing (and access to healthcare) may have influenced the use of blood tests in patients presenting in primary care.

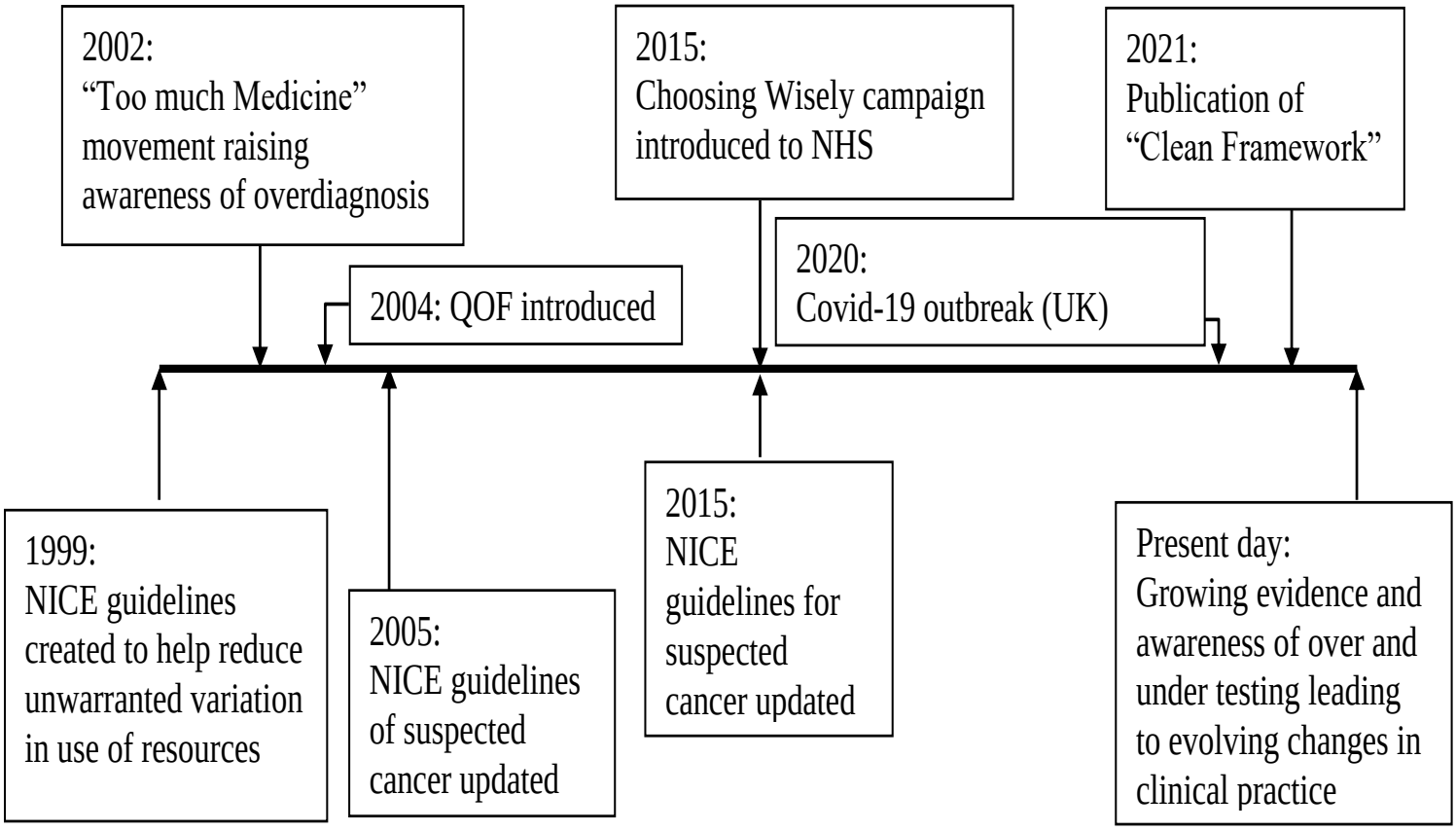


Figure 4: Timeline showing overlap of relevant campaigns and events.

Figure 5: Examples of initiatives that support optimal use of primary care blood tests: A). Too Much Medicine, B). Choosing Wisely, C). NHS Right Care, D). Getting It Right First Time.

2.1.2 Strategies for tackling inappropriate primary care blood testing

The above initiatives influence how blood tests are used in patients who present with possible cancer symptoms and for the conceptualisation of interventions for tackling both over and underuse. Critical to the development of interventions is an understanding of the drivers and consequences of unwarranted test use. Growing use of primary care blood tests in England may raise concerns about overtesting, where around 2 in 5 initially ordered laboratory tests trigger diagnostic investigation cascades leading to overuse (70). The downstream implications of such testing for patients includes increased anxiety, higher risk of false positive results and iatrogenic harm from subsequent investigations (71–74). Overtesting can also result from clinicians safeguarding against medicolegal litigation associated with undertesting (75). On the other hand the consequences of undertesting are well published, including higher risk of delayed or missed diagnosis and ineffective subsequent treatments, leading to worse patient outcomes (76,77).

Inappropriate testing can arise from increased workloads and time constraints, and the challenge GPs face with keeping themselves up-to-date with new evidence (78–80). NICE

guidelines (1999) aimed to address unwarranted variation associated with sub-optimal testing, including possible underuse of blood tests where the average use in UK primary care was lower than other European countries (Mean: 5.1% vs 15.5% in Switzerland between 1989-1991; (81). Laboratory test use steadily increased after the NICE guidelines were introduced from 13091 tests per 10000 person years in 2000/2001 to 44847 tests in 2015/2016 (52,55). It is prudent to acknowledge that A.) increased test use may also reflect general population growth and subsequent increased primary care use, and B.) variation in test use would be different by disease state (general population test use may vary from suspected cancer populations). Nevertheless, the risk of inappropriate testing necessitates interventions to improve care.

Evaluated interventions for addressing inappropriate test use include educational strategies (82–84), cost displays (85), changing order forms (86) and exploring different methods of communicating guidelines to test users (87,88). These interventions have provided short-term positive effects for reducing test use, with behaviour change techniques being suggested to provide lasting effects on clinician's test ordering behaviour (89,90).

The range of available options for clinical management can influence decision-making (i.e. the choice architecture;(91,92), as previously highlighted by changes in test ordering frequencies as a result of modified ordering forms (86). Following this principle, the above stated strategies relating to cost displays, ordering forms and guideline communication methods could be reverse-engineered to reduce underuse of blood tests. There is evidence to suggest that changing the format of test ordering forms can increase test use (93). Such strategies could be targeted to reduce delayed, missed or incorrect diagnoses and subsequent treatments associated with underuse of tests (94). Furthermore, strategies to increase blood test use may present a diagnostic strategy for GPs to aid decision-making for patients who present with symptoms of possible cancer in primary care.

2.2 Blood tests for cancer – evidence for commonly used tests.

2.2.1 Evidence supporting predictiveness: The diagnostic utility of blood tests

In primary care, a small number of cancer-specific blood tests (biomarker tests) are available. However, they are considered to have limited usefulness for diagnosing patients who present with non-specific symptoms (95). After the publication of the 2015 NICE guidelines for suspected cancer, evidence has emerged supporting the utility of information arising from routinely used blood tests in patients with possible cancer symptoms (see Table 1). The usefulness of these tests for suspecting cancer largely depends on their predictive value, which is often denoted by their ability to rule in (positive predictive value - PPV) or rule out (negative predictive value - NPV) disease. The NICE guidelines use these metrics when developing clinical recommendations for suspected cancer to assess the risk of cancer and aid subsequent decision-making. A PPV $\geq$3% was adopted by NICE as the threshold for urgent cancer referral, whilst a PPV from 1-3% should instigate further primary care-based investigations (96). If only symptoms with low PPV are present (i.e. <1% PPV), the patient will not be referred. However, there are several common blood tests that that if combined with presenting features they can confer predictive values that can select patients at higher risk (47).

In Denmark, a cohort study assessed the use of routine blood tests and the probability of cancer in patients referred with non-specific symptoms and found the risk of cancer increased with a growing number of abnormal blood tests (ranging between 23-62%; (97). Less generic blood test results including high human chorionic gonadotropin (hCG), M protein and cancer antigen 125 (CA-125) appeared to be more predictive of cancer (with the probability of cancer after testing, so-termed “post-test probability”, being 44.4%, 37.4% & 36.8%, respectively), with many abnormal results from less-specific blood tests indicating post-test probabilities of a positive test of over 25% (including low platelet count, low immunoglobin A, high bilirubin, high calcium, high metamyelocyte count, high alkaline phosphatase and high neutrophil count). In general, however, a single abnormal blood test result has limited diagnostic value (in the absence of symptom information). Further evidence from Denmark highlighted the use of inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as a strategy for predicting cancer in patients subsequently referred to outpatient clinics after presenting with non-specific symptoms (98). After adjusting for age and sex, the odds

ratio (OR) for cancer with raised CRP was 1.41. This association has also been identified in UK primary care populations (99). Incorporating data from over 150,000 primary care patients who had a CRP, ESR or plasma viscosity (PV) inflammatory marker test, Watson and Colleagues identified that raised inflammatory markers are associated with one-year cancer incidence that exceeds the NICE threshold for urgent investigation (i.e. >3%). Inflammatory marker tests are not incorporated within current guidelines for cancer diagnosis, except for suspected multiple myeloma (96). Suspected myeloma patients characteristically present with non-specific symptoms such as musculoskeletal pain and back pain and are associated with many pre-referral consultations and the longest diagnostic intervals among common cancers (33,37). Symptoms often need to be combined with abnormal test results to reach the threshold for referral. Recent evidence demonstrates that combining full blood counts (FBC), ESR, or PV and calcium in certain cases can identify patients with underlying cancer (100).

Several components of FBC tests can also aid cancer prediction. Anaemia (i.e. low haemoglobin) is a well-established feature of colorectal cancer (101). Evidence on risk thresholds for colorectal cancer with anaemia by age, sex and haemoglobin levels, have guided guideline production (102). Another feature of possible cancer is raised platelet counts (thrombocytosis), with short-term cancer risk in UK adults with thrombocytosis exceeding 3% (103). Two-thirds of patients presenting with thrombocytosis had other relevant symptoms of lung cancer, which may prompt GPs to assess platelet counts to confirm their suspicions. Abnormally large or small red blood cells (macrocytosis and microcytosis) measured using FBC can also be associated with possible malignancy in some primary care populations (100,104).

Table 1: Summary of evidence supporting risk stratification using blood markers for cancer.

Type of blood test	Blood test result(s)	Patient group	Risk estimation value	Cancer-site	Reference
Inflammatory markers	Raised inflammatory markers (C-reactive protein - CRP, erythrocyte sedimentation rate – ESR, and plasma viscosity - PV)	Adults	3.53% PPV (one-year cancer incidence)	All cancer-sites	Watson et al., 2019 (99)
Inflammatory markers and FBC	Normal inflammatory markers (ESR and PV) and FBC (haemoglobin - Hb)	Adults (>40 years old)	Normal Hb and PV = 0.12 (negative likelihood ratio – LR-)	Multiple Myeloma	Koshiaris et al., 2018 (100)
Platelets	Thrombocytosis	Adults (>40 years old)	11.6% PPV in males and 6.2% PPV in females (one-year cancer incidence) compared to normal platelet counts	22 common cancer-sites	Bailey et al., 2017 (103)
28 different blood tests	Abnormal results (i.e. high or low levels)	Patients with non-specific symptoms	Probability of cancer with 6-8 abnormal results = 25.5%, and ≥9 abnormal results = 35.4% 25/28 blood tests had estimated LR for cancer above 1.0 when abnormal (post-test probabilities ranging from 13.4-44.4%) Combinations of two abnormal results resulted in twofold increased probability of cancer.	≥15 cancer types	Naeser et al., 2017 (97)
Inflammatory markers	CRP and soluble urokinase plasminogen activator receptor (suPAR)	Patients with non-specific symptoms	Combination of CRP and suPAR blood tests (also accounting for age, sex and previous cancer) had associated NPV of 93.4%, sensitivity of 80.6% and specificity of 72.8% for	Any cancer	Rasmussen et al., 2017 (98)

			cancer (incident cancer within one-year)		
Full blood count	Haemoglobin (anaemia)	Men over 60 and women	For men over 60 years with a haemoglobin <11 g dl-1 and features of iron deficiency, the PPV was 13.3% (9.7, 18) For women with a haemoglobin <10 g dl-1 and iron deficiency, the PPV was 7.7% (5.7, 11)	Colorectal cancer	Hamilton et al., 2008 (102)
Full blood count	Mean corpuscular volume - MCV (assessing for microcytosis)	Patients aged ≥40	Overall 1-year cancer incidence in those patients with microcytosis was 4.0% compared with 2.0% in those with a normal MCV	13 cancer-sites	Hopkins et al., 2020 (104)
Cancer biomarker	CA125	Women with symptoms of possible ovarian cancer who had CA125 tests	Risk threshold models for ovarian cancer (accounting for age and CA125 level, split into ≥1%, ≥2% & ≥3% thresholds) with equivalent sensitivities to CA125 cut-offs (at ≥23, ≥35 & ≥39 U/mL) estimated higher specificities and PPVs compared to each CA125 cut-off, supporting risk-based triaging for possible ovarian cancer.	Ovarian	Funston et al., 2021 (105)
Inflammatory markers	CRP, albumin, lymphocyte count (LC), neutrophil count (NC) and platelet count.	Patients ≥18 years old with unexpected weight loss	Combinations of CRP & albumin, neutrophil & lymphocyte and platelet & lymphocyte had PPVs above 3% for all age groups (≥18, 40-59, 60-79, 80+). Although typically lower than combined scores, individual inflammatory	Any cancer	Nicholson et al., 2021 (106)

			markers had PPVs above 3% for most age groups.		
Cancer biomarker	CA125	Women receiving a CA125	For all ages, CA125 had PPV and specificity of 10.1% and 93.8% for ovarian cancer, respectively. In women <50 years old, CA125 had PPV and specificity of 3.4% and 92.7% for ovarian cancer, respectively. In women ≥50 years old, CA125 had PPV and specificity of 15.2% and 94.5% for ovarian cancer, respectively.	Ovarian	Funston et al., 2020 (107)

2.2.2 Window of opportunity: Earlier blood testing for supporting diagnostic timeliness?

The above evidence highlights the diagnostic utility of blood tests for early cancer detection, yet understanding opportunities for implementing this promising evidence to achieve timely cancer diagnosis is important. Exploring the pre-diagnostic period in patients diagnosed with bladder and renal cancer, recent evidence suggests that abnormal results from both common and less generic blood tests start from 6-8 months before diagnosis (108). Many of these tests were used in the earlier half of the diagnostic window, indicating missed opportunities to optimise blood test use to expedite subsequent renal or bladder cancer diagnosis. Earlier diagnosis of ovarian cancer in symptomatic women can also be achieved through CA-125 testing in women presenting with symptoms that raise diagnostic suspicion (105). In patients diagnosed with Hodgkin lymphoma, inflammatory marker requests in primary care and inflammatory marker levels in patients increase in the year preceding the diagnosis, indicating that earlier diagnosis might have been possible (109). Evidence of increasing rates of blood test abnormalities (including low haemoglobin, high platelet counts and high inflammatory markers) in symptomatic patients in the year before diagnosis of colorectal cancer suggest earlier diagnostic opportunities (110).

2.2.3 Is evidence for blood tests captured within the 2015 NICE suspected cancer guidelines?

For many common and rarer cancer populations, earlier blood testing may present diagnostic benefits. However, translating this evidence into practice is challenging (78,111). Therefore, ensuring this growing evidence-base that supports blood test use is incorporated into clinical guidelines is important as it may help GPs use blood tests for suspected cancer. However, much of the emergent evidence arrived subsequently to the publication of the most recent review update by NICE (2015). The majority of recommendations are based on the presence or absence of a presenting symptom or symptoms (79%). Most of the recommendations mandate referral (115 recommendations, or 53% of total) rather than investigation (94 recommendations, or 44% of total), while few recommend both (7, or 3% - Table 1).

***Table 2**: Characterising the NICE 2015 Guideline [NG12] Recommendations for Suspected Cancer*

	Presenting Symptom	Abnormal Test Result	Both alarm symptom and Abnormal result	Total
Recommendations for urgent referral:	85 (39%)	12 (6%)	18 (8%)	**115 (53%)**
Recommendations for investigation:	80 (37%)	1 (<1%)	13 (6%)	**94 (44%)**
Of which involve blood tests:	*32 (15%)*	*0 (0%)*	*2 (1%)*	***34 (16%)***
Recommendations for Investigation and referral:	5 (2%)	2 (1%)	0 (0%)	**7 (3%)**
Total:	**170 (79%)**	**15 (7%)**	**31 (14%)**	**216 Recommendations**

**Percentages (%) are based on the total number of NICE Guidelines recommendations for suspected cancer (Total: 216).*

Currently, only around one in ten NICE guideline recommendations for referral or investigation of suspected cancer endorse a blood test (96). If the promising evidence supporting the use of blood tests for cancer investigations are to be incorporated into clinical guidelines, aspects of their implementation concerning the patient, the GP and the healthcare system need considering.

2.3 Translation of blood tests for cancer – Situativity Perspective (Diagnosis "in the real world")

Given the limited input of blood tests within the clinical guidelines, understanding how blood tests are used by GPs requires an in-depth appreciation of clinical reasoning. GPs decisions to use a blood test may be triggered by symptomatic presentation, however many other motives for testing may be related to situational and contextual factors of the diagnostic process (112).

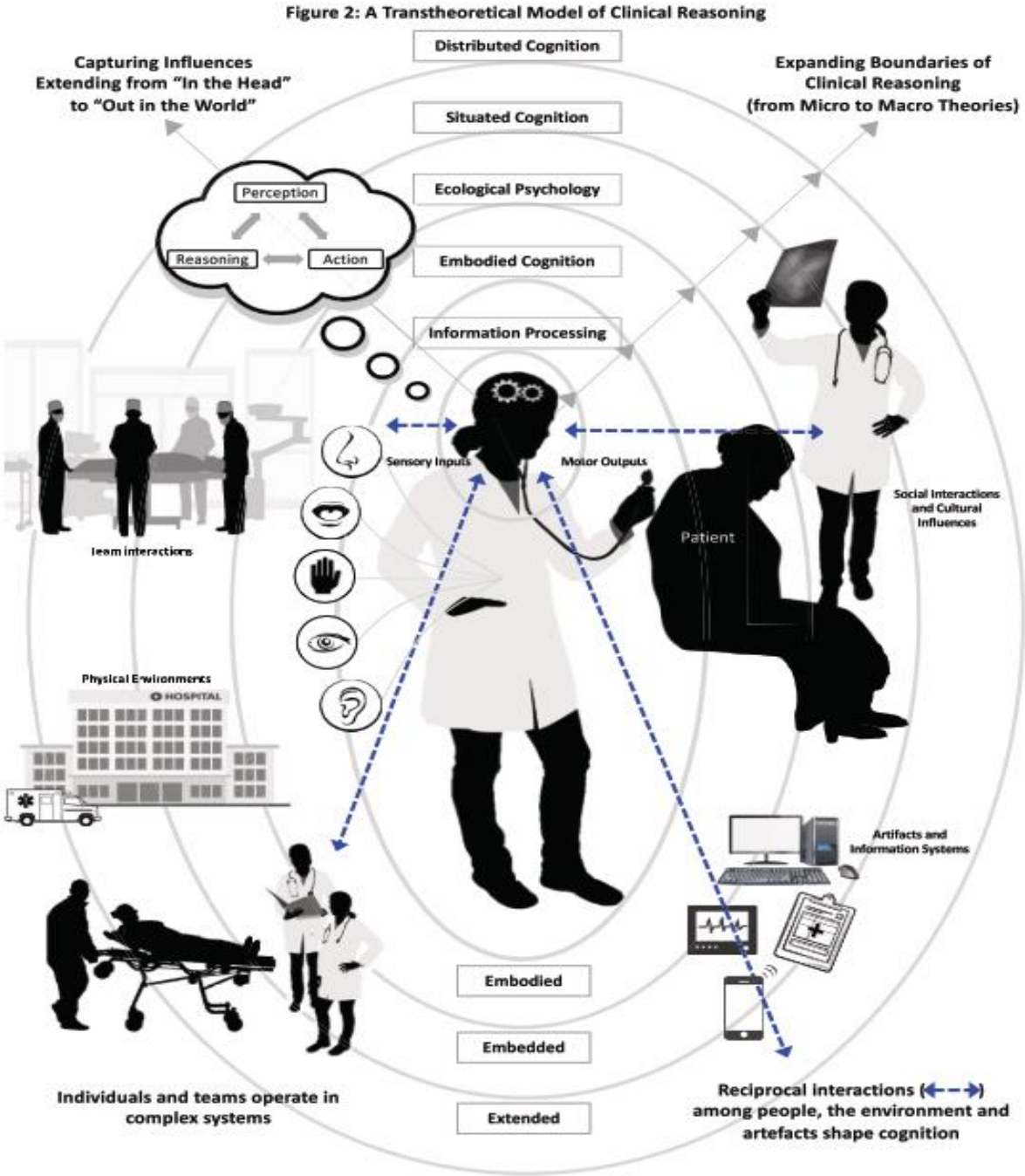


Figure 6: Situativity Perspective Framework - Illustrating the complexity of diagnostic clinical reasoning. (113)

Clinical reasoning becomes more challenging when patients present with non-alarm symptoms (i.e. decision-making is less intuitive). The social and contextual aspects of the diagnostic process therefore start to have more influence on GPs thought processes. The Situativity Perspective (which posits that diagnosis is a social and situated process and describes decision-making in terms of embodied, embedded and extended interactions) enables us to understand how the GP is influenced by different aspects of the diagnostic process during clinical reasoning (see Chapter 6; section 6.1.3, for further details). Decisions to perform blood tests are typically made by the GP during the consultation, however these decisions may be influenced by factors extending to the entire testing process (Figure 6: Adapted version of Situativity Perspective for blood testing process).

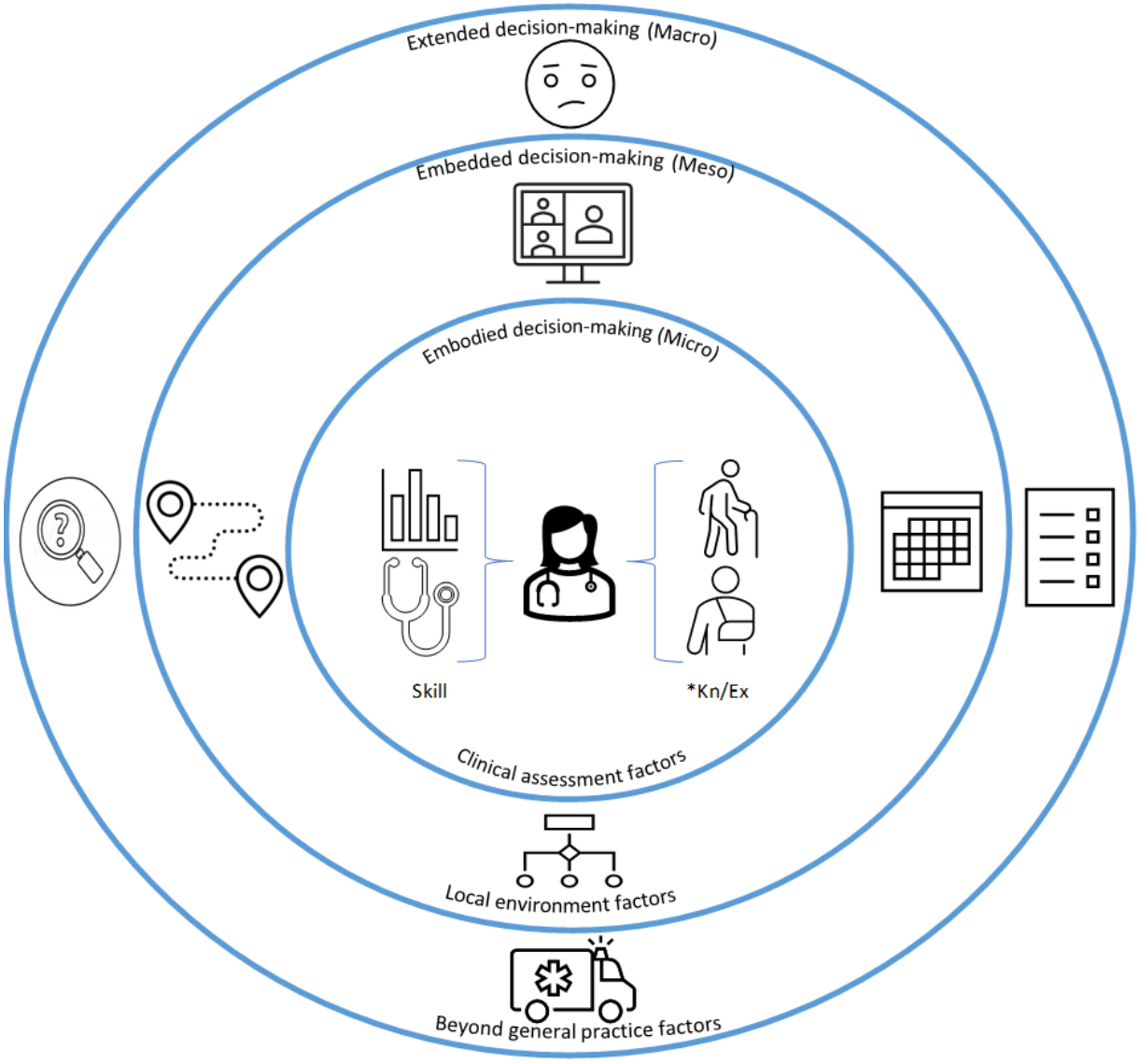


Figure 7: Situativity Perspective - related to primary care blood testing.

Embodied decision-making to use a blood test is likely to start during the GPs clinical assessment of the patient. The GP uses their clinical knowledge and experience (Kn/Ex) to assess the patient, while also using their investigative skills to gather more information (interacting with available diagnostic tools and interpreting information from the medical records). Patient factors including their presenting symptoms, their demographics and history of prior comorbidities will further influence the assessment. Embedded decision-making to use a blood test is influenced by factors within the local environment such as phlebotomy access/availability, the modality of consultations (face-face/online) and workflows within the practice. Extended decision-making accounts for factors that exist outside the clinical practice context, including patients demanding blood tests, courier service arrangements, concerns about overdiagnosis and clinical guidelines.

The situativity perspective helps to illustrate the complexity of decisions to use blood tests, partly derived from a convoluted phlebotomy process. The scope for error during the complex processes involved in blood testing (and therefore risk for worse patient outcomes) need considering.

2.4 Total Testing Process for Blood testing (Is it unnecessarily complex?)

Timely cancer diagnosis may depend on efficient blood testing, yet their use in primary care involves a complex multistep process from test ordering to communication of results and, where needed, follow-up actions. Effective test ordering partly depends on practice resources, where those patients registered to a practice with an on-site phlebotomist or with availability to same day blood tests have greater opportunities to expedite sample dispatch to a laboratory. At the laboratory, a process of sample identification, analysis and subsequent result communication occurs. Successful laboratory operations primarily rely on accurate analytical tests, but effective logistical and administration processes are necessary to ensure timely result feedback to primary care. Once blood test results are successfully received back in primary care, the GP interprets the clinical implications of the results and attempts to communicate this with the patient.

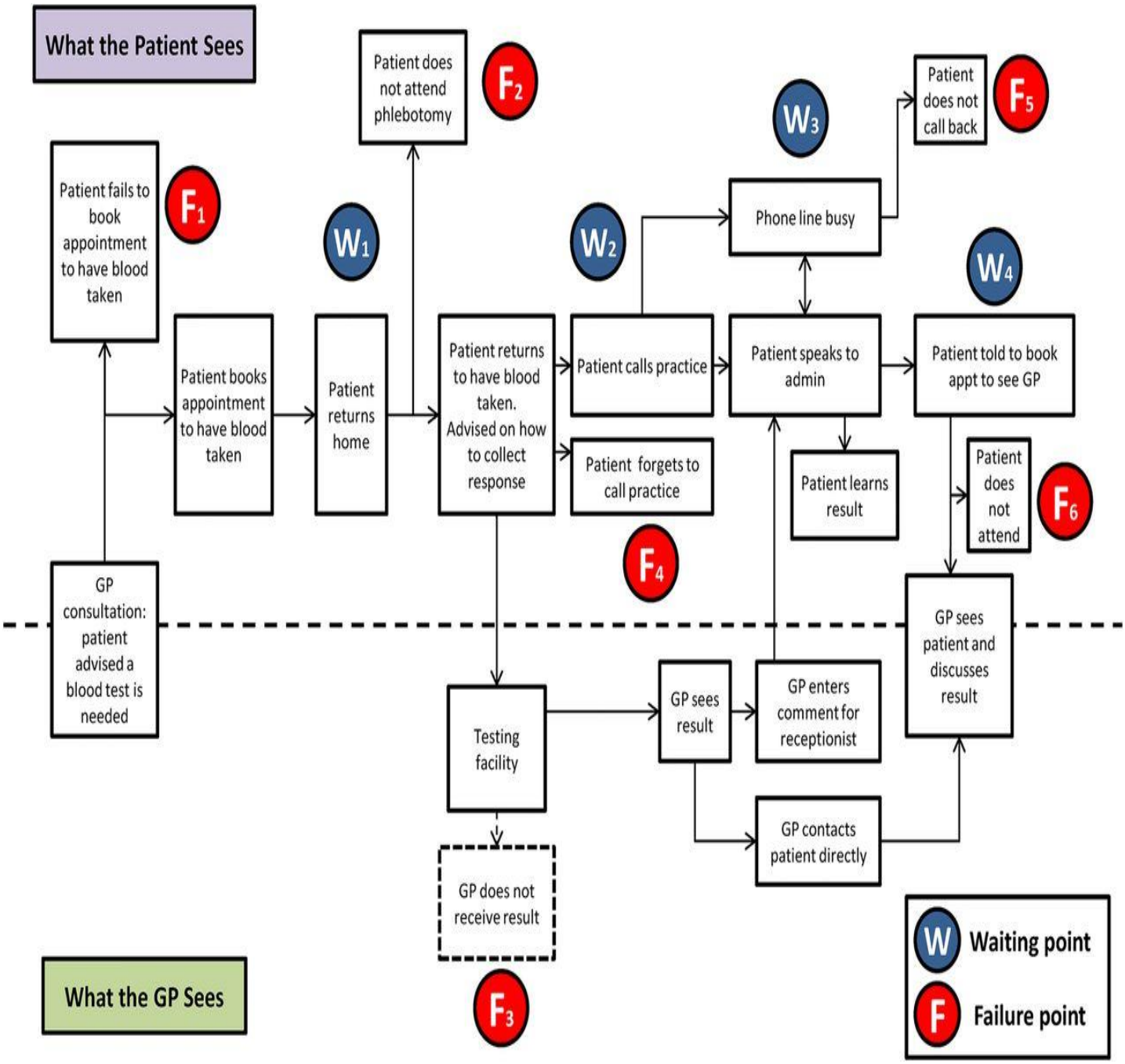


Figure 8: Waiting and failure points during the blood testing process between the patient and the GP (Litchfield et al)

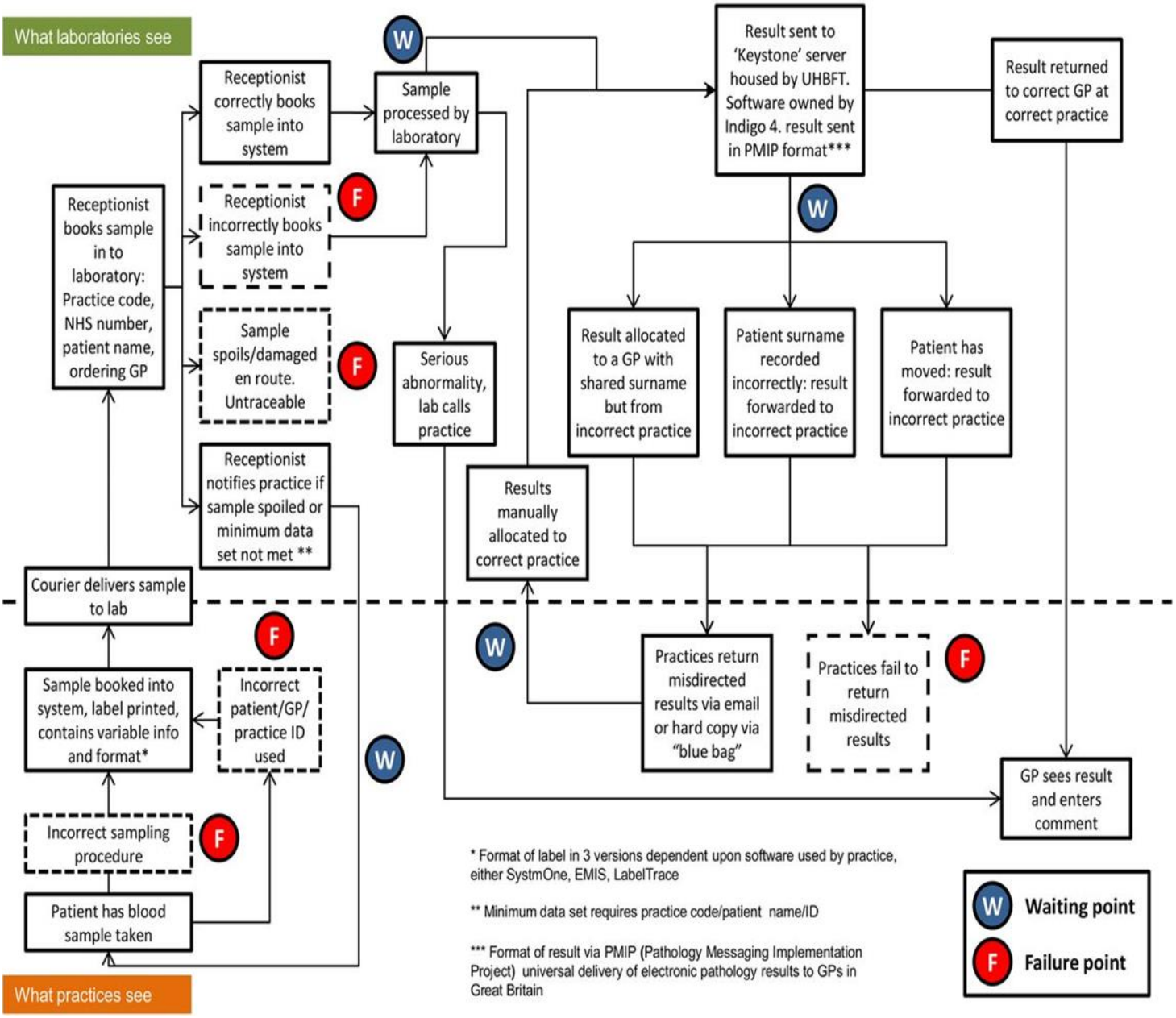


Figure 9: Waiting and failure points during the blood testing process between the general practice and the laboratory (Litchfield et al).

Litchfield and colleagues have mapped the total testing process for blood testing and illustrated its practical and logistical vulnerabilities (see figures 8 & 9; (114,115). This intricate process is prone to errors occurring at different stages of the diagnostic process, previously categorised as pre-analytic, analytic and post-analytic (116,117). Result communication in primary care can be hindered by errors associated with phlebotomy, delayed GP notification,

and failing to detect and notify patients of abnormal or missing results (115). These breakdowns that originate from complicated testing processes can impact patient care (118), presenting barriers that impede effective blood testing for cancer diagnosis.

The recently published Clean Framework aims to improve end to end pathology processes (from the perspective of the patient), focusing on optimising appropriate use and digitalisation and quality of pathology service delivery (69). Given that many errors associated with the blood testing process are situated in primary care (i.e. those in the pre- and post-analytical phase), interventions could be targeted on general practice. Diagnostic technologies embedded in clinical practice can support the diagnostic process, including access to and availability of point of care tests (POCTs). The next section explores the possible solution that “current” POCTs could offer in optimising the use of blood tests for early cancer investigations.

2.5 Point of Care Tests (POCTs) as a solution?

2.5.1 Using POCTs in Primary care settings

In 2018, an international consensus was reached for the definition of POCT use in primary care:

"a point-of- care test in family practice is a test to support clinical decision making, which is performed by a qualified member of the practice staff nearby the patient and on any part of the patient's body or its derivatives, during or very close to the time of consultation, to help the patient and physician to decide upon the best suited approach, and of which the results should be known at the time of the clinical decision making." (119)

The introduction of POCTs into primary care assumes that by providing test results during the consultation, timely and improved clinical decision-making is more likely. In the UK, blood-based POCTs have been successfully implemented in the management of several conditions in general practice including blood glucose measurements in diabetic patients, and assessment of coagulation (International Normalised Ratio) for patients on warfarin. Importantly, their implementation may reduce the complexity associated with conventional blood testing processes and could in principle enable the inclusion of more clinical recommendations within NICE guidelines that endorse blood test use as supported by the evidence.

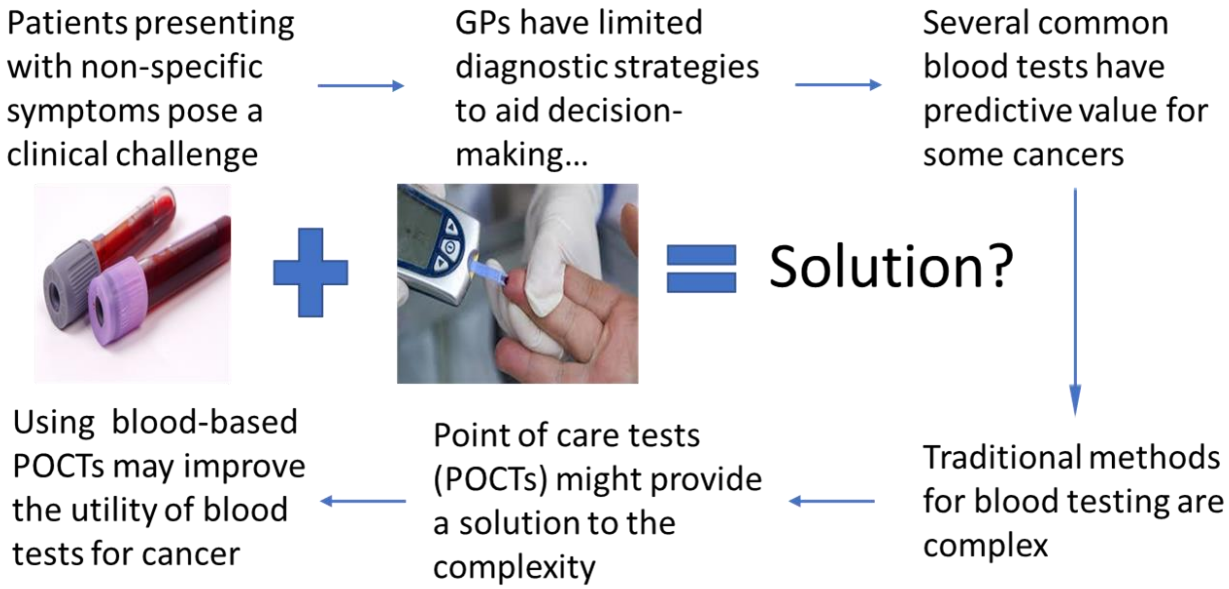


Figure 10: The promise of using POCTs for optimising blood test use to support cancer diagnosis?

In line with the NHS Long-Term Plan commitment to care provision closer to home by introducing community-based care models, POCTs are becoming more integrated into primary care settings (including their expansion into NHS pharmacy settings; (120). However, there is limited availability of primary care-based diagnostic services in the UK (121), although there is a growing desire to use them (122). The reason there are so few POCTs in primary care circulation is partly explained both by slow technological development but also by the complex evaluation cycle for new innovations to be adopted (123). However, the pace of POCT development and their adoption in practice has hastened due to global attempts to expedite the detection and prevention of Covid-19 (124,125). Technological advances are likely to correlate with improved accuracy, yet other determinants relating to their implementation and cost-effectiveness may still be overlooked (126). Nonetheless, POCT accuracy and implementation are both causes for concern for healthcare professionals which will need to be overcome to support implementation (127,128).

2.5.2 Current evidence for blood-based POCTs

POCT developers have previously been slow to recognise the importance of implementation factors when designing POCTs (126). Evaluation studies of new POCTs often fail to document implementation aspects that GP's find important (129). A large UK survey identified barriers and facilitators that GPs perceived to influence their use of blood-based POCTs (130). The potential for increased diagnostic certainty and better treatment decisions during the consultation, fewer re-consultations/referrals and greater patient satisfaction were deemed as facilitators. Conversely, how their use influenced GPs clinical skills (encouraging over-dependence of POCTs) and the associated costs and time constraints with their use were described as barriers. Concerns about diagnostic accuracy were also highlighted as a significant barrier, supporting previously documented concerns over POCTs producing false positive results and being less accurate than laboratory counterparts (127). Despite accuracy concerns, blood-based POCTs are used in secondary care settings. Translating diagnostic tests from different clinical settings poses challenges due to the disease prevalence in different clinical populations (Spectrum Bias; (131–135). However, unless implementation is considered in the designing stage of POCT development, their adoption in primary care will be limited, no matter their diagnostic accuracy.

Outside the UK, POCTs have been adopted more widely, therefore much relevant evidence pertains to healthcare systems other than the UK NHS. Nonetheless, evidence from European countries with similar medical infrastructure (136,137), provides a useful model for interpreting evidence on POCT use. In the Netherlands, primary care practitioners consider the clinical value of POCTs to be important, above that of laboratory equivalent tests (128). In Dutch primary care, healthcare professionals (nurses and GPs), perceive HbA1c and blood glucose POCTs positively, while patients appreciate the speed of testing; Dutch nurses and GPs confidently interpret POCT results, although the associated extra workload and workflow interruptions are seen as a disadvantage in the context of a time constrained environment; (138). In Germany, the most commonly used blood-based POCTs in primary care are blood glucose tests, and Troponin I/T, for assessing acute cardiovascular syndromes (139). However, most POCTs (out of 27 different types assessed) were deemed unhelpful owing to the implementation barriers described above.

2.6 Summary

Blood tests are commonly used in primary care for aiding diagnosis and there are opposing narratives as to balancing risk of over- and under-testing. Patients who present with non-specific symptoms of possible cancer may benefit from the appropriate use of a blood test, as documented by recent evidence. However, most of the relevant evidence emerged after the publication of the NICE 2015 guidelines for suspected cancer in primary care, therefore the potential to use blood tests to support the diagnostic process is not reflected in current NICE guidelines. Presenting clinical features and published guidelines may not entirely explain GPs' use of blood tests for suspected cancer, advocating social cognitive theory to help explain contextual and situational factors that influence testing decisions. POCTs may provide a solution to the complexity of the blood testing process and associated cognitive burdens; evidence evaluating their use in primary care is growing (highlighting many implementation-based barriers to their use).

Chapter 3: PhD rational and aims (Are common blood tests under-used for early cancer detection?)

3.1 Rationale

The purpose of this PhD was to provide evidence for how blood tests are used for patients presenting with new symptoms of cancer and infer possible solutions for improved implementation.

3.2 Thesis Aims

To identify missed opportunities and barriers to using blood tests for suspected cancer and provide possible solutions. The objectives were to explore:

- How primary care ordered blood tests are currently being used for suspected cancer;
- How clinical presentation influences this use, and;
- What factors beyond the clinical presentation influence GPs' use of blood tests for aiding their decision-making for possible cancer.

3.3 Specific Objectives

To achieve the above objectives, this PhD has:

1. Summarised the evidence for blood tests in the context of primary care cancer diagnosis, the complexity of phlebotomy, the influence of clinical context on GP decision-making to use blood tests and the potential promise of POCTs (Chapter 2);

2. Explored variation in common blood test use in pre-diagnosed cancer patients presenting in English general practice by diagnostic process factors (Chapter 4);

3. Described the frequency of blood test use in pre-diagnosed cancer patients by symptom presentation (Chapter 5);

4. Summarised theories of cognition and clinical reasoning to better appreciate the complexity of GPs decision-making to use blood tests (Chapter 6 & Appendix 3. K);

5. Investigated GPs perceptions towards blood test use in suspected cancer patients, exploring factors beyond the clinical presentation using behavioural and Implementation science theory to help explore solutions to practical and logistical barriers to testing (Chapter 6).

Considering the above objectives, the Discussion Chapter (Chapter 7) reflected on the findings in terms of the design and methods employed and Chapter 8 considers their implications for primary care policy, healthcare interventions and future research opportunities.

Chapter 4: Exploring variation in blood test use in patients subsequently diagnosed with cancer (How blood tests are currently being used).

Given the emergent evidence for the predictive value of common blood tests (Chapter 2), the next two Chapters explores frequency and variation in common blood test use by patient characteristics (Chapter 4) and the proportions of blood test use by symptom type (Chapter 5) using routinely collected data of patients subsequently diagnosed with cancer. Opportunities for intervention to support blood testing in cancer populations are discussed.

4.1. Background: Using NCDA data to explore cancer investigations

Between 2009/2010, the first national audit of cancer diagnosis in primary care (NACDPC) was conducted to gather evidence on the diagnostic pathway of primary care patients who were subsequently diagnosis with cancer (140). Building on the previous NACDPC dataset, in two different waves either side of the 2015 publication of NICE guidelines on suspecting cancer in primary care, the national cancer diagnosis audit (NCDA) provides a comprehensive overview of the diagnostic process for cancer patients diagnosed in 2014 and 2018. The NCDA used cancer registry data to assign incident malignant cancer cases in England to practices they were registered at when they were diagnosed with cancer. Participating practices in the NCDA were provided their list of patients who were diagnosed with cancer during the audit year, and GPs were asked to complete an online audit template providing primary care data for these cases across a range of diagnostic process characteristics (31).

In contrast to the NCDA, other databases (Clinical Practice Research Datalink – CPRD; The Health Improvement Network – THIN, and QResearch) rely on data input directly occurring as part of the clinical encounter into the patient's electronic health record (EHR). Numerous challenges exist however with repurposing information from the EHR for research, including problems concerning data quality and validation, completeness of data capture and heterogeneity among systems (141). Restricted consultation time frames and complex patients may contribute to substantial under-recording of problems in the medical notes (142). Furthermore, GPs may not be able to capture all presenting symptoms, particularly in complex presentations (143).

An advance of the NCDA audit waves 2014 and 2018 over the original NACDPC wave (2009-10) is that it provides more recent data that is representative of the national incident cohort in terms of sex, age and cancer site (compared with the population-based incident cohorts of cancer patients). Crucially for the purposes of this enquiry, the NCDA also collected information for multiple types of blood tests that were recorded for each case. Previous

evidence from patients captured in the NACDPC subsequently diagnosed with six common cancers (lung, colorectal, oesophagus, stomach, pancreas and ovarian) suggests that between 24% (ovarian cancer) and 55% (stomach cancer) had at least one blood test during their primary care management before referral (48). It remains unclear however if opportunities for greater use of common blood tests are being missed in patients subsequently diagnosed with cancer.

Therefore, the main analysis in this Chapter used NCDA 2018 data to explore factors associated with variation in blood test use and identify patient groups where targeted interventions might encourage more optimal blood testing. Comparisons are also made between 2014 and 2018 NCDA populations, acknowledging differences in sample size (2018 n=64,490 vs 2014 n=17,042).

4.1.1 Aims

To explore variation in blood test use by patient characteristic (assessing predictors of blood test use) and associations with intervals to referral (primary care interval) and diagnosis (diagnostic interval).

4.2 Methods

4.2.1 Study Design and Population (NCDA 2018)

I analysed cross-sectional data obtained by the 2018 version of the NCDA from 1876 general practices (~5% of all general practices in England) on 64,490 malignant cancer cases diagnosed in the year 2018. This data was collected during the 2019/2020 period. All cancers were included for analysis to incorporate those where there is growing evidence that blood tests have predictive value, but to also identify trends in blood test use across cancers where observed variation is not explained by clinical guidelines. Screen-detected cases were dropped from subsequent analysis (n=5922). Furthermore, cases were excluded from the analysis if they did not present in general practice (n=16907) as those patients could not have been subject to primary care-led blood test investigations. Information indicating unknown or not applicable investigations were excluded (n=1755) as whether blood tests or other test types were used could not be inferred. In line with previous research, patients aged 15 years or more were analysed (n=153 cases <15 years old excluded; (49). There was no missing information recorded for demographic factors including age, sex and indexes of deprivation. Therefore, 39,752 cases were included in the analysis (see appendix 3. A for sample derivation), of which around 1% (n=571) had more than one tumour recorded.

4.2.2. Outcome and exposure variables

The audit questionnaire collected information on whether blood tests were used in primary care prior to cancer diagnosis, as a series of binary items: “Primary care led investigations that were ordered as part of the diagnostic assessment, and prior to referral, decided by the GP and in response to symptoms complained of, signs elicited, or abnormal test results”. We defined common blood tests as a binary variable indicating the use of at least one of: full blood count (FBC), urea and electrolytes (U&E) or liver function tests (LFTs). Less often used blood tests were considered in addition (see supplementary analysis).

Exposure variables comprising categorical information on age group (15-29, 30-49, 50-69, 70+ years), gender at diagnosis (denoted as ‘sex’ hereafter; male and female), ethnicity (white, non-white, and unknown), index of multiple deprivation quintile group (based on income domain), count of pre-existing morbidities (0, 1, 2 and 3+ conditions, and missing), cancer site (a 29-group categorical variable) and presenting symptom group were generated (31). Additionally, factors related to the diagnostic process including the number of pre-referral consultations (i.e. 0, 1, 2 or 3+) and the type of subsequent referral (i.e. type of referral that

led directly to a cancer diagnosis; Routine, Urgent – not for suspected cancer, TWW/USC – "Urgent Specialist Consultation" for suspected cancer, referral to private health care, emergency referral – including patient self-referral, screening detected, other, not known, direct access and MDC – multidisciplinary diagnostic centre) were created for univariate analysis. Trends in blood test use by the number of consultations were examined as previous evidence indicates that three or more pre-referral consultations are likely for several cancers (33). However, these diagnostic process measures were not included for multivariate analysis due to their limited clinical meaningfulness (i.e. how the patient is subsequently referred is unlikely to be associated with blood test use) and for avoiding spurious assumptions (i.e. some consultations may be a result of repeat blood tests for monitoring purposes for pre-existing conditions, rather than testing for cancer).

The length of the primary care interval (PCI) was defined consistent with the Aarhus statement: the time from first symptomatic presentation to first referral to specialist care, as was the diagnostic interval (DI): the time from first symptomatic presentation to diagnosis by investigation status (17).

4.2.3. Categorising symptoms

Unexplained complaints have been associated with blood test use (144). In the context of cancer diagnosis, understanding the association between presenting non-alarm symptoms and blood test use might help identify opportunities where blood tests could be more effectively utilised as a diagnostic strategy. Information on presenting symptoms was collected regarding the presence of one or more of 83 pre-specified symptoms in the audit questionnaire. We defined alarm symptoms as those where the 2015 NICE guidelines recommended urgent or immediate referral or specialist investigation (appendix 3. B; (96). Three main groups are defined: patients presenting with alarm symptoms (for which urgent referral is recommended); those with non-alarm symptoms; and those with both alarm and non-alarm symptoms. Two further groups were also considered, one comprising alarm symptoms likely to indicate a medical emergency in whom primary care blood testing is not expected to be used, and a group with missing information on the nature of symptoms.

4.2.4. Statistical Analysis

Patients in the audit were recorded as having a blood test or not, across 9 blood test types. I described the proportion of patients who received a blood test by fixed patient characteristics (see table 2). Post estimations using Joint Wald tests explained the significance of the explanatory variables on predicting blood test use. The distribution of the primary care interval (PCI) and diagnostic interval (DI) were described using the median, and interquartile range (IQR), restricting to patients with non-negative values ranging from 0 to 730 in keeping with prior research. Additionally, I stratified the analysis by symptom category to explore the association of symptom specificity on interval length based on blood test use. Differences between symptom type groups and cancers were assessed using Kruskal-Wallis tests. Logistic regression was used to estimate crude and adjusted ORs of whether a blood test was used or not by age group, sex, ethnicity, deprivation (based on income), symptom category, comorbidities and cancer-site. Reference groups for categorical variables were white, men, aged 50-69, lowest indexes of deprivation, lung cancer, no comorbidities and presentation with alarm symptoms. Quantile regression was used to control for possible confounding or effect mediation with the crude observations associated between blood test use and interval lengths. Adjustments were made for blood test use, sex, cancer-site and symptom categories, while the model did not account for age group due to nonconvergence issues (related to the primary care interval, likely due to low numbers of cases in lower percentiles). An interaction term was also incorporated into the model to explore potential interactions between blood test use and symptom category. All statistical analyses were conducted using STATA SE V.15 (StataCorp).

4.2.5. Supplementary and Sensitivity Analysis

I calculated the proportion of tested patients who received a specific common blood test or combination of tests (hereafter, I refer to patients who had a common blood test as ‘tested’ patients for brevity) and the distribution of blood tests by cancer-site (appendix 3. C & Table 5, respectively). Using an item that coded pre-referral primary care-led investigations, two additional binary variables for ‘use of other blood tests’ and ‘use of other pre-referral investigations’ were also created (see appendix 3. D for details on included blood tests and investigations). This allowed me to explore how use of common blood tests related to the use of these two other types of investigations. Crucially, these investigation variables could not be included in the main multivariate model (i.e. the analysis was done in a separate model)

because of concerns with multicollinearity (i.e. other investigations being highly correlated with blood test use).

A sensitivity analysis repeated the main analysis after excluding patients recorded as having no consultations after presenting to their GP surgery (n=2048, 5% of the main analysis sample). This group were kept in the main analysis, as a large proportion of them (n=1554, 76%) were diagnosed after being referred via 2WW or routinely by their GP.

4.2.6. Comparison with NCDA 2014

In January 2022, I obtained access to the 2018 version of the NCDA. Up until this point, all analysis had been completed using data from the 2014 NCDA. Between the release of these two audits, the NICE guidelines for suspected cancer recognition were updated (2015). Additionally, during the timeframe between the recent and prior guideline updates (10 years; 2005 - 2015), evidence supporting blood test use for early detection of cancer was growing. Variation in blood test use in populations of patients diagnosed in 2014 and 2018 may be explained by the growing evidence base on blood testing for suspected cancer. Therefore, we expanded the above-described methods to explore variation in blood test use across both audits.

4.3 . Results

4.3.1. Main study Population

The main study population (n=39,752) predominantly included patients who were aged below 70 years old (see Table 2), yet those over 70 years of age accounted for a substantial minority of the population (49%). Half the population were aged between 30 – 69 years old (50%), while few were below 30 years of age (1%). Most patients were of white ethnicity (87%), with nearly 1 in 10 cases representing non-white populations (9%). There was a slight preponderance of men within the study population (55% vs 45%). Over a quarter of the study population had no comorbidities (n=10145, 26%). Around 1 in 3 patients had one comorbidity (n=12370, 31%) while comparatively fewer patients had 3 or more comorbidities (n=7401, 19%). Patients were more frequently diagnosed with prostate (19%), breast (12%), or lung cancer (11%), while few were diagnosed with vulval, Hodgkin lymphoma or oral cavity related cancers (<1%). Patients more often presented with symptoms of lower specificity (non-alarm: 41%), with over a third of patients presenting with alarm symptoms (35%). The remaining quarter of patients presented in primary care with either both alarm and non-alarm symptoms (15%), emergency symptoms (<1%) or not-known or not-applicable symptoms (9%). The median (IQR) PCI was 3 (0-20) days, and the median (IQR) DI was 39 (17-81) days.

4.3.2. Use of common blood tests

Two fifths of the study population had at least one common blood test in primary care before being diagnosed with cancer (16427/39752, 41% - see Table 2). Blood test use varied across exposure variables. Considering fixed patient characteristics, blood tests were more frequently used in older patients (ranging from <32% in patients younger than 50 and 46% in those 70 years or older, p<0.001). Higher proportions of blood test use are observed among patients aged 15-29 compared to those aged 30-49 years. Nearly half of men diagnosed with cancer had a common blood test, while just over a third of women did (48% vs 34%, respectively, p<0.001). In adjusted analysis, variation by sex remained, i.e. odds ratios of 0.92 (95% CI: 0.87-0.98) for women compared with men. Blood tests were predominantly used in white populations compared to non-white ethnicities (38% vs 42%, respectively, p=0.002), with variation remaining in adjusted analysis, i.e. odds ratios of 0.89 (95% CI: 0.82-0.97) for non-white groups compared to white populations. Furthermore, over two-fifths of patients coded as having unknown ethnicity had common blood tests (42%). The distribution of

common blood tests by deprivation quintile was even (ranging from 41% - 42%), with no clear pattern of variation ($p>0.05$).

Observing patient characteristics associated with clinical factors, the use of blood tests increased with greater number of morbidities (no morbidities: 36%, 3+ morbidities: 45%, $p<0.001$). Univariate analysis provided concordant findings, yet there was no evidence of variation by number of comorbidities in adjusted analysis. There was considerable variation in the use of common blood tests by subsequently diagnosed cancer ($p<0.001$). Patients eventually diagnosed with either leukemia, myeloma or pancreatic cancer experienced the highest proportions of common blood test use (i.e. 84%, 76% 71%, respectively), while less than one-tenth of patients diagnosed with vulval cancer, breast cancer or melanoma had common blood tests (8%, 4% and 2%, respectively). Comparable patterns of variation remained by cancer-site in adjusted analysis. At least half of patients presenting in primary care with non-alarm symptoms alone or both alarm and non-alarm symptoms had common blood tests prior to being diagnosed with cancer (50% and 56%, respectively). Nearly a quarter of patients presenting with alarm symptoms alone also had a blood test prior to being diagnosed with cancer (24%). Multivariate analysis supported variation by presenting symptom group, i.e. odds ratios of 2.75 (95% CI: 2.61-2.89) and 3.68 (95% CI: 3.44-3.93) for non-alarm symptoms alone and both alarm and non-alarm symptoms together respectively, compared with patients presenting with alarm symptoms alone. After adjusting for cancer-site, the odds were attenuated yet evidence of variation remained, i.e. odds ratios decreased to 1.58 (95% CI: 1.49-1.69) and 2.13 (95% CI: 1.98-2.30), respectively.

***Table 3**: Proportions and crude/adjusted ORs examining variation in common blood test use in primary care among individuals diagnosed with cancer.*

	Population total (column %)	**Received a blood test (row %)**	**Crude OR (95% CI)***	**Adjusted OR* (95% CI) (excluding cancer-site)**	**Adjusted OR* (95% CI) (including cancer-site)**
Total	39752 (100%)	16427 (41%)			
Age group			P<0.001	P<0.001	P=0.001
15-29 years	553 (1%)	172 (31%)	0.66 (0.55-0.79)	0.85 (0.70-1.04)	0.98 (0.77-1.23)
30-49 years	4009 (10%)	1053 (26%)	0.53 (0.49-0.57)	0.69 (0.63-0.75)	0.99 (0.90-1.10)
50-69 years	15746 (40%)	6293 (40%)	Ref	Ref	Ref
70+ years	19444 (49%)	8909 (46%)	1.26 (1.21-1.32)	1.23 (1.18-1.29)	1.12 (1.06-1.18)
Sex			P<0.001	P<0.001	P=0.009
Male	21854 (55%)	10391 (48%)	Ref	Ref	Ref
Female	17898 (45%)	6036 (34%)	0.55 (0.53-0.58)	0.67 (0.64-0.70)	0.92 (0.87-0.98)
Ethnicity			P=0.002	P=0.475	P=0.024
White	34421 (87%)	14310 (42%)	Ref	Ref	Ref
Non-white	3400 (9%)	1308 (38%)	0.88 (0.81-0.94)	0.96 (0.89-1.04)	0.89 (0.82-0.97)
Unknown	1931 (5%)	809 (42%)	1.01 (0.92-1.11)	1.04 (0.94-1.15)	1.02 (0.92-1.14)
Index of Multiple Deprivation (IMD)			P=0.222	P=0.106	P=0.115
1-Least deprived	8408 (21%)	3422 (41%)	Ref	Ref	Ref
2	8222 (21%)	3474 (42%)	1.07 (1.00-1.13)	1.08 (1.01-1.15)	1.08 (1.01-1.16)
3	7839 (20%)	3219 (41%)	1.02 (0.96-1.09)	1.04 (0.97-1.11)	1.01 (0.94-1.08)
4	7529 (19%)	3131 (42%)	1.04 (0.98-1.11)	1.07 (1.01-1.15)	1.03 (0.96-1.11)
5-Most deprived	7754 (20%)	3181 (41%)	1.01 (0.95-1.07)	1.04 (0.98-1.12)	0.99 (0.92-1.07)
Cancer			P<0.001	N/A	P<0.001
Leukaemia	661 (2%)	552 (84%)	7.69 (6.18-9.55)		9.24 (7.41-11.52)
Myeloma	599 (2%)	455 (76%)	4.68 (3.84-5.71)		5.16 (4.22-6.31)
Pancreatic	1165 (3%)	826 (71%)	3.61 (3.13-4.16)		3.52 (3.06-4.07)
Liver	471 (1%)	331 (70%)	3.50 (2.85-4.31)		3.69 (2.99-4.55)
Colon	2991 (8%)	2093 (70%)	3.47 (3.14-3.83)		3.84 (3.46-4.25)
Stomach	727 (2%)	448 (62%)	2.39 (2.03-2.81)		2.43 (2.06-2.87)
Rectal	1261 (3%)	764 (61%)	2.29 (2.02-2.61)		2.86 (2.50-3.28)
CUP	629 (2%)	368 (59%)	2.08 (1.75-2.46)		2.19 (1.84-2.60)
Hodgkin Lymphoma	218 (<1%)	121 (56%)	1.83 (1.38-2.41)		2.27 (1.70-3.04)
Ovarian	874 (2%)	482 (55%)	1.81 (1.56-2.10)		1.90 (1.63-2.21)
Non-Hodgkin Lymphoma	1545 (4%)	852 (55%)	1.82 (1.62-2.05)		2.15 (1.91-2.43)
Kidney	969 (2%)	477 (49%)	1.44 (1.25-1.66)		1.62 (1.41-1.87)
Oesophageal	1074 (3%)	504 (47%)	1.30 (1.13-1.49)		1.38 (1.20-1.59)
Prostate	7499 (19%)	3518 (47%)	1.32 (1.23-1.43)		1.42 (1.31-1.55)
Other	2184 (5%)	1004 (46%)	1.28 (1.16-1.42)		1.51 (1.36-1.68)
Bladder	1112 (3%)	481 (43%)	1.13 (0.99-1.29)		1.33 (1.15-1.52)
Mesothelioma	331 (<1%)	143 (43%)	1.14 (0.91-1.43)		1.04 (0.82-1.31)
Lung	4430 (11%)	1785 (40%)	Ref		Ref
Thyroid	467 (1%)	179 (38%)	0.95 (0.78-1.15)		1.38 (1.11-1.70)
Brain	328 (<1%)	123 (38%)	0.88 (0.70-1.12)		0.96 (0.76-1.23)
Cervical	194 (<1%)	59 (30%)	0.63 (0.46-0.87)		0.74 (0.54-1.03)
Oropharynx	523 (1%)	145 (28%)	0.57 (0.46-0.70)		0.70 (0.57-0.86)
Uterus	1266 (3%)	318 (25%)	0.49 (0.43-0.57)		0.65 (0.56-0.76)
Larynx	297 (<1%)	64 (22%)	0.41 (0.31-0.55)		0.50 (0.37-0.66)
Oral cavity	248 (<1%)	28 (11%)	0.18 (0.12-0.28)		0.26 (0.17-0.39)
Testicular	340 (<1%)	33 (10%)	0.16 (0.11-0.23)		0.19 (0.13-0.28)
Vulval	133 (<1%)	10 (8%)	0.12 (0.06-0.23)		0.17 (0.09-0.33)
Breast	4919 (12%)	209 (4%)	0.07 (0.06-0.08)		0.09 (0.07-0.10)
Melanoma	2297 (6%)	55 (2%)	0.04 (0.03-0.05)		0.05 (0.03-0.06)
Morbidities			P<0.001	P=0.908	P=0.409
0	10145 (26%)	3698 (36%)	Ref	Ref	Ref
1	12370 (31%)	5111 (41%)	1.22 (1.16-1.29)	1.01 (0.94-1.06)	0.94 (0.88-1.01)
2	9144 (23%)	4039 (44%)	1.37 (1.30-1.46)	1.01 (0.95-1.08)	0.97 (0.91-1.04)

	Population total (column %)	Received a blood test (row %)	Crude OR (95% CI)*	Adjusted OR* (95% CI) (excluding cancer-site)	Adjusted OR* (95% CI) (including cancer-site)
3+	7401 (19%)	3318 (45%)	1.41 (1.33-1.50)	1.01 (0.93-1.07)	0.96 (0.89-1.03)
missing	692 (2%)	261 (38%)	N/A	N/A	N/A
Symptom types			P<0.001	P<0.001	P<0.001
Alarm only	13778 (35%)	3341 (24%)	Ref	Ref	Ref
Non-alarm only	16487 (41%)	8223 (50%)	3.12 (2.97-3.28)	2.75 (2.61-2.89)	1.58 (1.49-1.69)
Alarm/non-alarm	5832 (15%)	3262 (56%)	3.97 (3.72-4.23)	3.68 (3.44-3.93)	2.13 (1.98-2.30)
Emergency only	173 (<1%)	62 (36%)	1.70 (1.24-2.34)	1.60 (1.16-2.21)	0.94 (0.66-1.32)
Not known/not applicable	3482 (9%)	1539 (44%)	2.48 (2.30-2.69)	2.01 (1.86-2.18)	1.01 (0.92-1.10)

*After excluding 692 patients with missing information on morbidities, 39060 cases remained for the logistic regression models. **Post estimations using Wald tests explained the significance of the explanatory variables on predicting blood test use. CUP = carcinoma of unknown primary; CNS = central nervous system; Ref = reference group.

4.3.3. Diagnostic process measures and blood test use

Common blood test use varied by consultation rate and referral type (see Table 3). Around half of patients had one consultation prior to referral (n=19443, 49%), with over a quarter receiving a blood test (n=5428, 28%). The proportion of blood test use increased with consultation rates (0 consultations = 25%, 1 consultation = 28%, 2 consultations = 54%, 3+ consultations = 64%, P<0.001). Univariate analysis supported this variation, suggesting increasingly higher odds of blood test use with growing consultation rates.

Three quarters of patients in the study sample were referred for TWW/USC for suspected cancer (n=29476, 74%), while the second most referred population were those being admitted to emergency care (n=3617, 9%). Less than half of referred patients had a common blood test (≤49%), where the distribution of blood test use between referral types remained within a 13% range (between: 36% - 49%). Univariate analysis confirms similar patterns of variation among those patients referred urgently (not for suspected cancer) or for emergency care, i.e. 1.33 (95% CI:1.16-1.52) and 1.25 (1.13-1.38), respectively. Conversely, lower odds of blood test use were observed among patients referred via TWW, for private health care, via direct access and for not-known referral routes, i.e. 0.89 (0.82-0.97), 0.74 (0.62-0.89), 0.67 (0.55-0.83) and 0.73 (0.59-0.91), respectively.

***Table 4**: Variation in common blood test use by diagnostic process variables.*

	Population total (column %)	Receiving a blood test (row %)	Crude OR (95% CI*)
Total:	39752 (100%)	16427 (41%)	
Number of consultations			P<0.001
0	2048 (5%)	515 (25%)	Ref
1	19443 (49%)	5428 (28%)	1.13 (1.02-1.26)
2	10508 (26%)	5680 (54%)	3.48 (3.12-3.88)
3+	6983 (18%)	4494 (64%)	5.30 (4.74-5.94)
Missing	770 (2%)	310 (40%)	N/A
Referral Type			P<0.001
Routine	2776 (7%)	1176 (42%)	Ref
Urgent (not for suspected cancer)	1293 (3%)	640 (49%)	1.33 (1.16-1.52)
TWW/USC – "Urgent Specialist Consultation" for suspected cancer	29476 (74%)	11806 (40%)	0.89 (0.82-0.97)
referral to private health care	645 (2%)	231 (36%)	0.74 (0.62-0.89)
emergency referral – including patient self-referral	3617 (9%)	1746 (48%)	1.25 (1.13-1.38)
screening detected	20 (<1%)	9 (45%)	0.97 (0.39-2.43)
other	835 (2%)	363 (43%)	1.01 (0.86-1.18)
Direct Access	538 (1%)	218 (41%)	0.67 (0.55-0.83)
MDC	94 (<1%)	44 (47%)	0.86 (0.56-1.32)
Not known	458 (1%)	194 (42%)	0.73 (0.59-0.91)

*After excluding 692 patients with missing information on morbidities, 39060 cases remained for the logistic regression models

4.3.4. Diagnostic timeliness by use of common blood tests

Patients who had a blood test experienced longer intervals between symptomatic presentation in primary care and subsequent referral compared to those not having a blood test (see Table 4), i.e. the median (IQR) PCI was 10 (1-30) days with blood testing and 0 (0-13) days without, p=0.001. The median diagnostic interval also increased among tested patients compared to those not tested, i.e. 49 (26-95) days vs 32 (14-70) days, p=0.001. Blood test use was associated with longer PCI and DI across all symptom presentation groups, although there was no evidence of variation in the DI among those presenting with emergency or not-known/not applicable symptoms (p>0.05). The largest absolute difference in interval length by blood test use was observed among patients presenting with alarm symptoms (19 days). Those patients presenting with non-alarm symptoms experienced longer differences in the PCI with test use (i.e. tested vs non-tested difference: +9 median days) compared to the DI (i.e. +7 median days).

The adjusted model showed attenuated associations between blood test use and the length of the PCI (from 10 days to 4 days). The attenuation was even stronger for the DI, dropping from 17 days in the observed data to three days. Further analysis identified cancer-site to be the predominant source for these changes, suggesting that when the likelihood of blood testing increases as does the diagnosis of cancers with longer intervals. After exploring interaction effects between blood test use and symptom category during adjustments for cancer-site and sex, variable reductions in the PCI were observed by testing status (yes/no) in those patients presenting with alarm (4 days to 1 day), non-alarm (9 to 7 days) or both alarm and non-alarm (6 to 4 days) symptoms. The DI experienced similar variable reduction by symptom category between tested and non-tested patients, decreasing by 16 (19 to 3 days), two (7 to 5 days) and nine (12 to 3 days) median days for patients presenting with alarm, non-alarm and both alarm and non-alarm symptoms, respectively.

***Table 5**: Median and inter-quartile range for the Primary Care Interval and the Diagnostic Interval by blood test use, stratified by symptom type.*

	All patients (independently of blood test status) (n=37752)	Patients having a common blood test (n=16427)	Patients not having a common blood test (n=23325)	Difference by common blood test use	P value*	**Adjusted difference in interval by common blood test use and symptom group	P value
Primary care interval (PCI)	Median (IQR) days	Median (IQR) days	Median (IQR) days	Median days		Median days (95% CI)	
Overall (n=35962)	3 (0-20)	10 (1-30)	0 (0-13)	10	<0.001	4 (3 – 5)	<0.001
Alarm only (n=18627)	0 (0-8)	4 (0-20.5)	0 (0-1)	4	<0.001	1 (1 – 1)	<0.001
Non-alarm only (n=19813)	8 (0-29)	13 (2-34)	4 (0-23)	9	<0.001	7 (6 – 8)	<0.001
Alarm/non-alarm (n=5363)	2 (0-17)	6 (0-22)	0 (0-8)	6	<0.001	4 (3 – 8)	<0.001
Emergency only (n=145)	0 (0-17)	9 (0-25)	0 (0-5)	9	0.017	9 (2 – 16)	0.01
Not known/not applicable (n=2837)	6 (0-27)	9 (1-34)	3 (0-22)	6	<0.001	6 (4 – 8)	<0.001
Diagnostic Interval (DI)	Median (IQR) days	Median (IQR) days	Median (IQR) days	Median days		Median days	
Overall (n=37883)	39 (17-81)	49 (26-95)	32 (14-70)	17	<0.001	3 (1 – 5)	0.001
Alarm only (n=19190)	28 (14-61)	41 (21-79)	22 (13-51)	19	<0.001	3 (1 – 5)	<0.001
Non-alarm only (n=21478)	46 (23-91)	49 (27-97)	42 (20-85)	7	<0.001	5 (3 – 7)	<0.001
Alarm/non-alarm (n=5708)	35 (16-69)	40 (21-77)	28 (14-59)	12	<0.001	3 (1 – 5)	0.007
Emergency only (n=162)	42 (17-86)	51 (22-100)	37 (11-78)	14	0.57	14 (-11– 40)	0.28
Not known/not applicable (n=2872)	56 (29-107)	62 (31-117)	52 (28-100)	10	0.21	11 (6 – 16)	<0.001

*P value from Kruskal-Wallis test, comparing intervals in tested vs non-tested patient groups

4.3.5. Blood test signatures and variation in use by cancer-site.

Common blood tests were used for over half of patients subsequently diagnosed with leukaemia (84%), myeloma (76%), pancreatic cancer (71%), liver cancer (70%), colon cancer (70%), stomach cancer (62%), rectal cancer (61%), carcinoma of unknown primary (59%), ovary cancer (55%) and non-Hodgkin lymphoma (55%). Conversely, their use was infrequent in patients diagnosed with breast cancer (4%) and melanoma (2%).

The association between cancer-site and blood test use changes when considering less generic blood tests with greater affinity to specific cancer-sites. Cancer biomarker tests were most used in patients diagnosed with prostate (86%) and ovarian (47%) cancer, with a background rate of 24% across all patients. Most patients having cancer biomarker tests were men (7828/9289, 84%). Around one-fifth of all patients received inflammatory marker tests (19%), with more prolific use occurring in those patients diagnosed with myeloma (49%), pancreatic cancer (42%), liver cancer (37%), carcinoma of unknown primary (36%), non-Hodgkin lymphoma (35%), leukaemia (33%) and colon cancer (33%). All other cancer-sites accounted for less than a third of inflammatory marker use. Most patients diagnosed with myeloma had a serum protein test prior to diagnosis (53%), while over a third had bone-profile tests (36%) and around one-fifth had ferritin blood tests (22%). The latter was used most frequently in patients diagnosed with colon cancer (34%) and in over a quarter of patients diagnosed with stomach and rectal cancers (28% and 26%, respectively). Few patients received amylase blood tests prior to cancer diagnosis, with the highest use observed among patients diagnosed with pancreatic cancer (17%).

***Table 6**: Frequency of blood test use by cancer-site*

Cancer	Common Blood tests	%	FBC	%	U&E	%	LFT	%	Inflammatory Markers	%	Cancer Biomarkers*** Use in Men	%	Use in Women	%	Serum protein	%	Ferritin	%	Bone profile	%	Amylase	%
Leukaemia (n=661)	552	84	543	82	370	56	340	51	216	33	39	6	5	1	46	7	115	17	117	18	9	1
Multiple myeloma (n=599)	455	76	439	73	387	65	345	58	295	49	62	10	29	5	320	53	129	22	217	36	9	2
Pancreas (n=1165)	826	71	790	68	763	65	773	66	488	42	89	8	110	9	45	4	224	19	239	21	194	17
Liver (n=471)	331	70	289	61	273	58	301	64	172	37	32	7	31	7	28	6	88	19	91	19	37	8
Colon (n=2991)	2093	70	2075	69	1751	59	1608	54	980	33	192	6	208	7	76	3	1029	34	450	15	98	3
Stomach (n=727)	448	62	444	61	388	53	371	51	205	28	45	6	23	3	16	2	207	28	121	17	36	5
Rectum (n=1261)	764	61	751	60	677	54	621	49	361	29	94	7	58	5	22	2	325	26	141	11	21	2
Unknown primary (n=629)	368	59	349	55	327	52	317	50	228	36	45	7	61	10	29	5	92	15	110	17	34	5
Ovary (n=874)	482	55	476	54	439	50	393	45	258	30	0	0	408	47	14	2	121	14	128	15	33	4
Non-hodgkin lymphoma (n=1545)	852	55	842	54	727	47	666	43	534	35	83	5	60	4	147	10	230	15	288	19	47	3
Kidney (n=969)	477	49	448	46	432	45	358	37	230	24	112	12	26	3	30	3	125	13	120	12	22	2
Oesophagus (n=1074)	504	47	496	46	456	42	422	39	230	21	36	3	18	2	19	2	190	18	125	12	37	3
Prostate (n=7499)	3518	47	3,025	40	3332	44	2337	31	1002	13	6420	86	1	<1%	160	2	374	5	896	12	36	<1%
Other (n=2184)	1004	46	967	44	845	39	764	35	478	22	121	6	100	5	83	4	240	11	266	12	70	3
Bladder (n=1112)	481	43	441	40	458	41	271	24	137	12	247	22	11	1	13	1	76	7	88	8	7	1
Lung (n=4430)	1785	40	1,720	39	1624	37	1420	32	1020	23	142	3	93	2	121	3	399	9	580	13	46	1
Thyroid (n=467)	179	38	175	37	153	33	124	27	81	17	2	<1%	7	1	4	1	21	4	37	8	0	0
Oropharynx (n=523)	145	28	143	27	127	24	103	20	105	20	6	1	1	<1%	8	2	21	4	32	6	0	0
Uterus (n=1266)	318	25	311	25	261	21	222	18	120	9	0	0	146	12	12	1	106	8	69	5	6	<1%
Breast (n=4919)	209	4	192	4	195	4	159	3	98	2	2	<1%	26	1	15	<1%	42	1	76	2	8	<1%
Melanoma (n=2297)	55	2	53	2	49	2	36	2	25	1	2	<1%	1	1	3	<1%	11	<1%	12	1	0	0
All other Cancers (n=2089)**	581	28	571	27	521	25	463	22	335	16	57	3	38	2	29	1	134	6	164	8	11	1
All Patients (n=39752)	16427	41	15,540	39	14555	37	12414	31	7598	19	7828	20	1461	4	1240	3	4299	11	4367	11	761	2

* The boundaries for green-yellow-red are set at the upper, median and lower values for each blood test. All other values are coloured proportionally.

** Cancer-sites with less than 397 cases (i.e. <1% of study population) were grouped together, including Hodgkin lymphoma, Mesothelioma, Brain, Cervical, Larynx, Oral Cavity, Testicular and vulval cancers.

***Cancer biomarkers are stratified by sex and includes PSA, CEA, CA125, CA19.9, other.

4.3.6 Supplementary Analysis: How often are common blood tests used concurrently and do other investigations influence their use?

After exploring the frequency of common blood test use in cancer patients prior to their diagnosis, I aimed to assess how often common blood tests are used in combination (Appendix 3. C). Most tested patients received at least one common blood test, with 95%, 88% and 74% receiving FBC, U&Es and LFTs, respectively. Most tested patients had at least two of the three common blood tests (87%), while nearly three quarters had all three (72%).

Use of other investigations (including imaging, endoscopy or other non-blood tests) was associated with more frequent use of common blood tests (i.e. 54% of patients having common blood tests had one or more non-blood test investigations – Appendix 3. D). These associations prevailed after adjustment for other variables, i.e. adjusted ORs for use of blood test in the presence of other (non-blood) tests of 1.83 (95% CI: 1.70-1.98).

In populations aged over 70 years old, evidence of variation in common blood test use remained after further adjustment for non-blood test investigations, i.e. OR of 1.16 (95% CI: 1.08-1.24).

By cancer-site, the odds of having a common blood test were higher in patients diagnosed with leukemia and lower in patients diagnosed with prostate and ovarian cancers after considering other investigations, i.e. ORs of 21.80 (95% CI: 16.66-28.52), 0.11 (95% CI: 0.09-0.13) and 0.46 (95% CI: 0.35-0.60), respectively.

4.3.7 Sensitivity Analysis: Accounting for patients with zero consultations

The findings of the sensitivity analysis excluding patients with ‘zero’ consultations were concordant with the main analysis (see Appendix 3. E). Associations with common blood test use remained consistent across patient characteristics compared with the main study results, observing a 1% difference in overall common blood test use.

4.3.8 Comparative analysis (NCDA 2018 vs NCDA 2014)

Overall, there was little difference across all measured outcomes between the two audits.

The composition of the two populations were very comparable (Appendix 3. F), with minor differences by ethnicity (5% increase in non-white populations in 2018 NCDA) and symptom

category (5% decrease in patients presenting with both alarm and non-alarm symptoms in 2018 NCDA).

Total common blood test use varied little between NCDA study populations (2018; 41% vs 2014; 39% - see Appendix 3. G), with concordant patterns of variation in blood test use by patient characteristic between the NCDA audits. Similarly, the difference in blood test use by consultation rate and referral types were minimal between the two audit waves (Appendix 3. H).

Between the 2014 and 2018 NCDA samples, the overall median PCI and DI shortened, i.e. 2014 NCDA PCI = 5 (IQR: 0-28) days & DI = 44 (20-94) days; 2018 NCDA PCI = 3 (0-20) days & DI = 39 (17-81) days (Appendix 3. I). This trend is also observed in populations receiving blood tests, where intervals were reduced in the 2018 cohort. Use of blood tests in patients presenting with alarm symptoms only or non-alarm symptoms only was associated with longer DIs compared to the overall (average) DI, consistently in both audits.

4.4 Discussion

4.4.1 Summary

A substantial minority of patients in the study population subsequently diagnosed with cancer experienced primary care blood tests (i.e. around two in five having a common blood test). However, cancer patients who were women, non-white or younger were less likely to receive a blood test. Patients who presented with symptoms of lower specificity received a greater amount of common blood tests, yet many presenting with alarm symptoms also had blood tests. Most patients were subsequently referred via TWW, many of whom had common blood tests prior to referral. Less generic blood tests (those which were not categorised as common) were used less in tested patients, yet increments are observed across a few cancer-sites (such as increased cancer biomarker use in patients diagnosed with prostate cancer). Those patients having a common blood test experienced longer intervals to diagnosis. Between 2014 and 2018 NCDA audits, common blood test use has increased marginally.

4.4.2 Strengths and Limitations

The study benefits from analysing data from a large and nationally representative sample of cancer incident cohorts in 2018, where the characteristics of participating and non-participating practices are not dissimilar (31). The findings of the main analysis are based on people diagnosed with cancer in 2018, and although the guidelines were updated in 2015, they mainly concern symptom-based recommendations. Auditing clinicians benefited from access to EHRs where relevant free-text information pertaining to presenting symptoms could support the interpretation of structured symptom data to estimate diagnostic intervals more accurately. One exception is noted, whereby the 2015 guidelines introduced a new recommendation for using FBC and inflammatory marker tests for patients presenting with symptoms suspicious of myeloma (96).

Interpreting the conclusions from this study require some caution. The chronological details relating to blood test use cannot be inferred from the NCDA data, such as the timing of test use in relation to symptom presentation and consultations. The addition of temporal information, which is routinely captured in EHR, might have provided more informative interpretations. However, the disadvantage with using EHRs relates to complications with determining the first relevant consultation where the patient is presenting symptoms of possible cancer. As such, establishing the length of diagnostic intervals becomes challenging.

Using the NCDA, the PCI could be restricted to assess more synchronous use of blood tests after symptom presentation, however concerns with sample representativeness and result interpretation might discourage such analysis. The majority of presenting symptoms are also under-recorded in coded data (145). An inherent assumption also must be made when using the NCDA that symptom recall and interpretation from the patient and GP is accurate, and subsequently recorded into the patient records with no errors (as is true for other clinical databases using information from medical records). Finally, although most common blood tests are ordered as part of a battery of tests, it may have been useful to separate specific components of these tests for sensitivity analysis (i.e. the breakdown of cancer biomarker tests by type, such as PSA and CA-125).

4.4.3 Comparison with the literature

The findings from this study expand on previous research (48) describing the frequency of blood test use and subsequent timeliness of cancer diagnosis by additionally assessing factors that influence the use of blood tests across a greater number of cancer-sites (including common and rarer cancers); variation by different types of blood tests, and the influence of investigations on the primary care and diagnostic interval.

Findings from a cross-sectional study of patients presenting with unexplained complaints (presenting with either fatigue, abdominal or musculoskeletal complaints) in Dutch general practice (n=100) suggest that just over half of these patients had a blood test (144). Similarly, half of patients in the NCDA study population who presented with symptoms of lower specificity had a blood test (50%). The results of the NCDA analysis also concord with evidence on primary care investigation use in the general population, whereby older age was correlated with incremental use of tests over time (52). By contrasting both the 2014 and 2018 NCDA datasets, I could crudely assess similar associations in test use over time but within populations of patients subsequently diagnosed with cancer. The evident lack of change in blood test use between NCDA datasets during this timeframe might reflect the delay associated with diffusing and translating new clinical evidence (supporting blood test use for early cancer diagnosis) into practice, where time lags for research evidence reaching clinical practice can average 17 years (146).

Blood tests forming part of the primary care appraisal process in patients subsequently diagnosed with cancer are found to lengthen the PCI and assumed to have little influence on reducing the DI within secondary or tertiary care settings, given their typically non-confirmative nature for diagnosis (48). In the present study, blood testing was associated with longer primary care and diagnostic intervals. The NCDA does not capture contextual information, therefore judging the appropriateness of test use is difficult. However, longer intervals may imply that situations exist where GPs must offset the diagnostic value of common blood tests against the probable delays in a subsequent referral (if required). Protracted DIs may in part constitute avoidable diagnostic delays in cancer patients, of which a quarter of avoidable delays are attributed to test requests/performance (48,147). Conversely, GPs may order common blood tests when they are uncertain about an underlying diagnosis. In some patient groups (i.e. those presenting with non-alarm symptoms) diagnostic delays resulting from common blood test use might be necessary for supporting GP decision-making, where arguably such delays might be longer without the blood test. Therefore, longer DIs from using blood tests in such patients may be deemed acceptable for informing decision-making to support the diagnostic process. Earlier versions of the NCDA (2014 data) captures information on attributes to avoidable delay, which might inform further qualitative exploration into the appropriateness of blood testing in cancer populations.

Blood testing was found to be less likely in women, non-white and younger populations before cancer diagnosis. However, laboratory testing in the general population is increasing across both genders and all age groups, and ethnic inequalities in access to primary healthcare are negligible in the NHS (52,148). Artifacts of the study design may partly explain this variation in blood test use. Nearly one in five patients included in the study population are diagnosed with prostate cancer (19%), which was 3% more than recorded in the 2014 NCDA. Celebrity endorsement at the beginning of 2018 (February - March) about prostate cancer awareness, encouraging more men to help-seek and consequently increasing 2WW referrals for (and subsequent diagnosis of) prostate cancer may explain this difference (149). Yet many of the NCDA study population were diagnosed with breast cancer (12%), i.e. a female-specific cancer. Around half of patients diagnosed with prostate cancer had common blood tests while just 4% of those diagnosed with breast cancer did (as they rarely form part of the

diagnostic process for suspected breast cancer). Consequently, the proportion of blood test use by sex might be artificially inflated or diluted by gender specific cancer-sites.

Blood tests were used less in younger patients, possibly reflecting the tendency of clinical recommendations for these populations that advocate referral over investigation (96). Recommendations for investigation in children and young people only concern those presenting with symptoms suspicious of leukaemia, where urgent FBC is encouraged.

Nevertheless, ethnicity is a well-recognised determinant in resource use, where inflexible working hours (limiting time to attend healthcare), unaffordable transportation (compromising access to care due to limited funds for travelling) and increased bureaucracy and documentation (complicating access to care) can act as pathways of discrimination among minority groups and impact access to healthcare (150,151). Prior cancer diagnosis audits have identified differences by ethnicity in number of pre-referral consultations (National Cancer Patient Experience Survey, 2010), indicating increased consultation rates in minority ethnic groups before cancer diagnosis in England (33) Level of education by ethnicity may influence these findings (i.e. lower education status might lead to greater consultation rates) and warrants future research to explore the impact of education on healthcare access (including blood test use) by ethnicity. Some primary care investigations including tests for cholesterol or HbA1c monitoring are however accessed equally by white and non-white populations with psychosis (152). Yet, the above-described social disparities may contribute towards extended DI's across all cancers in Black and Asian groups compared to White patients (153)

4.4.4 Implications

This research provides detailed analysis about how common blood tests are used in primary care prior to cancer diagnosis. Given the increasing trends in lifetime cancer risk and blood test use in the UK (2,52), it is important to explore variation in their use so that strategies can be developed to optimise their diagnostic utility for suspected cancer. At the population level, this study identifies possible unmet need for increased use of blood tests in certain patient groups.

The low predictive value of non-alarm symptoms may have prompted greater use of common blood tests due to their diagnostic versatility. Moreover, those presenting with both alarm

and non-alarm symptoms had the highest likelihood of having a blood test, possibly reflecting a larger degree of diagnostic uncertainty in this patient group, or that the presentation of the non-alarm symptom preceded the alarm symptom. Nonetheless, half of patients presenting with non-alarm symptoms did not have a common blood test. While the NCDA cannot support direct inferences about opportunities for using blood tests, its plausible that this patient group could benefit from greater use. It may not be unreasonable, for example, to use blood tests for selecting (triaging) patients for possible referral to multidisciplinary ('rapid') diagnostic centres (42,47,104,154).

Although patients presenting with alarm symptoms were less likely to have a blood test compared to those with non-alarm symptoms, a quarter still received blood tests before diagnosis. Recommendations for urgent suspected cancer referral within clinical guidelines based on the presentation of alarm symptoms should permit fast-tracked diagnostic pathways, yet many experience long care intervals. Given the publication of referral guidelines for patients presenting with alarm symptoms, the use of blood tests might be superfluous to requirements. Qualitative approaches might further explain this phenomenon by exploring the contextual reasons that motivate GPs to use blood tests. Anecdotally, red-flag cancer symptoms may prompt same-day blood testing for some patients (see Chapter 6; Theme 1; GP-11).

Variation in GPs' use of blood tests may infer opportunities for interventions to improve their use. Given the heterogeneous nature of cancer, solutions for optimising blood test use may reside in less clinical methods. Enhanced blood test use might be achieved through interventions aimed at addressing current logistical and practical barriers (rather than clinical reasoning), such as simple modifications to the selection (choice architecture) of blood tests on ordering forms (93,115). On the other hand, over-diagnosis (diagnosis of cancers that would not have caused any harm during a patient's lifetime) may be a concern (65,155). The results of common blood tests however are more likely to be used in a Bayesian-fashion combined with the information arising from the presenting symptom/ clinical picture (i.e. the probability of cancer given a specific symptomatic presentation provides an informative prior which helps to interpret the results of a blood test, making cancer more or less likely an explanation) to support clinical decision-making (rather than confirming a diagnosis),

therefore the consequences of over-diagnosis with common blood test use is unlikely to discourage GPs from using them.

The NCDA is an asset for early cancer diagnosis researchers, yet opportunities exist for enhancing this data source. The inclusion of non-cancer populations with relevant presenting symptoms would have allowed for further elicitation of variation in test use, above and beyond what was observed among cancer cases. Furthermore, data linkage to other healthcare settings (e.g. secondary care) may provide a more complete picture of patients diagnostic journey after receiving blood tests (compared to those who did not). In future, researchers may consider other platforms like OpenSAFELY, and CPRD and linkage to secondary care (156).

In conclusion, a detailed description of blood test use before cancer diagnosis has been illustrated in the above analysis. Some patient characteristics are associated with variable use of blood tests in pre-diagnosed cancer patients. A substantial minority of these patients have a common blood test, where demographic (i.e. age) and clinical (i.e. symptom presentation and cancer-site) information can predict their use. Blood test use by symptom category reveals potential unmet need for interventions to reduce the risk of underuse and overuse of blood tests within certain populations of cancer patients. Future research should explore variation in blood test use within specific populations of cancer patients and clinical scenarios and incorporate qualitative methods to help understand likely drivers of use (or lack of use) of common blood tests in patients presenting to a GP with new symptoms.

4.4.5 Chapter Summary

This analysis offers a reference point for understanding common blood test use in patients presenting with possible cancer symptoms to their GP. This study reveals patient groups where opportunities for more appropriate blood testing may yet be recognised. Analysis of symptoms uncovered variation in test use that may infer both underuse (in around half of patients presenting with non-alarm symptoms) and overuse (in a quarter of patients presenting with alarm symptoms) of blood tests. This quantitative insight into blood test use may help inform recommendations for optimising blood test use in suspected cancer populations. An important implication of this work however relates to opportunities to further explore the influence of presenting symptoms on blood test use. Given that variation

in blood test use by symptom category exists, an extension of this quantitative enquiry would be to study blood test use by symptom type. In doing so, a more detailed account of blood testing can be described and cross-referenced with relevant clinical recommendations to better understand patterns in blood test use.

Chapter 5: Exploring the frequency of blood test use by symptom type.

5.1. Background:

Most recommendations for suspected cancer are based on the presence of symptoms with relatively high predictive value for cancer, often denoted as 'alarm' or 'red-flag' symptoms (see Chapter 2, section 2.2.1). However, within the NICE referral guidelines, only about 1 in 6 recommendations relate to a blood test based on symptomatic presentation (16% - see Chapter 2, Table 1). In Chapter 4, findings indicate that blood test use in patients subsequently diagnosed with cancer varies by symptom category (suggesting that symptom type influences GPs' use of blood tests). However, such categorisation of symptoms limits the assessment of blood test use by individual symptoms, which might offer greater insights for researchers and policy makers regarding clinical recommendations. Additionally, the main analysis of Chapter 4 was restricted to common blood tests, excluding organ-specific and biomarker tests.

Therefore, this Chapter expands of Chapter 4 by benchmarking blood test use by individual symptoms across nine blood tests in patients subsequently diagnosed with cancer. In doing so, a better understanding of the initial clinical scenarios that influence GPs' use of blood tests in patients presenting with possible cancer symptoms can be achieved.

5.2 Methods:

5.2.1 Study Design and Participants

As previously described in Chapter 4, data from the NCDA (2018) was analysed. Similarly, the analysis sample was acquired after applying the same restrictions as per Chapter 4 (i.e. the sample included 39, 752 non-screen-detected cancer patients aged 15 years or older, first presenting to general practice and with complete information on investigation status). However, one additional case with biologically discordant sex-cancer-site was removed, leaving 39, 751 patients for the analysis (Appendix 3. J).

5.2.2 Variables of interest

Concordant with Chapter 4, we extracted information from the NCDA on the use of blood tests in primary care before cancer diagnosis. However, rather than focusing on common blood tests, information on all blood tests captured within the NCDA were extracted, including FBC, U&E, LFT, inflammatory marker, cancer biomarker, serum protein, ferritin, bone profile and amylase tests.

Symptom information was obtained from pre-specified drop-down menus within the NCDA as described in Chapter 4. A total of 83 symptoms are captured, around half of which (n=46) are recorded in less than 1% of the study sample. To avoid skewing the interpretation of blood test use by symptom type in populations where symptoms were rarely recorded, a new symptom variable was generated to group these uncommon symptoms together ("All other symptoms" – representing 17% of cases).

5.2.3 Analysis

The distribution of blood test use among patients presenting with symptoms was calculated. The proportion of cancer biomarker use was further stratified by sex to account for gender-specific tests, such as assumed PSA testing in men and assumed CA-125 testing in women.

5.3. Results:

5.3.1 Commonly used generic blood tests by symptom presentation

As observed previously, common blood tests are used frequently in primary care prior to cancer diagnosis (see Chapter 4). Considering common 'generic' blood tests (i.e. those without particular affinity with a body organ or system) around a third of all patients were tested by FBC (39%), U&E (37%), and LFTs (31%), and around one in five by inflammatory marker tests (19%).

The specificity of the presenting symptom for cancer seems to be driving variation in the use of the above common blood tests, with symptoms of lower specificity (for example, such as fatigue, loss of appetite and weight loss) being associated with greater use of common blood tests (although at a lower absolute frequency for inflammatory marker tests - see Table 6 & Figure 11).

***Table 7**: Frequency of generic blood tests based on presenting symptom.*

	Common 'generic' blood tests										Less common blood tests					
Symptom name	**FBC**	**%**	**U&E**	**%**	**LFT**	**%**	**Inflammatory Markers**	**%**	**Bone Profile**	**%**	**Ferritin**	**%**	**Serum Protein**	**%**	**Amylase**	**%**
Fatigue (n=1771)	1398	79	1267	72	1177	66	808	46	509	29	581	33	185	10	62	4
Loss of appetite (n=1264)	939	74	887	70	842	67	583	46	367	29	379	30	92	7	88	7
Weight loss (n=3408)	2331	68	2183	64	2090	61	1428	42	878	26	913	27	236	7	187	5
Upper abdominal pain (n=1192)	805	68	741	62	736	62	492	41	210	18	252	21	44	4	172	14
Diarrhoea (n=1013)	673	66	621	61	574	57	404	40	162	16	279	28	21	2	64	6
Change in bowel habit (n=1675)	1107	66	1013	60	941	56	633	38	287	17	483	29	35	2	75	4
Nausea and/or vomiting (n=1067)	693	65	666	62	648	61	433	41	229	21	238	22	37	3	97	9
Abdominal pain (NOS) (n=1932)	1233	64	1163	60	1114	58	736	38	339	18	387	20	61	3	179	9
Lower abdominal pain (n=1060)	683	64	631	60	584	55	407	38	195	18	233	22	23	2	39	4
Constipation (n=831)	527	63	484	58	448	54	297	36	185	22	204	25	34	4	39	5
Distension (n=980)	609	62	593	61	539	55	352	36	169	17	179	18	17	2	55	6
Back pain (n=1405)	837	60	797	57	719	51	578	41	425	30	207	15	251	18	37	3
Dyspepsia (n=805)	468	58	436	54	414	51	247	31	120	15	175	22	22	3	59	7
Rectal bleeding (n=1662)	907	55	805	48	723	44	411	25	175	11	411	25	18	1	24	1
Bone pain (n=490)	262	53	249	51	222	45	185	38	155	32	60	12	79	16	10	2
Other symptom (n=2131)	1093	51	1021	48	926	43	589	28	368	17	368	17	136	6	56	3
Dyspnoea (n=1751)	863	49	818	47	714	41	457	26	243	14	254	15	44	3	14	1
Dysuria (n=551)	255	46	263	48	199	36	110	20	60	11	33	6	11	2	11	2
Urinary tract infection (n=477)	209	44	217	45	148	31	93	19	42	9	33	7	11	2	5	1
LUTS (nocturia, frequency, hesitancy, urgency, retention) (n=4434)	1893	43	2139	48	1360	31	545	12	498	11	213	5	69	2	18	<1%
Haematuria (n=1465)	599	41	588	40	367	25	186	13	118	8	79	5	11	1	9	1
Neck lump/mass (n=1201)	498	41	422	35	367	31	325	27	125	10	78	6	30	2	5	<1%
N/A (n=2795)	1129	40	912	33	734	26	326	12	259	9	334	12	151	5	20	1
Chest pain (n=960)	387	40	365	38	330	34	236	25	138	14	96	10	49	5	19	2
N/K (n=687)	270	39	219	32	200	29	76	11	49	7	69	10	29	4	2	<1%
Dysphagia (n=997)	383	39	366	37	341	35	190	19	98	10	136	14	5	1	22	2
Cough (n=2577)	982	38	944	37	807	31	620	24	312	12	240	9	68	3	25	1
All other symptoms (n=6828)* **	2310	37	2115	34	1900	30	1316	21	722	11	551	9	233	4	153	2
Chest infection (n=686)	251	37	239	35	212	31	159	23	74	11	48	7	15	2	8	1
Other vaginal bleeding (n=421)	131	31	91	22	74	18	37	9	20	5	46	11	5	1	1	<1%
Haemoptysis (n=469)	143	30	131	28	111	24	80	17	38	8	29	6	3	1	3	1
Sore throat (n=478)	132	28	113	24	96	20	88	18	27	6	28	6	6	1	3	1
Hoarseness (n=468)	109	23	102	22	97	21	62	13	26	6	30	6	5	1	2	<1%
Post-menopausal bleeding (n=896)	166	19	145	16	124	14	61	7	34	4	44	5	2	<1%	1	<1%
Breast pain (n=768)	21	3	24	3	20	3	9	1	4	1	7	1	3	<1%	0	0
Breast lump/mass (n=4074)	102	3	109	3	80	2	44	1	35	1	17	<1%	6	<1%	2	<1%
Abnormal mole (n=1764)	18	1	17	1	8	0	5	0	4	<1%	4	<1%	0	0	0	0
All Patients (n=39752)	15540	39	14555	37	12414	31	7598	19	4367	11	4299	11	1240	3	761	2

*The boundaries for blue – white - red are set at the upper, median and lower values for each blood test. All other values are coloured proportionally.

**LUTS = lower urinary tract symptoms.

***46 symptoms accounting for less than 1% (n=398) of cases were grouped together, including nipple changes, pelvic pain, lymphadenopathy (localised), jaundice, night sweats, gastroesophageal reflux, testicular lump, headache, erectile dysfunction, prog/sub-acute loss of central neuro function, pruritis, lip/oral cavity/ tongue lump/mass, testicular pain, loin pain, fever, non-pigmented lesion, axillary lump/mass, unexplained lump suspicious of sarcoma, lesions suspicious of BCC, nipple discharge, thyroid lump/mass, lip/oral cavity/ tongue ulcer, ulceration, early satiety, bruising, bleeding or petechiae, pallor, vaginal discharge, anal mass, deep vein thrombosis, visual disturbance or loss, vulval mass, epistaxis, vulval ulceration, penile ulceration, vaginal mass, lymphadenopathy (generalised), fit/seizure, new onset diabetes, stridor, leukoplakia, fracture, lymph node pain with alcohol, renal colic, clubbing, haematemesis and vulval bleeding.

****Proportions presented in white boxes represent cases whereby testing might be associated with guideline recommendations for suspected cancer (based on the type of symptom and blood test).

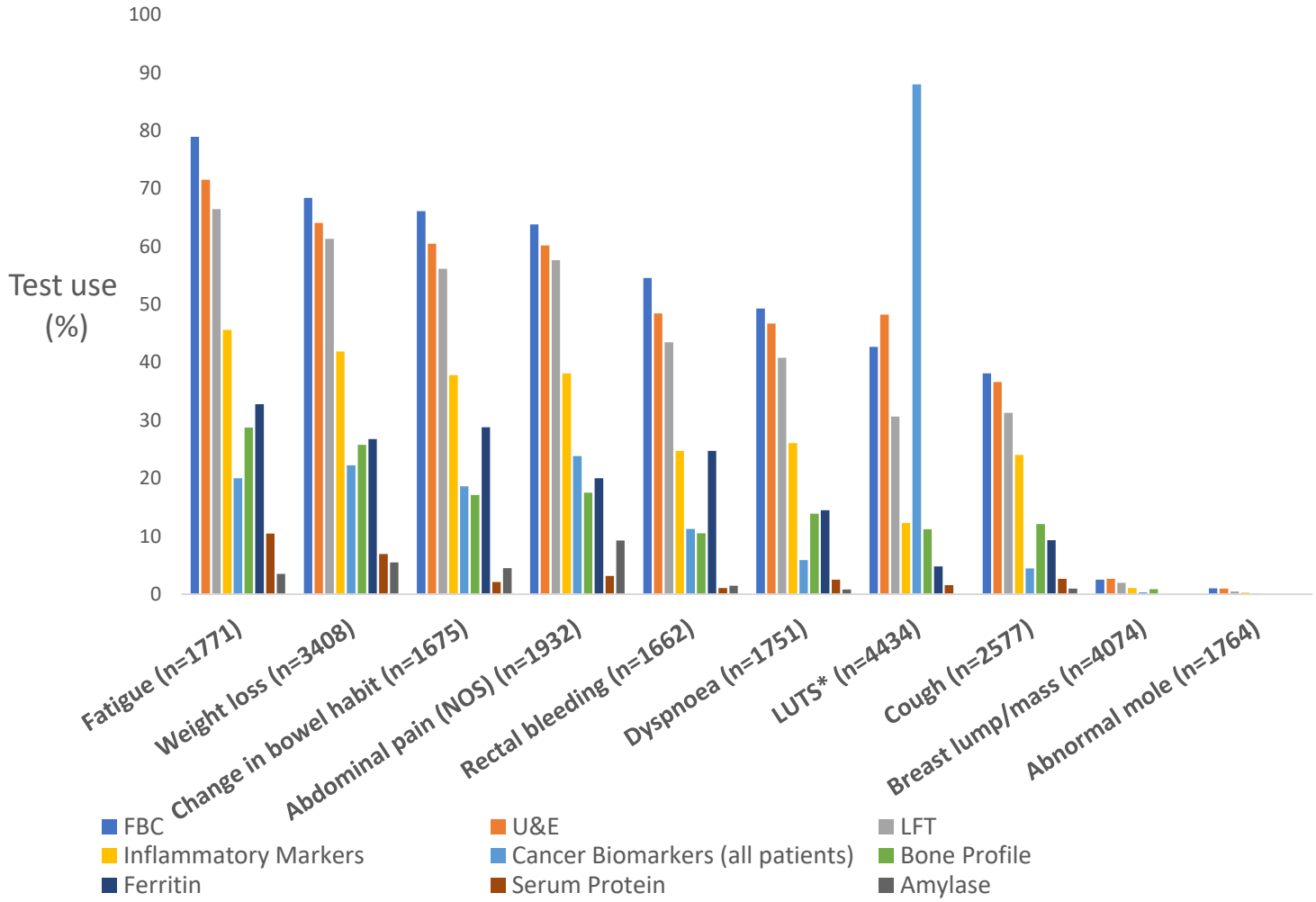
5.3.2 Less commonly used blood tests by symptom presentation

Specific blood tests including bone profile, ferritin, serum protein and amylase tests were used less frequently than generic blood tests, ranging from 2% for amylase to 11% for bone profile.

Bone profile and ferritin tests followed a similar pattern of use to common blood tests, whereby lower specificity symptoms (including fatigue, loss of appetite, weight loss) were associated with higher proportions of test use (26-33%).

Serum protein tests were used in about one-in-six patients presenting with back or bone pain (18% and 16%, respectively), compared with percentages <10% in all patients presenting with all other symptoms. Between 7-10% of patients presenting with fatigue, loss of appetite and weight loss had serum protein tests, compared with <6% among patients presenting with all other symptoms.

Amylase tests were more commonly used in patients presenting with upper abdominal pain (14%) compared with <9% of patients with all other symptoms.



*Lower urinary tract symptoms; cancer biomarker use by LUTs is restricted to men (88%).
**Symptoms presented in descending order by FBC use

Figure 11: Proportion of blood test use across top ten presenting symptoms.

5.3.3 Cancer biomarker use by symptom type

Cancer biomarker (PSA) testing was mainly concentrated in patients with urological symptoms, such as LUTS, dysuria and UTI symptoms, and haematuria (35%-88%). Men presenting with the latter symptom had PSA use comparable to the average (35%) and its frequency was also high among men presenting with back pain and bone pain (35% and 47%, respectively). Over half of men presenting asymptomatically (i.e. not-known – N/K, or not-applicable – N/A symptoms) also had biomarker tests (56% and 63%, respectively).

***Table 8**: Frequency of cancer biomarker use based on symptom presentation.*

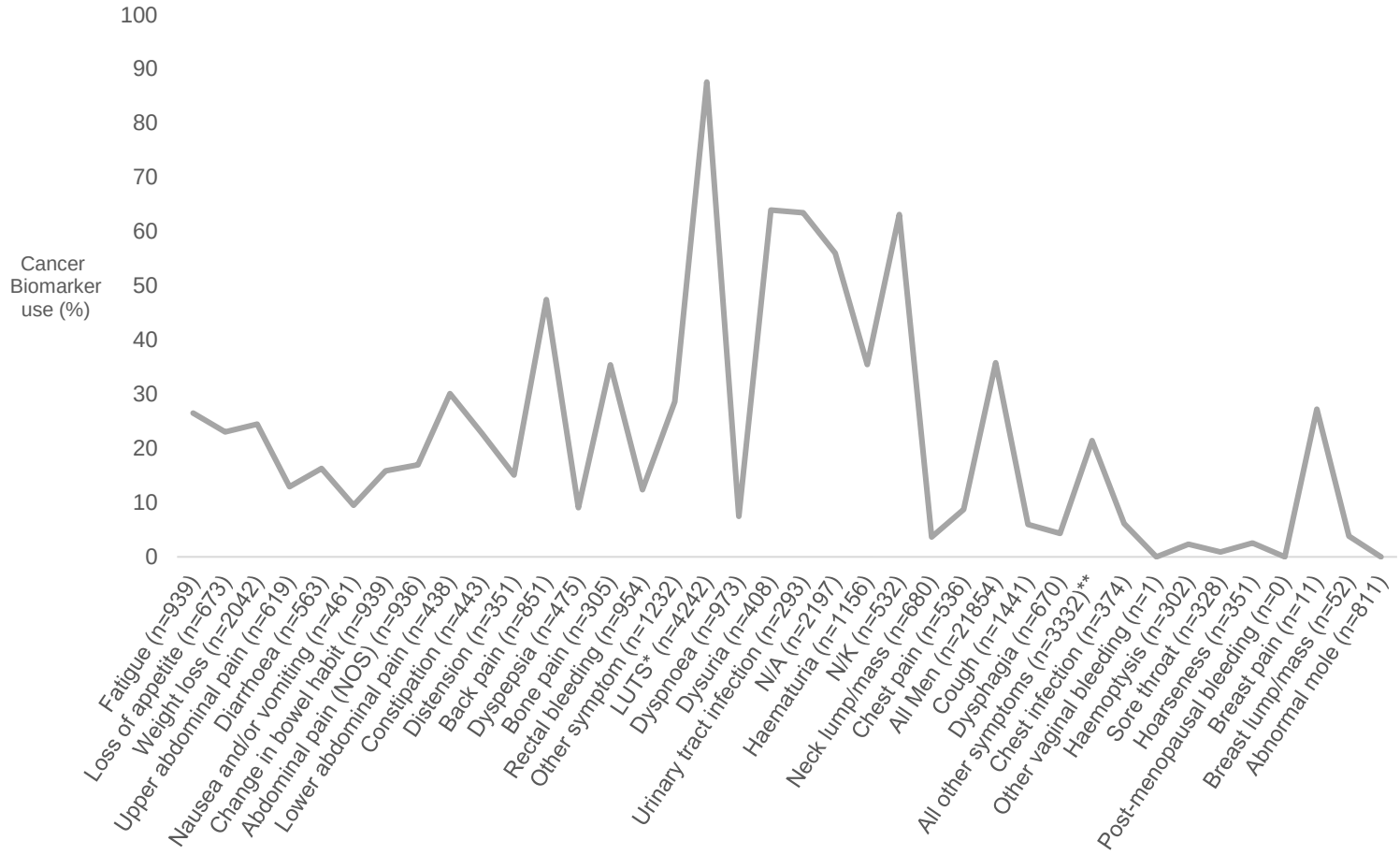
	Cancer Biomarkers					
	Men			Women		
Symptom name	Number of men with symptom	Biomarker use	%	Number of women with symptom	Biomarker use	%
Fatigue (n=1771)	939	249	27	832	105	13
Loss of appetite (n=1264)	673	155	23	591	136	23
Weight loss (n=3408)	2042	500	24	1366	259	19
Upper abdominal pain (n=1192)	619	80	13	573	105	18
Diarrhoea (n=1013)	563	92	16	450	74	16
Nausea and/or vomiting (n=1067)	461	44	10	606	110	18
Change in bowel habit (n=1675)	939	149	16	736	163	22
Abdominal pain (NOS) (n=1932)	936	159	17	996	302	30
Lower abdominal pain (n=1060)	438	132	30	622	199	32
Constipation (n=831)	443	101	23	388	102	26
Distension (n=980)	351	53	15	629	332	53
Back pain (n=1405)	851	404	47	554	64	12
Dyspepsia (n=805)	475	43	9	330	45	14
Bone pain (n=490)	305	108	35	185	13	7
Rectal bleeding (n=1662)	954	118	12	708	69	10
Other symptom (n=2131)	1232	353	29	899	81	9
LUTS (nocturia, frequency, hesitancy, urgency, retention) (n=4434)	4242	3716	88	192	50	26
Dyspnoea (n=1751)	973	73	8	778	30	4
Dysuria (n=551)	408	261	64	143	19	13
Urinary tract infection (n=477)	293	186	63	184	26	14
N/A (n=2795)	2197	1231	56	598	33	6
Haematuria (n=1465)	1156	410	35	309	8	3
N/K (n=687)	532	336	63	155	7	5
Neck lump/mass (n=1201)	680	25	4	521	8	2
Chest pain (n=960)	536	47	9	424	19	4
Cough (n=2577)	1441	86	6	1136	29	3
Dysphagia (n=997)	670	29	4	307	16	5
All other symptoms (n=6828)**	3332	715	21	2949	239	8
Chest infection (n=686)	374	23	6	312	9	3
Other vaginal bleeding (n=421)	0	***≤3	≤0	421	56	13
Haemoptysis (n=469)	302	7	2	167	1	1
Sore throat (n=478)	328	≤3	≤1	150	4	3
Hoarseness (n=468)	351	9	3	117	2	2
Post-menopausal bleeding (n=896)	0	≤3	≤0	896	76	8
Breast pain (n=768)	11	≤3	≤27	757	3	<1%
Breast lump/mass (n=4074)	52	≤3	≤6	4022	12	<1%
Abnormal mole (n=1764)	811	≤3	≤1%	953	0	0
All Patients (n=39752)	21854	7828	36	17898	1461	8

*The boundaries for blue – white - red are set at the upper, median and lower values for each blood test. All other values are coloured proportionally.

**Symptoms accounting for less than 1% (n=398) of cases were grouped together, including nipple changes, pelvic pain, lymphadenopathy (localised), jaundice, night sweats, gastroesophageal reflux, testicular lump, headache, erectile dysfunction, prog/sub-acute loss of central neuro function, pruritis, lip/oral cavity/ tongue lump/mass, testicular pain, loin pain, fever, non-pigmented lesion, axillary lump/mass, unexplained lump suspicious of sarcoma, lesions suspicious of BCC, nipple discharge, thyroid lump/mass, lip/oral cavity/ tongue ulcer, ulceration, early satiety, bruising, bleeding or petechiae, pallor, vaginal discharge, anal mass, deep vein thrombosis, visual disturbance or loss, vulval mass, epistaxis, vulval ulceration, penile ulceration, vaginal mass, lymphadenopathy (generalised), fit/seizure, New onset Diabetes, stridor, leukoplakia and fracture.

***Biomarker use between 0-3 is represented as "≤3" to reduce risk of residual disclosure, with corresponding percentages.

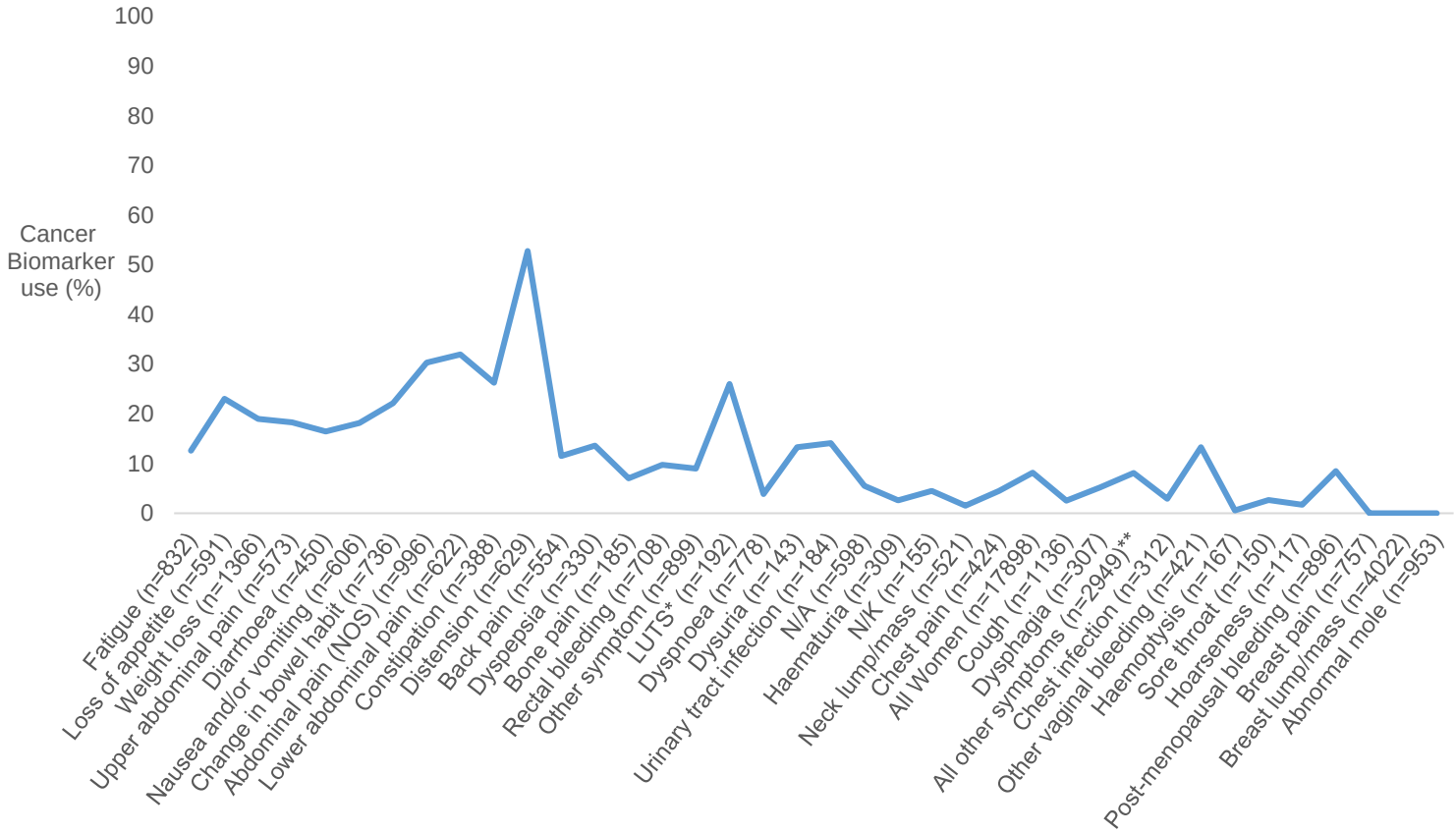
****Proportions presented in white boxes represent cases whereby testing might be associated with guideline recommendations for suspected cancer (based on the type of symptom and blood test).



*Other symptoms includes those accounting for less than 1% (n=398) of cases, including nipple changes, pelvic pain, lymphadenopathy (localised), jaundice, night sweats, gastroesophageal reflux, testicular lump, headache, erectile dysfunction, prog/sub-acute loss of central neuro function, pruritis, lip/oral cavity/ tongue lump/mass, testicular pain, loin pain, fever, non-pigmented lesion, axillary lump/mass, unexplained lump suspicious of sarcoma, lesions suspicious of BCC, nipple discharge, thyroid lump/mass, lip/oral cavity/ tongue ulcer, ulceration, early satiety, bruising, bleeding or petechiae, pallor, vaginal discharge, anal mass, deep vein thrombosis, visual disturbance or loss, vulval mass, epistaxis, vulval ulceration, penile ulceration, vaginal mass, lymphadenopathy (generalised), fit/seizure, New onset Diabetes, stridor, leukoplakia and fracture.

Figure 12: Line graph showing the proportion of cancer biomarker use by symptom type in men.

In women, abdominal distension was most commonly associated with cancer biomarker use (CA125). Around one in three women presenting with abdominal pain (30%) and lower abdominal pain (32%) had a biomarker test, as did around a quarter of women presenting constipation, LUTS, loss of appetite and changes in bowel habit (22% - 26%). In contrast to men, women with not known/not applicable symptoms had comparatively low biomarker test use (≤6%).



*All other symptoms includes those accounting for less than 1% (n=398) of cases, including nipple changes, pelvic pain, lymphadenopathy (localised), jaundice, night sweats, gastroesophageal reflux, testicular lump, headache, erectile dysfunction, prog/sub-acute loss of central neuro function, pruritis, lip/oral cavity/ tongue lump/mass, testicular pain, loin pain, fever, non-pigmented lesion, axillary lump/mass, unexplained lump suspicious of sarcoma, lesions suspicious of BCC, nipple discharge, thyroid lump/mass, lip/oral cavity/ tongue ulcer, ulceration, early satiety, bruising, bleeding or petechiae, pallor, vaginal discharge, anal mass, deep vein thrombosis, visual disturbance or loss, vulval mass, epistaxis, vulval ulceration, penile ulceration, vaginal mass, lymphadenopathy (generalised), fit/seizure, New onset Diabetes, stridor, leukoplakia and fracture.

Figure 13: Line graph showing the proportion of cancer biomarker use by symptom type in women.

5.4 Discussion

5.4.1 Summary

Building on findings from Chapter 4, this study explores the influence of individual symptoms in patients subsequently diagnosed with cancer. Lower specificity symptoms are predominantly associated with increased use of generic blood tests (and vice versa). Less generic blood tests (including cancer biomarker tests) fluctuated in their use according to when patients presented with symptoms that had greater affinity to features of certain cancer-sites. A better insight into the clinical circumstances in which blood tests are used has been obtained.

5.4.2 Strengths and limitations

In line with Chapter 4, this study shares many of the limitations and strengths inherent in the design of the NCDA dataset. Namely, although this study uses representative data, the precise timeframe with respect to symptom presentation, blood test use and subsequent referral actions were not captured (although the recording of investigation information was specified as pre-referral) and a possible under-reporting of symptom codes. Auditing GPs, however, benefited from access to patient records (including free-text) when entering audit data, improving the quality of symptom data capture and the assessment of symptom presentation synchronicity with blood test use.

Other databases may have provided additional information on blood tests beyond those studied, although the nine tests included represent the majority of common uses of blood tests in primary care. Common blood tests such as FBC, U&E and LFT tests provide information across a range of sub-component tests, which were not captured in the NCDA. Information on individual sub-components of the studied tests might provide opportunities to robustly assess their use against clinical guidelines where they are recommended.

5.4.3 Implications

Blood test ordering in patients subsequently diagnosed with cancer varied by the specificity of the presenting symptom and the clinical information arising from the chosen test. For commonly used generic blood tests, their use tended to increase with the presentation of symptoms of lower specificity. Myeloma is characterised by the presentation of non-specific symptoms, such as back pain which has a PPV of 0.1%. The predictive value of this symptom for myeloma increases to 4.0% (exceeding the 3% threshold for referral (96) when combined

with blood test results indicating hypercalcemia (157). Conversely, blood test use declines when patients present with symptoms of higher specificity of possible cancer. Site-specific symptoms such as signs and features of breast cancer often have PPVs that surpass thresholds for relevant referral (for instance, breast lump in 40+ year olds has a PPV of ≥4.8%; (158) and therefore obviate potentially unnecessary primary care investigations (such as blood tests).

Blood tests that were more specific were generally used less than common blood tests, but for some symptoms that represented specific features for certain cancers their use increased. The locality of the symptom to the suspected cancer-site (i.e. whether the symptom was generalised or organ-specific) and GPs awareness of recommendations for testing may partly determine the use of specified blood tests. To illustrate, most men presenting with LUTS had a cancer biomarker test (88% - a likely response to suspected prostate cancer and increased PSA testing endorsed by the NICE guidelines (96). Observed greater than average use of PSA testing in men with LUTS may reflect guideline-based action, yet the frequency drops when other relevant guideline symptoms for suspected prostate cancer are presented (i.e. haematuria, 35% in men). Two-thirds of men with this symptom therefore may be missing opportunities for more PSA tests, given that guidelines recommend PSA testing (alongside a digital rectal examination) to assess for prostate cancer in people with visible haematuria (96). Furthermore, most patients presenting with haematuria are less likely to be offered an urgent referral (159).

Congruent to specified blood tests for cancer, less common generic blood tests follow indistinct patterns of use based on symptom specificity. Serum protein tests are infrequently ordered (used in 3% of study population), yet almost one in five patients who present with symptoms of back pain have this test prior to diagnosis. In this scenario, it is plausible that serum proteins are being used concurrently with symptoms suggestive of multiple myeloma (possibly in response to current recommendations, although how much can be explained by this is uncertain).

The findings help to illuminate previously anecdotal and expected patterns in blood test use prior to cancer diagnosis. By assessing individual symptoms, this Chapter builds on the evidence of possible overuse and underuse in Chapter 4 by highlighting patient populations where blood test use varies by symptom type. Symptom affinity to organ-specific cancer-sites or more generalised body locations may account for this variation, where commonly used

blood tests may be underused in non-tested patients presenting with symptoms that are more vague (I.e. in 21%, 26% and 32% of patients presenting with fatigue, loss of appetite or weight loss, respectively, not having an FBC) and possibly overused in tested patients presenting with organ-specific features (I.e. in over 350 patients having one or more FBC, U&E or LFTs after presenting with breast-related symptoms).

Observed proportions of blood test use may serve as targets for markers of diagnostic process quality, either in a piloting/formative (indicating possible improvement) or evaluative (indicating that a quality marker has/has not been achieved) fashion. Such pilot targets can for example, posit the expected minimum proportion of patients with a given cancer who had specific blood tests as part of their diagnostic process after presentation to primary care with relevant symptoms, and before referral. These pilot targets can directly relate to the implementation of relevant, existing or future, guideline recommendations. For example, in our data we observe that 35% of men with haematuria were tested by PSA as part of their diagnostic process, although the 2015 NICE guidelines recommend a PSA test is performed to assess prostate cancer risk in men presenting with haematuria. Given this, a putative pilot target can recommend that a higher than 35% percentage of men presenting with haematuria ought to have a PSA test as part of their diagnostic process – though what that higher percentage value ought to be should be determined deliberatively by a guideline development group with appropriate remit. Generally, the development of quality markers for the diagnostic process is a broad subject that requires other factors (such as practitioner acceptability, the potential role of chance variation and influence of case-mix) to be considered until a quality measure, formative or evaluative, is developed. Such pilot targets can also be revised periodically, particularly if there is ongoing surveillance of the diagnostic process.

Further exploration of guideline recommended blood testing is warranted within databases that have precise chronological information to help determine the relationship between test use and relevant symptom presentation. This timeline information is important because the assumed relevant symptoms recorded by the NCDA auditor may not be the reason why blood tests were ordered (i.e. a prior symptom might have triggered the blood test). It would be possible to explore restricted intervals within the NCDA (attempting to simulate synchronous testing with symptom presentation), although this method would not entirely eliminate the

uncertainty regarding chronicity. Specifically, further assessment is required in symptomatic populations where relevant blood tests are expected (according to clinical recommendations) in order to appreciate opportunities to support GPs' use of blood tests. The growing evidence supporting the predictive value of blood tests for cancer warrants the continued monitoring of testing patterns for quality and safety purposes.

5.4.4 Chapter Summary

This research substantiates the importance of clinical presentation, as highlighted in Chapter 4, on GPs' use of blood tests in patients subsequently diagnosed with cancer. Increases and decreases in common blood test use correlate with the presentation of low and high specificity symptoms, respectively. More specific blood tests and cancer biomarker tests are used in a less indicative fashion based on the symptoms affinity to a given cancer-site and are generally adopted to a lesser extent. Symptom presentation explains some of the variation in blood test use, suggesting that interactions between GPs and patients during clinical assessments are important in determining the use of blood tests. Counterfactually, large variance in test use also signifies the possibility that other factors might be influencing decision-making. What cannot be accounted for in this study is the context in which blood tests were ordered (i.e. how factors beyond the clinical assessment influenced decision-making). Therefore, a qualitative approach is adopted in Chapter 6 to better understand the influence of non-clinical factors on GPs decisions to use blood tests.

Chapter 6: Understanding factors beyond the clinical presentation that influence GPs' use of blood tests in patients with possible cancer. A GP interview study

6.1 *Background:*

6.1.1 The process of decision-making (1. Psychological theories to explain decision-making for blood testing: "In the head of the GP"):

The use of common blood tests in primary care is determined by the clinicians' decision-making processes.

Theoretical frameworks for clinical reasoning can help to understand GPs' decisions regarding blood test use. These include the Normalisation Process Theory (NPT) and the Dual Process Theory (DPT), both established in psychological and implementation science research. They can illuminate the complexity of such decisions. These two theories can help to understand how tests are normalised into practice and how decisions about the use of tests can be 'slow' (analytical) or 'fast' (automatic) depending on certain factors. Below follows a brief account of these theories and their relation to decision-making to use blood tests.

Normalisation Process Theory (NPT)

The complex decision-making pathways related to use of blood tests are captured within the NPT, whereby test use is dependent on how it is embedded into clinical practice (i.e. how the test 'disappears' from view and becomes normalised (160). The NPT allows researchers to better appreciate barriers and facilitators to implementation based on how individuals adopt interventions to their own practice. Normalisation of interventions requires individuals to meet the requirements of four underlying principles, coherence (i.e. GPs understanding the value of blood tests), cognitive participation (i.e. GPs considering blood test use in their decision-making), collective action (i.e. having a general practice configuration that enables blood testing) and reflective monitoring (i.e. appraising the costs and benefits of blood test use; (160).

Dual Process Theory (DPT)

Decision-making behaviour was originally described as putting intentions into action, where implicit or explicit plans are required to guide actions to achieve goals (161). The understanding of this two-sided thinking was further developed over decades and their functional differences emphasised to highlight two distinct cognitive systems encapsulated within the Dual Process Theory (DPT). Largely recognised as a leading theory for describing

decision-making processes (162–171), the DPT posits that cognition can be dichotomised into type 1 (fast/automatic) and type 2 (slow/analytical) processes.

In the context of deciding to use a blood test, automatic "type 1" decision making is an indication of clinical certainty. The individual deciding the appropriateness to use a blood test relies on cognitive heuristics to support their decision (i.e. the rate of change or progression of symptoms might be a simple rule for GPs to employ to guide their decisions to use a test). Importantly, clinical certainty does not necessarily result in accurate diagnosis, as this can manifest as overconfidence and subsequent missed diagnostic opportunities (potentially to use blood tests more effectively; (172,173).

Conversely, when an element of deliberation is required (i.e. analytical "type 2" decision-making) decision-making becomes more complex and suggests clinical ambiguity. When deciding to use blood tests, GPs have to account for the probability of disease and the associated harms and benefits with testing. Rationalising such risks is formally understood and described using threshold models (174,175) where GPs will order a test when the risk of not doing so outweigh the harms of doing so. In this context, 'harm' should not be considered as simply in terms of clinical harm but also psychological consequences and even practical considerations such as the inconvenience and time needed by the patient and resources required by the health system. Thresholds for testing can vary depending on the individual and also circumstances. Decision-making for diagnostic testing can be influenced by emotions such as regret derived from test action or inaction (176), which is considered an important probability threshold for diagnostic test decisions (177–179). Risk aversion offers another driver that could act as a promoter of decisions to test. For example, GPs desire to minimise risks can lead to increased referral and laboratory testing rates (180,181). Evidently, a lower threshold for acceptable diagnostic probability of a certain disease (such as cancer) may encourage physicians to use more deliberative "type 2" cognitive processes that are linked to risk averse decisions (such as ordering further blood tests; (182). Decision-making is also influenced by knowledge and experience because more experienced GPs may intuitively identify clinically relevant aspects of a situation more efficiently than less experienced peers, leading to fewer testing decisions because a perceived lower level of additional information to be gained from the tests (183,184). This might also impact how GPs' use of common blood tests in a Bayesian fashion to assess the likelihood of cancer (i.e. using blood test results in

combination with presenting symptoms, whereby a "positive test" makes cancer a more likely explanation; (42).

Theories help to contextualise how GPs' decide to use blood tests, however external influences may also exist, including the availability and configuration of phlebotomy services, patient preferences (through their desires or expectations for testing), time constraints during the consultation, and the existence of clinical guidelines. Their influence is considered below:

Factors influencing decision-making to use blood tests.

Primary Care Context: Given the multiplicity of factors influencing cancer care pathways (see appendix 3. K; (185), GPs decision-making may be predetermined (and even limited) by the environment in which they operate. In the context of increasing workloads, rational decision-making during primary care consultations is likely to be restricted because GPs have to process limited information within a time-constrained situation (Bounded rationality; (78,79,186–188)).

Wider-system context: Factors beyond the clinical encounter might negatively influence decision-making processes to use blood tests. These may include testing capacity, medicolegal concerns relating to inappropriate use of blood tests and possible litigation, GPs' use of other tests (overlooking the diagnostic value of blood tests) to achieve clinical performance targets, for example, those outlined by the Quality and Outcomes Framework, QOF) and challenges with keeping up-to-date with relevant evidence (65,79,80,189,190). Regarding testing capacity, access and availability of phlebotomy remains an important factor for testing; not all practices have access to on-site phlebotomy (requiring patients to travel beyond their primary care practice for testing) and appointment availability will vary by practice.

Importantly, understanding prior decision-making theory and practical aspects of blood testing (illustrated above) was necessary to better appreciate the range of factors that may influence blood test use in patients presenting with possible cancer symptoms. The above paragraphs highlight the complexity of decision-making, illuminating a holistic range of psychological and physical factors to using blood tests (existing in the mind of the GP and

within their environment). Therefore, the development of questions within this qualitative Chapter is informed by a framework that accounts for attributes of the entire diagnostic process that might influence decisions to use blood tests.

6.1.3 The Situativity Perspective Framework (Bringing theoretical and practical factors together)

The Situativity Perspective Framework (SPF), a relatively new social cognitive theory, can help to illustrate how clinical reasoning occurs within (and might be influenced by) the social environment (191). The SPF draws on social cognitive theory and environmental contexts to portray clinical decision-making as a 'situated' process. The framework helps to integrate theories of decision-making (largely arising from the field of cognitive psychology) with social science and human factors research highlighting the influence of social norms, and of operational and practical enablers or barriers to diagnostic testing. In doing so, perspectives of clinical reasoning from both cognitive psychology and implementation science can be brought together into a broader framework acknowledging the influence of both internal (to the clinician) and external behavioural drivers. Importantly, the SPF highlights that clinical reasoning occurs within a specific context where the "thinker" interacts with already acquired knowledge (embodied factors), with the local practice environment (embedded factors) and with the wider healthcare system (extended factors).

Embodied decision-making: the cognitive processes "in the head of the GP":

The embodied level of decision-making captures how GPs initial thought processes are derived from their clinical knowledge, their prior experience of using blood tests and the information value that can be attained from their use (also refer to Chapter 2 illustration of situativity perspective for blood testing). The SPF helps to understand GPs decision-making from the perspective of their primary responsibility to assess risk and advise patients on possible diagnoses.

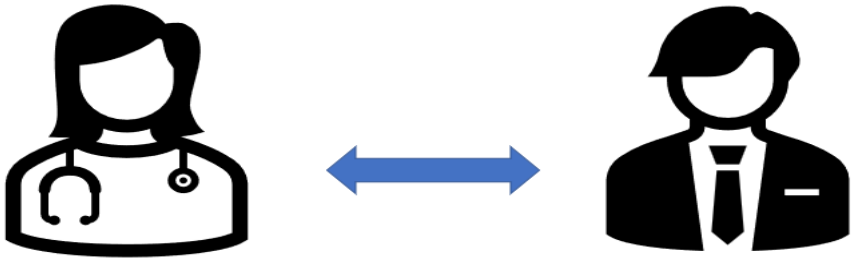


Figure 14: Embodied decision-making - occurs during clinical interactions between the GP and patient.

Embedded decision-making: "within the local environment":

How the GP interacts with their environment may influence management decisions on whether blood tests are to be used. Embedded decision-making is explained less by medical knowledge but more by service factors, i.e. access and availability of phlebotomy (on-site vs off-site), patient transport arrangements to phlebotomy sites (where applicable) and local protocols and knowledge (192). In that respect decision-making shifts from internal (cognitive) to external (contextual) drivers. Embodied decision-making is likely to precede embedded decision-making, where the GP considers environmental factors after initial consideration of clinical workup. Embedded decision-making may be vulnerable to so-termed 'operational failures' (defined as "disruptions, errors, or inadequacies in information, supplies, or equipment needed for patient care"; (193), where GPs diagnostic decisions are hampered by external factors across the primary care setting.

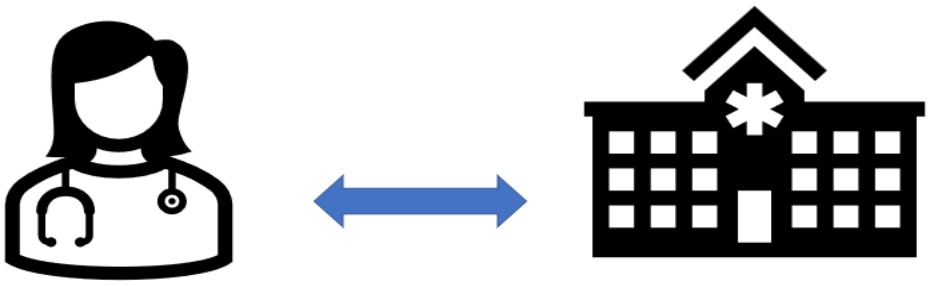


Figure 15: Embedded decision-making - occurs during interactions between the GP and their local environment.

Extended decision-making: "diagnosis in the real-world"

Building on the notion of embedded decision-making, extended decision-making accounts for how GPs make decisions within the broader healthcare system and societal norms and expectations. This includes the influence of clinical guidelines (i.e. recommendations for using blood tests in certain clinical presentations), and organisational structures (i.e. being aware of local commissioning policies). To overcome the cognitive burden and risk of ambiguous

decision-making based on externalised factors of the healthcare system, multidisciplinary shared decision-making is encouraged to support extended cognition processes by clinicians (194–196).

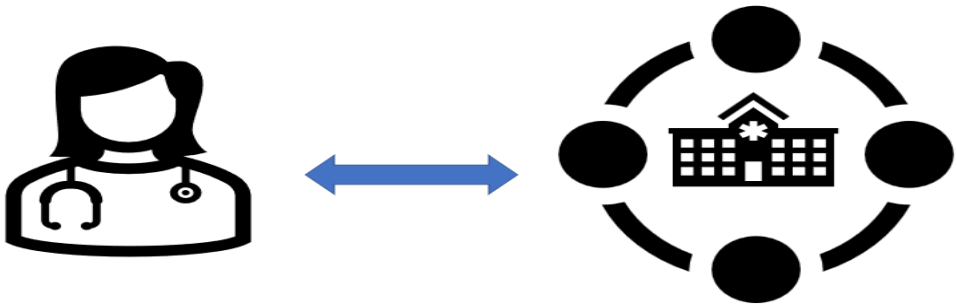


Figure 16: Extended decision-making - occurs during interactions between the GP and wider societal and healthcare system factors.

6.1.4 Summary of evidence on factors influencing clinical decision-making

This Thesis acknowledges the contribution of cognitive as well as the social and contextual factors in the diagnostic process using the SPF. The SPF could help to support and guide researchers and policymakers about factors that influence GPs decision-making for using blood tests, potentially highlighting opportunities to optimise their use. To this end, the SPFs sensitivity to many aspects of clinical reasoning processes made it a valuable tool for informing the construct of questions and development of themes related to blood test use in this Chapter (see Methods for details). The subsequent section reviews prior evidence on what influences GPs' use of blood tests.

6.2 *Introduction: Understanding GP decision-making to use blood tests*

Blood testing is common in general practice (52), often used to support decision-making where information additional to medical history and clinical examination is deemed beneficial, particularly in patients presenting with non-specific symptoms (144). The decision to use blood tests however might be based on prior experiences and not clinically motivated (i.e. used as a social function; (197). Although variation in common blood test use is observed by patient characteristics (see Chapter 4), the influence of factors beyond the clinical presentation on GPs' decision-making to use blood tests needs further exploration.

An important consideration regarding factors influencing GP decisions on blood test use is the complexity of the blood testing process itself. Litchfield and colleagues highlight logistical and communication challenges with the blood testing process in UK primary care, and possible avenues for simplifying the testing process (114,115,198). Some of the factors that may

hinder decision-making to use blood tests may be solved by technological innovations, such as point of care tests (POCTs – see Chapter 2).

A GP with easy access to phlebotomists may be more inclined to using blood tests than GPs with limited access (often dependent on phlebotomy service configuration – i.e. on-site/off-site; and whether a separate appointment is required after the consultation with the GP). GPs may also consider that they are expected to be seen to 'do' something (either in response to patient expectations or to minimise risk of medico-legal complaints; (199).

Some blood-based POCTs have been adopted in primary care for conditions such as diabetes monitoring (i.e. blood glucose measurements) and anticoagulation monitoring - see Chapter 2). A wider range of POCTs that are the equivalent of conventional common blood tests have been developed but are principally used in secondary care. These include full blood count (FBC) and inflammatory marker tests, used in emergency departments to help expedite diagnosis and support management of patients. Similar applications may also exist in primary care though their exact potential is uncertain (200). Process breakdowns that arise from laboratory services and phlebotomy access barriers may be obviated by the use of POCTs. For patients presenting with non-specific symptoms, POCTs could potentially offer a fast diagnostic strategy for assessing whether abnormalities (such as anaemia and thrombocytosis) are present.

These putative benefits of POCT testing need to be counter-balanced by the unavoidable interruption of GP workflows, and longer consultation duration (if POCTs were to form part of the consultation). A suitable model might be one where POCT testing takes place post-consultation by an on-site phlebotomist; such a model obviates the transporting of samples and associated process steps and delays, and also the need for out-of-site / different- day phlebotomy appointments.

Innovation in point of care technology and solutions to adoption have been further realised during the Covid-19 pandemic. The scientific pursuit of rapid diagnostic solutions for the virus resulted in unprecedented innovations and adoption of community-based POCTs (e.g. in the form of lateral flow or rapid tests). This successful implementation might translate into

further technological breakthroughs that support POCT use during primary care consultations.

6.2.1 Summary of GP motives for blood testing (and what else is needed):

Blood test use might be influenced by physical and psychological factors beyond the clinical presentation, which may form part of embedded and extended clinical reasoning. The relative contribution of these factors on GPs decisions to use blood tests remains less well explored. Furthermore, given the complexity of the blood testing process, the extent to which POCTs can support blood testing decisions for suspected cancer patients also warrants further investigation.

6.2.2 Aims

To better understand GPs perceptions of blood testing by exploring GPs experiences and attitudes towards their use in relation to embedded and extended factors of decision-making (beyond the clinical presentation associated with embodied decision-making).

6.3 Methods

6.3.1 Conducting semi-structured Interviews

The study was designed with input and training offered by Dr Alice Forster, Principal Senior Research Associate and Dr Christian von Wagner, Reader in Health Psychology, with research assistance from Zainab Kazaz.

Recruitment/sampling

Prior to conducting the interviews, the schedule was piloted with a practicing GP working within the UCL Epidemiology of Cancer Healthcare and Outcomes (ECHO) group (Dr Meena Rafiq), a senior health psychology researcher (Dr Christian Von Wagner) and an epidemiologist (Prof Georgios Lyratzopoulos) and revised based on their feedback. Recruitment for the semi-structured interviews was achieved through a network of academic GPs (affiliated with the CanTest Collaboration – an international group of primary care cancer researchers). Recruitment was not limited by saturation restrictions, as I wanted to obtain as much information as possible on the factors that influenced blood test use. Interviews were

conducted using Microsoft Teams which recorded the interviews as MP4 files. For transcription and anonymity purposes, these recordings were converted into MP3 audio files and then transcribed verbatim (outsourced to Devon Transcription) and anonymised. Ethics approval was obtained from the UCL Research Ethics Committee on 21/08/2020, following initial application on 29/05/2020.

6.3.2 Question conceptualisation and development of interview schedule

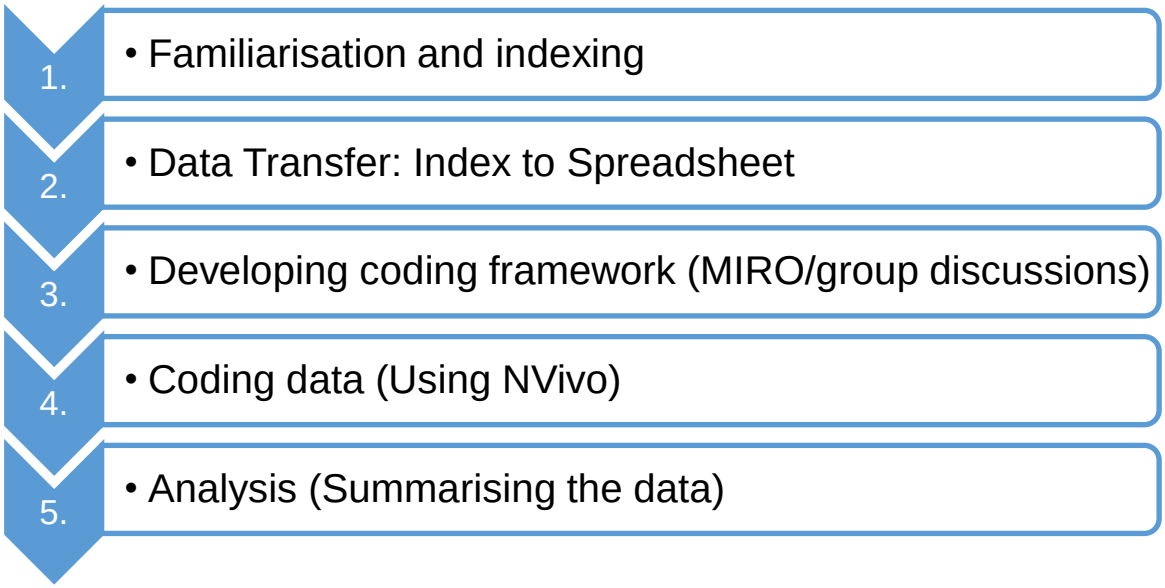
Theory behind interview schedule

Previously identified factors in the literature associated with test use formed the broad themes of an interview schedule (see appendix 3. L for outline of interview schedule). The first 5 interviews included a prioritisation task using a Likert-scale which revisited the determinants explored during the interview and measured how influential they are in affecting GP decision-making to use a blood test. This enabled further iterations of the interview schedule.

6.3.3 Data Analysis

Process for content analysis

Qualitative content analysis enabled content sensitive assessment (192). Specifically, I used inductive thematic analysis to explore themes in blood test use, which was comprised of several phases:



Step 1: Familiarisation and indexing (Preparation for analysis: part 1)

Before analysing the transcripts, two raters (B.C and Z.K.) went through an independent process of familiarisation with the transcript content. The raters initially read through several transcripts and highlighted sections of text where themes were emergent in relation to how GPs used blood tests (preceding text before the quote was highlighted if required for context). This process assured that relevant questions were being asked (judged on the relevance of the responses provided by GPs) and identified additional themes or subthemes that may not have been considered during the development of the interview schedule (supplementing further iterations of the interview schedule). Relatedly, this process "filtered out" themes that were irrelevant and could therefore be removed from subsequent iterations (such as GPs perceptions about their ability to communicate with the laboratory). Comments were linked to highlighted themes to help create an index (see appendix 3. M, for example), which helped theme categorisation. Indexes were initially created independently (between B.C and Z.K) and subsequently merged during a joint review process, agreeing a final index to expedite data transfer (I.e., quotes) from interviews into pre-structured spreadsheets.

Step 2: Data Transfer and Preparation for coding (Preparation for analysis: part 2)

Before developing a coding framework, some preliminary organisational tasks were required. Firstly, relevant quotes from the interview transcripts that were indexed were transferred into a spreadsheet (Spreadsheet 1). Having access to that data in this format was necessary to better manage the information and filter specific quotes by GPs.

With all relevant quotes in spreadsheet 1, B.C and Z.K independently developed another (spreadsheet 2) where "headings" were created (I.e. themes/sub-themes) to categorise quotes (factors) arising from the transcripts. Spreadsheet 2 was split into three levels; domains, sub-themes and factors (quotes). The domains broadly covered clinical presentation/patient factors, GP professional practice factors, health care system/ process factors, test implementation factors and Covid pandemic-related factors. Under each domain were empty cells which B.C and Z.K independently populated with "headings" (sub-themes), allowing subjective and impartial decisions about the most appropriate heading based on the entered quotes (relating to factors that influence blood test use). This helped to avoid biasing the analysis to any themes they may have been predisposed to during the indexing phase and provided opportunities to modify previous themes and expand on new ones. Quotes where

the researchers were unsure about the appropriate theme were labelled “other” so that they could be subsequently discussed.

Step 3: Developing the coding framework

Quotes from the indexing spreadsheet were added to a second spreadsheet, used to organise data into a framework to aid the coding process). B.C and Z.K independently allocated quotes to themes depending on their relevance to how they influenced use of blood tests.

Once quotes were allocated to themes, the researchers collaborated to agree on a coding framework, using MIRO; an online software that allowed sharing of the generated themes and sub-themes (i.e. the codes to be used in NVivo – see Appendix 3. N, for MIRO example). Consensus about inclusion (i.e. agreeing with the relevance of themes, sometimes altering or merging themes if deemed similar) and exclusion (i.e. agreeing a particular theme to be irrelevant) of themes was achieved through discussions. Disagreements were solved by a third senior team member (A.F).

Step 4: Coding the transcripts

After the development of the coding framework (Step 3), the interview transcripts were uploaded into a qualitative analysis programme (NVivo) where they would be categorised and coded before analysis. Within NVivo, data was contained within a three-level coding system. Congruent to SPF, three higher-level categories were generated to capture data that corresponded with embodied, embedded and extended decision-making. Within these higher-level constructs, relevant themes that captured factors related to blood test use were generated. In the final level of construction, sub-themes (level 3) associated with factors of blood test use were embedded into the broader themes (level 2) that were categorised within aspects of the SPF (level 1 - see figure 17).

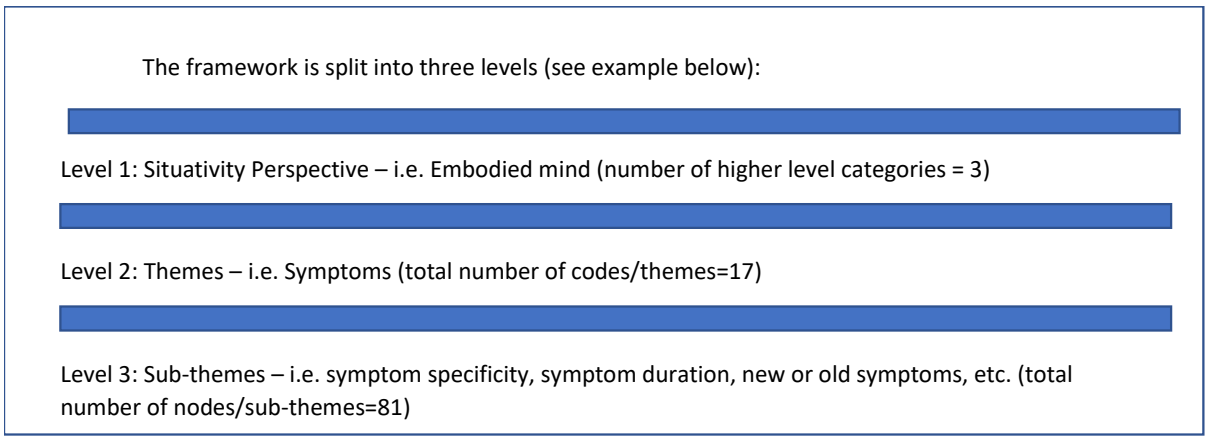


Figure 17: Levels of information in coding framework.

Relevant quotes were contained within each sub-theme. Some quotes failed to converge with the coding framework, potentially highlighting imperfections with its design or uncertainty in the mind of the coder. Therefore, the coding process remained iterative so that new codes could be generated if necessary. Coding commenced with the recording of relevant textual information about GPs' use of blood tests into so-termed 'nodes' (representing sub-themes), which was then placed within coded themes related to GPs' use of blood tests. The original coding framework contained 78 nodes. After identifying unassigned quotes and allocating them into either pre-existing or new nodes (n=14), the framework included 81 nodes.

Step 5: Analysis (Summarising the data)

The prior steps were necessary to categorise the data arising from the interviews into emergent themes, which was crucial before analysis. By assessing textual data within nodes (I.e. quotes) in the context of their allocated sub-themes, broader themes and constructs of the Situativity Perspective Framework, I attempted to summarise and describe the data within paragraphs of text. This allowed for a summation process without losing in-depth information. Subsequently, discussions with A.F helped to concentrate the summarising process, considering the physical and psychological factors arising from the data.

6.3.4 Interpreting the data (informing the discussion using Behavioural Change Theory):

Identifying behavioural barriers (Theoretical Domains Framework):

The Theoretical Domains Framework (TDF - (201) helped to link GPs motives for using blood tests (identified using the SPF) to possible behavioural barriers impeding their use. The TDF was established using an amalgamation of 33 behavioural change theories to better understand what influences health professionals implementation of evidence-based recommendations (202). The TDF is commonly used for exploring behavioural tendencies for reducing low value healthcare (203); being increasingly employed for understanding primary care and pre-operative laboratory testing decisions (204–206). The TDF categorises different behavioural domains into constructs that further refine that behaviour (see appendix 3.O for more detailed description of domains).

This framework was adopted to inform my interpretation of behavioural barriers identified throughout the thematic analysis. For example, GPs sometimes had concerns about the accuracy of blood tests being misleading, relating to the TDF domain "beliefs about consequences".

Identifying solutions to behavioural barriers (Behavioural Change Wheel):

The TDF domains can fit within the Behavioural Change Wheel (BCW - see Figure 14). The BCW characterises interventions and policies for behavioural change, which encircle a focal behavioural system (formally the COM-B model, a theoretical model of behaviour which posits how behaviour is conditionally-based on capabilities, opportunities and motivations; with the TDF being latterly considered within the wheel; (201,207). The outer two circles of the BCW can be used to highlight solutions (intervention and policy-based) relating to sources of behaviour identified by the TDF.

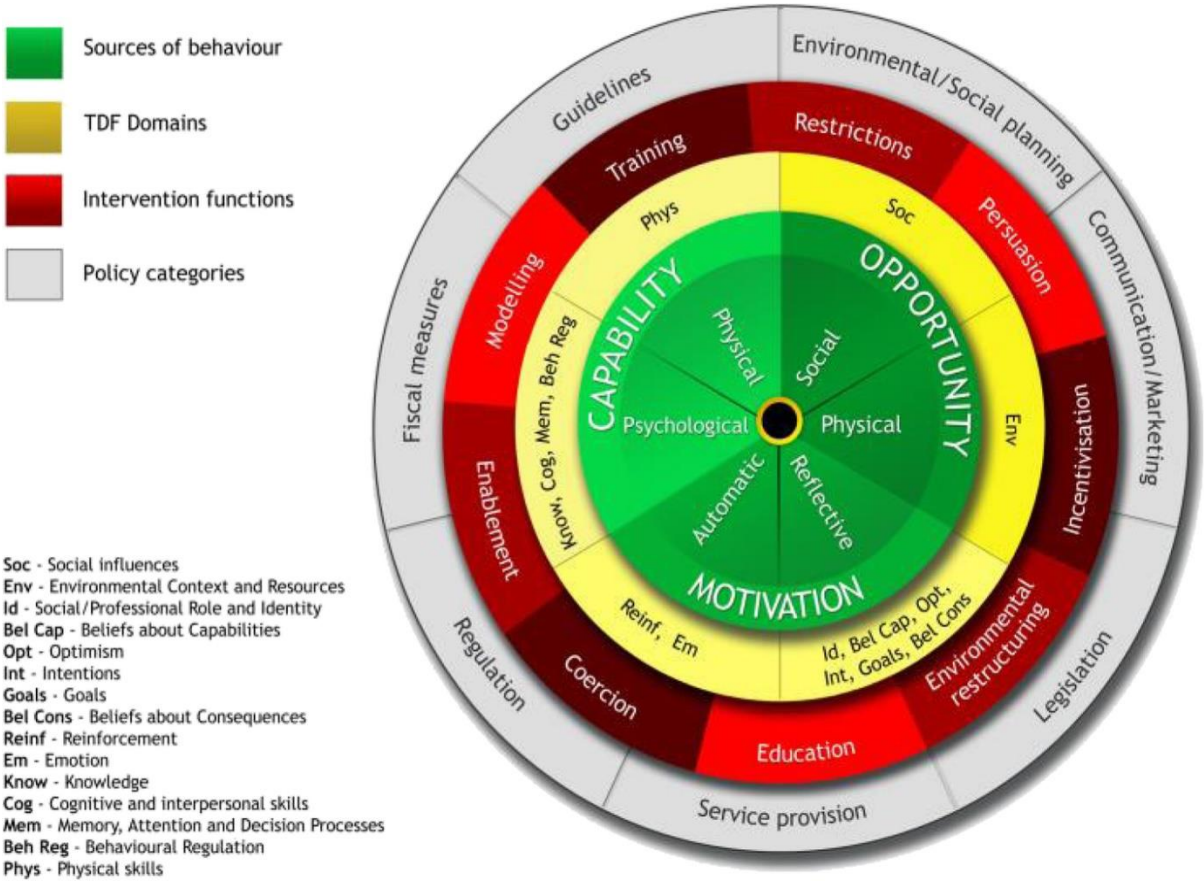


Figure 18: Theoretical Domains Framework linked with COM-B model within the Wheel of Behavioural Change (207,208).

I used the BCW (with the embedded TDF) as a theory-based approach to consider appropriate interventions for optimising blood test use. Solutions for reducing and encouraging GP use of tests have previously been recognised through adopting the BCW (209,210). Implementing a previously employed three-phased analysis, I firstly performed the inductive thematic analysis (steps 1-5 above), mapped emergent themes to the TDF domains (identifying barriers) and then finally mapped TDF domains to the BCW intervention functions (identifying solutions) to study behaviour change in primary care clinicians (211).

In brief, the coding process helped to categorise relevant factors of blood test use (using the coding framework) into themes and sub-themes (with iterative generation of new themes if required). For example, participants often reported concerns with blood test use that related to logistical aspects of testing, such as the availability of phlebotomists. Given the great number of such quotes, a broad theme relating to phlebotomy service processes was generated to capture relevant sub-themes, including the testing capacity of phlebotomy services. Emergent themes were summarised during the analysis to inform the discussion.

My interpretation of the findings was chiefly based on the emergent themes from the data, yet generated sub-themes (providing more precise detail) enabled opportunities to assess their fit to behavioural domains of the TDF (supporting my interpretation of possible barriers to blood test use). After matching sub-themes to relevant TDF domains, I further cross-referenced the identified domains to the intervention functions of the BCW to identify intervention targets.

6.4. Results

6.4.1 Participant Characteristics

Fifteen GPs were invited, of whom 11 (5 female and 6 male) responded and participated in interviews ranging from 27-68 minutes. Most participants were based in urban practices. Interviews were completed in two batches, the first five were conducted between October and November, 2020, while the latter six were completed between March and April, 2021.

6.4.2 Thematic Analysis:

Beyond presentation and other clinical factors, three major themes were identified to influence GPs' use of blood tests:

- phlebotomy service configuration and related processes,
- GPs' expectations and their perceptions of patient expectations, and
- perceptions of diagnostic accuracy of blood tests.

Throughout these themes several sub-themes were also identified, including concerns about possible overdiagnosis (related to the third main theme, on perceptions about the diagnostic accuracy of blood tests) and the potential use of blood-based POCTs (embedded throughout all three themes). Where relevant, the influence of Covid-19 was also considered given that the field work was conducted intra-pandemic and while societal and health service use changes were occurring.

Theme 1: Access to phlebotomy services

The availability of phlebotomy services influenced GPs perceptions about their use of blood tests:

"I think that when phlebotomy is easily available, I am much more likely to request it." [GP-1]

Conversely, GPs willingness to use blood tests appeared to decrease when phlebotomists were not available (appendix 3. P; workflow; GP-11). Participants also expressed that they factor patients access to phlebotomy appointments into their decision-making to use blood tests (aiming to reduce repeat visits and travel burden for patients residing in distant areas - appendix 3. P; logistics; GP-6). Improving access to phlebotomy was deemed advantageous for both patients and GPs, providing the test was performed after the consultation. The challenge of transitioning from testing to consulting was suggested to be inefficient and time-consuming within the limits of a 10-minute consultation (appendix 3. P; workflow; GP-4, GP-11).

Given the limited time available for a GP consultation, access to same-day phlebotomy was favoured over in-consultation POCT use. Decision-making for using same-day blood tests was dependent on clinical severity. In very urgent cases, blood testing was less likely as GPs tended to opt for admitting these patients directly to hospital, while a safety-netting approach was adopted in patients presenting with concerning but not urgent symptoms (whereby a blood test was booked to help inform subsequent decisions - appendix 3. P; GP Skills; GP-9). In semi-urgent cases same-day blood tests were deemed necessary, including for patients with red-flag symptoms for cancer:

"I think, very severe symptoms or worrying symptoms, or red flags of cancer or something else serious, would be the ones you'd want to do same day." [GP-11]

Decision-making for same-day blood testing could be guided by referral criteria within guidelines (96)- appendix 3. P; GP Skills; GP-6). Although GPs expressed the importance of remaining astute to updates of national clinical guidelines (appendix 3. P; Guidelines; GP-1), some were further influenced by local processes and pathways, which may dictate different requirements for blood testing (appendix 3. P; Workflow; GP-11).

GPs expressed concerns about the logistics of blood sample transportation. Several were cognisant of the time slot at which blood tests were ordered and obtained; reflecting on both

the time schedule for courier services to collect samples (i.e. not ordering blood tests after the courier has visited the practice) and risk of blood sample degrading if stored for an extended period:

"logistics of couriering and getting the samples from a practice to the lab sometimes is critical because samples need to be refrigerated or need to be analysed within a certain time frame, so there's definitely, yes, logistics and transport that come into it." [GP-3]

Waiting times for test results were not considered to prevent using blood tests (appendix 3. P; Guidelines; GP-3). In the context of cancer, two days was deemed a tolerable period for awaiting result feedback (precluding the need for blood-based POCTs – appendix 3. P; POCTs; GP-9).

When prompted about possible use of blood-based POCTs, some GPs indicated that their use may increase blood testing (appendix 3. P; POCTs; GP-9) and reduce patient visits for subsequent phlebotomy appointments (appendix 3. P; POCTs; GP-11). The ease of use and the avoidance of venepuncture were deemed as potential benefits of POCTs:

"Certainly, if it was as easy to use as a diabetic finger prick or something, I think you would be doing it a lot more." [GP- 11]

However, participants affirmed that unless more time was provided for consultations (to incorporate testing and decision-making), POCTs were unlikely to be adopted (appendix 3. P; POCTs; GP-7). Procedural aspects of POCT use were also considered to be time-consuming, as GPs reflected on the multiple practical steps required with intra-consultation urine testing (implying similar or greater pitfalls apply to blood-based POCTs – appendix 3. P; POCTs; GP-10). Use of POCTs as part of consultation was deemed to likely result in increasing workloads (appendix 3. P; POCTs; GP-3).

GPs also had reservations about the need to explain unexpected findings during a POCT-including consultation (appendix 3. P; POCTs; GP-6). POCT use also diminished time available for decision-making and communication with the patient (i.e. watchful-wait strategy)(appendix 3. P; POCTs; GP-10).

GPs have had to modify their use of blood tests in response to Covid-19. Most GPs described fewer physical examinations as remote (video or telehealth) consultations became very

common during the pandemic. Therefore, blood tests were ordered prior to subsequent consultations to support decision-making:

"we are trying to assess things remotely at the starting point. So some conditions, I can do the history over the phone, fine, they are not in front of me at that time, so I can't do an examination yet, but sometimes I might feel it's still important and if I felt even with the examination I still wanted to do a blood test, I might do the blood test first and then bring them in" [GP-3]

Summary of factors relating to phlebotomy:
• Availability and ease of access of phlebotomy services • Traveling requirements for patients attending phlebotomy • Variation in local and national phlebotomy processes and pathways • Timeframes and logistics of sample collection and processing

***Box 1**: Summary of factors relating to phlebotomy*

Theme 2: Clinicians' expectations and perceptions about patients'

When GPs tell patients that a blood test is required, they report that there is typically little hesitancy from patients (see appendix 3. P; Patient Expectations; GP-8). Some patients consult expecting a blood test to be ordered (appendix 3. P; Patient Expectations; GP-3) (appendix 3. P; Patient Expectations; GP-9). Anxiety is also considered to play a role in patient expectations of blood tests:

"I definitely do more, depending on patient anxiety and their desire for them, which isn't probably a good reason to do blood tests. But I bet it's not just me that's in that boat."[GP-10]

Many GPs were amenable to patient requests for blood tests, considering that tests are relatively harmless and cost little (appendix 3. P; Patient Expectations; GP-4). Presenting symptoms influenced GPs receptiveness to patient requested blood tests, with GPs being more willing to agree to testing in patients with vague symptoms (appendix 3. P; Patient Expectations; GP-8). Similarly, GPs appreciated the reassurance that could be obtained by blood tests in anxious patients independently of whether a strong clinical indication exists for their use:

"So if you really don't think there is something wrong with somebody and the patient is anxious or you don't think they believe you or they want some reassurance, some normal blood tests, especially routine ones like we are discussing, are sometimes quite helpful to reassure the patient that there is nothing wrong." [GP-10]

GPs perceived that patient reassurance from (normal) blood test results benefit the patients' experience of GP empathy and interpersonal skills (i.e. showing that GPs are taking them seriously – appendix 3. P; GPs perception of blood test use; GP-4) and boosting patient confidence in GPs' decisions (appendix 3. P; GPs' perception of blood test use; GP-6). Although normal blood test results are reassuring, there may be instances where results promote patient anxiety (appendix 3. P; GPs perception of blood test use; GP-11), which may tame GPs using them (appendix 3. P; POCTs; GP-10). Furthermore, GPs also considered the value of blood tests for providing reassurance to themselves for urgent referral decisions:

"I suppose if there is someone who is very ill and there is something that can help me decide whether he or she needs to go to hospital right now – yes that would be helpful." [GP-2]

Blood test use to support clinical decision-making was a widely accepted motive among participants (appendix 3. P; GPs Beliefs; GP-4), though contingent on GPs' previous

professional experiences and the nature of the result. Early-stage career GPs considered their use of blood tests to be higher than those in their later stages, reflecting varying degrees of confidence in clinical acumen and desire for reassurance (appendix 3. P, GPs experience; GP-11). Late-career GPs however may have been more exposed to misdiagnosis, which may also encourage blood test use (appendix 3. P; GPs Experience; GP-8). Independently of GPs career stage, concerns about explaining abnormal results to patients and the associated risk of increased patient anxiety may moderate GPs desire for using blood tests:

"if you have got slightly off tests that are meaningless, but they are slightly off, that can create anxieties as well. I am slightly careful with using blood tests just as a reassurance, because you can end up with potentially more anxiety than you are solving". [GP-9]

Although GPs acknowledged that increased blood test use could contribute towards patient anxiety and subsequent testing, this did not necessarily translate into concerns about over-testing:

"It's not necessarily that the blood test was the wrong thing to do, but it can sometimes lead you to other investigations and anxiety and worry for patients." [GP-6]

Summary of factors relating to GP and patient expectations:
• Patients demands/expectations that a blood test would be ordered (GPs sometimes had concerns about these requests leading to overtesting and increased patient anxiety). • GPs' use of blood tests as a tool to gain more reassurance in their diagnostic decision-making. • GP experience (i.e. more experience might reduce GPs dependency on blood test use).

***Box 2**: Summary of factors relating to GP and patient expectations*

Theme 3: Accuracy of blood tests

The diagnostic accuracy of blood tests was deemed important (appendix 3. P; GPs Beliefs; GP-1), particularly regarding normal blood test results allowing the ruling-out multiple pathologies (appendix 3. P, GPs perceptions of blood test results, GP-11). However GPs are aware that:

"no test is perfect and will be 100% specific and 100% sensitive." [GP-2]

GPs mitigate such concerns by using blood tests in conjunction with information from clinical assessments. This is deemed important for reducing the risk of false reassurance (appendix 3. P; GPs perception of blood test results; GP-1), which may arise when considering normal blood tests results as confirmatory of absence of a disease (appendix 3. P; GPs perception of blood test results; GP-4).

Blood-based POCTs may offer opportunities for GPs to rapidly assess symptom and blood test information during the same consultation. However, GPs were sceptical that their accuracy might not be comparable with laboratory-analysed blood tests:

"I'm not convinced that point of care tests are going to be comparably accurate, so I'm not sure that what you gain in speed is worth a trade-off in terms of accuracy" [GP-4]

Participants additionally recognised that blood test use in very ill patients was more likely to indicate GPs clinical uncertainty. Vague presenting symptoms may prompt GPs to rely on the accuracy of blood tests (disregarding their analytical limitations - appendix 3. P; GPs perception of blood test results; GP-4). GPs level of diagnostic uncertainty influenced the diagnostic value entrusted upon blood test results. Increased pre-test uncertainty reduced the value placed on normal test results, whilst unexpectedly abnormal findings were welcome:

"If I'm really worried and a test is normal doesn't mean I just 100% trust the test. And equally, if I'm not that worried and a test comes back abnormal, it's like, oh okay, well that changes things a bit." [GP-3]

GPs awareness of potential overdiagnosis

Participants' awareness of potential overdiagnosis was evident yet caused little concern when considering the use of common blood tests. Some GPs explained that the diagnostic value derived from common blood tests is gleaned from the assessment of trends overtime, suggesting that it was unlikely that a single common blood test result would lead to over-diagnosis (see appendix 3. P; Overdiagnosis; GP-11). With slightly raised blood test results, GPs sometimes relied on their clinical intuition to confidently rule-out the possibility of overdiagnosis based on the overall clinical picture:

"Sometimes you'll get results of questionable clinical significance but I think you get pretty good at just knowing that, "it doesn't matter if that's a little bit raised or if that's a little bit raised," it's not in keeping with the overall clinical picture so, no, I am pretty happy that I don't over-diagnose" [GP-7]

Nonetheless, concerns were expressed about slightly abnormal liver function tests and the requirement for repeat testing leading to increased workloads (appendix 3. P; Overdiagnosis; GP-9). Raised blood test results also increased concerns about the requirement for more specialist investigations and medical appointment-related travel burden for patients (appendix 3. P, Overdiagnosis; GP-10).

Worried patients demanding blood tests may increase overdiagnosis, particularly in patients with unexplained complaints (see appendix 3. P; Overdiagnosis; GP-8). In this situation, having access to blood-based POCTs may tempt GPs to comply with patient demands in a way that increases chances of incidental abnormal findings being detected. When prompted about blood-based POCTs however, GPs considered the ease of access provided by POCTs to have the potential to contribute to over-testing (encouraging over-testing - appendix 3. P; POCTs; GP-9).

Summary of factors related to accuracy concerns:

- Overall, GPs were aware that blood tests are imperfect (often relying on additional symptom information)
- The presentation of low specificity symptoms increases GPs propensity to use blood tests
- GPs prior index of suspicion influenced their interpretation of blood test results
- GPs expressed little concern about potential overdiagnosis with using common blood tests (although they acknowledge that liberal testing may increase the risk)
- There is a perceived risk of repeat testing, increased patient anxiety and increased workloads with slightly raised test results.

***Box 3**: Summary of factors related to accuracy concerns*

Factors that can act as barriers or facilitators to blood-based POCT use throughout emergent themes

Facilitators:

- Opportunity for enabling greater use of blood tests (through ease of access)
- Potential for reducing subsequent visits to a health service facility (for phlebotomy)
- Considered a less invasive blood sampling method than venipuncture
- Potential value in expediting decision-making in unwell patients in whom an emergency referral may be considered.

Barriers:

- Accuracy on POCTs not comparable to laboratory standard tests
- Increased volume of false-positives (in response to easier access to blood tests).
- Limited time to explain, use and interpret blood-based POCTs during the consultation
- Perceived as unnecessary in patients with "progressive" disease like cancer
- Concerns regarding potential overtesting through easier access to blood tests with POCT use.

***Box 4**: Barriers and Facilitators to using blood-based POCTs*

6.4.3 Exploring potential strategies to reduce barriers to blood testing:

As explained in the methods, identified themes (issues) were mapped to the Theoretical Domains Framework and the Behavioural Change Wheel to link these constructs to potential interventions targeting specific issues deemed to constrain the diagnostic process (see Table 8). For example, access and availability of phlebotomists were identified as issues that can be targeted by interventions, which were deemed to map to the "Environmental Context and Resources" domain of the TDF (defined as: "Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior";(202). Given the nature of this theme, the BCW intervention functions including "Enablement" (Increasing means/reducing barriers to increase capability or opportunity) and "Environmental restructuring" (Changing the physical or social context) were deemed appropriate solutions. Interventions might include ensuring practices have adequate staffing levels to cope with testing demands and increasing access to on-site phlebotomists.

***Table 9**: Using theories of behaviour change to explore possible targets for intervention.*

Mechanisms of action		*Intervention content*	
Identified Themes	**Relevant constructs of the theoretical domains framework**	**Relevant Functions (Wheel of Bahaviour Change)**	***Example targets**
Access and availability of phlebotomists	Environmental Context and Resources	Enablement / Environmental restructuring	Ensure that phlebotomy services/general practices have adequate phlebotomy staff to meet demands for blood tests Improve 'within-practice' as opposed to off-site phlebotomy (I.e. increased opportunities for same-day blood testing).
Logistics of sampling process and patient access	Environmental Context and Resources	Enablement / Environmental restructuring	Improve courier services for processing without need for blood sample storage in general practice Enhance practice capacity for phlebotomy home-visits or, where appropriate diagnostic technology is available, introduce blood-based POCTs to reduce patient repeat visits.
Digital vs face to face consultations	Environmental Context and Resources/ Intentions / Beliefs about consequences	Incentivisation / Training	Digital: Encourage GPs to request blood tests to support decision-making (in the absence of physical exams, or after inconclusive examination and concerning, unexplained, symptoms) Face to face: Increase GPs awareness on the value of combining blood tests with other presenting signs and symptoms.
Local and national pathways/ cultures	Environmental Context and Resources	Environmental restructuring / Enablement	Introduce standardised measures to reduce variation by practice in the use of blood tests (i.e. update/enforce guidelines for using blood tests for symptoms of possible cancer– possibility for e-trigger/prompt approaches embedded into electronic health record systems to appropriately prompt GPs about relevant guidelines).
GPs perceptions of patients demands	Beliefs about Capabilities / Social or professional role and identity / Skills	Enablement	Enable GPs to manage patient expectations through shared decision-making, evaluating the harms/benefits and discussion of action plans
GPs' use of blood tests as a social function: reassuring patients	Knowledge / Skills / Beliefs about Capabilities	Training/Enablement	Remind GPs/increasing awareness about the potential benefits and pitfalls to using blood tests as a method for reassuring patients.
GPs concerns with sensitivity/ specificity	Beliefs about capabilities / Beliefs about consequences	Education/Enablement	Encourage increased awareness of the diagnostic capabilities of common blood tests.
GPs concerns with false reassurance	Beliefs about consequences	Education/Enablement	Encourage increasing awareness of the risks associated with interpreting results from tests that are not 100% accurate.
GPs concerns with over-testing/ overdiagnosis	Beliefs about consequences	Education / Environmental restructuring	Increase awareness about the potential risk of overdiagnosis

6.5 Discussion

6.5.1 Summary

Several factors influence GPs' decision-making to use blood tests, beyond medical knowledge and skills; those encompass logistical and practical issues of the total testing process (TTP), patient factors, and considerations of test accuracy. Determinants of blood test use were broadly correlated with aspects of the phlebotomy process, clinicians expectations and their perceptions of patients' attitudes towards blood testing, and GPs concerns about the accuracy of blood tests and possible overtesting. Participants described barriers to using blood-based POCTs, expressing an overarching view that they will remain unhelpful unless time-constraints within the GP consultation are addressed.

The context in which blood tests are ordered in patients presenting with possible cancer symptoms can be dichotomised into psychological and physical components of decision-making. Logistical and practical aspects of the phlebotomy service may act as physical barriers to using blood tests, whereas GPs prior knowledge relating to how they manage patient expectations and their perceptions about the diagnostic accuracy of blood tests may act as psychological factors influencing test use. Interventions focusing on environmental restructuring may usefully target "physical" artefacts of the blood testing process currently acting as barriers to using common blood tests.

6.5.2 Strengths and Limitations

This qualitative study provides an overview of GPs perceptions and factors they consider influential towards their use of blood tests in patients presenting with symptoms of possible cancer. We explored determinants of blood test use beyond the context of the clinical presentation by employing the Situativity Perspective Framework, which allowed for a more extensive assessment of factors operating throughout the TTP for blood testing.

The small sample size and potential selection bias from interviewing GPs with an interest in cancer research (and possibly blood tests) is a limitation that restricts the representativeness of the study.

6.5.3 Comparison with the Literature

Psychological factors - Embodied decision-making for blood testing:

The findings both corroborate and expand on previous literature. Blood test use can be motivated by GPs need to reassure themselves of their clinical decision-making, as shown previously (199). Diagnostic uncertainty increased GPs' propensity to use blood tests, e.g., to confirm or refute diagnostic suspicions. The perceived diagnostic value of blood test results is an important factor for using blood tests to manage clinical uncertainty (212). Although no formal statistical evidence can be inferred to exist from the qualitative data, an emergent hypothesis from the findings suggest that less experienced and less confident GPs order more tests (and vice versa; congruent with past research; (212,213), with those in the later stages of their career sometimes being perceived to also use more tests to avoid misdiagnosis. Increased testing may help to mitigate misdiagnosis concerns for cancer, yet risk creating new anxieties related to overtesting (214,215). Relatedly, overtesting might reflect uncertainty from miscalibration between GPs diagnostic confidence and their diagnostic accuracy, resulting in inefficient testing and unnecessary diagnostic delays (172,173). However, given the non-confirmative nature of common blood tests and their use for supplementing decision-making (providing clues for cancer diagnosis (47), the risk of overdiagnosis is minimised.

The finding regarding use blood tests for reassurance purposes concords with evidence from a semi-structured interview study of GPs (n=23), indicating blood test use as both an option for managing uncertainty and for providing a 'gift' to patients (where the test result would illuminate the 'truth'; (199). Concordantly, participating GPs often accepted patient blood test requests motivated by health concerns by patients, in order to provide reassurance, using blood tests to mitigate patient worry. Shared decision-making for blood testing might also reduce subsequent patient anxieties arising from testing expectations that are not aligned with their GP (216).

Physical factors – Extended decision-making for blood testing:

While psychological factors undoubtedly influence decision-making, practical aspects also influence blood test use. GPs wish for greater access and availability of phlebotomists, and same-day testing. A focus group study with general practice staff and patients from four UK

primary care centres highlighted healthcare professional frustrations about delays between decisions to order blood tests and subsequent phlebotomy appointments (114).

The risk of patients not attending phlebotomy appointments due to extensive traveling was a concern for some GPs, yet this issue of 'distance decay' is not common within centralised primary healthcare structures (217). A more prominent concern among GPs related to the logistics involved with sample transportation (i.e. courier timetables) and the scheduling of blood tests, describing a small but critical timeframe between sample collection and analysis. Poorly timed ordering of blood tests could contribute to delayed sample transportation to laboratories (117), which might perpetuate waiting times relating to the laboratories communication with the practice about degraded blood samples and patient re-testing (115).

Although interventions for reducing ambiguity within guidelines for laboratory testing may optimise test use (215), we found little evidence of concern among GPs referring to blood test-based recommendations within 'suspected cancer' guidelines.

Factors relating to blood-based POCT use:

Participants were largely ambivalent towards their implementation of POCTs in practice. In line with prior evidence (127,130,218), GPs indicated concerns about their accuracy, issues with their use during consultation, possible over-reliance on blood test results and increase in workload. GPs expressed concerns shared by prior research that blood-based POCTs would have limited diagnostic value for suspected cancer (122). In concordance, this large national survey (n=1109) identified less than one in ten GPs (8%) in the UK who would find a POCT helpful in supporting cancer diagnosis.

Factors relating to Covid-19:

Covid-19 emerged as influencing GPs' use of blood tests. We found GPs limited ordering of non-urgent blood tests intra-pandemic. Coincidentally, national shortages in blood test tubes during covid-19 prompted reduced use of blood tests (219). Online consultations became more common, with GPs modifying their use of blood tests so results could be assessed during consultations (i.e. ordering tests ahead of consultation).

6.5.4 Implications

Service-level interventions may be preferrable, as current GP workloads and time pressures may limit the effectiveness and uptake of GP-level interventions (such as behavioural interventions including training and educational programs). Increasing access to on-site phlebotomists (and opportunities for phlebotomy home-visits) may help to remove logistical barriers to intended blood test use. Interventions to optimise courier services should also be considered.

Practical modifications of the diagnostic process could help to bypass complicated decision-making with blood testing, such as changing the available selection of tests (the choice architecture) on blood test ordering forms to optimise blood test requests (87). The development of clinical guidelines recommending blood test use for specific clinical scenarios may encourage appropriate use, whilst "reminder" alerts/prompts embedded within electronic health records could reduce GP missed opportunities to use guideline recommended blood tests. However, these electronic health record flags can be limited by GPs cognitive capacity to manage information overload and alert-fatigue (220,221).

Many perceived limitations in using POCTs could be modifiable (i.e. delegating responsibility of POCT use to onsite phlebotomists, to avoid prolonged consultations). Evaluation studies suggest that pre-analytical errors with using blood-based POCT are more important to solve than concerns about their accuracy (222,223). The sensitivity of blood tests for cancer (see Chapter 2.2.1) may help to reduce diagnostic accuracy concerns about POCT use, if they provide a solution for more frequent testing. Implementation barriers related to both conventional and POCT-based blood testing may impede the adoption of novel blood-based technologies for supporting early cancer diagnosis (such as the Galleri test marketed by Grail and currently trialed in the NHS). It would not be unreasonable to foresee such technologies being embedded into conventional blood testing strategies. Further research could focus on practice-level interventions to enable the incorporation of blood-based POCTs in primary care and the clinical scenarios where their use may be appropriate.

In response to Covid-19, GPs adjusted their use of blood tests to mitigate viral transmission. Change in service provision models may have longer-term influences on decision-making to use blood tests in patients unable or unwilling to attend phlebotomy appointments. Recommendations to encourage GPs to anticipate blood test use prior to consultation (or

earlier assessment of blood test results within the medical records) may help with decision-making during online patient assessments and avoid delays from ordering subsequent phlebotomy appointments. Although these implications relate to a pandemic which has since subsided, a degree of pandemic-induced changes in consultation mode patterns are expected to prevail in the future.

In conclusion, decision-making to use blood tests is influenced by factors beyond the context of presenting symptoms. Logistical and practical factors that are situated within the local and wider healthcare system may contribute towards variation in blood test use. Holistic interventions that account for the total blood testing process may better support GPs' decision-making.

6.5.5 Chapter Summary

In summary, the study documented that decision-making to use blood tests is not determined by clinical presentation alone. After considering decision-making through the SPF, complexities of decisions to use blood tests can be better understood. Elements of the physical environment that influence testing decisions may be less amenable to behavioural interventions (such as the capacity that practices have for on-site phlebotomy), yet modifications aimed at reengineering blood testing procedures might better support GPs' use of blood tests (where interventions are "normalised" into testing processes, with minimal interference on GPs clinical practice). Importantly, through qualitative analysis of GPs perceptions I have elaborated on Chapters 4 and 5 by assessing contextual factors of blood test use. Together, these three Chapters provide patient population and GP-generated data on primary care blood test use in patients presenting with possible cancer symptoms. In the context of mounting diagnostic evidence for using blood tests to aid decision-making for suspected cancer and a growing interest among public and policymakers in early cancer diagnosis research, the next Chapter summarises the findings of this Thesis by considering the aims, limitations, and implications of this PhD project.

Chapter 7: Discussion

The growing burden of cancer has prompted a proliferation of research into understanding opportunities for supporting earlier diagnosis. Primary care is situated on the frontline of healthcare, where most patients first present symptoms and the first opportunities for diagnostic intervention occur. GP diagnostic assessment and decision-making is partly influenced by their interpretation of presenting symptoms. Currently, clinical guidelines centre on patients who present with alarm symptoms, though only half of all patients with cancer present with those (34). Conversely, the other half of patients subsequently diagnosed with cancers characterised by vague symptoms with low PPV experience protracted diagnostic journeys and poorer outcomes.

Blood tests could represent an underused diagnostic strategy in patients not meeting eligibility criteria for suspected cancer pathways. Recent research has greatly expanded the evidence-base regarding the diagnostic utility of blood tests for supporting GP decision-making in patients presenting with possible cancer symptoms. Much of this new evidence has emerged after the publication of the 2015 NICE guidelines for suspected cancer, therefore the potential for blood tests in supporting GPs seems not fully explored.

However, the complexity of the blood testing process may limit the implementation of evidence-based recommendations suggesting the use of blood tests. The practical and logistical realities of blood testing expand beyond the clinical encounter. These relate to the complexity of the blood sampling process, that involves accessing phlebotomy services, often out of site and typically at a different day after the consultation.

POCTs may help to extenuate challenges in the blood testing process. Evidence supports their analytical performance across a range of settings, yet POCTs that are equivalent to common blood tests using tube sampling have not yet been widely implemented in primary care. The potential of POCTs in general practice may be realised once barriers to their implementation are addressed. In the meantime, changes in phlebotomy services may be beneficial.

Comprehending solutions for improving blood test use requires an understanding of the clinical scenarios in which blood tests are used. By studying the influence of patient characteristics of blood test use, Chapter 4 expands on this previous research by exploring factors that may contribute to such variation in blood test use (i.e. things that might influence GPs testing decisions across different populations).

The patients' presenting symptoms represent an important factor influencing blood test use. Patients presenting with lower specificity symptoms have higher odds of blood test use compared to patients presenting with alarm symptoms). Given the importance of symptoms, Chapter 5 further explored the frequency in which primary care blood tests were used by individual symptom. Generic blood testing patterns conform with the specificity of presenting symptoms as identified in Chapter 4 (i.e. higher symptom specificity resulted in lower testing rates, and vice versa). The use of cancer biomarker tests and other blood tests with higher organ-specific affinity varied depending on the relevance of symptomatic features of cancer-sites.

Yet an array of factors beyond the clinical presentation are also influential in how GPs decide to use blood tests. Theories of cognition help to explain the nuances of testing decisions by elaborating on how diagnostic tests are normalised into practice (Normalisation Process Theory - (160), how clinician's rationale for testing may be autonomous or analytical (Dual Process Theory - (161) and how such decisions may be influenced by a wider range of contextual and situational factors beyond clinical reasoning (Situativity Perspective Framework - (191). Importantly, the latter theory illustrates how physical attributes of the testing environment and logistical and practical factors also influence GPs decision making. POCTs currently offer limited solutions for supporting GPs' use of blood tests, although reconfiguring physical components of the testing process may provide more rapid short-term benefits.

7.1 Summary of main findings:

This Thesis specified three aims at the outset. The research inquiry started by studying population groups (Chapters 4 to 5) and then explored perceptions of blood test use among GPs (Chapter 7).

7.1.1 Aim 1: To explore how often common blood test are used in patients subsequently diagnosed with cancer and variation in use by patient characteristics

The study illustrated in Chapter 4 was the first to systematically explore the frequency and variation in common blood test use in patients subsequently diagnosed with cancer in England. Prior research using the previous NCDA wave (2014) did not address this question (31,147,224,225). Research on an earlier version of the cancer audit (National Audit of Cancer Diagnosis in Primary Care – diagnosis date: 2009/2010) profiled primary care investigations without a focus on blood tests, was restricted to patients with only 6 common cancers; and did not examine the influence of specific symptoms (32,48,49,226,227). Ongoing research, including projects in this Thesis, are exploring cancer diagnostic pathways in patients diagnosed in 2018 (228).

Chapter 4 findings show how common blood tests are used in a substantial minority of cancer patients (41%), and that use varies by presenting symptom (24% for alarm only patients and 50% for non-alarm only patients). Blood test use in the NHS has been increasing very slowly (47), which may explain the marginal difference in common blood test use between 2014 (39%) and 2018 (41%) NCDA versions (acknowledging our study population of incident cancer cases does don't correspond to all patients). However, most likely the limited increase reflects that practice recommendations in NICE's 2015 clinical guidelines for suspected cancer did not generally include blood test recommendations and reflect genuinely stable practice.

Concordant with prior studies using cancer diagnosis audit data, the use of primary care blood tests prolonged the PCI length (Rubin et al (43): 15 vs 4 median days, Chapter 4: 10 vs 0 median days). Chapter 4 highlights a similar pattern of lengthening in the DI with blood test use, although the difference is more pronounced compared to the PCI (Test use vs non-use on DI: 49 vs 32 median days). After allowing for confounding by other variables, I found that the impact of test use on prolonging the intervals was shorter than observed. The attenuation was greater in the DI, suggesting that much of the delay associated with primary care blood

testing is, paradoxically, occurring after the referral. Cancer-site was a major confounder, i.e. patients tested with blood tests are also those with cancers associated with longer intervals. After interactions were explored between test use and symptom category, further attenuation of differences in the length of the DI by blood test status were observed. This finding might represent GPs recognition of symptoms with higher PPVs (i.e. alarm symptoms) who are then fast-tracked. It is also plausible that blood testing would prolong DI's for other non-cancerous conditions, though the interpretation of appropriate test use would be dependent on the clinical context.

There was little difference in the frequency of blood testing between the 2018 and the 2014 audits (see appendix 3.G). It would be prudent to further explore these comparisons over time (potentially in 2022 cancer populations and subsequent audit waves), particularly as supportive diagnostic evidence for blood tests is growing and slowly being incorporated into published recommendations of suspected cancer. However, a third wave of the NCDA initiative is not currently planned.

The findings in this Chapter build on prior literature, and highlights opportunities for targeting possible overuse (i.e. in alarm symptom patients) and underuse (i.e. among those without alarm symptoms) of blood tests in patients presenting with possible cancer. Additionally, given the findings regarding blood test and symptom category, this study inspired the research for Chapter 5 (aim 2).

7.1.2 Aim 2: To explore the how often blood tests are used in patients subsequently diagnosed with cancer after presenting with symptoms

Chapter 5 continues the description of blood test use in patients subsequently diagnosed with cancer, focusing on symptom types across a broader range of blood tests. As evident from Chapter 4, symptom category influences blood test use, yet the exact nature of this association by symptom type is now further detailed. Recommendations within NICE suspected cancer guidelines (often based on clinical and demographical information, e.g. presenting symptoms and age) may dictate many of the patterns in test use. For example, in men presenting with lower urinary tract symptoms (229), prostate specific antigen tests are recommended for detecting possible prostate cancer (93). Cancer biomarker tests and blood tests with organ-specific affinity in general may have limited diagnostic utility across most presenting symptoms, but have high diagnostic value for features relevant to particular cancer-sites (where their use is higher). Conversely, patients presenting with symptoms of lower specificity are more likely to have blood tests than those with more specific symptoms, suggesting an inverse relationship between common blood test use and symptom specificity.

As identified in Chapter 4, the presentation of non-specific symptoms correlated will more frequent blood testing. Concordantly, prior research using NCDA symptom data found similar blood test use in such populations (57%; (224). Further, I found that over three-thirds of patients (range: 61-79%) presenting with fatigue, loss of appetite or weight loss had a common blood test before diagnosis. These symptoms represent early features of some cancers including lung (230,231) and pancreatic cancer (232), where blood testing ranges between 40-41% and 63-71%, respectively (48,228).

Blood test use appeared to be quite variable among patients presenting with abdominal and urinary-related symptoms, including abdominal pain, change in bowel habit, rectal bleeding, UTIs, LUTs and haematuria. Given that abdominal symptoms are common in pre-diagnosed cancer patients (225), between 25% - 66% of patients presenting with abdominal symptoms had a common blood test. In contrast, fewer patients received common blood tests after presenting with urinary-related symptoms (12-44%).

Patients presenting with higher specificity symptoms (such as skin or breast-related symptoms) had the lowest frequency of blood tests, indicating that blood tests have limited diagnostic value in cancers with obvious signs/symptoms (such as breast cancer and

melanoma, where common blood tests are used in 4% and 2% of cases, respectively – see Chapter 4).

With the exception of ferritin tests that followed a similar testing pattern to common blood tests (and were more frequently used in patients presenting with symptoms of possible colorectal cancer), the use of other less generic blood tests were typically guideline driven and less predicated on symptom specificity. Bone profile and serum protein tests were associated with higher use in patients presenting with back or bone pain (relative to all other symptoms), while amylase test use is comparatively higher in patients presenting with upper abdominal pain.

Taken together, Chapter 5 focuses on the relationship between blood test use and symptom presentation in pre-diagnosed cancer patients. As discussed in Chapter 5, the proportions of tested patients with certain cancer sites could facilitate the production of pilot targets for markers of diagnostic process quality. In benchmarking blood test use in populations characterised by symptom type, policy makers and guideline developers may be able to better inform recommendations for suspected cancer. An important next step is to explore blood test use by symptom type within relevant demographic groups. It would be prudent to establish how often guideline recommended blood tests are being used in the desired populations to appreciate strategies for optimising their use.

7.1.3 Aim 3: To explore factors beyond the clinical presentation that influence GPs' use of blood tests

This study complements the quantitative research in earlier Chapters and aims to better understand the context in which blood tests are being ordered. The motivating question for this Thesis is whether blood tests are an underused strategy in patients presenting with non-specific symptoms of possible cancer (explored further in Chapters 4-5). Patients' clinical features at presentation may indeed determine blood test use, but other factors that influence how GPs decide and act on ordering (or not ordering) tests should not be overlooked. Therefore, understanding cognitive processes during consultation is important for explaining test use. Prior cognitive theory attempts to explain decision-making as an automatic or analytical processes, with the latter leading to slower and more complex decision-making based around risk thresholds (see appendix 3.K). For example, blood testing to avoid the risks of misdiagnosis (and associated anxieties) is a well reported motive for testing (199,215). GPs may also decide to use blood tests in a Bayesian fashion alongside presenting symptoms to support decision-making for cancer (47). Importantly, social and environmental factors influence decision-making beyond the cognitive aspects of decision-making. As previously stated (Chapter 2), a landmark study conducted in NHS primary care has illustrated the complexity (and vulnerability) of the blood testing process (114,115). The evidence highlights practical issues that may influence decision-making to use tests beyond the clinical presentation. Relatedly, point of care technologies may present solutions to these practical problems, therefore understanding how GPs would consider their use in practice may reveal opportunities for supporting blood test use.

Overall, the complex psychological and practical attributes of the blood testing process may represent barriers to optimal primary care blood testing in patients presenting with possible cancer symptoms. Except for Litchfield and Colleagues, much of the evidence describing practical and logistical factors that influence diagnostic testing originates from the US, and relates to human factors experts identifying procedural and organisational failures or errors associating with testing processes. Conversely, evidence pertaining diagnostic decision-making derived from Europe predominantly consider psychological theories when explaining factors that influence decisions for test use. Only in recent years have these two approaches been combined to provide a more holistic understanding of both intrinsic and extrinsic factors that influence diagnostic testing decisions. This innovation has given rise to more expansive

theories, including the Situativity Perspective Framework, which can help conceptualise factors of decision-making into those that are 'embodied' in clinician cognitive processes (i.e. past experiences and knowledge), embedded in their local environment (i.e. workflows) and extended into the wider healthcare system (i.e. national guidelines).

Being guided by the situativity theory, my interviews with GPs identified a range of themes related to how they perceive their use of blood tests. It was remarkable that capacity issues with phlebotomy services (i.e. access and availability of phlebotomy/opportunities for same-day testing) have been consistently identified as playing a significant role in GPs' use of blood tests. The service configuration of phlebotomy access therefore may predetermine blood testing use, including the logistical aspects of sample collection, preparation and transportation. GPs often mentioned blood testing decisions were sometimes based on their ability to reassure anxious patients (and indeed themselves in situations of diagnostic uncertainty), a finding that supports prior literature (199,215). Similarly, it was also evident that decision-making to use blood tests was influenced by concerns about false reassurance by false negative or indeterminant test results particularly regarding POCTs.

Chapter 6 confirmed that many factors beyond the clinical presentation itself influence how GPs decide to use blood tests. Solutions for psychological barriers to testing may be derived from applying behavioural change techniques/strategies, whereas practical and logistical modifications to the blood testing process may be applied. Such interventions do not assume diagnostic reasoning is altered, but that GPs are able to order blood tests more easily in a greater proportion of patients.

7.2 Limitations (Chapters 4 & 5):

Two cross-sectional observational studies of patients subsequently diagnosed with cancer and a thematic analysis of interview data were used in this Thesis. I discuss the strengths and weaknesses of these studies, critically appraising their study design, and possible bias and the role of chance that may have influenced the findings.

7.2.1 Strengths and weakness of NCDA as a data source

The NCDA provides opportunities to conduct cross-sectional analyses of the diagnostic process in cancer patients. The included populations and participating general practices in the NCDA have previously been assessed to be representative of the general population of incident cancer cases; the source has been established in other literature independent of my Thesis (31,140,233). Therefore, I will explore limitations beyond the generalisability of the findings. A limitation of the source is that it only includes cancer cases. While information on controls (as in the case-control studies) or cohort design including patients who did not develop cancer can offer advantages, NCDA studies follow the tradition of population-based cancer registry-based studies which are by their nature focused only on cancer cases.

7.2.2 Strengths and Weaknesses of blood test information in the NCDA

The NCDA captures data pertaining to nine blood test types, yet components of blood tests (e.g haemoglobin concentration or platelet count, within Full Blood Count) are not specified. However, many blood tests (for example Full Blood Count, Urea and Electrolytes, Liver Function Tests etc.) comprise the measurement of multiple metabolites or biomarkers. Unlike the NCDA, the CPRD database has access to sub-components of blood tests making additional analysis of specific blood tests within relevant populations more achievable, for example, the assessment of inflammatory marker test components for early detection of multiple myeloma (100). Nonetheless, it was appropriate for my study to focus on blood test type per se (as opposed to their sub-components) to show how these 'composite' tests that comprise many sub-measurements are ordered in practice.

7.2.3 Strengths and weaknesses of symptom information in the NCDA

There are inherent limitations that need considering when capturing symptom information within the medical records and the retrospective extraction of this data for research purposes. This is a methodologically challenging area that has no formal solution in this research field. Firstly, coded (structured) data is variable within primary care medical records

(234–236), potentially limiting GPs' complete and accurate recording of symptoms. Another problem relates to how clinicians "filter" the recording of symptoms based on their judgements of relative importance (i.e. less-specific symptoms are generally under-recorded), and the under-use of structured data in preference of free-text. The NCDA methods will not be able to 'better' the former (i.e. symptom representation will possibly be biased towards more specific symptoms), however because auditors could inspect the whole patient record, it is plausible that symptom information is more complete than in routine data sources reliant on coded data such as the CPRD. Nonetheless, the full symptom burden recorded in NCDA cases may fall short of the true value compared to other data sources, such as patient surveys ((237). Importantly, the extraction of symptom data may unknowingly be influenced by the auditors' knowledge of cancer diagnosis. Therefore, fewer non-specific symptoms (perhaps considered to be less relevant to the cancer diagnosis) may be recorded in the NCDA, particularly if they were reported together with alarm symptoms.

The availability of both coded and free-text data will have contributed to mitigating biases arising from estimating symptom frequencies using only coded data (145). It is worth considering the established role of clinical audits using data collection methods employed by the NCDA in the literature (31,140,238).

As shown in Chapter 5, small counts in certain patient strata confer residual disclosure risk (based on cross-referencing symptom and blood test information, and possible prior knowledge of other features of such patients by 'motivated intruders' from other sources) although such risks are often theoretical. Once identified, the risk was removed by dropping these cases a priori following good practice guidelines.

A small proportion of patients were identified (n=571, 1%) with more than one tumour (Appendix A). This minority of the study population were included in the analysis sample (to avoid missing symptom information which might be relevant, with little risk of biasing the overall findings), yet the relevance of recorded symptoms in relation to recorded cancer diagnosis in these cases is challenging.

7.2.4 Information on diagnostic timeliness (Interval data)

Missing values

It is common in epidemiological studies for patients to have missing information on important outcome data, in my study context for example this relates to time interval data from symptom presentation to referral (16% missing) or diagnosis (12% missing - see Chapter 4). The capture of PCI data has improved between the release of the NACDPC and NCDA datasets, with NACDPC missing values ranging from 17% (across six cancer-sites (48) to 21% (225). The degree of missing DI data was comparable with prior studies, for example missing information of DI in the NCDA (12%) was similar to primary care cancer registries in Denmark (8.9%; (35).

Confounders

Although the number of variables adjusted for was limited, residual confounding in cancer populations after adjusting for age is reportedly minimal (239). Additionally, although the number of comorbidities were assessed, I did not explore comorbidity categories (given no evidence for variability). It is plausible, however, that the GPs assessment of symptoms may have been influenced by the patients' comorbidities, potentially contributing to the length of the PCI and DI (240–243).

Sensitivity analysis in Chapter 4 aimed to explore the potential impact of excluded patients who were recorded as having presented in primary care but had no consultations recorded (two different NCDA data items). Around three-quarters of these patients were referred by their GP, indicating that the fact that they had no recorded consultation must have been a data entry error, and concordant findings from the sensitivity analysis suggest minimal potential from bias. Nevertheless, the remaining quarter of these patients (n=494, 24%) were not referred (i.e. may not have had the opportunity to have a primary care blood test). Their inclusion may have reduced effect sizes in our analysis, although possible bias would be limited due to the small number of patients in this group.

Methodological considerations

The distribution of primary care and diagnostic interval data is typically positive skewed (see figure 15). When assessing associations across interval data, linear models are suboptimal (although linear regression has been implemented for assessing PCI in the NACDPC; 43) as they assume that mean differences in blood test use is consistent across the distribution of

the interval variable (i.e. across all centiles, not only the median/50th centile). Given this quantile regression was appropriately used.

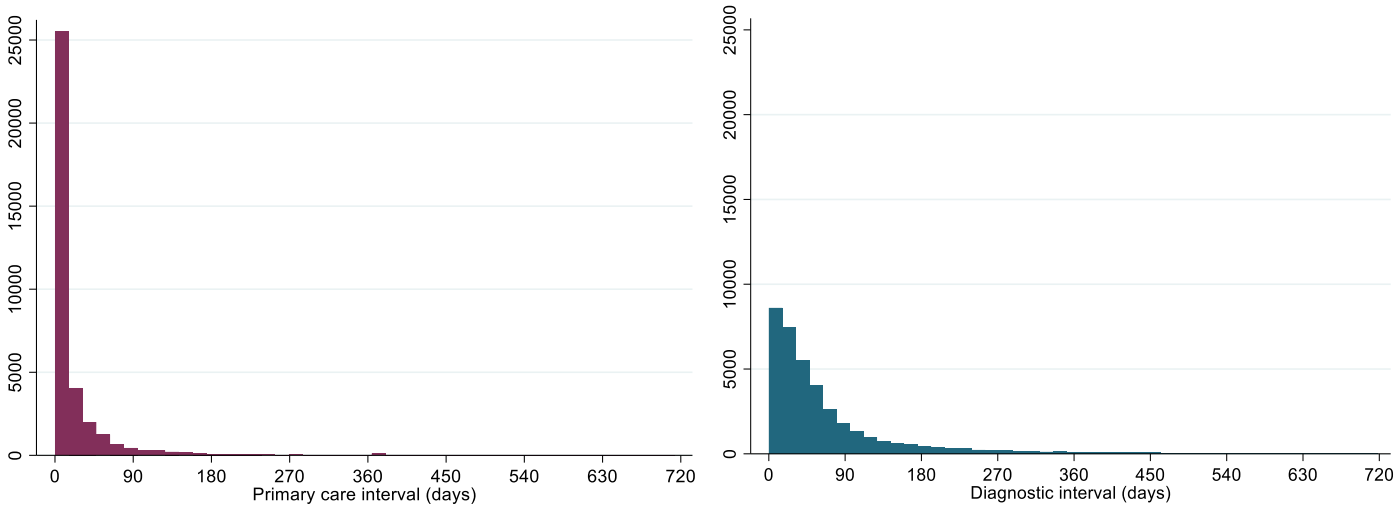


Figure 19: Distribution of the primary care (left) and diagnostic interval (right) among the NCDA 2018 population. Tests for skew and kurtosis indicated p<0.001 for both intervals.

In Chapter 4, I initially described observed values within intervals using summary metrics (medians, interquartile ranges). Quantile regression helped to expand on crude observations on interval data by accounting for covariates (potential confounders), with interaction effects exploring the association between blood test use and symptom category.

Quantile regression is commonly used for assessing diagnostic timeliness and is indeed considered the optimal method for analysing such data (244), although may have relatively limited statistical power over parametric methods (such as generalised linear models (GLM) that have previously been adopted to assess patient interval data in the NACDPC (225). Moreover, accelerated failure time models (a type of survival analysis) may provide a useful alternative to the standard Cox regression model (previously adopted for assessing factors associated with diagnostic intervals in cancer cohorts (230,232) that avoids violating the proportional hazards assumption for analysis of diagnostic intervals (more recently implemented in CPRD cancer cohorts (245).

7.2.5 Generalisability

The findings may partly be an artifact of the NCDA structure and how data was captured and extracted. As previously stated, the NCDA population and participating practices are representative of incident cases and of English general practices, respectively.

The interpretability of the NCDA analysis on blood test use among cancer populations requires deliberation, particularly the challenges with translating this evidence into current populations. Although blood test use was comparable between NCDA versions (in fact marginally higher in the 2018 wave), variation in use in contemporary cancer populations may be less comparable with NCDA 2018 populations. Firstly, with the growing awareness of and campaigning against inappropriate testing since 2018, GPs attitudes to using laboratory tests may have changed. Secondly, given the reductions in urgent referrals for cancer during the covid-19 pandemic (indicating fewer primary care consultations; (246), analysis of blood test use in the proceeding years after the NCDA 2018 audit may not reflect typical patterns of testing for cancer patients. To illustrate, primary care blood testing rates dropped by around 80% in the first week of pandemic induced lockdowns (March, 2020) in response to Covid-19 and were still below 50% of normal levels in June (247). The deficit will in part reflect indirect influences on blood test use for suspected cancer due to reduced consultation rates, thus interpreting this data is challenging. Going forward primary care EHR data sources such as OpenSAFELY offer methodological advantages to traditional audits (such as the NCDA) by including patients with cancer, and by providing the possibility of automated updates for monitoring blood test use. The prescription of pancreatic enzyme replacement therapy was assessed during Covid-19 using OpenSAFELY and highlights how such platforms can reduce the resource burden of maintaining manual audits and expedite access to real-time data (248).

7.3 Limitations (Chapter 6)

7.3.1 Participants:

Considering why the selected participants were chosen is important for appreciating researcher influences on the study outcomes. Achieving sample representativeness is important for extrapolating findings into real world populations. For several reasons however, my interview study lacks external validity.

Selection Bias

Convenience sampling was employed to recruit participants from an academic network of GPs interested in early cancer diagnosis research (CanTest collaboration – see Appendix 3.Q for recruitment documents). This was necessary, particularly as field work took place during pandemic-related lockdowns and GP availability for interviews is difficult in general. Selection bias is however a concern, as the sample included research active GPs who are likely to be sensitised to primary care blood testing for possible cancer and may not reflect the perceptions of the average GPs. Conversely, academic GPs may provide more in-depth and contextual insight into barriers of blood testing within suspected cancer populations. Additionally, not all GPs who received an invite participated in the study (n=4, 27%), however it is unlikely that their non-participation is a source of substantial non-response bias. Future studies may endeavor to replicate this study across both academic and non-academic GPs to establish the perceptions of blood test use more broadly across a larger sample of GPs.

7.3.2 Study design:

Study design could have influenced the interpretations of the findings. The accuracy of qualitative data depends on GPs ability to recall information (recall bias). At times some of the interview questions may have been perceived as leading questions (limiting participants responses) or encouraging participants to appease the interviewer with responses they think would benefit the researcher's objectives (social desirability bias). Nonetheless, as far as possible I have asked questions factually.

As alluded earlier, interviews were conducted online due to governmental social distancing measures during the covid-19 pandemic. Using digital platforms to conduct this study offered a fast, cheap, logistically simple and wide-reaching method for interviewing GPs. However, information gathering during face-to-face interviews may have generated different quality and quantity of data – though the effect of 'mode' of interview is difficult to decipher. For

example, online interviews may have led to missed opportunities for further probing questions that could have ensured in-person.

7.3.3 Sample size (qualitative interviews)

The limited sample size (n=11) also represents a concern. Power calculations do not typically apply in qualitative research, however semi-structured interviews in primary care can be highly meaningful with as few as 10 participants (249,250). Furthermore, based on the concept of "information power", the quality and quantity of information held within such sample sizes can obviate the need for recruiting more participants (251). After interviewing 11 participants, I considered that the emergent factors were judged to no longer be expanding on previously developed themes. Data saturation, however, is hard to judge and dependent on the adopted analytical methods. If more resources were available additional participants would have enabled me to draw more specific comparisons across GPs from different backgrounds.

7.3.4 Theoretical Approach

The theoretical underpinning for this study had strengths and weaknesses. Two frameworks were implemented, for conceptualisation and interpretation purposes. The Situativity Perspective Framework was used for guiding the interview schedule and was a key strength for this study. The TDF helped with the identification of cognitive barriers to using blood tests (predominantly linked to embodied decision-making). However, many of the themes arising from the data indicated physical barriers to using blood tests, beyond the clinical presentation. Therefore adopting the TDF might have offered a less detailed assessment of these factors compared to alternative theories.

At the conceptual level, combining the TDF with the consolidated framework for implementation research (CFIR) may have led to a better understanding of the contextual mechanisms influencing blood test use at different organisational levels (252). The CRIF categorises factors influencing implementation into five domains, four of which relate to the 'intervention' (in this instance the blood test), 'outer-setting' (in our instance primary care organisation beyond the consultation), 'inner-setting' (in our instance the consultation) and processes (such as the process of ordering, performing and analysing the test and communicating results), while the remaining domain relating to the individual (in our instance the practitioner; (253). These domains may have offered complementary interpretations of

the results and possible helped to identify additional practical and logistical barriers to blood testing. However, the objective of the qualitative project was to identify as many factors as possible that influence GPs decisions to use blood tests and the TDF usefully (but quite broadly) illuminates barriers to testing that exist through the lens of the SPF. Post-hoc, the CRIF may have provided finer interpretations for embedded and extended factors beyond the domains offered by the TDF (which was useful for illustrating cognitive barriers relating to embodied decision-making processes).

The combination of theories addressing both individual (i.e. TDF) and organisational factors (i.e. CRIF) has been proposed in implementation science literature (254). Although these two frameworks can identify barriers to implementation, the offered solutions for improving implementation are often too generic to support specific changes in practice (given the diverse contexts in which these frameworks are used), therefore additional translational effort is typically needed, e.g. through expert opinion elicitation to guide intervention design; (255). The SPF also has similar limitations that prevent its use for guiding specific solutions (i.e. clinical reasoning is not categorised beyond embodied, embedded and extended), therefore the intervention functions of the BCW (linking with the TDF) was deemed more appropriate for identifying possible targets for interventions.

7.3.5 Confounding and other factors

The perceptions elicited from participants may be influenced by unmeasured factors to the study design. The Covid-19 pandemic is a source of likely confounding, as GPs may have been primed to consider process/practical-related barriers to blood testing given the restrictions and modifications to blood testing processes (due to social distancing interventions to reduce Covid-19 transmission).

Concerns about overdiagnosis and inappropriate test use might also influence professional attitudes towards blood tests, given the growing evidence that illuminates this issue in primary care (65).

7.3.6 Research and Researcher effects (Reflexivity)

Responses from participants during the interviews may partly be influenced by attributes of the research and researcher. The researcher's lack of medical training was beneficial for seeming non-judgemental, yet potentially limiting opportunities to probe for further relevant information (see Chapter 6). The topic guide developed iteratively during earlier interviews,

with subsequent iterations likely improving data capture in participants in the latter phase of the field work. Similarly, my questioning skills will have improved as more interviews were completed (I.e. low quality data captured during earlier interviews may be mitigated by higher quality data captured in later interviews). The design of the topic guide, coding of data, creation of themes and interpretation of findings will likely be influenced by preconceptions relating to prior literature, and the opinions of behavioural science supervisors who guided me.

7.3.7 Reliability and validity of measures

The reproducibility and trustworthiness of this research is subject to contention. Generated themes relating to phlebotomy services, GP perceptions about patients and blood test accuracy concerns were based on GP responses to open-ended probing questions (inductive analysis). However, themes around POCTs and Covid-19 were in response to more closed questions (primarily deductive analysis). Therefore, there might have been greater scope within the former themes to identify unexplored factors that may be acting as barriers to blood test use than the latter themes.

The validity of my interpretations relating to behavioural barriers of blood test use was supported by theory (TDF) that has been previously validated, even for using blood tests in primary care settings (see Chapter 6). The transparency and the reproducibility of the research was further improved by referring to the standards for reporting qualitative research (SRQR) checklist, which helped to ensure high standard qualitative research practices were employed.

Chapter 8: Implications

8.1 Implications for future research

The Thesis findings highlight opportunities for further research in several areas. I used the NCDA 2018 to explore the determinants of blood test use, with particular focus on the influence of presenting symptoms, before cancer diagnosis (Chapters 4 & 5). Replicating these studies in both historical and more recent populations of patients with cancer, and broader populations of patients presenting with symptoms of possible cancer, would improve the generalisability of the findings. Exploring blood test use in other sources of primary care data should also be considered. There are also opportunities to explore variation in blood test use among suspected cancer guideline populations where blood tests are recommended -i.e. examining guideline-concordant diagnostic care, though acknowledging that such blood test recommendations are generally rare. Such analysis may reveal opportunities for interventions to optimise blood test use, given evidence supporting their predictive value into clinical practice in primary care.

Future research should also explore variation by contextual factors and service characteristics (additional to patient characteristics), given the evidence provided in Chapter 6 regarding the numerous non-clinical presentation factors that influence GPs decisions to order a blood test. For example, future research should consider exploring general practice variation in blood test use (given that the configuration of phlebotomy services may vary in different geographical areas, i.e. on-site vs off-site phlebotomy), which may help to reveal local mechanisms responsible for inappropriate levels of testing and highlight opportunities for intervention. Prior observational studies could usefully inform the design of such research, such as using video recordings during primary care consultations to explore clinical decision-making processes (256) Additionally, inequitable blood testing by sex and ethnicity as apparent in the findings reported in Chapter 4 (i.e. lower test use in both women and ethnic minority groups) should prompt future research to help explain such differences (rather than rely on peoples' recall of individual experiences).

This Thesis elaborates on previous service evaluation studies, namely by Litchfield and colleagues. Factors related to embedded and extended decision-making highlighted in Chapter 6 may have some influence on practical errors described by Litchfield's total testing framework. For example, there might be an association between limited phlebotomy access and patients returning home after booking their blood test (described as a waiting point)

where the waiting time is longer when phlebotomy access is limited. Furthermore, Litchfield also describes the testing process between the GP and the laboratory. The courier service's responsibility in delivering the blood sample to the laboratory is described yet there is no acknowledgement of a possible failure in terms of "time-taken" to transport the sample, which was considered a critical timeframe by primary care clinicians (to avoid haemolysis - see Chapter 6). However, the different testing contexts within the aforementioned studies (i.e. blood testing in general vs blood testing for suspected cancer) do limit how synergistic the findings are (given that the waiting and failure points described by Litchfield and colleagues may only apply to two in five cancer patients).

Future research could merge process-mapping evaluations with qualitative research methods to understand the intricacies of the blood testing process to mitigate potential barriers to blood testing. For example, a significant event audit (SEA) is a quality improvement technique (a type of narrative analysis for understanding the circumstances of an event - (257) previously used for understanding cancer diagnostic pathways that could be adopted for exploring SEA documents related to the blood testing process (258).

The findings from this Thesis may be different if data on symptoms and intervals were self-reported by patients, as opposed to the collection of this information from their medical records as used in this Thesis. However, obtaining such evidence from large and representative samples of patients would be challenging, and non-response and selection bias are prevalent in studies using patient-generated data. The CPRD offers a large study population (covering 7% of the UK population) whose demographic composition is representative of the UK population (259,260), and could allow for matched case-controlled or cohort studies to help explore and contrast variation in blood test use against symptomatic populations who were not subsequently diagnosed with cancer. This might be particularly useful for exploring blood test use after presentations for which their use is recommended by guidelines.

The diagnostic utility of blood tests has been considered as part of early detection strategies for cancer, yet contextual and environmental factors that contribute to decisions about their use requires further deliberation. Most GPs are not academic (<10% of the GP workforce in the UK are academic; (261), therefore understanding the perceptions of the broad body of GPs about blood test use would provide a more informative (generalisable) research enquiry.

The Situativity Perspective Framework provides a holistic approach to understand the context of diagnostic decision-making, incorporating elements of cognitive psychology, human factors approaches and implementation science. The constructs of the framework provided a useful tool for guiding my research questions. Future research may consider further detailing of the framework structure into sub-components of decision-making (building on the embodied, embedded and extended components) to improve its utility for exploring barriers to decision-making in practice.

The theoretical domains framework (TDF) and COM-B model facilitated the identification of behavioural-based barriers and solutions to blood testing, although may have been less applicable for logistical and practical-related barriers (associated with embedded and extended decision-making). Future research should consider additional implementation science frameworks (such as the consolidated framework for implementation research – CFIR) to better explore wider barriers to blood testing in primary care. Such frameworks may better inform researchers interpretation of the complexity and inherent errors associated with the blood testing process.

A different avenue to further exploring the research questions that motivated my research is to explore the health economics aspects of greater or lower use of the studied blood tests, together with possible use of specialist referrals or other, primary care or specialist tests. Such an approach will have to consider clinical (e.g. diagnostic interval length) and patient experience outcomes relating to different levels of testing and associated costs.

Vignette experiments could be considered for validating identified factors that influence blood testing decisions, whereby putative contexts can be modified to explore GP preferences for ordering of blood tests. Furthermore, vignettes could usefully ascertain preferences for using blood-based POCTs as a strategy for supporting blood test use in patients with non-specific symptoms. Although my qualitative research predominantly found GPs consider POCTs unhelpful for supporting blood testing for suspected cancer, research should continue to assess GPs perceptions of their diagnostic utility in primary care given ongoing technological innovations in this field.

The evidence generated from this Thesis builds on a relatively unexplored question regarding how blood tests are used in primary care, both locally and internationally. The

configuration of phlebotomy services and blood testing processes will vary by country and their evaluation should be part of future enquiries. International variation in cancer referral pathways has recently been explored using the International Cancer Benchmarking Partnership (ICBP), which may offer opportunities to explore how primary care diagnostics (such as blood tests) are used for suspected cancer in future (262).

8.2 Implications for practice

This Thesis is motivated by the complexity of cancer diagnosis and the evolving discipline of early cancer detection in primary care (see Chapter 1). Early diagnosis can be supported by commonly used blood tests (see Chapter 2.2.3), thus evaluating their use as part of early diagnosis strategies is important (24). Moreover, the complexity of blood testing in primary care and the related factors that influence decisions to use them are receiving greater recognition (see Chapter 2.3 / 2.4). The findings from this Thesis are timely, given my objectives for better understanding associations between blood test use and patient characteristics (i.e. how often blood tests are being used) and determinants that influence GPs' use of blood tests (i.e. why are blood tests being used or not used) in populations subsequently diagnosed with cancer.

Findings from Chapter 4 indicate that among people diagnosed with cancer, certain patient characteristics are associated with GPs' use of blood tests. is the nature of presenting symptoms as appraised by the GP is integral to testing decisions, with blood testing being more likely in patients presenting with less-specific symptoms (although half of patients presenting with less specific symptoms don't have blood tests before diagnosis). Given the growing evidence supporting blood test use in suspected cancer patients, the overriding narrative of this Thesis pertains to a potential under-appreciation of blood tests in low-risk patients with non-specific symptoms as part of the diagnostic process. Conversely, this PhD further illuminates the extent to which certain populations presenting with higher specificity symptoms might be having unnecessary primary care-led blood tests (a potential indication of overdiagnosis). With the development of more sensitive blood marker tests (such as the Galleri blood test), mitigating the risk of overdiagnosis will become increasingly important.

Regarding new, so-termed, Multi-Cancer Early Detection (MCED) tests, two possible uses arise, first as screening tools in asymptomatic individuals, and second, as risk stratification tests in symptomatic individuals. It is likely that the latter use will also be guided by or accompanied with conventional blood tests such as those assessed in the present study, with some of the learning being relevant and 'portable' to this new context.

The time penalty associated with blood test use on patient's primary care and diagnostic intervals is important for locating opportunities to expedite diagnostic processes. While patients who had a blood test experienced longer diagnostic care intervals, this may have

been potentially necessary if it would have reduced even longer intervals that could have been associated with not testing. This finding compliments the results of Chapter 6, whereby practical and logistical attributes of the wider testing process appear to offer important targets for supporting the diagnostic process. Overcoming implementation barriers to testing may promote opportunities for novel tests (such as the Galleri 'multi-cancer early detection' blood test) to be integrated into practice.

The findings from Chapter 5 illustrate how GPs' use of common blood tests closely follows symptom specificity. Blood tests are frequently used for symptoms of lower specificity, where they are likely used in a Bayesian fashion to provide additional priors to inform decision-making. Guidelines may in the future include a greater number of recommendations for blood test use in patients presenting with non-specific symptoms. Implicitly, the influence of guidelines can already be observed through testing frequencies of less generic blood tests (For example, higher cancer-biomarker use in men presenting with urinary symptoms may reflect effective utilisation of blood-based recommendations by GPs).

Important barriers to using blood tests are highlighted in Chapter 6, which broadly relate to phlebotomy processes, GP perceptions of patient's expectations and the accuracy of blood tests. In the short-term, process re-engineering with regard to phlebotomy services may be a favourable approach for supporting GP blood test use. Policymakers could also consider other changes to what is already a complex blood testing process to minimise pre- and post-analytical errors. Furthermore, GPs concerns about appointment scheduling to off-site phlebotomy services could be mitigated by increasing access to on-site phlebotomy, potentially facilitating and expediting blood test use). In the long-term, behavioural interventions may support GPs decision-making to use blood tests. The modality and delivery of interventions is important however, considering the complex nature of clinical reasoning. New blood tests and innovations in diagnostic technologies, including point-of-care tests, may offer additional opportunities for supporting the diagnostic process, beyond those offered by currently available common blood tests.

8.3 Concluding remarks

Blood tests form an important part of the diagnostic process in primary care, and their role is likely going to increase in the future, given likely emergent epidemiological evidence on the predictive value of blood tests for cancer, and the introduction of MCED testing in combination or in sequence with common blood tests. Despite evidence supporting the diagnostic utility of blood tests for cancer, half of cancer patients who presented with non-specific symptoms did not have a common blood test as part of their diagnostic process in primary care. My research enquiry used cross-sectional audit data and general practitioner interviews to explore blood tests as a diagnostic strategy in cancer patients presenting with symptoms of low specificity.

My research assessed the frequency and related variation in blood test use in patients subsequently diagnosed with cancer and the factors that influence GPs decisions to order such tests. The findings can guide implementation research efforts regarding use of blood tests for patients presenting with new symptoms in primary care to support the diagnostic process for cancer and other diseases, and inform the development of interventions. The evidence presented contributes to a growing evidence base on diagnostic interventions for early cancer detection that can translate to improved outcomes for cancer patients.

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Appendix 1. (Academic research profile)

These Chapters have resulted in publications (some pending) at peer-reviewed academic journals:

- Cranfield, B; Koo, MM; Abel, G; Swann, R; McPhail, S; Rubin, G; Lyratzopoulos, G (2022) **Primary care blood tests before cancer diagnosis: National Cancer Diagnosis Audit data.** *British Journal of General Practice***.** 0265. **DOI**: https://doi.org/10.3399/BJGP.2022.0265

  Based on work relating to Chapter 4.

- Cranfield, B; Abel, G; Swann, R; McPhail, S; Rubin, G; Lyratzopoulos, G (2022) **Primary care blood tests and symptom presentation before cancer diagnosis: National Cancer Diagnosis Audit data**. *Cancers* [Epub ahead of print].

  Based on work relating to Chapter 5.

- Cranfield, B; Forster, A, Rafiq, M; Rubin, G; Lyratzopoulos, G; Wagner C von (2022) **Factors other than clinical presentation influencing the use of common blood tests in patients with new symptoms: A qualitative interview study of GPs.** *British Journal of General Practice / BJGP Open* [Epub ahead of print].

  Based on work relating to Chapter 6.

Research dissemination

Conference/meeting contributions and attendance:

- *International CanTest Schools (1st: Attendance, 2nd – 4th: Oral Presentations/updates; 2018 - 2022*): These meetings attracted primary care cancer researchers from across international academic institutions and provided platforms for discussion relating to my work as described in Chapters 4 and 6.

- *Health Services Research (HSR) UK Conference (2019 – Attendance):* I attended this conference to understand more about current research for health technology in primary care and implementation issues (coming from a POCT perspective, this conference was useful for informing components of Chapter 6 and for previous – but never completed – reviews about POCT use in primary care).

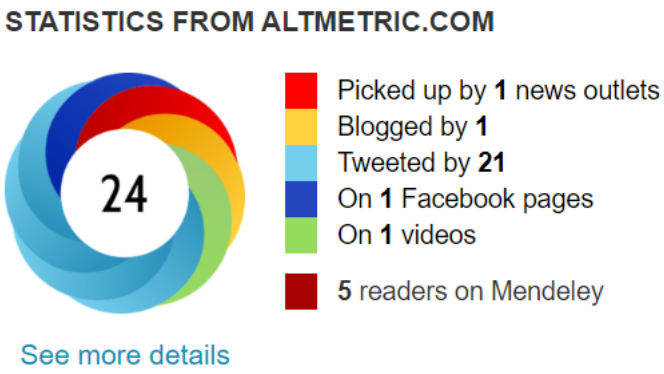
- *Early Diagnosis – Cancer Research UK (ED-CRUK) Conference (2019 – Attendance)*: I attended this conference to better immerse myself within the field of early cancer diagnosis and to network, building on possible future collaborations. Some of these researchers I have since collaborated with.

- *Cancer and Primary Care Research International Network (Ca-Pri – 2021 - Oral Presentation*): I presented preliminary findings from Chapter 4.

- *Research Department of Epidemiology and Public Health (Poster presentation – UCL; 2020):* Poster competition where I presented the plans and objectives of my PhD (winning first Prize).
- Three Minute Thesis (UCL Poster Competition – 2020): Competed in poster competition.

Media coverage:

- BJGP Life (Podcast – Episode 091): "Common blood tests before cancer diagnosis and implications for primary care" (25th October, 2022). Available at: https://bjgplife.com/episode-091-common-blood-tests-before-cancer-diagnosis-and-implications-for-primary-care/



- ENGLEMED Health News: *"Backing for primary care blood tests for cancer diagnosis"* (18th October, 2022). Available at: http://www.englemed.co.uk/22/22oct182_cancer_diagnosis_blood_tests.php
- PRACTICE INDEX News: *"Backing for primary care blood tests for cancer diagnosis"* (18th October, 2022). Available at: https://practiceindex.co.uk/gp/blog/news-backing-for-primary-care-blood-tests-for-cancer-diagnosis/

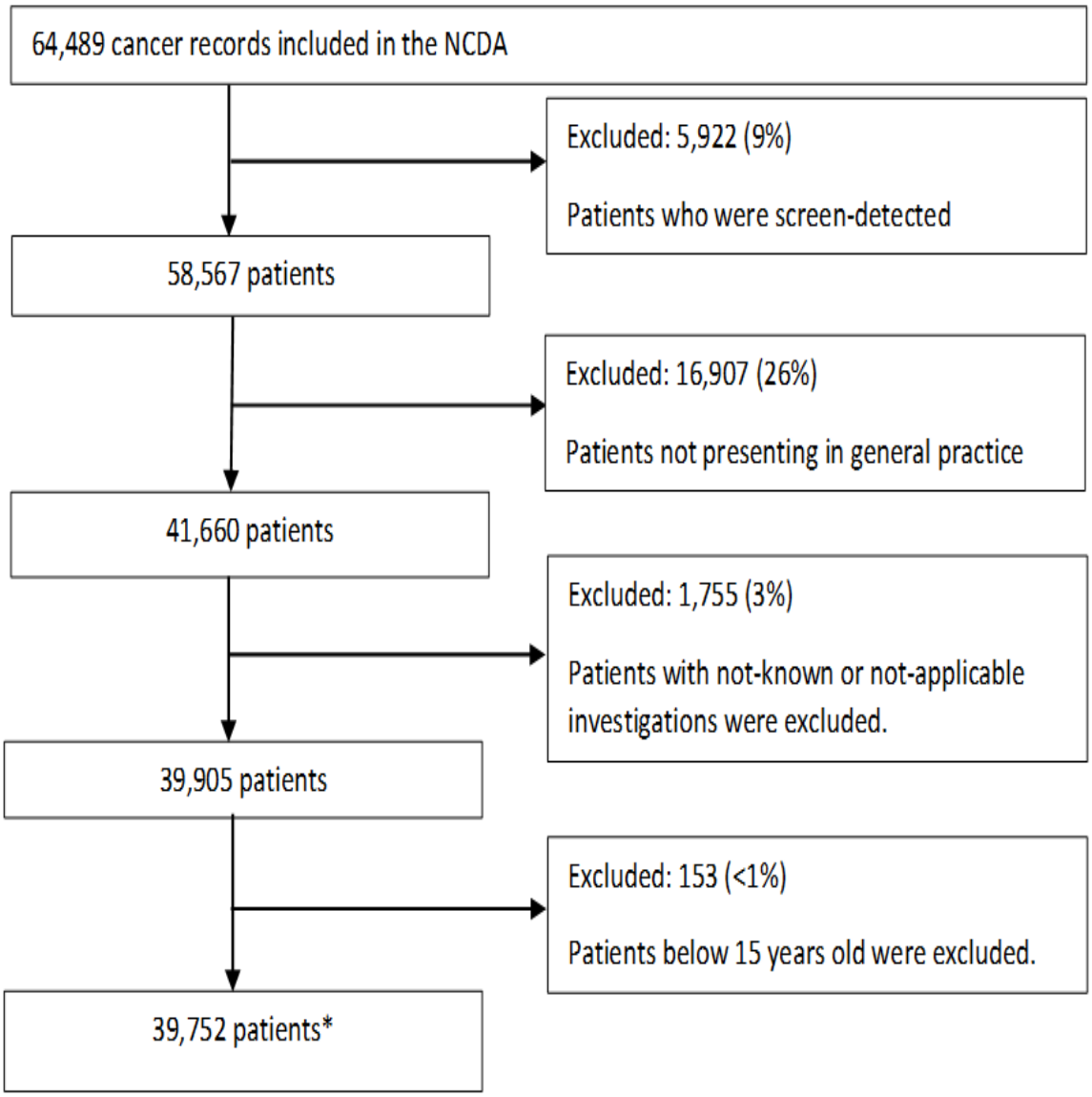
Appendix 2. (Professional development during PhD)

Courses undertaken as part of doctoral training:

- Statistics and Research Methodology (Centre of Applied Statistics Courses – weeklong short course pre-PhD)
- Research Methods for Quantitative Data (Four-day course: 11th February 2021)
- Arena One: Gate (Postgraduate teaching assistant (PGTA) course: 19th January 2022)
- Short course: Introduction to search strategies for systematic reviews of interventions (13th November 2019).
- Cumberland Lodge Retreat: A weekend conference/training with fellow PhD Students regarding research methods (14th – 16th June 2019).
- Short course: Critical appraisal of a randomised controlled trial for life and medical sciences students (01/05/2019)
- Short course: Potential Energy – Effective Presentations (5th February 2019)
- Short course: Academic Writing (14th January 2019)
- Short course: Advanced Rapid Qualitative Data Analysis (28th May 2021)
- Short course: Process/Pathway Mapping in Rapid Qualitative Research (21st May 2021)
- Student Mentor (2021 - 2022)

Appendix 3. A (4.2.1): Derivation of the analysis sample

Figure 1. Derivation of the analysis sample (n=39752)



*Includes 571 patients with more than one tumour.

Appendix 3. B (4.2.3): List of symptoms by categorisation

Emergency symptoms (n=5)	Alarm symptoms (n=36)	Non-alarm symptoms (n=40)	Not-known/Not-Applicable Symptoms (n=2)
Fracture	Breast Lump/mass	Abdominal pain (NOS)	N/A
Stridor	Haematuria	Back pain	N/K
Haematemesis	Lesions suspicious of melanoma	Bone pain	
Fit/seizure	Change in bowel habit	Breast pain	
Visual disturbance	Neck lump/mass	Upper abdominal pain	
	Dysphagia	Chest infection	
	Post-menopausal bleeding	Chest pain	
	Haemoptysis	Cough	
	Rectal bleeding	Deep vein thrombosis	
	Constipation	Distension	
	Jaundice	Dyspepsia	
	Lymphadenopathy (localised)	Dysuria	
	Hoarseness	Early satiety	
	Testicular lump	Dyspnoea	
	Vulval bleeding	Erectile dysfunction	
	Thyroid lump/mass	Fatigue	
	Nipple Change	Fever	
	Clubbing	Gastroesophageal reflux	
	Nipple discharge	Headache	
	Penile ulceration	Infection	
	Axillary lump/mass	Diarrhoea	
	Bruising, bleeding or petechiae	Loin pain	
	Epistaxis	Loss of appetite	
	Lymphadenopathy (generalised)	Lower abdominal pain	
	Vulval ulceration	LUTS (nocturia, frequency,hesitancy, urgency, retention)	
	Anal mass	Nausea and/or vomiting	
	Lip/oral cavity/togue ulcer	New onset Diabetes	
	Lymph node pain with alcohol	Night sweats	
	Lesions suspicious of BCC	Non-pigmented lesion	
	Leukoplakia	Other symptom	
	Lip/oral cavity/tongue lump/mass	Other vaginal bleeding	
	Ulceration	Pallor	
	Unexplained lump suspicious of sarcoma	Pelvic pain	
	Vaginal mass	Prog/sub-acute loss of central neuro funct	
	Vulval mass	Pruritus	
	Weight loss	Renal colic	
		Sore throat	
		Testicular pain	
		Urinary tract infection	
		Vaginal discharge	

Appendix3. C (4.2.5): Table showing individual and combined frequencies of common blood test use before cancer diagnosis

Investigation Signatures	**Total (%)**
Patients having FBC blood tests	15540 (95%)
Patients having U&E blood tests	14555 (88%)
Patients having LFT blood tests	12414 (74%)
Patients having two or more common blood tests	14321 (87%)
Patients have all three common blood tests	11761 (72%)

Appendix 3. D (4.2.5): Table showing adjustment for different investigations

Table showing c*haracteristics of blood test requests, and crude/adjusted ORs of blood tests (including different investigations as an additional covariate [column 5])*

	Received a blood test (%)	Crude OR (95% CI)*	Adjusted OR* (excluding cancer-site and different investigations)	Adjusted OR (excluding different investigations)	Adjusted OR (95% CI)
Total Number:	16427 (41%)				
Age group		P<0.001	P<0.001	P=0.001	P=0.002
15-29 years	172 (31%)	0.66 (0.55-0.79)	0.85 (0.70-1.04)	0.98 (0.77-1.23)	1.02 (0.72-1.44)
30-49 years	1053 (26%)	0.53 (0.49-0.57)	0.69 (0.63-0.75)	0.99 (0.90-1.10)	1.01 (0.87-1.17)
50-69 years	6293 (40%)	Ref	Ref	Ref	Ref
70+ years	8909 (46%)	1.26 (1.21-1.32)	1.23 (1.18-1.29)	1.12 (1.06-1.18)	1.16 (1.08-1.24)
Sex		P<0.001	P<0.001	P=0.009	P=0.079
Male	10391 (48%)	Ref	Ref	Ref	Ref
Female	6036 (34%)	0.55 (0.53-0.58)	0.67 (0.64-0.70)	0.92 (0.87-0.98)	0.92 (0.84-1.00)
Ethnicity		P=0.003	P=0.475	P=0.024	P=0.269
White	14310 (42%)	Ref	Ref	Ref	Ref
Non-white	1308 (38%)	0.88 (0.81-0.94)	0.96 (0.89-1.04)	0.89 (0.82-0.97)	0.91 (0.81-1.02)
Unknown	809 (42%)	1.01 (0.92-1.11)	1.04 (0.94-1.15)	1.02 (0.92-1.14)	0.98 (0.85-1.13)
Index of Multiple Deprivation (IMD)		P=0.222	P=0.106	P=0.115	P=0.260
1-Least deprived	3422 (41%)	Ref	Ref	Ref	Ref
2	3474 (42%)	1.07 (1.00-1.13)	1.08 (1.01-1.15)	1.08 (1.01-1.16)	1.04 (0.94-1.14)
3	3219 (41%)	1.02 (0.96-1.09)	1.04 (0.97-1.11)	1.01 (0.94-1.08)	1.07 (0.97-1.18)
4	3131 (42%)	1.04 (0.98-1.11)	1.07 (1.01-1.15)	1.03 (0.96-1.11)	1.11 (1.01-1.23)
5-Most deprived	3181 (41%)	1.01 (0.95-1.07)	1.04 (0.98-1.12)	0.99 (0.92-1.07)	1.06 (0.96-1.17)
Cancer		P<0.001		P<0.001	P<0.001
Leukaemia	552 (84%)	7.69 (6.18-9.55)		9.24 (7.41-11.52)	21.80 (16.66-28.52)
Myeloma	455 (76%)	4.68 (3.84-5.71)		5.16 (4.22-6.31)	1.34 (0.97-1.86)
Pancreatic	826 (71%)	3.61 (3.13-4.16)		3.52 (3.06-4.07)	3.09 (2.48-3.84)
Liver	331 (70%)	3.50 (2.85-4.31)		3.69 (2.99-4.55)	4.66 (3.48-6.24)
Colon	2093 (70%)	3.47 (3.14-3.83)		3.84 (3.46-4.25)	4.14 (3.54-4.85)

Stomach	448 (62%)	2.39 (2.03-2.81)	N/A	2.43 (2.06-2.87)	2.61 (2.03-3.37)
Rectal	764 (61%)	2.29 (2.02-2.61)		2.86 (2.50-3.28)	3.19 (2.58-3.94)
CUP	368 (59%)	2.08 (1.75-2.46)		2.19 (1.84-2.60)	1.81 (1.37-2.39)
Hodgkin Lymphoma	121 (56%)	1.83 (1.38-2.41)		2.27 (1.70-3.04)	1.86 (1.18-2.94)
Ovarian	482 (55%)	1.81 (1.56-2.10)		1.90 (1.63-2.21)	0.46 (0.35-0.60)
Non-Hodgkin Lymphoma	852 (55%)	1.82 (1.62-2.05)		2.15 (1.91-2.43)	1.82 (1.50-2.22)
Kidney	477 (49%)	1.44 (1.25-1.66)		1.62 (1.41-1.87)	1.58 (1.26-1.98)
Oesophageal	504 (47%)	1.30 (1.13-1.49)		1.38 (1.20-1.59)	2.16 (1.75-2.66)
Prostate	3518 (47%)	1.32 (1.23-1.43)		1.42 (1.31-1.55)	0.11 (0.09-0.13)
Other	1004 (46%)	1.28 (1.16-1.42)		1.51 (1.36-1.68)	1.98 (1.67-2.34)
Bladder	481 (43%)	1.13 (0.99-1.29)		1.33 (1.15-1.52)	1.45 (1.17-1.79)
Mesothelioma	143 (43%)	1.14 (0.91-1.43)		1.04 (0.82-1.31)	1.30 (0.92-1.84)
Lung	1785 (40%)	Ref		Ref	Ref
Thyroid	179 (38%)	0.95 (0.78-1.15)		1.38 (1.11-1.70)	0.35 (0.25-0.50)
Brain	123 (38%)	0.88 (0.70-1.12)		0.96 (0.76-1.23)	1.14 (0.76-1.70)
Cervical	59 (30%)	0.63 (0.46-0.87)		0.74 (0.54-1.03)	1.13 (0.69-1.86)
Oropharynx	145 (28%)	0.57 (0.46-0.70)		0.70 (0.57-0.86)	0.88 (0.63-1.23)
Uterus	318 (25%)	0.49 (0.43-0.57)		0.65 (0.56-0.76)	0.68 (0.53-0.86)
Larynx	64 (22%)	0.41 (0.31-0.55)		0.50 (0.37-0.66)	0.63 (0.40-1.00)
Oral cavity	28 (11%)	0.18 (0.12-0.28)		0.26 (0.17-0.39)	0.51 (0.28-0.92)
Testicular	33 (10%)	0.16 (0.11-0.23)		0.19 (0.13-0.28)	0.25 (0.14-0.43)
Vulval	10 (8%)	0.12 (0.06-0.23)		0.17 (0.09-0.33)	0.37 (0.15-0.90)
Breast	209 (4%)	0.07 (0.06-0.08)		0.09 (0.07-0.10)	0.24 (0.19-0.30)
Melanoma	55 (2%)	0.04 (0.03-0.05)		0.05 (0.03-0.06)	0.15 (0.10-0.21)
Morbidities		P<0.001	P=0.908	P=0.409	P=0.345
0	3698 (36%)	Ref	Ref	Ref	Ref
1	5111 (41%)	1.22 (1.16-1.29)	1.01 (0.94-1.06)	0.94 (0.88-1.01)	1.01 (0.92-1.09)
2	4039 (44%)	1.37 (1.30-1.46)	1.01 (0.95-1.08)	0.97 (0.91-1.04)	1.07 (0.97-1.17)
3+	3318 (45%)	1.41 (1.33-1.50)	1.01 (0.93-1.07)	0.96 (0.89-1.03)	1.04 (0.94-1.16)

missing	261 (38%)	N/A	N/A	N/A	N/A
Symptoms		P<0.001	P<0.001	P<0.001	P<0.001
Alarm	3341 (24%)	Ref	Ref	Ref	Ref
Non-alarm	8223 (50%)	3.12 (2.97-3.28)	2.75 (2.61-2.89)	1.58 (1.49-1.69)	1.07 (0.97-1.17)
Alarm/non-alarm	3262 (56%)	3.97 (3.72-4.23)	3.68 (3.44-3.93)	2.13 (1.98-2.30)	1.36 (1.21-1.52)
Emergency	62 (36%)	1.70 (1.24-2.34)	1.60 (1.16-2.21)	0.94 (0.66-1.32)	0.84 (0.50-1.42)
Not known/not applicable	1539 (44%)	2.48 (2.30-2.69)	2.01 (1.86-2.18)	1.01 (0.92-1.10)	0.70 (0.62-0.79)
Other Pre-referral Investigations* **		P<0.001	N/A	N/A	P<0.001
None	9467 (35%)	Ref	N/A	N/A	Ref
One or more	6960 (54%)	2.15 (2.06-2.24)	N/A	N/A	1.83 (1.70-1.98)
Other Blood tests* **		P<0.001	N/A	N/A	P<0.001
None	2637 (12%)	Ref	N/A	N/A	Ref
One or more	13790 (79%)	27.97 (26.47-29.55)	N/A	N/A	106 (95.59-117.87)

*After excluding 692 patients with missing information on morbidities, 39060 cases remained for the logistic regression models. **Post estimations using Wald tests explained the significance of the explanatory variables on predicting blood test use. ***Based on answers to the Audit questionnaire item: "Primary care led investigations that were ordered as part of the diagnostic assessment, and prior to referral, decided by the GP in response to symptoms complained of, signs elicited, or abnormal test results" with possible options comprising: FBC, U&Es, LFTs (as used in main analysis), imaging (chest x-ray, skeletal x-ray, other x-ray, contrast radiology including barruim, swallow, meal, enema and other, ultrasound abdomen, ultrasound transvaginal, ultrasound neck, ultrasound pelvis, ultrasound other, CT chest, CT abdomen, CT brain, CT other, MRI brain, MRI spine, MRI other), endoscopy (upper GI, colonoscopy, flexible sigmoidoscopy, bronchoscopy, colposcopy, flexible cystoscopy), urinary (cytology); other blood tests (cancer biomarkers, inflammatory markers, bone profile, ferritin, serum protein and amylase tests); symptomatic FIT test (only included in the 2018 audit, and not used in the present paper); and other investigations.

Appendix 3. E (4.2.5): Sensitivity Analysis (removing cases with no recorded consultations after presenting in general practice).

Table showing frequency of blood test use by patient characteristics, after excluding cases with zero consultations

	Population Total (column %)		Received a blood test (row %)	
	Main	**Sensitivity**	**Main**	**Sensitivity**
Total:	39752 (100%)	37704 (100%)	16427 (41%)	15912 (42%)
Age group				
15-29	553 (1%)	532 (1%)	172 (31%)	170 (32%)
30-49	4009 (10%)	3728 (10%)	1053 (26%)	1021 (27%)
50-69	15746 (40%)	14898 (40%)	6293 (40%)	6079 (41%)
70+	19444 (49%)	18546 (49%)	8909 (46%)	8642 (47%)
Sex				
Male	21854 (55%)	20885 (55%)	10391 (48%)	10065 (48%)
Female	17898 (45%)	16819 (45%)	6036 (34%)	5847 (35%)
Ethnicity				
White	34421 (87%)	32681 (87%)	14310 (42%)	13885 (42%)
Non-white	3400 (9%)	3184 (8%)	1308 (38%)	1253 (39%)
Unknown	1931 (5%)	1839 (5%)	809 (42%)	774 (42%)
Index of Multiple Deprivation				
1- Least Deprived	8408 (21%)	8040 (21%)	3422 (41%)	3336 (42%)
2	8222 (21%)	7831 (21%)	3474 (42%)	3361 (43%)
3	7839 (20%)	7417 (20%)	3219 (41%)	3115 (42%)
4	7529 (19%)	7090 (19%)	3131 (42%)	3025 (43%)
5 - Most Deprived	7754 (20%)	7326 (19%)	3181 (41%)	3075 (42%)
Cancer				
Leukaemia	661 (2%)	629 (2%)	552 (84%)	528 (84%)
Multiple myeloma	599 (2%)	579 (2%)	455 (76%)	442 (76%)
Pancreas	1165 (3%)	1120 (3%)	826 (71%)	805 (72%)
Liver	471 (1%)	456 (1%)	331 (70%)	323 (71%)
Colon	2991 (8%)	2846 (8%)	2093 (70%)	2016 (71%)
Stomach	727 (2%)	692 (2%)	448 (62%)	432 (62%)
Rectum	1261 (3%)	1188 (3%)	764 (61%)	727 (61%)
Unknown primary	629 (2%)	602 (2%)	368 (59%)	359 (60%)
Hodgkin lymphoma	218 (<1%)	208 (1%)	121 (56%)	120 (58%)
Ovary	874 (2%)	834 (2%)	482 (55%)	467 (56%)
Non-hodgkin lymphoma	1545 (4%)	1488 (4%)	852 (55%)	836 (56%)
Kidney	969 (2%)	925 (2%)	477 (49%)	459 (50%)
Oesophagus	1074 (3%)	1013 (3%)	504 (47%)	484 (48%)
Prostate	7499 (19%)	7261 (19%)	3518 (47%)	3426 (47%)
Other	2184 (5%)	2090 (6%)	1004 (46%)	973 (47%)

Bladder	1112 (3%)	1072 (3%)	481 (43%)	465 (43%)
Mesothelioma	331 (<1%)	315 (1%)	143 (43%)	136 (43%)
Lung	4430 (11%)	4279 (11%)	1785 (40%)	1751 (41%)
Brain	467 (1%)	315 (1%)	179 (38%)	122 (39%)
Thyroid	328 (<1%)	444 (1%)	123 (38%)	170 (38%)
Cervix	194 (<1%)	175 (<1%)	59 (30%)	55 (31%)
Oropharynx	523 (1%)	495 (1%)	145 (28%)	140 (28%)
Uterus	1266 (3%)	1172 (3%)	318 (25%)	302 (26%)
Larynx	297 (<1%)	284 (1%)	64 (22%)	63 (22%)
Oral cavity	248 (<1%)	226 (1%)	28 (11%)	23 (10%)
Testis	340 (<1%)	320 (1%)	33 (10%)	33 (10%)
Vulva	133 (<1%)	124 (<1%)	10 (8%)	10 (8%)
Breast	4919 (12%)	4452 (12%)	209 (4%)	192 (4%)
Melanoma	2297 (6%)	2100 (6%)	55 (2%)	53 (3%)
Morbidities				
0	10145 (26%)	9583 (25%)	3698 (36%)	3589 (37%)
1	12370 (31%)	11709 (31%)	5111 (41%)	4933 (42%)
2	9144 (23%)	8718 (23%)	4039 (44%)	3923 (45%)
3+	7401 (19%)	7061 (19%)	3318 (45%)	3217 (46%)
Symptom Types				
Alarm only	13778 (35%)	12720 (34%)	3341 (24%)	3167 (25%)
Non-alarm	16487 (41%)	15967 (42%)	8223 (50%)	8052 (50%)
Alarm/non-alarm	5832 (15%)	5570 (15%)	3262 (56%)	3169 (57%)
Emergency only	173 (<1%)	167 (<1%)	62 (36%)	62 (37%)
Not-known/not-applicable	3482 (9%)	3280 (9%)	1539 (44%)	1462 (45%)

Appendix 3. F (4.3.7): Comparison of study compositions

Table showing composition of populations in the 2014 and 2018 NCDA audits

	NCDA 2014 study sample	NCDA 2018 study sample
Total:	10951 (100%)	39752 (100%)
Age group		
15-29 years	164 (2%)	553 (1%)
30-49 years	1143 (10%)	4009 (10%)
50-69 years	4379 (40%)	15746 (40%)
70+ years	5268 (48%)	19444 (49%)
Sex		
Male	5854 (53%)	21854 (55%)
Female	5093 (47%)	17898 (45%)
Ethnicity		
White	9547 (87%)	34421 (87%)
Non-white	473 (4%)	3400 (9%)
Unknown	931 (9%)	1931 (5%)
Index of Multiple Deprivation (IMD)		
1-Least deprived	2389 (22%)	8408 (21%)
2	2474 (23%)	8222 (21%)
3	2386 (22%)	7839 (20%)
4	1980 (18%)	7529 (19%)
5-Most deprived	1722 (16%)	7754 (20%)
Cancer*		
Prostate	1707 (16%)	7499 (19%)
Breast	1373 (13%)	4919 (12%)
Lung	1296 (12%)	4430 (11%)
Colon	787 (7%)	2991 (8%)
Melanoma	670 (6%)	2297 (6%)
Rectal	473 (4%)	1261 (3%)
Other	421 (4%)	2184 (5%)
Bladder	347 (3%)	1112 (3%)
Oesophageal	321 (3%)	1074 (3%)
Pancreatic	311 (3%)	1165 (3%)
Leukaemia	280 (3%)	661 (2%)
Ovarian	255 (2%)	874 (2%)
Stomach	212 (2%)	727 (2%)
CUP	202 (2%)	629 (2%)
Oral/Oropharyngeal	181 (2%)	523 (1%)
Myeloma	164 (2%)	599 (2%)
Liver	135 (1%)	471 (1%)
Mesothelioma	114 (1%)	331 (<1%)
Thyroid	105 (1%)	467 (1%)
Testicular	104 (1%)	340 (<1%)

Brain/CNS	100 (1%)	328 (<1%)
Laryngeal	84 (1%)	297 (<1%)
Cervical	59 (1%)	194 (<1%)
Vulval	39 (<1%)	133 (<1%)
Morbidities		
0	2965 (27%)	10145 (26%)
1	3400 (31%)	12370 (31%)
2	2489 (23%)	9144 (23%)
3+	1954 (18%)	7401 (19%)
missing	143 (1%)	692 (2%)
Symptoms		
Alarm only	4828 (44%)	17306 (44%)
Non-alarm only	2981 (27%)	12007 (30%)
Alarm/non-alarm	2471 (23%)	6957 (18%)
Not known/not applicable	671 (6%)	3482 (9%)

*Disparity in the recording of cancer-sites between NCDA datasets means not all cancers are shown in this comparison.

Appendix 3. G (4.3.8): Comparing blood test use between 2014 and 2018 NCDA versions

Table showing variation in common blood test use by patient characteristic between 2014 and 2018 NCDA audits

	Received a blood test (%) - 2014	Received a blood test (%) - 2018	Crude OR (95% CI)* - 2014	Crude OR (95% CI)* - 2018	Adjusted OR* (95% CI) (excluding cancer-site) - 2014	Adjusted OR* (95% CI) (excluding cancer-site) - 2018	Adjusted OR* (95% CI) (including cancer-site) - 2014	Adjusted OR* (95% CI) (including cancer-site) - 2018
Total	4266 (39%)	16427 (41%)						
Age group			P<0.001	P<0.001	P<0.001	P<0.001	P=0.004	P<0.001
15-29 years	43 (26%)	172 (31%)	0.56 (0.39-0.82)	0.66 (0.55-0.79)	0.66 (0.45-0.96)	0.78 (0.64-0.95)	0.61 (0.40-0.95)	0.95 (0.76-1.20)
30-49 years	276 (24%)	1053 (26%)	0.51 (0.44-0.60)	0.53 (0.49-0.57)	0.65 (0.55-0.77)	0.65 (0.60-0.71)	0.92 (0.76-1.11)	0.98 (0.89-1.09)
50-69 years	1660 (38%)	6293 (40%)	Ref	Ref	Ref	Ref	Ref	Ref
70+ years	2287 (43%)	8909 (46%)	1.25 (1.15-1.36)	1.26 (1.21-1.32)	1.24 (1.13-1.35)	1.26 (1.20-1.32)	1.13 (1.02-1.24)	1.12 (1.07-1.18)
Sex			P<0.001	P<0.001	P<0.001	P<0.001	P=0.003	P=0.003
Male	2627 (45%)	10391 (48%)	Ref	Ref	Ref	Ref	Ref	Ref
Female	1639 (32%)	6036 (34%)	0.58 (0.53-0.63)	0.55 (0.53-0.58)	0.67 (0.62-0.73)	0.62 (0.59-0.65)	0.85 (0.76-0.94)	0.91 (0.86-0.97)
Ethnicity			P=0.298	P=0.003	P=0.066	P=0.561	P=0.187	P=0.033
White	3696 (39%)	14310 (42%)	Ref	Ref	Ref	Ref	Ref	Ref
Non-white	193 (41%)	1308 (38%)	1.11 (0.91-1.34)	0.88 (0.81-0.94)	1.19 (0.97-1.46)	0.97 (0.89-1.04)	1.07 (0.86-1.34)	0.89 (0.82-0.97)
Unknown	377 (40%)	809 (42%)	1.08 (0.94-1.24)	1.01 (0.92-1.11)	1.13 (0.97-1.30)	1.03 (0.93-1.14)	1.15 (0.98-1.35)	1.03 (0.92-1.14)
Index of Multiple Deprivation (IMD)			P=0.062	P=0.222	P=0.010	P=0.034	P=0.005	P=0.133
1-Least deprived	903 (38%)	3422 (41%)	Ref	Ref	Ref	Ref	Ref	Ref
2	965 (39%)	3474 (42%)	1.04 (0.91-1.17)	1.07 (1.00-1.13)	1.03 (0.91-1.16)	1.09 (1.02-1.16)	1.02 (0.89-1.16)	1.08 (1.01-1.16)

3	919 (39%)	3219 (41%)	1.03 (0.92-1.16)	1.02 (0.96-1.09)	1.01 (0.89-1.14)	1.05 (0.99-1.12)	0.98 (0.86-1.30)	1.01 (0.94-1.08)
4	828 (42%)	3131 (42%)	1.18 (1.04-1.33)	1.04 (0.98-1.11)	1.21 (1.06-1.38)	1.09 (1.02-1.17)	1.19 (1.03-1.37)	1.03 (0.96-1.11)
5-Most deprived	651 (38%)	3181 (41%)	0.99 (0.87-1.13)	1.01 (0.95-1.07)	0.97 (0.85-1.11)	1.07 (1.01-1.15)	0.90 (0.77-1.04)	0.99 (0.92-1.07)
Morbidities			P<0.001	P<0.001	P=0.832	P=0.625	P=0.986	P=0.344
0	1015 (34%)	3698 (36%)	Ref	Ref	Ref	Ref	Ref	Ref
1	1346 (40%)	5111 (41%)	1.25 (1.13-1.39)	1.22 (1.16-1.29)	1.05 (0.94-1.17)	1.01 (0.95-1.07)	0.98 (0.87-1.11)	0.94 (0.88-1.00)
2	1012 (41%)	4039 (44%)	1.31 (1.17-1.46)	1.37 (1.30-1.46)	1.03 (0.91-1.17)	1.04 (0.97-1.11)	1.003 (0.87-1.14)	0.97 (0.91-1.04)
3+	836 (43%)	3318 (45%)	1.43 (1.27-1.61)	1.41 (1.33-1.50)	1.04 (0.91-1.19)	1.01 (0.94-1.08)	1.01 (0.87-1.17)	0.95 (0.88-1.02)
missing	57 (40%)	261 (38%)	N/A	N/A	N/A	N/A	N/A	N/A
Symptom types			P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
Alarm only	1202 (25%)	3341 (24%)	Ref	Ref	Ref	Ref	Ref	Ref
Non-alarm only	1438 (48%)	8223 (50%)	2.80 (2.54-3.08)	3.12 (2.97-3.28)	2.54 (2.30-2.81)	2.75 (2.61-2.89)	1.66 (1.47-1.88)	1.58 (1.49-1.69)
Alarm/non-alarm	1357 (55%)	3262 (56%)	3.64 (3.28-4.04)	3.97 (3.72-4.23)	3.41 (3.07-3.79)	3.68 (3.44-3.93)	2.06 (1.83-2.32)	2.33 (1.98-2.30)
Not known/not applicable	269 (40%)	1539 (44%)	2.02 (1.70-2.39)	1.89 (1.75-2.04)	1.69 (1.43-2.01)	1.54 (1.42-1.66)	0.91 (0.75-1.11)	0.91 (0.83-0.99)

*After excluding patients with missing information on morbidities, 10,808 cases and 39,060 cases remained for logistic regression analysis in the NCDA 2014 (i.e. 143 cases excluded) and 2018 (i.e. 692 cases excluded) populations, respectively.

Appendix 3. H (4.3.8): Comparison of Diagnostic process measures

Table showing comparisons between NCDA audits in blood test use by consultation rate and referral type.

	NCDA 2014		NCDA 2018	
	Total/Received a common blood test (% tested)	Crude ORs (95% CI)*	Total/Received a common blood test (% tested)	Crude ORs (95% CI)*
Total Number:	10951/4776 (39%)		39752/16427 (41%)	
		P<0.001		P<0.001
Number of Consultations				
0	797/163 (20%)	Ref	2048/515 (25%)	Ref
1	4612/1102 (24%)	1.21 (1.00-1.46)	19443/5428 (28%)	1.13 (1.02-1.26)
2	2718/1294 (48%)	3.49 (2.88-4.22)	10508/5680 (54%)	3.48 (3.12-3.88)
3+	2645/1634 (62%)	6.24 (5.16-7.56)	6983/4494 (64%)	5.30 (4.74-5.94)
Missing	179/73 (41%)	N/A	770/310 (40%)	N/A
p<0.001*				
Referral Type**		P<0.001		P<0.001
Routine	1107/463 (42%)	Ref	2776/1176 (42%)	Ref
Urgent - not for suspected cancer	563/256 (45%)	1.15 (0.93-1.41)	1293/640 (49%)	1.33 (1.16-1.52)
TWW/USC for suspected cancer	7470/2717 (36%)	0.79 (0.69-0.90)	29476/11806 (40%)	0.89 (0.82-0.97)
Referral to private healthcare	242/86 (36%)	0.74 (0.55-1.00)	645/231 (36%)	0.74 (0.62-0.89)
Emergency Referral (including patient self-referral)	1207/602 (50%)	1.36 (1.16-1.61)	3617/1746 (48%)	1.25 (1.13-1.38)
Screening detected	14/3 (21%)	0.37 (0.10-1.36)	20/9 (45%)	0.97 (0.39-2.43)
Other	248/98 (40%)	0.88 (0.66-1.17)	835/363 (43%)	1.01 (0.86-1.18)
Not known	100/41 (41%)	0.97 (0.63-1.48)	458/194 (42%)	0.73 (0.59-0.91)
p<0.001				

* Chi-squared tests examined the differences in explanatory variables by blood test request.**Information on direct access and MDC referrals were only captured in the 2018 NCDA, therefore no comparisons were made for these referral options.

Appendix 3. I (4.3.8): Comparison of NCDA intervals

Table showing the distribution of PCI and DI by blood test use, stratified by symptom type between NCDA versions

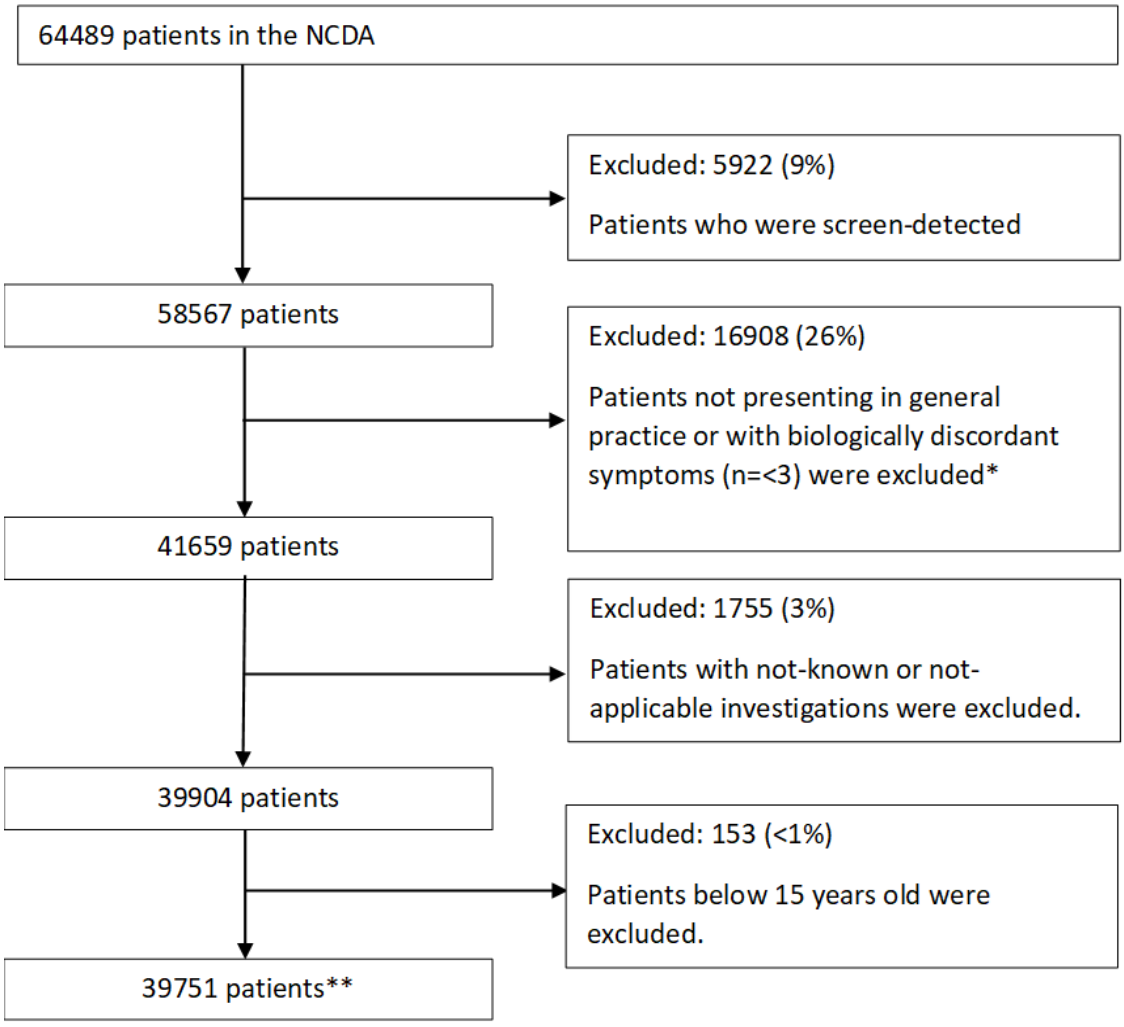
	All patients (independently of blood test status) (n=10951)	Patients having a common blood test (n=4266)	Patients not having a common blood test (n=6685)	Difference by common blood test use	P value*
2014 NCDA	Median (IQR) days	Median (IQR) days	Median (IQR) days	Median days	
Primary care Interval					
Overall (n=8920)	5 (0-28)	15 (3-43)	1 (0-16)	14	0.001
Alarm only (n=6023)	2 (0-22)	14 (2-42)	0 (0-10)	14	0.001
Non-alarm only (n=4357)	13 (1-38)	17 (5-48)	7 (0-28)	10	0.001
Alarm/non-alarm (n=1978)	11 (0-38)	17 (4-47)	4 (0-26)	13	0.001
Not known/not applicable (n=518)	6 (0-30)	6 (0-33)	6 (0-28)	0	0.141
Diagnostic Interval					
Overall (n=9582)	44 (20-94)	59 (30-119)	35 (15-77)	24	0.001
Alarm only (n=6477)	38 (15-84)	58 (29-113)	29 (14-66)	29	0.001
Non-alarm only (n=4786)	53 (26-107)	60 (31-122)	46 (21-95)	14	0.002
Alarm/non-alarm (n=2218)	50 (22-102)	59 (30-115)	38 (17-84)	21	0.001
Not known/not applicable (n=537)	63 (31-116)	68 (35-120)	59 (29-115)	9	0.45
2018 NCDA	(n=37752)	(n=16427)	(n=23325)		
Primary care Interval					
Overall (n=35962)	3 (0-20)	10 (1-30)	0 (0-13)	10	<0.001
Alarm only (n=22410)	0 (0-8)	4 (0-20.5)	0 (0-1)	4	<0.001
Non-alarm only (n=16927)	8 (0-29)	13 (2-34)	4 (0-23)	9	<0.001
Alarm/non-alarm (n=6212)	2 (0-17)	6 (0-22)	0 (0-8)	6	<0.001
Not known/not applicable (n=2837)	6 (0-27)	9 (1-34)	3 (0-22)	6	<0.001
Diagnostic Interval					
Overall (n=37883)	39 (17-81)	49 (26-95)	32 (14-70)	17	<0.001
Alarm only (n=23615)	28 (14-61)	41 (21-79)	22 (13-51)	19	<0.001
Non-alarm only (n=18144)	46 (23-91)	49 (27-97)	42 (20-85)	7	<0.001
Alarm/non-alarm (n=6748)	35 (16-69)	40 (21-77)	28 (14-59)	12	<0.001

Not known/not applicable (n=2872)	56 (29-107)	62 (31-117)	52 (28-100)	10	0.21

*P value from Kruskal-Wallis test, comparing intervals in tested vs non-tested patient groups

Appendix 3. J (5.2.1): Sample derivation (accounting for residual disclosure)

Figure showing sample derivation for Chapter 5 analysis

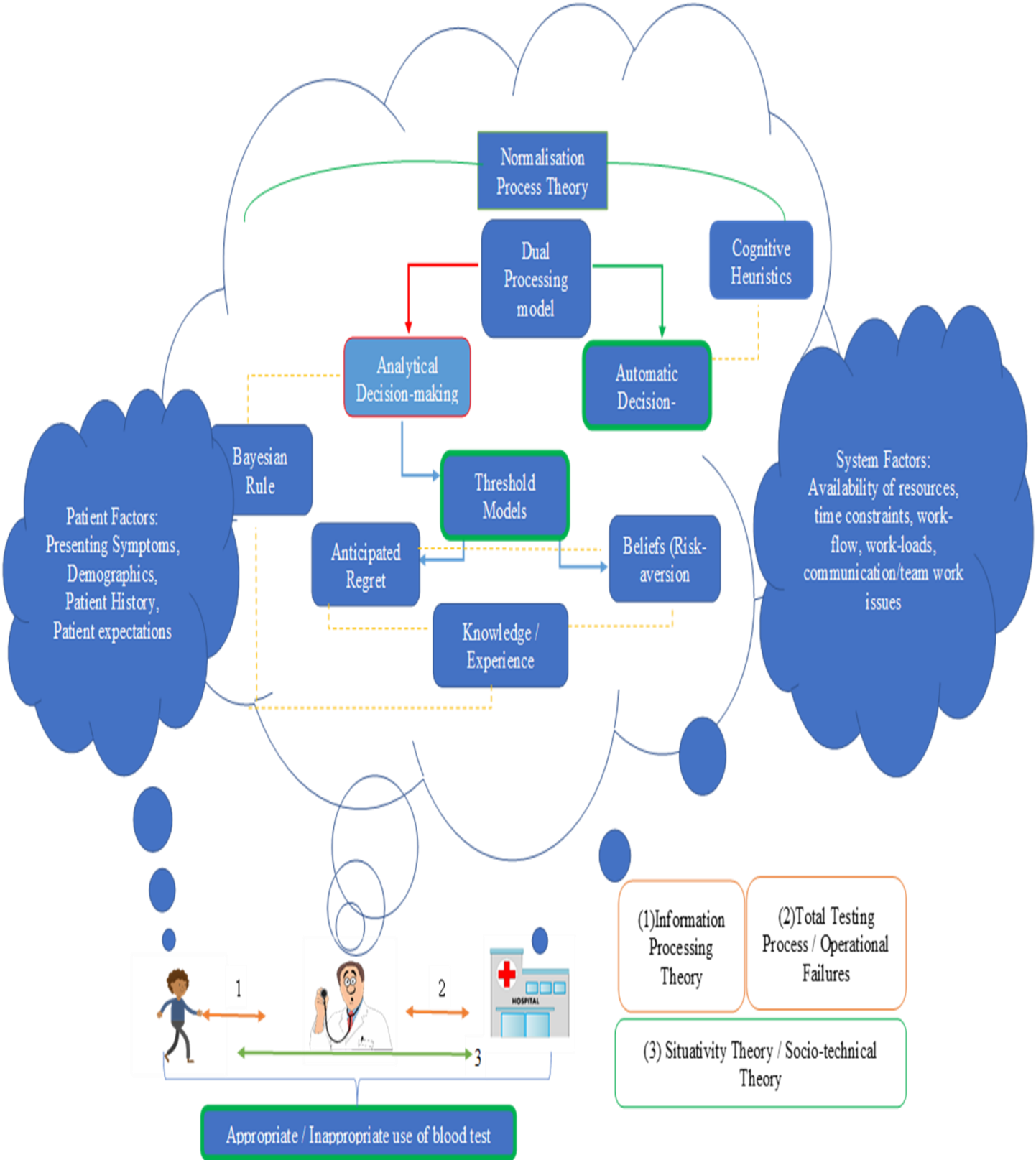


*Cases that risked residual disclosure were removed to protect data that might breach confidentiality requirements.

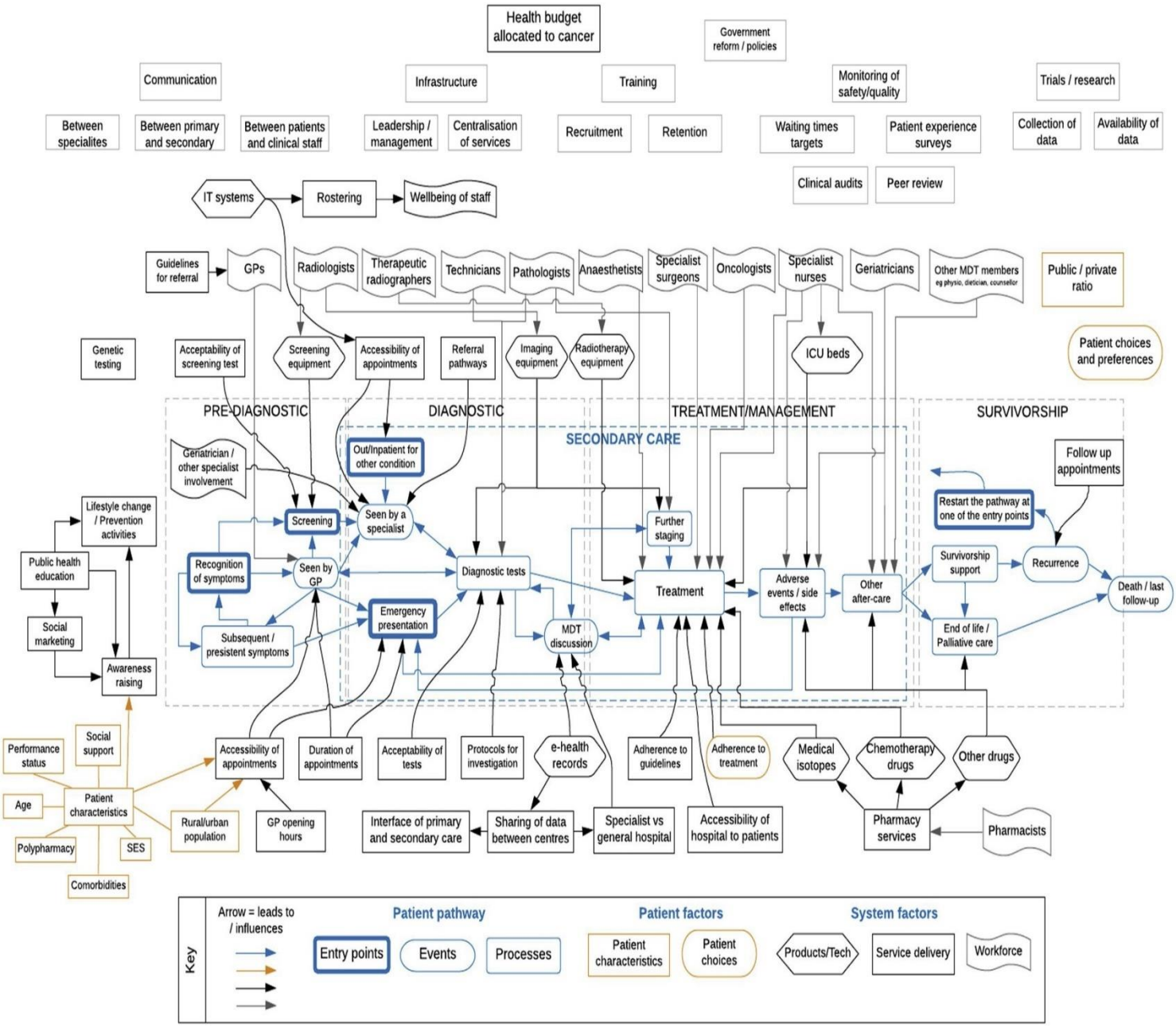
**Includes 571 patients with more than one tumour.

Appendix 3. K (6.1.1): The complexity of blood testing decisions.

Part A: Illustration of cognitive and external factors that may influence how a GP decides to use a blood test.



Part B: *Figure illustrating mechanistic model of factors that influence cancer care pathways* (185)



Appendix 3. L: (6.3.2): – Interview Schedule
Figure showing interview schedule for semi-structured interview study (Chapter 6)

QUALITATIVE DISCUSSION

I. Theme 1: Clinical presentation factors that influence the use of blood tests

Question:

1. *"Imagine that you see a patient presenting with new symptoms. Could you tell me a bit about **how often and when** you would feel the need to order a common blood test for these patients?"*

Prompts / closed questions (if necessary):

- *"How would your decision-making to use a blood test for this patient be influenced by the **nature** of the symptoms, for example, whether they were **localising or non-localising?**"*

    - *If Alarm symptoms haven't been mentioned: "Would your decision-making to use a common blood test change if the patient was presenting with **alarm (also called 'red-flag') symptoms such as those covered by NICE referral guidelines**?"*

- *"How often if at all do you feel that it would have been useful if patients with new symptoms had a **blood test before seeing you**? Perhaps at booking the appointment or even earlier (for the same complaint)?"*

*"Imagine two patients of the same age and sex and have the exact same symptoms, how is **history of chronic conditions** likely to influence your decision-making about use of blood tests?" Please expand.*

If not mentioned spontaneously you can ask: Do **patients with morbidity** tend to have more historical / old blood tests, and are they of any use in practice if and when patients present with new symptoms.

- *"If a patient who has not been blood-tested previously **presents again** with the persistent or worsening symptoms, how would this influence how you decide to use a common blood test?"*

I. <u>Theme 2: Factors relating to GP professional practice that influence the use of blood tests.</u>

Question**:**

- *"Would you ever use a blood test to help **manage patient expectations**?"*
    - "For instance, when you believe the information that will be gained is unlikely to be useful medically, but may be useful for reassuring an anxious patient?"

- *"In your own understanding, **how do you think your own propensity to order common blood tests differs to other GPs**, e.g. in your practice? – i.e. do you order tests on average more or less often than other GPs?" If you are uncertain this is not a problem – just say do not know / cannot tell.*

  *<u>TO BE ASKED ONLY IF THE ANSWER IS 'YES, I THINK I AM ABOVE/BELOW AVERAGE</u>: If you think that your practice is different to average, **why** do you think this may be the case?*

- Do you ever worry about possible **over-diagnosis** (e.g. of asymptomatic illness that will be detected incidentally) through testing? Either way (i.e. whether you are or not concerned about such possibilities), please expand.

- When a result comes back and it is **borderline**, what do you tend to do next?

II. <u>Theme 3: Factors relating to process/system-related factors that influence blood test use.</u>

Question:

I would now be interested to find out about how factors associated with healthcare system processes may affect your use of blood tests.

"Imagine you see a patient today who presents with new symptoms which you feel require further investigation using a common blood test. I have a few questions about the practical steps that are required for testing, and how they may influence the use of common blood tests in patients with new symptoms?"

- (<u>if not already mentioned above</u>): "*Have you ever had any concerns with **access** to phlebotomy services?"*

- *In your experience, does it happen that you ask for a blood test to be performed and the **patient did not manage to make the phlebotomy appointment** or did make it but missed it?*

- *"If required, could a blood test appointment be booked on the **same-day** as the consultation?"*

    - *"And under **what circumstances would you order a blood test on the same day**?*

- *"How do you find out about **abnormal blood test results**?" If you find that a test was abnormal, what do you usually do next?*

I. <u>Theme 4: Factors relating to blood tests that influence your use of blood tests</u>

Question:

"Lets assume that there is a **blood-based POCT** that is 100% accurate as conventional peripheral blood testing via phlebotomy etc. – e.g. Let's assume that the CRP POCT is as good as the standard measurement of CRP, and in future that we have as good POCT for the most important components of the FBC (e.g. haemoglobin concentration or platelet concentration) as we do now via tests using phlebotomy. In that hypothetical scenario, please tell me whether you would be testing patients complaining of new symptoms with a 'common blood-based' POCT more often than you currently do with normal 'common blood tests' **and if so why**?"

Or if Not, Why not?

II. <u>Theme 5: Factors influencing blood test use during the coronavirus pandemic</u>

Question:

"*How has the **impact of the coronavirus pandemic** impacted your use of blood tests and **how is this different to pre-covid times**?*"

*Before we finish the interview, **are there any other factors** that you can think of that impact your use of blood tests for patients presenting with new symptoms that have not been covered in the previous questions?*

That is the end of the interview. Thank you very much for your participation.

Appendix 3. M (6.3.3): Indexing process
Image showing example of indexing process for interview study

R: Yes.

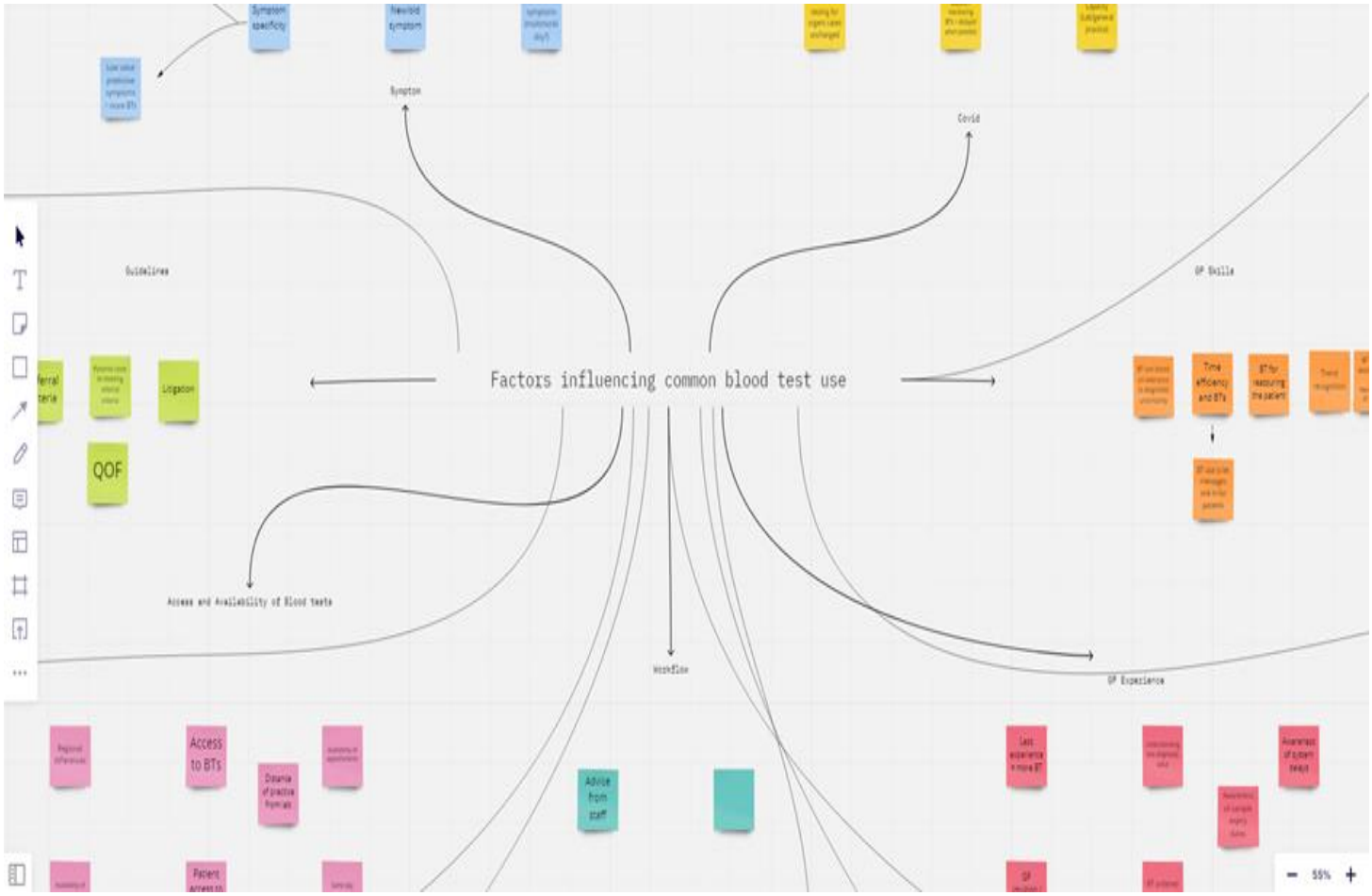
I: **Could you tell me a bit about how often, and when, you would feel the need to order a blood test for these patients?**

R: Yes. So, there's probably three situations that spring to mind, where I would order a blood test. So, one is where there's something specific you're worried about, and so you would want to get a specific blood test. So, there might be something to do with their kidneys or their liver and you'd specifically want to check those markers. Or you might be worried about cancer, so if somebody came in with lymphadenopathy that had been there for a while, you might want to get a full blood count just to check that it wasn't. So those are probably blood tests that you would do to rule out something bad going on, although you don't think there's something bad going on. There's another situation where you're not really sure what's going on, so you might do a bit more of a general screen of a few different blood tests, just to see. So, things like fatigue or general aches and pains often come into this kind of category, or sometimes neurological symptoms as well. Numbness and pins and needles and that kind of thing, you might be like, "Well, I'm not really sure what's going on here, so I'm just going to do a bit of a general screen of a few different things, just to see if anything comes up." And then, if everything's normal, it reassures you a bit that there's nothing serious going on, even though you can't really explain it. And then the other thing is probably if people come in and they need blood tests, you know they're on routine blood tests for medications or... [ringing] sorry, my phone... for medication or something. And, yes, then you might do blood tests as well. So, those are the three situations that spring to mind, the categories where I'd probably do blood tests most commonly.

I: **Yes.**

R: And then, sometimes the symptoms you can't explain or if you're worried about something specific, sometimes they're more urgent than others; sometimes you do them straight away, sometimes you might say, "Well, I'll

Appendix 3. N (6.3.3): Using MIRO
Image showing how an online visual collaboration software was used to facilitate the development of a coding framework.



Appendix 3. O (6.3.4): Domains of the Theoretical Domains Framework

Domain Number	Domain Type
1	**Knowledge** (An awareness of the existence of something)
2	**Skills** (An ability or proficiency acquired through practice)
3	**Social/professional role and identity** (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)
4	**Beliefs about capabilities** (Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use)
5	**Optimism** (The confidence that things will happen for the best or that desired goals will be attained)
6	**Beliefs about consequences** (Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)
7	**Reinforcement** (Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)
8	**Intentions** (A conscious decision to perform a behaviour or a resolve to act in a certain way)
9	**Goals** (Mental representations of outcomes or end states that an individual wants to achieve)
10	**Memory, attention and decision processes** (The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)
11	**Environmental context and resources** (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour)
12	**Social influences** (Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)
13	**Emotion** (A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)
14	**Behavioural regulation** (Anything aimed at managing or changing objectively observed or measured actions)

Appendix 3. P (6.4): Interview quotes

The following three tables contain quotes from GPs during interviews which relate to embodied, embedded and extended factors of decision-making to use blood tests. These quotes are additional to those embedded within Chapter 6.

Embodied factors

Theme Construct	Sub-theme (Factors of blood test use)	Quotes
GPs perception of blood test results	- Influence of the interpretability of blood test results on subsequent blood test use • Influence of slightly abnormal results (when compared to baseline levels and context) on blood test use • Influence of previous borderline blood test results on blood test use • Influence of trends in previous blood test results on blood test use • Influence of pre-test probability on blood test use - Influence of accuracy concerns on the use of blood tests • Influence of overtesting and overdiagnosis on blood test use	"And blood tests are often one of the simplest ones to get that have the greater scope for reassurance, because, essentially, if you've checked inflammatory markers, full blood count, LFTs, Us and Es; if all of those are normal, then it rules out an awful lot of significant pathology." [GP-11] "So I see tests being requested on people to rule out things that are so unlikely, sometimes to rule out things that the patient doesn't have the symptoms of or convincingly, so again I think this speaks to lack of confidence in the profession that we are trying to cover all bases. [GP-4] "we can sometimes be falsely reassured by blood tests and those are often the patients who are presenting unusually and you have delayed diagnosis and convoluted diagnostic pathways." [GP-1] "I think the issue with patient expectations, and patient anxiety is often the issue with this, is that they tend to want tests and tell you that getting the test will reassure them and that they'll feel better if they know that its normal but, actually, when they have that test, the anxiety continues, and it just shifts to a different point." [GP-11] "that's often a barrier that you need to overcome with somebody to make you think that you are taking their symptoms seriously and people often find what they perceive to be the more objective standard of a blood test more believable." [GP-4] "Its part of the doctor/patient relationship is the trust, that they trust you are doing the right thing and if you can't persuade them with the conversation then I don't think its unreasonable to get them the blood tests." [GP-6]
GPs' Beliefs	• Influence of fears about litigation on blood test use • Influence of GPs worries about the patient on their use of blood tests	"*I think its very forgivable to do blood tests to try and get reassurance*" [GP-4] "*I think they [blood tests] can be useful as both rule in and rule out tests*" [GP-1]

	• Perceived reassurance/ confidence gained by GPs with blood test use • Influence of gut-feeling on blood test use	
GPs' Experience	• Influence of GP experience on blood test use • Influence of GP understanding of test diagnostic value on blood test use • Influence of "old ordering habits" on blood test use • Awareness of system delays	*"being more junior, you're less certain of yourself and you're more inclined to test more, just to make sure you don't miss things." [GP-11]* "you're obviously biased by your previous experiences. You don't want to miss diagnoses. You always stick to either the cancers that you've had, maybe diagnoses, things you may have missed. So that does influence your level of risk." [GP-8]
GPs' Skills	• Influence of GPs tolerance of diagnostic uncertainty on their use of blood tests • Influence of patients nearly meeting referral on blood test use • Influence of the perceived ability of blood tests to change patient management on their use • Influence of clinical urgency on blood test use • Ability for blood tests to extend monitoring period for GPs (watchful-wait method) • Influence of blood test to provide reassurance for the patient on their use	"If something is needed on the same day, I would classify it as urgent. If it something that is really urgent, then obviously, I send them to A&E, [laughing] but with most things, I can take myself." [GP-9] some of the referral criteria, they want the bloods done. If I think the patient needs to be seen, I will do the referral that day and know that they are getting the bloods booked in. [GP-6]
Shared decision-making	• Influence of blood tests ability to provide a diagnostic label on their use • Influence of GPs ability to be flexible to patient requests on their use of blood tests	"*sometimes patients want blood tests and if its unlikely to be particularly harmful or costly then I'll often go along with that*." [GP-4]

Embedded Factors

Theme Construct	Sub-themes (Factors of blood test use)	Quotes
Practice-level logistics	• Influence of practice accessibility issues for the patient on blood test use. • Influence of practice mechanisms/tools for ordering blood tests (depending on clinical urgency) on blood test use	"*So some of them have quite a long distance to come back to the practice to get a blood test to then go back home…if they live 50 minutes away I'd rather just get them done and then I know they are in the system and the referral can be processed*". [GP-6]
Workflow	• Influence of other practice staff on blood test use • Influence of phlebotomy availability on blood test use • Influence of appointment availability on blood test use • Opportunity for same-day blood tests on blood test use • Influence of workload on blood test use	*"I've worked in places where you want someone to have a blood test and you look, and there's no blood tests with the nurse or the HCA clinics for two or three weeks. And I think it does play a part in your ordering, because then the only way you're going to get a blood test quickly is to do it yourself. And, obviously, that's going to take time, you're probably already behind in clinic" [GP-11]* "if you're having a coffee or lunch or something and you say, "Oh, I saw this patient with this, this morning," and you had not really thought a blood test, but somebody's like, "Oh, I always get some blood tests for that," then you change your practice to fit in with those around you." [GP-11] "*I think availability of blood tests does play a part in how much you use them, so I think, if there's no blood tests available and your only option is to do them yourselves, you probably are less likely to order them than if you can get a nurse to do them that afternoon, then that's ideal, you just get them to do it."* [GP-11] Previously, I've probably done more myself, but I find that transition from consulting to doing tests is actually a non-efficient way to do things and takes up a lot more time. [GP-4]

Extended Factors

Theme Construct	Sub-themes (Factors of blood test use)	Quotes
Guidelines	• Influence of referral criteria on blood test use • Influence of Quality Outcomes Framework (QOF) on blood test use • Influence of potential costs on blood test use	"*there is always new guidance coming out, like now a platelet over 400 you should refer for chest x-ray, so I think you have to stay up-to-date with things*" [GP-1] "*Things like costs and waiting times for results and that don't often come into my thinking*." [GP-3]

	• Influence of waiting time for results on blood test use • Influence of evidence-base for diagnostic value of blood tests on their use	
System-level logistics + POCT influence	• Influence of sample transport on blood test ordering • Influence of laboratory logistics on blood test use • Difference in blood test use by region • <u>Attitudes towards blood-based POCTs:</u> Facilitators: - Influence of GPs perceived diagnostic value of POCTs in practice on their use - Influence of POCT to provide reassurance on their use in practice - Influence of the usability of POCTs on their use in practice Barriers: - Influence of GPs concerns with the accuracy of POCTs on their use - Influence of GPs willingness to adapt/adopt new technology on the use of POCTs - Influence of time-availability during consultations on use of POCTs - Influence of accessibility of POCTs on their use - Influence of the perceived workload as a result of	"*if I have a point of care test that is just as accurate as the hospital ones, it is less burdensome to patients, in terms of time, and less burdensome in terms of repeat visits, I would use it more" [GP-9]* "Certainly, if it was as easy to use as a diabetic finger prick or something, I think you would be doing it a lot more. And you get the information straight away, which would be great, because you don't then need to wait a day or two and then have that second appointment to follow up, so you could do it straight away." [GP- 11] "*I could see it being used more, just because it's easily accessible. And for all those reassuring things, it would be helpful just to do*". [GP-10] "You mentioned CRP, [laughing] I would use that definitely more if I suspect infection, because that is really useful, and it is something [laughing] you really want to know at that point in time. If I am doing these tests and it might be cancer, then two days probably isn't the end of the world." [GP-9] "I don't see what the point of a point of care test is because it's just more time for me to do a test and process the sample myself" [GP-3] "But the reality is are you getting any longer with your patient? So if you are still in a 10minute appointment, good god, no, I'll send you to phlebotomy thank you very much. If it's built in to my appointment, yes, then that would be reasonable." [GP-7] Having said that, then all the ones that I want watchful waiting on, I've lost my time haven't I? So in some ways I might use it less because of that reason. [GP-10] "I would worry about the consequences of, not more false positives, because it's the same as a lab test, but you get false positives in everything and having to deal with more of those because you've done more tests." [GP-10] "*The practicalities of doing it when you've got ten minutes and queues of patients... With point of care testing that we've got at the moment that is sometimes not as easy as you might think. Even getting a urine*

	POCT use on their use in practice - Influence of cost implications on POCT use - Influence of GPs concerns regarding the explanation of slightly abnormal POCT results to patients on their use of POCTs - Influence of the immediacy of the results on GPs' use of POCTs - Influence of GPs concerns that the POCT result might override consultation messages on their use	*sample in ten minutes. You have to get them out of the room, get them to wee, get it in a bottle, get it brought back, put gloves on, dip, read the results, carry on. In ten minutes, that is hard to do*." [GP-10] "the thing about having them go off to the lab and come back is that you then have time to consider what that means, was that what you expected, where you go next? If you have point of care at the time the patient is there then you may get a surprise that you weren't expecting and you then have to tell the patient, you might want to look stuff up, there might be a vague symptom, there could be several, two-week wait pathways." [GP-6]
Patient behaviours/ expectations	• Influence of patient demand on blood test use • Influence of patient anxiety on blood test use • Influence of previous patient consultations on blood test use • Influence of patients acceptability of blood tests on their use	"There is a bit of patient demand there. Sometimes patients come to the consultation expecting a test and we have to have a conversation about that." [GP-3] "*I would say there is very little reluctance for blood tests*". [GP-8] "I think my decision to order a blood test is a joint decision between me and the patient, always. [laughing] I think that is key" [GP-9] "young patients who might contact us saying they are worried about tiredness or general symptoms and they just want to have a blood test because they are concerned." [GP-8]
Overdiagnosis	• Limited concern when deciding to use blood tests • Influence of slightly abnormal results on GPs risk perception of overdiagnosis • Influence of patients on GPs perception of overdiagnosis	And people wanting that diagnostic label. So people want to keep doing Google searches, especially if we have done a lot of tests and then we've ruled out stuff but they are still symptomatic. They are... That's the kind of pressure, then, to keep testing them. [GP-8] "sometimes blood tests are so non-specific they can find problems that aren't there. Like, if we use D-dimer for example. That is a blood test for a blood clot. It can be positive for hundreds of reasons but if it is positive you probably need to get them a scan of their lungs to check for a blood clot. And that comes with a trip to hospital and lots of extra resources." [GP-10] I think I, certainly, worry about it less with the more routine blood tests, the FBCs, the Us and Es, the CRP, because I think they're something that we see so regularly and it's observing the pattern over time, so I

		probably worry less about over-diagnosis with that. [GP-11] "I am definitely concerned about over-testing, because it creates anxiety. It creates all these kinds of problems. It creates more workload as well, because you have a slightly abnormal liver function test result, you have discussions with the patient, you have to repeat that test. So, it is workload as well, but in terms of over-diagnosis, yes, because you may refer the patient on, and they may get a diagnosis. That's not necessarily causing problems" [GP-9] "So, I think there are pros and cons; in terms of having information to hand when I see the patient, that is very useful, but on the negative side, we could end up with lots of unnecessary investigations causing lots of anxiety, which we don't need. So, I would be careful with blanket-testing everyone with that." [GP-9]

Appendix 3. Q (7.3.1): Recruitment Process documents (Ethical Approval, participant information sheet and consent form).

Ethical Approval:

UCL RESEARCH ETHICS COMMITTEE
OFFICE FOR THE VICE PROVOST RESEARCH

21/08/2020

Dr Christian Von Wagner
Department of Behavioural Science and Health
UCL

Cc: Ben Cranfield

Dear Dr Von Wagner,

Notification of Ethics Approval with Provisos
Project ID/Title: 17905/001: A qualitative study of general practitioner preferences to use a common blood test to aid decision-making for suspected cancer in primary care.

Further to your satisfactory responses to the reviewer's comments, I am pleased to confirm that your study has been ethically approved until **21/08/2021 with the following provisos:**

- Please provide UCL REC with written permission for use of any professional and private networks in recruitment, where necessary
- In consent form, correct Alex Potts contact to: data-protection@ucl.ac.uk
- Include the inclusion criteria as a clause, rather than as a line at the top of the consent form

Ethical approval is subject to the following conditions:

Notification of Amendments to the Research
You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing an 'Amendment Approval Request Form'
http://ethics.grad.ucl.ac.uk/responsibilities.php

Adverse Event Reporting – Serious and Non-Serious
It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Joint Chairs will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Joint Chairs of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Joint Chairs will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Office of the Vice Provost Research, 2 Taviton Street
University College London
Tel: +44 (0)20 7679 8717
Email: ethics@ucl.ac.uk
http://ethics.grad.ucl.ac.uk/

Final Report

At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

In addition, please:

- ensure that you follow all relevant guidance as laid out in UCL's Code of Conduct for Research: www.ucl.ac.uk/srs/governance-and-committees/research-governance
- note that you are required to adhere to all research data/records management and storage procedures agreed as part of your application. This will be expected even after completion of the study.

With best wishes for the research.

Yours sincerely

Catherine Collins
On behalf of the UCL Research Ethics Committee

Exploring the determinants associated with the blood testing process that influence their use for potentially serious illness: An online interview study with general practitioners.

Thank you for your interest in this research. We are interested in having a conversation with you about your experiences in using blood tests and how you use them for patients with potentially serious illness.

Before you decide whether you would like to join us for a conversation, it is important for you to know what taking part will involve. Please read this information sheet, which outlines the details of the study. This research has been reviewed and approved by UCL REC (ID number: 17905/001).

How to contact us

If after reading this, you have questions or would simply like to know more, please feel free to get in touch with me. I would be more than happy to answer any questions you may have:

Mr Ben Cranfield (Data Collector) ✉ ben.cranfield.18@ucl.ac.uk

Dr Christian Von Wagner (Principal Investigator) ✉ c.wagner@ucl.ac.uk

01. What is the purpose of the study?

The purpose of this study is to explore general practitioners' attitudes towards using blood tests for potentially serious illnesses, and to understand how different determinants of blood testing influence their decisions to use the test. The findings of the interviews will be used to inform the development of future research, which will focus on the determinants of blood testing identified from this interview study to be important for their use.

02. Why have I been invited?

As a GP, in this interview we aim to explore your views and experience regarding the factors that influence your use of blood tests. You have been invited because you are a primary care clinician (The only criterion for participation is that you are a GP). Diagnosing cancer is a challenge in primary care – and half of patients subsequently diagnosed with cancer present with non-specific symptoms. Diagnostic strategies for these patients are limited. However, recent evidence indicates that some common blood tests have predictive value for several cancers. Although this evidence is promising, in order for blood tests to help predict cancer and aid GP decision-making they must be used effectively. Thus, we want to understand your perceptions of using blood tests and which determinants of the blood testing process are important for triggering your use of the test. The information you provide will be very useful for the future development of targeted implementation research for optimising the use of blood tests for potentially serious illnesses.

03. What will taking part involve?

If you choose to take part, you will be invited to attend an online interview (e.g. via Teams) at a time and day that is convenient for you. The interview will last for about half an hour and will be led by a PhD student from UCL.

- Before the interview, you will be asked to sign and return consent form indicating that you have read this information sheet, are happy for the interview to be audio recorded, and understand that you are free to withdraw at any time. The consent form will also allow you to indicate whether you would like to know the results of the research when the project is over.
- During the interview, you will be asked questions about your experiences and perceptions of using blood tests as a general practitioner, specifically in relation to diagnosis of potentially serious illnesses. The researcher will take notes throughout the interview which will also be audio recorded. Audio recording must

be performed to enable subsequent transcription of interviews, with any details that could identify you removed so that your individual contribution will be anonymous.

- Audio recordings will be destroyed on completion of transcript

04. Do I have to take part?

Your participation is completely voluntary, and it is up to you to decide to join the project. If you do decide to take part, please keep this information sheet with the researcher's contact information in case you have any questions. Please contact the data collector to let them know of your interest so that a date and time for the interview can be arranged. You will be free to withdraw your contribution up to 14 days after to the interview without giving a reason.

05. What are the possible benefits of taking part?

We cannot promise that taking part in our project will benefit you directly, but many people find it rewarding to know that they have made an important contribution to research. Our hope is that this will ultimately lead to a better understanding of what determinants of the blood testing process are influential to their use, particularly for investigating potentially serious illnesses. The evidence generated would guide future research into blood test use for potentially serious illnesses by facilitating more targeted interventions for optimising the use of blood tests.

06. What are the possible risks and disadvantages of taking part?

Taking part in the interview carries very little risk. There is a slight possibility that you will feel uncomfortable discussing previous experiences of blood test use (I.e. missed opportunities to use a test). You do not have to answer any questions that make you feel uncomfortable, and you can withdraw from the study up until 2 weeks after completing the interviews without giving a reason.

07. Will my taking part be kept confidential?

Yes. Our procedures for storage, processing, handling and destroying the information you give us are in line with data protection legislation (GDPR and DPA 2018). All information which is collected about you during the interview will be kept strictly confidential and stored securely. The research team will not pass on your personal details to anyone else. Any personal information about you will be removed so that you cannot be recognised.

08. What will happen to the results of the research study?

The results will be reported in scientific journals and presented at academic conferences. While we may use quotes obtained from interviews, you will not be personally identified in any reports or publications from the study.

09. Who is organising the research?

This research is being organised by researchers at University College London (UCL). Mr Ben Cranfield, from the Department of Behavioural Science and Health, is leading this research.

10. Who has reviewed this study?

This study has been looked at and approved by the UCL Data Protection Officer (Registration Number: Z6364106/2020/05/58) and the UCL research ethics committee (REC - research ethics submission: 17905/001). It has been awarded registration on the basis that it is compliant with data protection legislation (GDPR and DPA 2018).

11. What if there is a problem or I want to make a complaint?

We do not expect there to be any problems and will do our best to ensure you are happy with your participation. However, if you wish to make a complaint, or have concerns about any aspect of the way you have been approached or treated during your participation in this research, please contact the PI in the first instance (Dr Christian Von Wagner ✉ c.wagner@ucl.ac.uk). If you are unsatisfied with the PI's response, then please contact UCL REC at ethics@ucl.ac.uk.

Local Data Protection Privacy Notice

Notice:

The controller for this project will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk

This 'local' privacy notice sets out the information that applies to this particular study. Further information on how UCL uses participant information can be found in our 'general' privacy notice:

For participants in health and care research studies, click here

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices.

The lawful basis that will be used to process your personal data are: ‘Public task’ for personal data.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk.

Research Department of
Behavioural Science and Health

CONSENT FORM

Exploring factors related to blood testing that influence their use for potentially serious illness: An interview study with general practitioners.

Please read the following statements carefully and initial each box to the right of each statement as you read through them. Please then print your name and sign and date the form in the box below. Please then return this completed form to the researcher. Your details will be treated in the strictest confidence.

How to contact us

If after reading this, you have questions or would simply like to know more, please feel free to get in touch with me. I would be more than happy to answer any questions you may have:

Mr Ben Cranfield (Data Collector) ✉ ben.cranfield.18@ucl.ac.uk

Dr Christian Von Wagner (Principal Investigator) ✉ c.wagner@ucl.ac.uk

Please read the following statements carefully and then put your initials in each box:

- I confirm that I have read the information sheet dated 15/04/2020 (Version 1.1) for the above study (which has been reviewed and approved by UCL REC - ID number: 17905/001), have been given the opportunity to ask questions and, if asked, have had these answered satisfactorily. ☐
- I understand that as a GP I am eligible to participate in this interview and confirm that I have had sufficient time to consider whether or not I want to take part in the study. ☐
- I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason (up until 14 days after the interview). ☐
- I understand that audio recording is mandatory for the interview I am participating in and I agree for anonymous direct quotes to be used alongside findings from the research in publications and reports as detailed in the information sheet. ☐
- I understand that all personal data relating to me (I.e. participant names and professional information) is held and processed in the strictest confidence (any identifiable information will be deleted immediately after interviews have been transcribed), under data protection legislation (GDPR and DPA 2018). Please contact the UCL data protection officer (Alex Potts: data-protection@ucl.ac.uk) if any queries arise. ☐
- I agree to take part in the above study. ☐

Name (please print): _____

Signature: _____ Date: _____

I would like a summary of the results at the end of this study Yes ☐ No ☐

If 'Yes' please print your postal and/or email address below so the researchers can contact you:

_____

_____

Researcher:	***Date***	***Signature:***
_____	_____/_____/____	_____