Patient preferences of genomic testing in precision cancer medicine

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Declaration

I declare this thesis has been written by myself and has not previously been submitted for a higher degree. The thesis was undertaken during my post as a Clinical Research Fellow at the University of Glasgow. All chapters were written by myself. Where others have been involved, this has been acknowledged**.**

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Abstract

Aims: The aim of this thesis was to identify and rate themed patient preference attributes of genomic testing in precision cancer medicine (PCM). The effect of clinical treatment intent and time since completing treatment was examined as a novel hypothesis that these factors influence identified preference attribute themes and/or ratings. This thesis then benchmarked the identified preference attributes against the ATLANTIS clinical trial design, in order to assess how a current clinical trial incorporates patient preferences.

Methods: A narrative review of current cancer treatment paradigms was undertaken alongside systematic review of the literature assessing patient preferences of genomic testing in PCM. In addition, mixed methods research, using Nominal Group Technique (NGT), identified and rated preference attribute themes of genomic testing amongst cancer patients. These preference attributes were then benchmarked against genomic testing undertaken within the ATLANTIS clinical trial, to determine how a novel PCM study design incorporated the attributes.

Results: Patient preferences of genomic testing in PCM are influenced by clinical treatment intent and time since completing treatment. Patients undergoing cancer treatment with radical intent demonstrated higher preference ratings for test sensitivity (true positive) and specificity (true negative). Invasiveness of testing and test turnaround time were higher rated preference attributes amongst patients undergoing treatment with palliative intent. Ten preference attribute themes of genomic testing were identified: regulatory/NHS approval, test turnaround time, invasiveness of testing, physician approval, test sensitivity (true positive), test specificity (true negative), prevalence of variant, distance to travel, implications for family and family endorsement for testing. The novel adaptive design of the ATLANTIS trial incorporated many of the preference attribute themes of genomic testing demonstrated in this thesis.

Conclusions: Patient preferences of genomic testing in PCM are influenced by clinical treatment intent. This thesis identified and rated preference attribute themes of genomic testing for patients, as well as benchmarking these against a current UK PCM clinical trial. The adaptive design of the ATLANTIS trial incorporated many of the preference attributes, but does not allow for assessment of interaction between multiple inter-related attributes. The results of this thesis augment novel clinical trial design for studies incorporating genomic testing in order they retain patient-centred values at their core.

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Abbreviations

ALK	Anaplastic lymphoma kinase
BAP1	Gene coding for ubiquitin carboxylterminal hydrolase
BCR-Abl	Chromosome 9:22 gene fusion (Philadelphia chromosome)
BIG	Breast international group
BRAF	Serine/threonine-specific protein kinase
BRCA	Breast cancer gene
BRR	Best response rate
ctDNA	Circulating tumour DNA
DNA	Deoxyribonucleic acid
ECOG	Eastern co-operative group
EGFR	Epidermal growth factor receptor
EMBASE	Excerpta medica database
EORTC	European organisation for research and treatment of cancer
ERCC2	Excision repair cross-complementation group 2
ETOP	European thoracic oncology platform
EU	European Union
FANCD2	Fanconi anaemia group D2
GCP	Good clinical practice
GLA	Alpha-galactosidase
HER2	Human epidermal growth factor receptor 2
HRD	Homologous recombination deficiency
HTA	Health technology agency
IDMC	Independent data monitoring committee
IMP	Investigative medicinal product

IQR	Inter-quartile range
KRAS	Oncogene first identified in Kirsten rat sarcoma
MAP	Molecular analysis for personalised therapy
MEDLINE	Medical literature analysis and retrieval online system
MET	MET proto-oncogene
MHRA	Medicines and healthcare products regulatory agency
MRC	Medical research council
NCRI	National cancer research institute
NGS	Next generation sequencing
NGT	Nominal group technique
NHS	National Health Service
NICE	National institute of clinical excellence
NRES	National research ethics service
OR	Odds ratio
OS	Overall survival
PALB2	Partner and localiser of BRCA2
PARP	Poly(ADP-ribose)polymerase
PCM	Precision cancer medicine
PCR	Polymerase chain reaction
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PMI	Precision Medicine Initiative
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PubMed	Database of references and abstracts on life sciences/biomedicine
QUOROM	Quality of reporting of meta-analyses
RAND	Research and Development Corporation

RE-AIM	Reach, effectiveness, adoption, implementation and maintenance
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acid
s.d.	Standard deviation
SMC	Scottish medicines consortium
SPIRIT	Standard protocol items: recommendations for international trials
UC	Urothelial cancer
UGT1A1	Gene locus encoding several UDP-glucuronosyltransferases
VEGF	Vascular endothelial growth factor
WTP	Willingness-to-pay

Chapter 1. Introduction

1.1. Overview of precision medicine

The last century has seen a marked evolution in healthcare from physician preference approaches to a largely evidence-based one. Whilst this has resulted in improved clinical outcomes for patients, it remains a mechanism whereby treatments are based on stratification by phenotypic markers and average response across a population that, to a large extent, ignores the variation between individuals. Precision medicine is an emerging approach in multiple disease treatment and prevention strategies, taking into account individual variability in genes, lifestyle and environment (Berger & Van Allen, 2016). The precision medicine approach subdivides individual patients into groups based on their risk of developing specific diseases or their response to particular therapies.

There are many inter-related variables influencing an individual's response to treatment (Schmidt, Chau, Price, & Figg, 2016). These include disease delineation and stratification, early detecting, monitoring, modelling around dynamics of disease evolution, improved surveillance and management (Beckmann & Lew, 2016). Precision medicine aims to provide adapted surveillance and therapies to delay onset of disease and, where possible, prevention strategies. This may lead to a paradigm shift in the focus of healthcare as well as development of new taxonomies for health conditions.

Distinct genetic variants cause conditions that respond to different treatments yet share similar symptoms. Precision medicine aims to provide a mechanism to determine the underlying genetic cause of a set of symptoms or disease. One such example lies in the understanding that many genetic lesions can lead to increased risk of cardiomyopathy and sudden cardiac death, but only patients with mutation in GLA gene respond to enzyme

replacement therapy (Morel & Clarke, 2009). Even in situations where the genetic cause of a disease is known, unrelated genomic variants can affect treatment efficacy by altering mechanisms for drug metabolism or increased likelihood of adverse events. This is demonstrated, for example, when some patients treated with conventional doses of Azathioprine, an immunosuppressive medication, are at risk of developing life-threatening myelosuppression if they harbour genetic variants preventing the drug being properly metabolized (Relling, 2013). These examples demonstrate the importance of identifying an individuals' genomic profile for providing optimal care.

Precision medicine has grown rapidly over recent years, fuelled globally by the Precision Medicine Initiative (PMI) launched in the United States in 2015. The PMI represents a $215 million investment aimed at accelerating biomedical research. The initiative has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to a wider range of health and illnesses (Allen, 2015). Both components are now within reach due to scientific advances including molecular biology, genomics, proteomics and bioinformatics, made possible by the Human Genome Project (Lander et al., 2001).

In the United Kingdom (UK), the 100,000 genomes project was launched in 2013 to establish the use of genomic sequencing within the National Health Service (NHS), drive change within health services and more widespread adoption of the technology (Rabesandratana, 2014). Genomics England was setup to deliver this national genomics project in partnership with the NHS. Rare diseases and cancer were selected as the areas with immediate potential for clinical benefit of genomic analysis. The previous UK Biobank and Deciphering Developmental Disorders framework highlighted the UK's role as a leading influence in human genomics (Sudlow et al., 2015). Such projects have the

aim of up-scaling population-based genomic sequencing and pivotal integration with clinical data. Previous treatment paradigms have targeted 'causative mutations' within just one gene segment at a time. Recent scientific advances in next generation sequencing allow for the sequencing of millions of DNA fragments simultaneously (Blumenthal, Mansfield, & Pazdur, 2016). This allows scientists to perform genetic testing for many more individuals and test many thousands of genes at a time. The initial sequencing of the human genome took 13 years to perform and cost over £2billion, where an individual genome can now be sequenced in around a day at a cost of less than £700 (Watson, et al. 1990).

1.2. The role of bioinformatics and genomics in precision medicine

The capacity to create and interpret large volume data, produced by technological and scientific innovations, is having a profound effect on the scientific community by deepening understanding of disease biology (Auffray et al., 2016). These advances facilitated genome sequencing from hundreds of thousands of individuals to define allele-specific compositions and relative abundances of RNA transcripts in numerous cell types and conditions, allowing exploration of protein and metabolite profiles. These genome sequences promote understanding of molecular, cellular and physiological mechanisms as well as integral pathways and networks. This comprehensive data, including both multi-scale and multi-level genomics requires increasingly complex multidimensional analyses to convert datasets into clinically meaningful information. Clinical bioinformatics refers to the multidisciplinary approach to the utilisation and integration of laboratory and clinical data and other resources (Breit, Baumgartner, Netzer, & Weinberger, 2016). This is an essential component of data-driven precision medicine, bridging the gap between clinical and laboratory research.

The production of high volume data from ‘omics, imaging, clinical and emerging data types, including data ranging from single cells to organs, provides a wealth of information. This ever-expanding volume of data generated by such transformative tools will lead to an inevitable shift in healthcare. This will be contingent on the data eventually being translated into clinical benefits for patients and populations. This may provide synergistic opportunities for integrative approaches and a shift from traditional organ-based treatment paradigms to a more inclusive and systemic assessment of health and disease based on large scale genomic data sets (Auffray, Chen, & Hood, 2009; Hood & Tian, 2012).

1.3. The role of genomic sequencing

Recent years have witnessed the decreasing fiscal cost of next-generation sequencing (NGS) technologies. This led to increased clinical application of these techniques. Targeted exome sequencing of a panel of genes for hotspot mutations, selected according to their relevance to specific disease, is the most common molecular profiling tool utilized at present. There are several advantages with this approach; being more cost and time efficient, as well as more manageable bio-informatic and computational requirements (Lopez, Harris, Roda, & Yap, 2015). NGS uses parallel sequencing arrays to interrogate DNA coding regions (whole exome sequencing) or entire eukaryotic genome (whole genome sequencing). Whole genome sequencing offers the most comprehensive strategy for tumour genomic analysis, though it is currently limited in clinical application by cost and turnaround time of sequencing and analysis. The sequencing of exome regions by whole exome sequencing may provide a more practical technique for use in clinical practice (Lopez et al., 2015). Drillon et al (Drillon, Wang, & Arcila, 2015) demonstrated whole exome sequencing identified actionable genomic alterations in a further 65% of non-small cell lung cancers, originally tested negative for mutations by non-NGS methods. Some groups incorporate whole exome sequencing into their patient selection strategies in

clinical trial units (Roychowdhury & Chinnaiyan, 2014). The ultimate selection of technique is likely to be driven by the specific scientific hypothesis.

As the cost-effective balance changes, NGS is shifting from being a research tool to frontline clinical practice. The application of NGS principles led to discovery of mendelian diseases in foetal-derived plasma DNA, such as foetal aneuploidies (Beaudet, 2016). The majority of current NGS focuses on DNA sequencing, though there is increasing awareness that whilst this can be informative and valuable, our genomic DNA sequences do not encapsulate the comprehensive information defining individual or population health status. The road from genomic to phenotypic health status is fraught with uncertainties. This is reflected in the fact that, besides germ line variants, somatic variants need to be considered given potential somatic mosaicism (Lupski, 2013). Venter and colleagues maintain the presence of the "dynamically changing nature of our genomes throughout our life." (Telenti, Perkins, & Venter, 2016). The potential for monitoring such dynamic genomic changes may necessitate repeated sequencing of an individuals' genomic profile throughout their disease process.

1.4. Evolution from evidence-based to precision medicine

Current treatment paradigms in medicine focus on organ-specific and disease phenotypic factors. This was propagated by data from population studies, from which statistical interpretations are applied to infer treatment recommendations applied across that population. This method means, for most traits, an individual may fall within the mean estimates, but may be an outlier for other traits which predispose towards poor response. Under these circumstances, current evidence-based medicine may fail to provide adequate response for a particular individual. This contrasts with the premise of precision medicine, where the focus is around an individual and production of large volume multi-faceted data.

The precision medicine approach, however, also has limitations, with the multiplicity of data producing a wealth of unique outputs that may put the patient in to an "n of one" category (Ciardiello et al., 2014). This may, in turn, lead to a significant reduction in the statistical power to define appropriate evidence-based guidelines.

The roles of evidence-based and precision medicine are, though, potentially complementary. There is added value gained from merging the strengths of both approaches and relies on an ability to perform analysis of large cohorts of patients with a wealth of genomic data. Conversion from single cases to an evidence-based precision medicine approach requires collation and meta-analysis of large-scale datasets from multi-institutional registers and cohorts. This facilitates detailed analysis and aggregation of similar "n of one" cases, resulting in reliable inferences made from such stratified subgroups.

1.5. Precision medicine in cancer

Oncology is the clear choice for enhancing the near-term impact of precision medicine. Cancers aggregate as a common disease process and are amongst the leading causes of death worldwide (Schmidt et al., 2016). Much of cancer biology is based on the central premise that it is a genetic disease, caused by a clone of cells proliferating in an unregulated fashion due to somatically-acquired mutations. We now understand that many malignant tumours display heterogeneity both within and between tumours (Yap, 2012). Further classifying tumours into more precise subgroups, by powerful methods and analytical tools, enables clinicians to develop more accurate diagnostic, prognostic and therapeutic strategies (Jamal-Hanjani, Quezada, Larkin, & Swanton, 2015).

The concept of precision cancer medicine (PCM) creates opportunities for innovative therapies with clinical benefit, whilst challenging current models of clinical practice. The application of the precision medicine concept, provides powerful methods for delineating individual patient characteristics supported by advances in proteomics and metabolomics (McShane, 2013). The application of these scientific principles herald a rapid increase in the number and diversity of precision medicine clinical trials which, it is hoped, will transfer into clinical practice in future (Sleijfer, Bogaerts, & Siu, 2013). The overriding premise of PCM is delivery of the 'right drug to the right patient at the right time' with the expectation that therapeutic selection based on individual tumour profiling may produce durable clinical benefits (Biankin, Piantadosi, & Hollingsworth, 2015).

PCM moves beyond previous models of cancer therapeutics based on clinical trials of largely unselected patients, beyond a simple phenotypic marker, to profiling an individual's cancer genome to optimize their clinical management (Chin, 2008). PCM offers the potential to deliver safe and effective cancer treatment that is individualized, targeted and biologically rational. One such example is the characterization of germline mutations that predict cisplatin-induced oto-toxicity and potentially provide a mechanism for prospective identification of at-risk patients (Ross, 2009).

The concept of oncogene addiction was first proposed by Weinstein in 2002, with ensuing innovative approaches to cancer treatment (Weinstein, 2002). The emergence of imatinib, the BCR-Abl tyrosine kinase inhibitor has revolutionised treatment of chronic myeloid leukaemia (Druker et al., 2006). This was the first targeted 'precision medicine' agent to illustrate proof of concept that treating the principle driving oncogene can have a powerful impact on response. The initiation of the 'Cancer Genome Project' at the Wellcome Trusts Sanger Institute, using exon Sanger sequencing, quickly identified somatic mutations in the

BRAF gene for the majority of malignant melanoma tumours (Flaherty et al., 2012). This opened a window into the biology of these tumours and clinical translation with development of novel BRAF-targeted tyrosine kinase inhibitors demonstrating clinical activity in melanoma. Subsequent generations of targeted agents have subcategorized tumours into molecular subsets, such as EGFR and ALK inhibition in non-small cell lung cancer (Maemondo et al., 2010; Shaw, 2013). One further example, trastuzumab, has demonstrated efficacy for gastro-oesophageal and breast cancers over-expressing HER2, challenging conventional organ-specific treatment paradigms (Schmidt et al., 2016). Targeting actionable mutations has potential to transcend tumour histology, effectively categorizing tumours based on an individual molecular profile rather than anatomical tumour origin.

The identification of genomic drivers of cancer progression has improved outcomes in many cancer subtypes. Scientific consensus from the 'Consensus of precision medicine for metastatic cancers Molecular Analysis for Personalised Therapy (MAP) Conference' suggests that it is best to assess the molecular profile of tumours at the time of treatment and avoid archival samples (Swanton C, Soria JC, et al, 2016). This is particularly relevant for genomic alterations involved in resistance to prior therapy, such as EGFR T790M mutations in lung cancer. There remains, though, a lack of robust clinical evidence around the validity of many of these genes, leading to the advent of molecular screening clinical trials and large collaborative data sets attempting to place molecular data within a clinical context.

Genomic testing provides information on cancer aetiology, prognosis and potential therapeutic responsiveness. Abbosh et al outline the potential role of PCM in sequencing circulating tumour DNA (ctDNA) to identify tumour recurrence in advance of

conventional imaging (Abbosh et al., 2018). This has potential to impact decisions on adjuvant therapy alongside development of therapeutic resistance. Precision medicine is emerging as a natural extension that integrating research disciplines and clinical practice, building a knowledge base that can guide individualized patient care. This occurs at a crucial time when efforts such as the UK 100,000 Genomes project (Rabesandratana, 2014) and the US Precision Medicine Initiative seek to scale up population-based genome sequencing and integrate it with clinical data (Abrams et al., 2014). The 100,000 Genomes project has driver the UK transformation process, leading to the established NHS Genomic Medicine Service. This aims to perform 500,000 whole genome sequences deployed in routine care for rare diseases and cancer, based on annual review by the NHS Genomic Test Directory (Samuel and Farsides, 2017).

The UK Stratified Medicine Paediatrics (SMPaeds) research study aims to test somatic and germline DNA and RNA tumour samples for genetic and gene-expression changes in children with cancer. This aims to identify children who may be eligible for new targeted precision medicine cancer therapies. Eligible patients include those with relapsed/refractory progressive solid tumours who undergo biopsy as part of their standard care. Testing on formalin fixed paraffin embedded tumour biopsy tissue will include customised next generation sequencing (NGS) panels and methylation sequencing. Testing on fresh frozen biopsy material includes whole exome sequencing (WES), RNA-sequencing (RNASeq) and low coverage whole genome sequencing (lcWGS). Circulating tumour DNA (ctDNA) will also undergo NGS panel testing, digital polymerase chain reaction (PCR) and germline exome or genome sequencing. This study will assess feasibility of delivering PCM testing within clinical timelines and proportion of patients with molecular alternations in tumour for whom a recommendation can be made of molecularly targeted therapy (George, SL., Izquierdo, E., et al, 2019).

In recent years, both medical research and legal landscape evolved as a result of developments in information technology. Medical researchers are collecting, re-using and linking health-related genomic data on an unprecedented scale, based on the presupposition that research will significantly improve patient outcomes. This has, however, led to an increasing concern about the effectiveness of existing data protection law and the need for more protection of personal data recognized by the European Union (EU) (Mostert, Bredenoord, Biesaart, & van Delden, 2016).

1.6. Barriers to clinical adoption of genomic testing

The widespread adoption of genomic testing is mired in complexity, with considerable challenges needing addressed. The widespread introduction of genomic sequencing challenges current clinical paradigms as they exist. For an individual patient, such factors include tumour heterogeneity, technical feasibility or validity of biomarkers, integration and interpretation of ever-increasing volume of data, associated information technology needs, as well as multiple dimensions of value and cost-effectiveness (Ciardiello et al., 2014).

Cancers are known to express significant heterogeneity both between and within tumours, driving phenotypic variation posing significant challenge to precision cancer medicine (R. Burrell, McGranahan, & Bartek, 2013). The extensive heterogeneity of common cancers, seen by expression of protein biomarkers and at multiple genetic and epigenetic levels, complicates our understanding of cancer pathways and potentially confounds biomarker validation through cancer sampling bias. It is evident the classical view of clonal architecture in cancers, manifest as driver mutations followed by linear accumulation of mutational insults, is too simplistic and there remains significant variation in genetic

profile of an individual tumour (R. A. Burrell & Swanton, 2014). A cancer may not comprise a single dominant clone, but contain multiple co-existing sub-clones with the implication that these can be spatially separated or intermixed within the same biopsy specimen. There is also co-existent tumour heterogeneity appreciated over the lifetime of cancer, with varying patterns of genetic changes from initiation through to formation of metastasis and relapse. Longitudinal tumour sampling approaches are an important factor aiding clinicians deciphering the impact of cancer evolution. This necessitates development of non-invasive methods of tumour profiling (Swanton, 2014).

The large volume of data produced by genomic testing must be validated, standardised, reproducible and delivered in a timeframe compliant with clinical care. An important component of this is the need for large, collaborative, translational research projects that link clinical, demographic and outcome data to histology and molecular profiles. This enriches clinical application of data within a rigorous evidence-based framework. Existing collaborations include the EORTC SPECTAcolor pan-European biomarker screening platform for patients with advanced colorectal cancer (SPECTAcolor). Other examples include the AURORA international programme developed by the Breast International Group (BIG) and Lungspace, run by the European Thoracic Oncology Platform (ETOP) (Aurora; LungScape). These platforms demonstrate importance of effective information transfer between laboratory and clinical research. The European Consensus Conference has published guidelines for external quality assessment of molecular genomics to ensure consistency of testing (van Krieken, Siebers, & Normanno, 2013).

1.7. Health economic assessment of genomic testing in PCM

Genomic testing and PCM have potential to improve health outcomes and cost-effectiveness in a healthcare system, though methods for economic assessment of the

approach are fraught with challenges (Ciardiello et al., 2014). PCM has attractive health economic principles because, in theory, only those patients who are likely to benefit receive treatment and avoids treating patients with potentially toxic therapy for which there is little clinical benefit.

The current cost-effectiveness analysis framework of using health gain to describe the value of complex health technology such as PCM is not likely to sufficiently capture all of its benefits (Buettner & Heydt, 2013). There remains a need for appropriate health outcome models for PCM. In the UK, patients receive health care provided by the nationally-funded NHS. In this setting, access to new cancer therapies and accompanying diagnostic testing may be restricted, such as cases where cost exceeds the applied cost-effectiveness thresholds. This is further confounded that regulatory pathways for drug and genomic diagnostic approval are disparate, paired often with different funding streams. Previous economic modelling of upfront KRAS testing in patients with metastatic colorectal cancer suggested cost savings could be made and spare patients from toxic and ineffective therapies (Nelson, 2009). A previous cost-effectiveness analysis of crizotinib for ALK-positive non-small cell lung cancer highlighted that this was not cost-effective due to the low frequency of the marker in this patient population and high cost of the drug, despite its clinical effectiveness (Djalalov, Beca, & Hoch, 2014).

As the cost of genomic sequencing continues to reduce, the costs of education, training and infrastructure as well as new clinical pathways need to be considered. The costs of any genomic test or new drug must continue to balance supporting innovation and investment with what an individual healthcare system can afford. There remains a need for innovative means around assessing cost-effectiveness of genomic testing in PCM with greater research to provide evidence of increased healthcare quality.

1.8. Current landscape of UK clinical trials in PCM

The over-riding principle of PCM is to match molecular, genomic and clinical data with underlying therapeutic mechanisms, providing biologically rational and clinically effective anti-cancer strategies. Despite the remarkable successes in understanding novel drivers of oncogenic processes, success rates for approval of therapeutics remains low. There remains a chasm between discoveries in laboratory-based research and development of successful therapeutics within the clinical arena. There is a tangible need for creative strategies to bridge this gap. One key element is the application of novel clinical trial designs and incorporation of predictive genomically defined biomarkers early in the process.

Despite the increasing recognition around genomic testing in cancer, evaluating targeted therapies presents a formidable challenge, especially when mutations are rare and can transcend tumour histology. Some eminently targetable tumour mutations may be so rare they are only discovered in the context of a negative trial. Such examples include durable clinical benefits for everolimus, a novel mTOR inhibitor, in patients with bladder and thyroid cancer. This study was negative for primary efficacy endpoints across the population, but exceptional clinical responders were subsequently discovered to harbour specific genomic signatures in mammalian target of rapamycin (mTOR) signalling pathways, rendering them uniquely sensitive to everolimus (Iyer, Hanrahan, et al, 2012). If a clinical trial had the ability to identify patients with similar genomic signature, it may well lead to enrichment regardless of tumour histology or anatomical origin.

A review by Roper et al in 2015 demonstrated an increase in proportion of clinical trials requiring a genomic alteration for enrolment. The review showed an increase in utilization

of PCM from 3% in 2006 to 16% in 2013 across all clinical trials in the UK (Roper, Stensland, Hendricks, & Galsky, 2015). Molecular biomarkers for precision medicine were included in 39% of global oncology trials in 2018 (Awad, K., Dalby, M., et al, 2019). Randomised clinical trials are an important tool for evidence-based medicine, historically incorporating a broadly defined population, representative of a specified primary cancer site and histology. The heterogeneous nature of tumours from the same anatomical subsite and histology, though, challenging existing clinical trial design. PCM offers the potential to tailor therapeutics to patients in order that more of the treated population will benefit. The average benefit across the population will be greater, with fewer patients exposed to cancer therapies without benefit. This led to novel clinical trial designs, such as umbrella and basket design trials (Berry, 2012).

Basket trial designs incorporate multiple tumour histologies sharing common genetic aberrations. Basket trials can be randomised or non-randomised and incorporate single or multiple therapeutic agents. Eligible patients have tumour sequencing performed, determining whether their tumour contains a genomic alteration with 'actionable' target. The basis of determining 'actionable' mutations may be based on clinical evidence of efficacy in patients with the same genomic pattern but different primary site of tumour, or pre-clinical tumour models demonstrating importance of the therapeutic target. The standard phase 2 basket trial design ignores the heterogeneity of primary disease site and pool patients containing actionable mutations. To separately analyse the patients of each primary site would require much larger sample sizes. Thall (Thall et al, 2003) developed a Bayesian hierarchical design used for making inferences about drug activity in primary-site subtypes of a basket clinical trial design.

The vemurafenib basket trial is one such study, where patients with BRAF V600 mutations were treated with vemurafenib regardless of primary histology (Hyman et al., 2015). Each arm of the trial had a specific histology and was analysed separately in the context of a Simon 2-stage design to allow for early stopping if no efficacy was seen. This study was noteworthy for showing preliminary efficacy in BRAF V600-mutated non-small cell lung cancer, but also for highlighting that tumour lineage might influence drug sensitivity as underscored by the lack of responses in colorectal cancer patients harbouring the same mutation.

Umbrella trial designs are restricted to patients with a single primary site cancer, but utilise therapeutic agents targeting genomic variants. Patients with potentially actionable mutation for one of the available targeted agents are assigned to receive that agent or a matched control. The analysis of umbrella trial designs are limited to the single primary site of disease.

One example of umbrella trial design is the on-going UK National Lung Matrix trial (Middleton et al., 2015). This trial involves multiple molecularly-targeted treatments against different subtypes of non-small cell lung cancer. A patients' tumour is molecularly profiled using hotspot panel within the Cancer Research UK Stratified Medicines Program 2 study. This determines allocated treatment arm of the trial based on detected driver mutations. The trial is an adaptive design and has been designed with flexibility in mind, so as to add or remove treatment arms as new data comes to light.

Basket and umbrella trials provide efficient designs predicated on the hypothesis that presence of a genomic or molecular marker predicts response to targeted therapy. This hypothesis incorporates precision cancer medicine into clinical trials, including rare

mutations difficult to study within a histology-specific context. This acts as proof-of-concept validation of putative target conducted within multiple cohorts of a single study, rather than having to run multiple separate trials. The success of these trial designs depends, in part, on the strength of data linking the genomic target with targeted therapy. Delivery of effective therapies relies on the tumour being dependent on the target pathway and that the targeted therapy reliably inhibits or promotes the target.

The understanding of oncogenic mechanisms influences risk assessment, diagnostic categorization and therapeutic strategies, with increasing use of therapies in clinical trials. The WINTHER trial (Kurzrock et al, 2019) selected patients for therapy based on fresh-biopsy derived DNA sequencing or RNA expression. The study included 107 patients deemed evaluable for therapy with matching scores calculated post-hoc for each patient according to drugs received. For DNA, this included the number of mutations divided by the total alteration number. For RNA, it incorporated expression-matched drug ranks. Amongst the 107 patients in the study, 26.2% had stable disease for greater than 6 months, partial or complete response. The study demonstrated that fewer prior therapies, improved baseline performance status and higher matching scores correlated with longer PFS. The study highlighted both genomic and transcriptonomic profiling are useful for improving therapy and patient outcomes, expanding the horizons for PCM trials.

Classical population-based clinical trials harvest a small number of measurements from a group, often led by a single study sponsor with single pharmaceutical company or drug agent. Precision medicine clinical trials require consideration of a myriad of genomic factors that may be unique to that individual. Increasingly complex trial designs evolve with additional numbers of clinical arms, targeted therapy combinations and complex collaborations. These complex collaborations may involve more than one genomic test

and more than one targeted agent, with potential to transcend study sponsors and pharmaceutical companies. These studies will rely on new collaborations between academic institutions, clinicians and pharmaceutical industry.

Sicklick and Kurzrock (2019) described the challenges of precision cancer medicine trials based on molecular matching with monotherapies and low matching rates correlating with low response rates. They hypothesized that personalised treatment with combination therapies could improve outcomes in patients with refractory malignancies. The I-PREDICT study used tumour DNA sequencing and timely recommendations for individualised treatment with combination therapies. Administration of multidrug regimens was feasible and 49% of patients received personalised treatment. This study demonstrated targeting a larger fraction of identified molecular alterations, yielding higher matching score, correlated with significant improvement in disease control rates, paired with improvements in progression-free and overall survival rates when compared to targeting fewer somatic mutations. The I-PREDICT study demonstrated current PCM clinical trial designs pairing one oncogenic driver with one drug may be optimised by treating molecularly complex and heterogeneous cancers with combination regimens (Sicklick, J.K., Kurkrock, R., et al, 2019).

Patients enrolling in conventional PCM clinical trials, often involving a single genomic profile, face the potential of screening, potentially including invasive biopsy, for a trial without prospect of intervention. Novel clinical trial designs attempt to increase efficiency and enrichment by linking patients in a common infrastructure for screening in the appropriate trial or sub-study. This has potential to benefit patients by increasing prospective intervention rates and reducing delays to targeted therapeutics. Being

performed under a single study design reduces the need for repeated invasive testing to assess tumour genomics.

The TARGET study (Rothwell, D., Ayub, M., et al, 2019) demonstrated the feasibility of blood-based genomic profiling by matching patients with different cancer types to early phase clinical trials on the basis of analysis of somatic mutations and copy number alterations across 641 cancer-associated gene panel in a single ctDNA assay. ctDNA from the first 100 patients in the study demonstrated good concordance with matched tumour, results being turned around within clinically acceptable timeframes for review by a molecular tumour board. Data from the TARGET study demonstrated that 41 out of 100 patients had actionable mutations and 11 of these received matched therapy. This data supports the application of ctDNA in early phase clinical trials.

Statistical considerations will continue to play a pivotal role in novel clinical trial design in PCM, incorporating small patient numbers and multiple tests. One key challenge for conventional clinical trial design is generalizability of results. Ensuring a trial design offers applicable results to an individual is challenging, given the ever increasing recognition of heterogeneity amongst cancer patient populations. Developing therapeutics with candidate biomarkers is more complex than traditional practice of developing drugs based on broad heterogeneous populations. Ensuring screening strategies reflect expected gene mutation frequencies will be a crucial calculation as complex trial designs evolve. Larger phase II studies with more extensive genomic profiling may be required in order to adequately understand the role of the candidate biomarkers in a specific disease.

1.9. Role of patient preferences for genomic testing

As discussed throughout this chapter, PCM moves beyond previous models of cancer therapeutics, based on trials of largely unselected patients, to molecular profiling of an individual's cancer genome. This has potential to offer efficacious, cost-effective cancer treatment that is targeted, biologically rational and reduces under- or over-treatment, thus preventing toxicities associated with non-specific modes of action of chemotherapy. PCM must incorporate genomic stratification with a holistic treatment approach which accords patient participation and preferences (Cribb & Owens, 2010). Tutton emphasised the importance of genomic and social aspects of healthcare in the UK, an important component to maintain the lasting legacy of scientific innovation (Tutton, 2012).

Novel clinical trial designs in PCM mean patients face different therapeutic and clinical trial decisions. Conventional clinical trial designs incorporate a small number of molecular profiles and targeted therapies, opening the possibility of patients enrolling and screening for a study for which they have little prospect of intervention. Patients may undergo further testing, including invasive biopsy, to determine eligibility. Novel clinical trial designs try to optimise this efficiency. However, with little empirical evidence around patients' preferences of genomic testing, there is a gap in understanding how best to do this. Without evidence of what matters to patients, it is difficult to predict uptake or understand what the barriers are to successful PCM implementation within clinical trials.

It is anticipated genomic testing in PCM will increasingly be utilized to select patients for specific and clinical trials. This has the potential to raise a number of ethical questions for patients beyond the provision of their cancer care. Genomic sequencing has potential to reveal increased risk of cancer syndromes and other diseases. This raises issues of privacy, data protection and discrimination for patients. In such cases, reporting of results could be

clinically meaningful and/or life-saving. Disclosure of such results from genetic testing that are clinically and analytically valid can be positive, helping patients take control of their lives. One such example could be patients with BRCA 1/2 mutations, who can benefit from prophylactic surgery to reduce cancer risk or from surveillance to detect cancer earlier. Providing feedback opportunities may also contribute to involving and educating patients and patient advocacy groups. Genomic testing could highlight genetic mutations with potential to affect other family members or have implications for an individual. In either setting, it is important to identify patients' preferences for genomic testing and its wider implications. Continuing research around developing ethical and legal frameworks, establish counselling recommendations and disclosure of information from genomic testing are paramount in this process. Patient and advocacy group participation is important to ensure acceptability of PCM and improve the translation of genomic testing data to the overall benefit of cancer patients.

Given the growing emphasis on providing patient-centred care, policy makers are increasingly seeking consumers' healthcare expectations, priorities and opinions. Involvement of patients' preferences is seen as an indicator of quality in modern cancer care (Muhlbacher, Bethge, Reed, & Schulman, 2016). Developing deeper understanding of patients' preferences around genomic testing in a rapidly emerging new era of cancer medicines may also allow further optimisation of patient-centred clinical trial design and recruitment. The inclusion of patient preferences can have beneficial effects including improved treatment compliance and clinical outcomes.

Within the promising scientific principles of genomic profiling, clinicians and patients will have to balance this plethora of information in order to make informed therapeutic decisions. Previous studies demonstrate patient preferences towards cancer diagnosis and

treatment are affected by a number of factors unique to that individual (McQuellon et al., 1995; Slevin, 1990; Weeks, 1998). These include factors such as perceived prognosis, disclosure of information and associated risks of testing (Gray et al., 2016). These factors have been studied in the pre-precision medicine era, but become of paramount importance in assessing the validity of precision cancer medicine and ensuring its lasting legacy beyond scientific promise.

1.10. Conclusions

As discussed throughout this chapter, the emergence of genomic testing in PCM challenges conventional clinical therapeutics and trial design, affecting clinical trialists, clinicians, pharmaceutical companies, regulatory and funding bodies as well as patients. Patients are now faced with increasingly complex decisions around genomic testing and its role in clinical trials. This thesis will identify and rate patient preferences of genomic testing within the rapidly evolving PCM paradigm and how these preferences are incorporated by a novel clinical trial design.

The overall aim of the thesis was to identify and rate patient-centred preference attribute themes of genomic testing and benchmarked these against a current UK clinical trial, to assess how current PCM clinical trial designs incorporate patient preferences. This thesis also explored the novel hypothesis that preference attribute themes and ratings of genomic testing may be influenced by clinical treatment intent and time since completing therapy.

The research questions for this thesis are as follows:

1. How are patient preference attributes of genomic testing in PCM defined and rated?
2. Do current clinical trial designs incorporate patient preference attributes of genomic testing in PCM?

The aims of this thesis will be addressed as follows:-

1. Conduct a narrative review of genomic testing and precision cancer medicine.
2. Undertake systematic review of the literature examining current evidence assessing patient preferences of genomic testing in precision cancer medicine.
3. Identify preference attribute themes of genomic testing for patients.
4. Identify rating scores for identified preference attribute themes.
5. Examine the effect of cancer treatment intent and time since completing therapy on identified preference attributes and rating scores.
6. Benchmark how a current precision medicine UK clinical trial design incorporates the identified patient preference attribute themes and ratings.

Chapter 2. Assessing patient preferences of genomic testing

2.1. Introduction

As discussed in Chapter 1, a key factor ensuring the legacy of PCM is incorporation of patient preferences of genomic testing in both clinical trial design (Tsimberidou, 2012) and widespread implementation in clinical practice (Lee & Nelson, 2012), (Fraeknel & McGraw, 2007), (Say & Thomson, 2003). Understanding patient preferences will deepen understanding of attitudes towards genomic testing (Rogausch & Prause, 2006). This chapter will consider methodologies to endorse the thesis research aims of identifying and rating patients' preference attributes of genomic testing in PCM.

2.2. Mixed methods research in defining and rating attributes

Qualitative approaches to healthcare research have their roots in social science and humanities disciplines such as sociology, social anthropology, psychology, history and geography. Health professionals have a long history of integrating social science insights into understanding of human health (Henderson, 1935), (Kleinman, 1973), (Helman, 2000). Social research methods have been adopted as part of the toolbox of approaches providing evidence for practitioners and policy-makers across fields such as global health, primary care, health promotion, health services and nursing. Although social sciences and humanities disciplines have their own distinct methodological and theoretical traditions, what they have in common is a focus on what people do, and why, in the context of social relationships (Green J, 2018). As the challenges of health policy and practice are increasingly recognized as rooted in the 'social,' it is not surprising that health care practitioners, managers and policy makers have turned to social enquiry to enhance understanding of health, health behaviour and health services (Murphy E, 2003).

Qualitative research has a particular role to play in generating useful knowledge about health and illness, from that of individual perceptions through to global systems. Qualitative methodologies include approaches answering questions of what happens, why and with what effects at different levels. There are differing ways of characterizing qualitative versus quantitative research. The most basic way of characterizing qualitative research is by describing the kind of data it generates (Holliday, 2002). In this delineation, qualitative data are usually in the form of words, in contrast to the numbers generated by quantitative research. Some have seen this division between qualitative and quantitative research as difficult, since many studies involve differing degrees of both. Another way of characterizing qualitative research is by the methods used to generate the data. There are some methods primarily associated with qualitative research, including interviews, ethnographic case studies and participant observation, where others, such as surveys or experiments, are more associated with quantitative research. Studies in health care literature often employ a mixed methods approach of qualitative and quantitative methodologies (Fielding, 2010).

Mixed methods research is becoming increasingly recognised as a third major research approach, along with qualitative and quantitative methodologies (Kuhn, 1962). Mixed methods research exists as a synergy between ideas of both qualitative and quantitative research. Within social science methodological literature, Campbell and Fiske's article (Campbell & Fiske, 1959) is often viewed as formalising the practice of using multiple research methods. In this article, Campbell and Fiske introduce the idea of triangulation, referring to "multiple operationalism." More than one method is used as part of a validation process ensuring explained variance is the result of the underlying phenomenon or trait and not of the method (such as qualitative or quantitative methods). Subsequent authors argued the convergence of findings stemming from two or more methods

"enhances our beliefs that the results are valid and not a methodological artefact." (Bouchard, 1976). Denzin (Denzin, 1978) was the first to outline how to triangulate methods. Denzin defined triangulation as "the combination of methodologies in the study of the same phenomenon." He outlined the following four types of triangulation:

1 - Data triangulation, such as the use of a variety of sources within the study

2 - Investigator triangulation such as the use of multiple different researchers

3 - Theory triangulation, where the use of multiple perspectives and theories interpret the results of the study

4 - Methodological triangulation, defined by use of multiple research methods to study a research problem.

Although recognizing triangulation may not be suitable for all research purposes, Jick (Jick, 1979) noted the following advantages:

- It allows researchers to be more confident of their results
- Stimulates development of creative ways of collecting data
- Can lead to thicker, richer data
- Can lead to synthesis or integration of theories
- Can uncover contradictions
- May serve as the litmus test for competing theories

Morse (Morse, 1991) outlined two types of methodological triangulation: simultaneous and sequential. According to Morse, simultaneous triangulation represents use of qualitative and quantitative research where there is limited interaction between two sources of data during the collection stage, but findings complement one another at the data interpretation stage. On the other hand, sequential triangulation is utilized when the results of one approach are necessary for planning the next.

Sieber (Sieber, 1973) outlined five reasons for combining qualitative and quantitative research. This included how combinations can be effective at the design, data collection and data analysis stage of the research process. Rossman and Wilson (Rossman & Wilson, 1985) identified three reasons for combining qualitative and quantitative research. Firstly, the combinations are used to enable confirmation or corroboration of each other through triangulation. Secondly, combinations are used to enable or develop analysis, providing richer data. Thirdly, combinations are used to initiate new models of thinking by attending to paradoxes emerging from different data sources.

Greene et al (Greene, 1989) inductively identified the following five purposes or rationale of mixed methodological studies:

Triangulation – seeking convergence and corroboration of results from different methods studying the same phenomenon

Complementarity – seeking elaboration, enhancement, illustration, clarification of the results from one method with results from the other

Development – using the results from one method to help inform the other

Initiation – discovering paradoxes and contradictions leading to reframing of the research question

Expansion – expanding the breadth and range of inquiry by using different methods for different inquiry components

Most recently, Collins (Collins, 2006) identified four rationale for conducting mixed methods research. They were:

1 - **Participant enrichment** – mixing quantitative and qualitative research using techniques including recruiting participants, engaging in activities and ensuring appropriate participant selection for inclusion.

2 - **Instrument fidelity** – assessing the appropriateness and/or utility of existing instruments, creating new instruments or monitoring performance of human instruments.

3 - **Treatment integrity** – assessing fidelity of intervention

4 - **Significant enhancement** – facilitating thickness and richness of data, augmenting interpretation and usefulness of findings.

Johnson, Onwuegbuzie and Turner (Johnson, Onwuegbuzie, & Turner, 2016) defined mixed methods research as "Intellectual and practical synthesis based on qualitative and quantitative research. It is the third methodological or research paradigm, along with qualitative and quantitative research. It recognizes the importance of traditional quantitative and qualitative research but offers a powerful third paradigm choice that may provide the most informative, complete, balanced and useful research results. "

The aim of the research presented in this thesis was to identify and rate themed patient preference attributes of genomic testing in PCM. This involved initially identifying preference attributes and associated rating scores. This thesis also assessed whether patient-centric factors such as clinical treatment intent and time since completing treatment affect patient preference attributes or ratings of genomic testing. The nexus of contingencies in this thesis, in relation to the thesis research question, suggests that mixed methods research design is anticipated to provide superior research findings and outcomes compared to either qualitative or quantitative research methods alone.

2.3. Consensus methods research

2.3.1. Background of consensus research

Formal consensus research methods have become increasingly visible tools for solving problems in health and cancer research. The main purpose is to define levels of agreement on controversial subjects in situations where there is insufficient evidence, or where there is an overload of, often contradictory, information (Rennie, 1981). Quantitative research methods, such as meta-analysis, have been developed to provide statistical overview of clinical trials and resolve inconsistencies in the results of published studies. Consensus methods are another means of dealing with conflicting scientific evidence. They allow a wider range of study types to be considered than is usual in statistical reviews. In addition, consensus methods research allows greater role for qualitative assessment of evidence (Fink, 1984). Consensus methods are primarily concerned with deriving quantitative estimates through qualitative approaches. They, therefore, complement the theory of mixed methods research.

The aim of consensus research methods is to determine the extent to which experts or lay people agree about a given issue. They seek to overcome some of the disadvantages normally found with decision making in groups or committees, which are commonly dominated by one individual or by coalitions representing vested interests (Jones & Hunter, 1995). The term ‘agreement’ takes two forms, which need to be distinguished. First, the extent to which each respondent agrees with the issue under consideration, typically rated on a numerical or categorical scale. Second, the extent to which respondents agree with each other, the consensus element of these studies, typically assessed by statistical measures of average and dispersion.

The focus of consensus methods research lies where unanimity of opinion does not exist owing to lack of evidence or where contradictory evidence exists on an issue. Consensus methods attempt to assess extent of agreement (consensus measurement) and to resolve disagreement (consensus development) (Perry, 1987). The most widely utilised consensus research methods are the Delphi Technique (DT) and nominal group technique (NGT). Both methods involve measuring consensus and NGT also incorporates developing consensus. Both of these techniques have a relatively long history of use in healthcare research, with formal rules for collecting and analysing information, emphasizing production of immediate solutions to healthcare problems. This chapter will discuss these methodologies in healthcare research and their application in this thesis study.

2.3.2. The Delphi Technique

The Delphi technique (DT) has been used widely in health research to obtain expert opinion in a systematic manner via highly structured group interaction. The Delphi method was developed by Norman Dalkey and associates at the RAND institute in 1953 and utilizes a multi-stage self-completed questionnaire with individual feedback (Linstone & Turoff, 1975). Delbecq, Van de ven and Gustafson (Delbecq, Van de Ven, & Gustafson, 1975) define this as a "method for the systematic solicitation and collation of judgments on a particular topic through a set of carefully designed sequential questionnaires interspersed with summarized information and feedback of opinions delivered from earlier responses." The technique, is used to achieve the following objectives:

- Determine or develop a range of possible program alternatives.
- Explore or expose underlying assumptions or information leading to different judgments.

- Seek out information which may generate consensus on the part of the respondent group.
- Correlate informed judgments on a topic spanning a wide range of disciplines
- Educate the respondent group as to the diverse and inter-related aspects of the topic.

The DT, according to Cyphert and Gant (Cyphert & Gant, 1971), attempts to overcome the numerous problems associated with the traditional round-table method for achieving a consensus. These include factors such as influence of psychosocial factors, dominant group members and the band-wagon effect. Participants within DT are polled individually, often anonymously. The survey is conducted over three to five 'rounds.' After each round results are elicited, tabulated and reported to the group. The Delphi method is considered complete when reported outcomes saturate and develop convergence of opinion.

Tersine and Riggs (Tersine & Riggs, 1976) point out that Delphi Technique has many advantages over more conventional means of gathering opinions on matters not subject to precise quantification. Tersine and Riggs observed that most benefits are the result of keeping the identification of participants' unknown, eliminating one form of bias. Participants are deemed to be less susceptible to the 'halo effect,' where opinion of one highly respected individual can influence others. The authors observed advantages in the DT with face-to-face groups, where full member participation is not restrained by increasing group size. DT imposes no restrictions on the number of participants.

The DT has advantages enabling each participant to express views impersonally, whilst ultimately providing information generated by the entire group (Proctor & Hunt, 1994). Since DT questionnaires are completed by mail, no geographical constraints on the

selection of experts need be imposed. Crawford and Cossitt (Crawford & Cossitt, 1980) compared three group processes, namely regular face-to-face interacting groups, the NGT and DT. They point out that one of the major strengths of the Delphi process is removal of inhibiting effect around face-to-face interactions of the group. This strength also proves to be one of its major weaknesses. In an attempt to measure participant satisfaction, Crawford and Cossitt had subjects respond to eight Likert-type statements on a five-point agree-disagree scale. The results supported the hypothesis that "the total removal of face-to-face interactions from decision-making processes tends to diminish social-emotional satisfaction among participants."

Anderson, Ball and Murphy (Anderson, Ball, & Murphy, 1981) observed DT has three main weaknesses:

1 - It is only the initial step and simply attempts to obtain consensus.

2 - This consensus may not necessarily be the "best" judgment.

3 - The technique entails considerable labour, including tabulations, record keeping and mailings.

Sackman (Sackman, 1975), in critical analysis of DT, concluded its liabilities outweighed its assets, often being characterized by crude questionnaire design, vulnerability with respect to who is an 'expert' and obliviousness to reliability of measurement and scientific validation of findings. Starkweather, Gelwicks and Newcomer (Starkweather, Gelwicks, & Newcomer, 1975) also highlighted the reliability of DT increases with the size of the group and number of rounds, but panellists sometimes become fatigued after two or three rounds.

2.3.3. The Nominal Group Technique

NGT is a highly structured face-to-face group interaction, providing orderly procedure for obtaining information from target participants about a selected issue. The NGT was initially devised by Van de ven and Delbecq (Van de Ven & Delbecq, 1972) as a "special purpose technique useful for situations where individual judgments must be tapped and combined to arrive at decisions which cannot be delivered by one person. They are problem-solving or idea-generating strategies."

Delbecq (Delbecq et al., 1975) described the step-by-step process associated with the Nominal Group Technique:

- The meeting room must be selected and prepared
- The necessary supplies must be ready
- The leader must make an opening statement
- The question must be presented
- Each member must write his or her key ideas silently and independently
- Ideas from all group members should be recorded in a round-robin fashion on a flip chart that is visible to the entire group.
- There should be serial discussion for clarification purposes. This means there will be a short period allowed for discussion of each idea listed on the flip chart. It is imperative that each item on the flip chart be discussed in order.
- The preliminary vote is taken
- The group discuss the preliminary vote. The purpose of this discussion is two-fold: to examine inconsistent voting patterns and provide opportunity to re-discuss items which appear to have received too many or too few votes.
- The final vote

Van de Ven and Delbecq further describe NGT as "a group process for generating qualitative insight regarding critical problem dimensions." Gallacher et al (Gallacher, Hares, Spencer, Bradshaw, & Webb, 1993) agree it is a structured procedure for gathering information but reinforce in their definition the importance of gathering it from 'people who have insight into a particular area of interest.' The decision of the group is the combined outcome of the individual votes.

Subsequent authors (Pendleton & Myles, 1991), (Carney, McIntosh, & Worth, 1996), (Hickson, Worrall, Yiu, & Barnett, 1996) presented variations of the original technique, but the process up to the point of ranking or scoring items appears based on the original outline. Twible (Twible, 1992) used a modified technique in which the question was written on a board and members called out relevant responses. In this setting, similar responses were grouped together and labelled alphabetically.

In their original work, Van de Ven and Delbecq (Van de Ven & Delbecq, 1972) outlined the advantages of NGT in allowing the target group to single out critical problems by means of a process which is non-threatening and depersonalized. It allows clarification of meaning and exploration of both subjective and objective dimensions. Katz (Katz, 1988) demonstrated that all group members can contribute effectively and feel valued by the process. Hickson (Hickson et al., 1996) highlighted the prioritization process enabling the resulting program to reflect values of the participants. NGT can also be used to survey a large number of participants and allow for efficient management of the data generated (Twible, 1992).

There are disadvantages associated with NGT. Pendleton and Myles (Pendleton & Myles, 1991) felt the technique was time consuming as it can take up to two hours to complete a

group. Scott and Deadrick (Scott & Deadrick, 1982) stated time can be wasted clarifying the question if it is not clearly stated. Fox (Fox, 1987) highlighted that NGT makes no provision for inputting and review of ideas before the meeting. The nominal group technique also permits only one person to input at any given time, which can create a 'bottleneck' around discussion topics. This sets a group size limit of around 10 participants for effective operation.

2.3.4. Discussion

The choice for utilization of either Delphi Technique or Nominal Group mixed methods research techniques is influenced by various factors, including the primary research question, perception of consensus required and associated practicalities such as limitations of time or geography. Examples of healthcare studies employing Nominal Group and Delphi Technique are shown in *Table 1* and *Table 2*, respectively.

Linstone and Turoff (Linstone & Turoff, 1975) suggest criteria for situations where DT should be considered:

- The research problem does not lend itself to precise analytical techniques but can benefit from subjective judgments on a collective basis.
- The research population presents diverse backgrounds with respect to experience or expertise.
- More subjects are required than can effectively interact face-to-face.
- Time, costs and logistics would make frequent meetings of all subjects unfeasible.

Cantrill, Sibbald and Buetow (Cantrill, Sibbald, & Buetow, 1996) highlight further advantages of the NGT lie in allowing peer support for participants identifying problems. NGT also has value in situations where participants value social interaction.

Table 1. Examples of healthcare studies using the Nominal Group Technique (NGT)

Authors	Aim					Participants						Prioritisation or ranking
	Develop guideline	Generate ideas	Problem solving	n	Size range	Doctors	Other AHP	Policy makers	Patients	Public	Academics	
Bissell et al	•			1	8	•	•	•				N/A
Bond&Watson	•			1	13	•	•	•	•	•		Ranking
Bradley et al		•		4	3-8	•					•	Prioritisation
Tully&Cantrill	•			1	10	•	•				•	Ranking
Rice et al		•		3	3-6					•		Mean rating
Gastelurrutia et al			•	2	7		•	•			•	Mean rating
McMillan et al		•		21	2-14		•				•	Ranking
Hutchings et al		•		6	4-9		•	•		•	•	Ranking
Aspinal et al	•	•	•	10	4-12		•		•	•	•	Ranking

AHP= Allied healthcare professional

Table 2. Examples of healthcare studies using the Delphi technique (DT)

Authors	Aim		No of experts			Experts				Rating
	Develop guideline	Generate ideas	Invited	Agreed	Completing	Doctors	Other AHP	Academics	Patients	
Campbell et al	•		305	305	79	•	•			Yes
Chan et al	•		23	9	9	•				Yes
McBride et al	•	•	164	109	47	•		•	•	Yes
Taylor et al	•	•	179	158	158	•	•	•		Yes
McDermott et al	•	•	58	53	48		•	•		Yes
Alahlafi&Burge	•	•	84	73	71	•	•	•	•	No
Meshkat et al	•		201	75	54	•	•			Yes
Masud&Blundell	•	•	67	53	49	•		•		No

AHP = Allied healthcare professional

2.4. Conclusions

This chapter discussed methodological considerations to identify and rate patient preference attributes of genomic testing in PCM. The primary research question required both qualitative identification of preference attributes and quantitative rating scores. Given genomic testing and PCM remains in its clinical infancy, it is hypothesized that patients will have little prior experience of the modality. The strengths of consensus research and NGT, in this setting, are that they support participants to better understand genomic testing and its role. Previous studies in this patient population have also highlighted the importance of social interaction in facilitating complex discussions for patients. Given these considerations, systematic review of the literature followed by mixed methods research methods employing NGT to identify and rate preference attributes is favoured for this study.

The first stage of the research design was to examine, via systematic review, the current literature identifying and rating patient preference attributes of genomic testing in PCM. It was anticipated the identified preference attributes or ratings could be utilised within the mixed methods study design. Chapter 3 will explore the employed methods and identified patient preference attributes from the systematic review of the existing literature.

Chapter 3. Assessing patients' preferences of genomic testing in PCM: A Systematic Review

3.1. Introduction

As discussed in chapter 1, understanding preference attributes will lead to greater understanding of patients' preferences of genomic testing, its subsequent therapeutic application and role in clinical trials (Rogausch & Prause, 2006). The aim of this systematic review was to identify, summarize and assess the validity of preference attributes and ratings of genomic testing for patients within existing literature.

3.2. Systematic Review Methods

3.2.1. Background

Systematic reviews have become increasingly important in healthcare research (Stephens, 2001). Healthcare professionals use them to keep up to date in their field (Oxman, Cook, & Guyatt, 1994), often used as a starting point for developing clinical guidelines (Swingler, Volmink, & Ioannidis, 2003). As with all research, the value of a systematic review depends on what was done, what was found and the clarity of reporting (Moher, Tetzlaff, Tricco, Sampson, & Altman, 2007). Several early studies evaluated the quality of systematic review reports (Mulrow, 1987), (Sacks, Berrier, Reitman, Ancona-Berk, & Chalmers, 1987) and found areas of inconsistency or perceived deficiency. In order to address this, the Quality of Reporting of Meta-analysis (QUOROM) statement (Moher et al., 1999) aimed to create international consensus on reporting and meta-analysis of randomised controlled trials. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines updated previous recommendations, reinforcing principles within systematic reviews (Moher, 2009).

The terminology used to describe a systematic review has evolved over time. The PRISMA statement (1999) utilised the definition provided by the Cochrane Collaboration (S. Green & Higgins, 2005): "A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, collect and analyse data from the studies that are included in the review."

3.2.2. Search strategy

A systematic review was conducted for publications up until January 2018 using Cochrane Library, MEDLINE, EMBASE and PubMed (Moja et al., 2005). A combination of the following search terms was used: 'precision/personalised cancer medicine/genomic testing' in combination with 'patient preferences/attitudes/satisfaction.' The initial search strategy was not restricted to a particular type of research design. Articles were eligible for consideration if they were published in English, within peer-reviewed journal, included precision/personalised cancer medicine and explored patient preferences and/or attitudes towards genomic testing. All retrieved studies were screened by title and abstract, following which the selection criteria were applied (Stephens, 2001). If this initial search strategy concluded that a title/abstract met eligibility criteria for literature review, then the full text article was obtained. Based on full manuscripts, studies were included for selection according to whether they met pre-defined eligibility criteria. The complete search strategy is included in *Figure 1*.

Figure 1. Search strategy for thesis systematic review of the literature

1 exp Individualized Medicine/ 7299

2 exp Molecular Targeted Therapy/ 13750

3 exp Pharmacogenetics/ 10507

4 exp Patient-Specific Modeling/ 104

5 (precision adj2 medicine).ti,ab. 370

6 (personali?ed adj2 medicine).ti,ab. 4699

7 ((precision or personali?ed or genomic) adj2 oncolog*).ti,ab. 107

8 1 or 2 or 3 or 4 or 5 or 6 or 7 32620

9 exp Attitude to Health/ 323484

10 exp Patient Preference/ 4128

11 exp Patient Satisfaction/ 68555

12 exp Patient Participation/ 19631

13 exp Patient-Centered Care/ 12900

14 (patient* adj (view* or attitude* or preference* or satisfaction or perception* or centered or centred)).ti,ab. 46918

15 9 or 10 or 11 or 12 or 13 or 14 353405

16 8 and 15 2014

17 limit 16 to english language 1805

3.2.3. Selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement provides guidelines for conducting a systematic review and suggests framing questions with five components to facilitate the systematic review and meta-analysis process (Moher, 2009). The PRISMA checklist is demonstrated in *Appendix 1*. Inclusion criteria are presented as five PICOS components (Methley, Campbell, Chew-Graham,

Mcnally, & Cheraghi-Sohi, 2014), namely the patient population or disease being assessed (P), the intervention or exposure (I), the comparator group (C), the outcome or endpoint (O) and chosen study design (S). The PICOS tool is commonly used to identify components of clinical evidence for systematic reviews and is endorsed by the Cochrane Collaboration (S. Green & Higgins, 2005). The pre-defined criteria for this systematic review were applied in order to choose the final studies to be included, presented using PICOS criteria as shown in *Table 3.*

Table 3. PICOS criteria applied to systematic review.

PICOS components	Inclusion criteria
Population (P)	Participants with history of cancer or healthy volunteers participating in hypothetical cancer-related scenarios
Intervention (I)	All precision/personalised cancer medicine/genomic testing studies
Comparative (C)	Any
Outcome (O)	Patient preferences, attitudes or perspectives
Study design (S)	Any study design (qualitative, quantitative or mixed methods)

This systematic review included original research articles, review articles were excluded. Studies were included if they empirically assessed patient attitudes/perspectives/preferences of genomic testing in precision cancer medicine via any qualitative, quantitative or mixed methods. Studies were excluded if they did not assess patient attitudes/preferences, did not involve cancer, precision medicine or genomic testing. The titles, abstracts and full texts of the identified studies were reviewed.

3.2.4. Data extraction

After screening, all eligible studies were reviewed and study characteristics were extracted to three data extraction tables (*Appendix 2*). *Appendix 2* contains the following elements: basic study characteristics (including author and year), country of study, number of patients and volunteer participants, recruitment criteria, study type, applied methodology for eligible studies, identified attributes and associated levels.

3.2.5. Critical appraisal

This systematic review applied and adopted the quality assessment list of previous reviews assessing patient perspectives in healthcare (Moja et al., 2005), (Stephens, 2001). The critical appraisal of included studies was assessed using the Mixed Methods Appraisal Tool (2018) due to mixed qualitative and quantitative methods employed by studies. The foundation of mixed methods research combines the strengths of qualitative research in providing in-depth description of complex phenomena, allied with the statistical generalizability of quantitative methods. Multiple validated tools exist assessing quantitative methodologies as well as some validated tools for qualitative methods. The MMAT was developed by Pluye et al in 2009 to address the challenges relating to appraisal of mixed methods studies (Pluye, P., Gegnon, M.P., et al, 2009). The first iteration of MMAT was developed in line with a social constructionist world view. This version of MMAT included 15 criteria for four categories of study design, namely qualitative, quantitative experimental, quantitative observational and mixed methods. Further refinement to the MMAT methods were published in 2012 (Pace, R., Pluye, P., et al, 2012) and latterly 2018 (Pluye, P., Garcia Bengoechea, E., et al, 2018).

The 2018 MMAT version includes 25 criteria and 2 screening questions. This appraises five different categories of study design: qualitative, randomised controlled, non-

randomised, quantitative descriptive and mixed methods. Each category contains five core criteria, rated as either yes, no or can't tell. Prior versions of the MMAT incorporated a summative score for each study, calculated by dividing the number of criteria met by four (Pluye et al, 2011). Increasing opinion suggests single numerical values do not reflect the strengths or deficiencies of a study, as well as being unclear whether it should be weighted (Higgins and Green, 2008). Current literature discourages use of summative scores for each criterion (Herbison, Hay-Smith and Gillespie, 2006; Viswanathan et al, 2012). MMAT has been validated in several studies, demonstrating reliability, usability and content validity (Hong et al, 2018).

Performing MMAT involved three main steps (Hong et al, 2018). This firstly involved two screening questions to determine suitability of MMAT appraisal. Secondly, selection of appropriate category of study design amongst the five MMAT categories: qualitative, randomised controlled, non-randomised, quantitative descriptive and mixed methods. Each qualitative or quantitative study was assigned one category. Studies employing mixed methods were assigned three categories, namely: the qualitative category, one quantitative category and the mixed methods category. In assigning appropriate study categories based on methodological approach, the MMAT acknowledges the distinctive methodological characteristics specific to each component used in mixed methods studies (O'Cathain, 2010). The third step of MMAT consists of rating the chosen category criteria. There were three response options: 'yes' meaning the criterion was met, 'no' meaning the criterion was not met or 'can't tell' when there is not enough information in the paper to judge whether criterion was met or not.

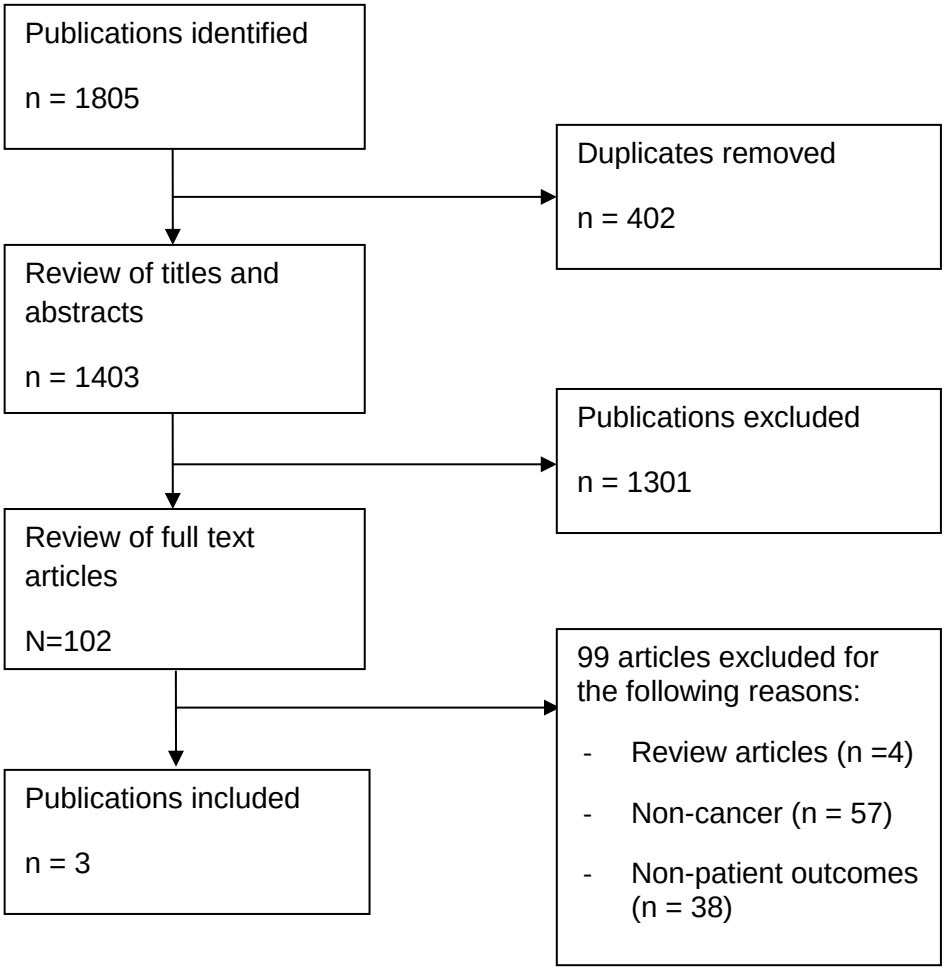
The studies were critically appraised using the MMAT and independent preference attributes and attribute levels for genomic testing in PCM were assessed descriptively, with

comparison between descriptive outcomes. This was performed due to heterogeneity of study design and methodologies employed within the small number of studies eligible for inclusion. No studies were excluded due to limited or reduced methodological quality based on MMAT assessment. The Mixed Methods Appraisal Tool quality criteria tables are shown in *Appendix 3*.

3.3. Results

The primary search strategy yielded 1805 articles. After removal of duplicate publications, titles and abstracts of 1403 studies were screened resulting in exclusion of 1301 studies. The full text articles of the remaining 102 studies were then screened based on the previous inclusion and exclusion PICOS criteria, of which 3 studies were eligible for inclusion in the systematic review. The PRISMA flow chart of the screening process is demonstrated in *Figure 2*.

Figure 2. PRISMA flow chart for systematic review.



This systematic search yielded three unique studies examining patient attitudes/preferences of genomic testing in precision cancer medicine. These studies, the identified themed preference attributes and ratings are discussed in turn below.

Genomic testing to determine drug response: measuring preferences of the public and patients using Discrete Choice Experiment (DCE) (Najafzadeh, 2013)

Methods

This study utilised a discrete choice experiment (DCE) to elicit preferences of both the public (n=1,058) and cancer patients (n=38) for differing attributes within a hypothetical genomic test aimed at guiding cancer treatment. The study presented a questionnaire to

patients previously or currently being treated for lymphoma, as well as healthy volunteers. Participants completed discrete choice questionnaires using scenarios either involving an aggressive curable cancer or non-aggressive incurable cancer (571 and 525 participants respectively), reflecting clinical treatment paradigms in lymphoma.

Factors examined

The study identified attribute characteristics of both patient and physician preferences towards pharmacogenomic testing using 3 pilot studies, published literature and physician opinion (Najafzadeh & Davis, 2013). The attributes selected were: genomic test sensitivity/specificity, severity of side effects, likelihood of side-effects, genetic test turnaround time, genetic test procedure and cost.

Results

This study highlighted the relative impact of attributes affecting uptake of genomically-guided cancer testing. It demonstrated preferences for uptake of genomic testing were different between the scenarios of an aggressive curable malignancy versus a non-aggressive incurable malignancy. The groups of patients and public within the study demonstrated significant variability in demographic characteristics: mean age (58.2 versus 47.9 years respectively), household income of greater than CAN$ 125,000 (36.1 versus 6.1 per cent respectively) and baseline education with 32.4% of patients having master or doctorate degree versus 3.3% in the public group.

Test sensitivity

The study demonstrated, in the case of an aggressive curable cancer, the preference weight of the public for a test sensitivity of 50% was -0.1686 (s.e. 0.466) and increased to 0.1748 (s.e. 0.0266) for a test with sensitivity of 95%. This effect is evident in the odds ratio for

willingness-to-pay (WTP) relative to test sensitivity, showing the odds of choosing a test with 95% sensitivity were 1.41 times the odds of choosing a test with 50% sensitivity. Respondents were willing to pay $1331 for increasing test sensitivity from 50% to 95%. Respondents were, however, only willing to pay $796 and $487 for increasing sensitivity to 80% and 65% respectively. In the setting of a non-aggressive incurable cancer, preference weights for 95% sensitivity and 50% sensitivity were 0.2577 (s.e. 0.270) and -0.2436 (s.e. 0.0479) respectively. Increasing test sensitivity from 50% to 95% increased the odds ratio of choice by 1.65 times.

Test specificity

In the scenario of an aggressive curable cancer, the odds of choosing a test with 95% specificity were 1.24 times the odds of choosing a test with 50% specificity and the public were willing to pay $827 for this amount of improvement in specificity level. The preference weight for 95% test specificity was more than two fold larger in the respondents for the scenario of non-aggressive incurable cancer (0.2452 versus 0.1008, p-value <0.001).

Severity of side effects

Reducing the severity of side effects from severe to mild was associated with large odds ratios in both aggressive curable and non-aggressive incurable cancers (2.10 and 2.24 respectively). Furthermore, the odds of choosing a treatment with 5% likelihood of side effects were 1.62 and 1.75 times the odds of choosing a treatment with 95% likelihood of side effects, for an aggressive curable and non-aggressive incurable cancer respectively.

Shortening test turnaround time

Shortening test turnaround time from 12 to either 7 or 2 days had the smallest impact on preference weights and odds ratios (OR) for both scenarios. In contrast, the invasiveness of testing procedure had a large impact on estimated preference weights and OR values for both scenarios. Respondents offered blood sample had an OR of 1.73 and 1.88 for an aggressive curable and non-aggressive incurable cancer respectively, versus OR of 1 for liver biopsy in both groups. This demonstrated strong preference for m less invasive testing modality.

Comparing patients versus healthy population

The authors of the study did attempt to compare selected subsamples of the public (n=83) with similar demographic characteristics of the patient group (n=38) to allow comparison between the groups for their preferences. The pooled data was examined using a fitted conditional logit model to estimate preference weights and OR with attribute levels. The study numbers within the patient group meant that for many factors, the study was underpowered to determine significant differences between the groups. It did demonstrate, however, that the preference weight for test sensitivity of 95% was larger for patients compared to the public (0.8794 versus 0.2480 respectively, p-value<0.001).

A national study of breast and colorectal cancer patients' decision-making for novel personalized medicine genomic diagnostics (Issa, Tufail, Atehortua, & McKeever, 2013)

Methods

This study employed discrete choice experiment to develop an understanding of breast and colorectal cancer patients decision-making and preference trade-offs around characteristics of specific molecular genomic tests, namely Oncotype DX and KRAS/UGT1A1

respectively. The study surveyed a nationally representative sample of 300 patients with breast or colorectal cancer using a web-administered discrete choice instrument. Amongst all respondents for the study, 76.5 % of breast and 70% of colorectal cancer patients were identified as having early-stage cancers.

Factors examined

The attributes and levels were allocated based on published literature and six focus groups of breast and colorectal cancer patients (Issa, Tufail, Hutchinson, Tenorio, & Baliga, 2009). The attributes were: personal cost of testing, individuals who would have access to results (confidentiality of results), how test results are used, chance the test will correctly predict patient response to treatment and what information the test will provide. There were up to 6 levels within each attribute, assessed across 20 scenarios presented in a randomized manner. For each participant, part-worth utilities or relative importance scores were computed, reflecting the influence of each attribute on participant choice.

Results

This study demonstrated all 5 preference attributes influence patient decision-making, however accuracy of the genomic test and cost appeared to have the most weight amongst both breast and colorectal cancer patients. Amongst all patients within the study, 22.5% were willing to pay for genomic testing and patients sought test accuracy of greater than 90%. The study demonstrated both groups of patients weighted the capability of genomic testing diagnostics to determine probability of treatment efficacy of greater importance than detecting adverse events. 78.6% of breast cancer patients ranked the possibility of false-negative test, leading to under-treatment, higher than false-positive resulting in over-treatment (68%). This finding contrasted that of the colorectal cancer patient group, who ranked the chance of false positive as greater significance than a false negative (72.8

versus 63%, p=0.0024). Overall, cancer patients demonstrated a high willingness to pay for these two specific genomic tests. Amongst all respondents, willingness-to-pay falls at a level of $500.

Cancer patients' acceptance, understanding and willingness-to-pay for pharmacogenomic testing (Cuffe et al., 2014)

Methods

This study employed patient questionnaire followed by interviews using hypothetical trade-off scenarios around use of chemotherapy. The questionnaire encompassed domains of socio-demographic characteristics, health status, patient preference for whom should decide on pharmacogenomic testing and level of agreement (using Likert scales) with a series of novel statements designed to elicit patient values on chemotherapy and pharmacogenomics. Patient preferences were determined by interviewer administered questionnaires and probability trade-off testing. This included 244 patients with diagnosis of malignancy. The population was divided into adjuvant (n=123) and metastatic (n=121) groups, based on patients self-reported perception of cancer stage.

Factors examined

Patients in the study were asked to trade off preferences against the burden of testing by systematically modifying the levels of attributes associated with testing. The primary attribute was therapy efficacy, in the adjuvant group, and risk of adverse events in the metastatic group. Other attributes included cost of testing, waiting time for results and prevalence of genetic variant of interest.

Results

Amongst the adjuvant patient group, 72% of patients were willing to accept chemotherapy for a 5% absolute improvement in cure rate and risk of severe side-effects less than 5%. A further 24% of patients would accept chemotherapy for a higher cure rate (median 15%, range 10-50%); thus only 4% refused chemotherapy at any level of benefit. Of the patients accepting chemotherapy, 99% were willing to accept pharmacogenomic testing that could improve prediction of response to chemotherapy when the test was free, had a 1 day turnaround time for results and the prevalence of the genetic variation associated with lack of response to chemotherapy was 50%.

Amongst the metastatic group, 92% were willing to accept chemotherapy for an 80% benefit (shrinkage or stable disease) and risk of severe side effects less than 5%. A further 2.5% of patients would accept chemotherapy for a higher response rate (median 95%, range 85-100%), where as 2.5% would accept chemotherapy for a lower risk of side-effects (median 0%, range 0-1%). Of the 97% of patients accepting chemotherapy, 97.4% were willing to accept pharmacogenomic testing that could stratify risk of toxicity when the test was free, had a 1 day turn around for results and the prevalence of the genetic variation associated with severe side-effects was 5%.

The median acceptable waiting time for pharmacogenomic test results was 16 days (range 0-90 days) for the adjuvant group and 14 days (range 1-90 days) in the metastatic group. Patient preferences for pharmacogenomic testing were not influenced by the prevalence of the genetic variant. The median lowest prevalence at which patients would no longer opt for pharmacogenomic testing was 5% (range 0-80%) and 1.5% (range 0-10%) for the adjuvant and metastatic groups respectively. Amongst the adjuvant patient group, 37% of

patients would accept testing even when the prevalence of the genetic variation of interest varied from 5-95%.

Within the study, 85% of patients agreed reducing chance of receiving ineffective treatment was a high priority. 77% of patients believed any additional test offered by the medical profession must be of benefit. 92% of patients were agreeable to an additional blood test to facilitate testing, whereas only 55% of patients were agreeable to repeat tissue biopsy. The median WTP for pharmacogenomic testing was CAD$2000 and CAD$1000 in the adjuvant and metastatic setting respectively.

3.4. Discussion

To the authors' knowledge, this is the first systematic review analysing the available evidence regarding patients' preferences and attribute rating of genomic testing within the precision cancer medicine paradigm. The core principles of precision cancer medicine remain around the concept of the 'right drug for the right person at the right time,' (Biankin, Piantadosi, & Hollingsworth, 2015) highlighting the importance of patient empowerment and involvement in decision making within precision medicine (Sleijfer, Bogaerts, & Siu, 2013),(Chin & Gray, 2008), (E. D. Green, Guyer, & National Human Genome Research, 2011). This systematic review highlights the paucity of prospective studies examining patient preference attributes of genomic testing within precision cancer medicine.

The study by Najafzadeh et al demonstrated the type and prognosis of cancer effect preference attributes for genomically-guided treatments. In the scenario of an aggressive curable cancer, individuals emphasized the importance of test sensitivity versus specificity. In contrast, for a non-aggressive incurable cancer, individuals put similar emphasis on

sensitivity and specificity attributes. The study enrolled both healthy volunteers and patients with previous diagnosis of lymphoma, but was limited by the small sample of cancer patients within the cohort, making valid conclusions for the wider cancer population challenging. Historical studies demonstrate differential decision-making and priorities amongst patients both after a cancer diagnosis and at varying points along their cancer journey. This, therefore, does make it difficult comparing this study group to the wider cancer population. The scenarios in this study also reflect current treatment paradigms in the management of patients with non-Hodgkins lymphoma, which are not necessarily applicable to the wider cancer patient population.

The study demonstrates the relative impact of different attributes of genomically-guided testing on uptake. The change in severity and likelihood of toxicity attributes, as well as invasiveness of the test procedure had the largest influence on decision-making. The study highlighted in the patient group that improving test sensitivity influenced patient preferences of genomic testing, but was underpowered to make inferences about other preference attributes within the patient group.

The study by Issa et al employed a discrete choice methodology to determine trade-offs and threshold values for patient preference attributes regarding two specific genomic cancer tests. The study provides insight into the relative importance of attributes affecting patients preferences of the two genomic tests assessed. Overall, the study demonstrates high willingness for colorectal and breast cancer patients to pay for genomic diagnostic tests. Since most cancer treatment decisions involve making 'trade-offs' between evidence of efficacy and potential for adverse events, this study explored patient preferences for the type of information provided by genomic testing. It demonstrated patients' high value genomic tests with accuracy of greater than 90%. The decisions of both groups of patients

within the study about use of genomic testing are influenced more by probability of being cured than desire to avoid potentially serious adverse events. It is noted within the study that privacy of results was not ranked highly amongst patients, but that oncologist/doctor recommendation was weighted strongly by both breast and colorectal cancer patients. This highlights the importance of both physician and patient education around complex decision-making process for these genomic tests.

This study identified patient preference attributes of two genomic tests testing utilised in clinical practice. The study assessed tests used to make decisions on benefits of adjuvant chemotherapy, one in each breast and colorectal cancer. The preference attributes used within this study all had weighting when assessed using the discrete choice experiment. The study looked at genomic testing within these two groups, but not all factors may be fully generalised to the wider cancer community and in particular different stages or anatomical subtypes of cancer. The scenarios in this study focus on patients having adjuvant therapy. The trade-offs and thresholds for patients with advanced disease may be different to this group and cannot be assumed to be similar to those in the study. It is, therefore, difficult to extrapolate the preference attributes used in this study to patients with more advanced cancer, or patients with cancers other than breast and colorectal anatomical subsites. This study enlisted patients willing to complete an online questionnaire, sourced from an independent web-based tool. These patients may, therefore not be entirely representative of the wider cancer patient community and may reflect those more willing to respond to a questionnaire.

The study be Cuffe et al included 244 patients with a cancer diagnosis, assessing preference attributes for pharmacogenomic testing in both the adjuvant and metastatic setting. The study employed hypothetical scenarios determining preferences of primary

outcome, efficacy and toxicity in the adjuvant and metastatic groups respectively, relative to systematically modified levels of preference attributes associated with testing. These attributes were: cost of testing, waiting time for results and prevalence of the genomic variant. Amongst both the adjuvant and metastatic groups, willingness to accept pharmacogenomic testing was high (99 and 92% for adjuvant and metastatic setting respectively). 85% of patients identified undergoing pharmacogenomic testing in order to define ineffectual therapies was important.

This study demonstrated patients were willing to accept and pay for pharmacogenomic testing when deemed clinically useful by their healthcare provider. The strength of patients' desire was evidenced by the considerable out-of-pocket costs they were willing to pay. This was within a universal healthcare setting, where most patients are familiar with a system that is reimbursed at point of use. Several studies have demonstrated willingness-to-pay may be a surrogate measure not only of patients perceptions of the net worth or benefit of a test but also their willingness to adopt novel technologies. The two hypothetical scenarios within the study were limited on only one primary outcome within each group and it is likely that they will systematically over-estimate the willingness for uptake of testing within the wider oncology patient community. This study did, though, elicit important preference attributes of genomic testing in PCM.

One limitation of this study is hypothetical scenarios performed based on patients self-reported cancer stage. In the adjuvant group, this focused on efficacy of therapy, where as in the metastatic group it focused on toxicity from therapy. Ideally, the study would have determined the role of both factors within each group and been able to look at trade-offs within these preference attributes, but the study authors felt this would lead to unacceptable complexity of design. It is, therefore, likely that the hypothetical scenarios utilised in this study will over-estimate the actual uptake rates if translated into clinical practice. The

study determined patient preferences, therefore elected not to address matters of physician resistance, insurance reimbursement and broader pharmacogenomic issues.

The strength of this systematic review is that it is the first to critically appraise and define themed patient preference attributes of genomic testing from the available evidence. It highlighted the sparsity of empirical studies assessing patient preferences of genomic testing within the clinical arena. This involved performing a systematic review of clinical research publications. One limitation of this design is that it utilised databases within medical and scientific literature, but did not assess the current evidence available within purely qualitative research databases. This has the potential to exclude further qualitative studies which may add weight to themed preference attributes within the identified evidence.

The overall aim of this systematic review was to identify preference attributes of genomic testing which could be utilised throughout the mixed methods design of this study. The review demonstrated the paucity of empirical research identifying and defining patient preference attributes applicable to this study population, so these preference themes will not be directly utilised within the study. This study will incorporate mixed methods design, in order to empirically identify themed preference attributes prior to quantitative rating.

3.5. Conclusions

The advent of genomic testing in precision cancer medicine relies on collective preferences of patients, providers and funding bodies (Greenberg, 2015). The diffusion of genomic technologies has been generally slow, with comparatively little empirical research reporting on the expectations and experiences of patients and providers. This systematic

review demonstrated the sparse empirical evidence identifying and rating preference attribute themes of genomic testing for patients.

This systematic review identified preference attribute themes which may be applicable to small subsets of patients and specific genomic tests, such as Oncotype DX, or specific histology-related scenarios such as in lymphoma. These attributes include predictive value of tests, cost of testing, efficacy of available therapy, potential toxicity and effects on quality of life. These preference attributes, though, are not universal to the wider population of patients where PCM may be applied.

The studies highlighted by this systematic review demonstrated patient preference attributes and trade-off thresholds of genomic testing are not homogeneous. Patients making decisions on perceived risks and benefits of curative versus palliative therapy identified different preference attributes and trade-offs, which must be taken into account when considering the potential promise of genomic testing.

This systematic review demonstrated patient preferences attributes and ratings of genomic testing across the breadth of solid tumour oncology are poorly understood. The identified preference attribute themes are not wholly transferrable to the patient group being considered in this thesis and would not provide sufficient evidence to support the research questions. The initial intention of this systematic review was to identify and describe themed preference attributes which could be used within the mixed methods study. Given the lack of empirical evidence within the current literature, the preference attribute themes identified by this systematic review will, therefore, not be incorporated into the mixed methods study of this thesis. The remainder of this thesis will explore the employed methodology and its role in addressing the research aims highlighted in Chapter 1.

Chapter 4. Methodology

4.1. Overview

The systematic review of the literature in Chapter 3 demonstrated the paucity of empirical evidence identifying and rating patient preference attribute themes of genomic testing in PCM. As discussed in the research aims of Chapter 1, this thesis identified and rated patient preference attributes for genomic testing, then assessed how these attributes were incorporated within a novel PCM clinical trial design. Given the lack of empirical evidence identifying and rating themed preference attributes, consensus research methodology was used to answer the thesis research questions, which will be outlined in the remainder of this chapter.

4.2. Research Aims

4.2.1. Hypothesis

The aim of this thesis was to identify and rate patient preference attribute themes of genomic testing. These were then benchmarked against a current UK clinical trial to determine how current clinical trial designs incorporate patient preferences of genomic testing. The study addressed the novel hypothesis that patient preference attributes and ratings are influenced by cancer treatment intent and time since completing therapy. This thesis chapter will discuss the research methodology used to address the thesis research questions.

4.2.2. Ethical approval

The study received ethical approval (REC ref no.16/LO/1665) from the NHS National Research Ethics Service (NRES), included in *Appendix 7*. Full details of the study methodology and copies of the study protocol, patient consent form and participant information sheet were submitted in parallel with the ethics application (*Appendix 8*).

Procedures of the Declaration of Helsinki and Good Clinical Practice (GCP) were followed. Written informed consent was provided by all participants prior to participation in any study-related activities.

4.3. Nominal Group Technique (NGT) design considerations

Although there is considerable consensus on how to conduct certain aspects of NGT, there is variability in its application (McMillan et al., 2014). As most studies involved small numbers, between one and five groups (Gastelurrutia et al., 2009), (Dening, Jones, & Sampson, 2012; Hiligsmann et al., 2013), there is limited information on how to conduct and analyse studies with larger data sets. This thesis aimed to address the research questions by descriptive assessment of preference attribute themes and associated quantitative attribute rating. This entailed large numbers of groups to ensure diversity with respect to participant demographics, such as cancer subtype, age and experience of previous cancer treatments.

Despite the diversity in application, McMillan et al (McMillan et al., 2014) demonstrated general consensus on four core NGT phases:

1 - Silent generation of ideas

2 - Round robin

3 - Clarification

4 - Ranking

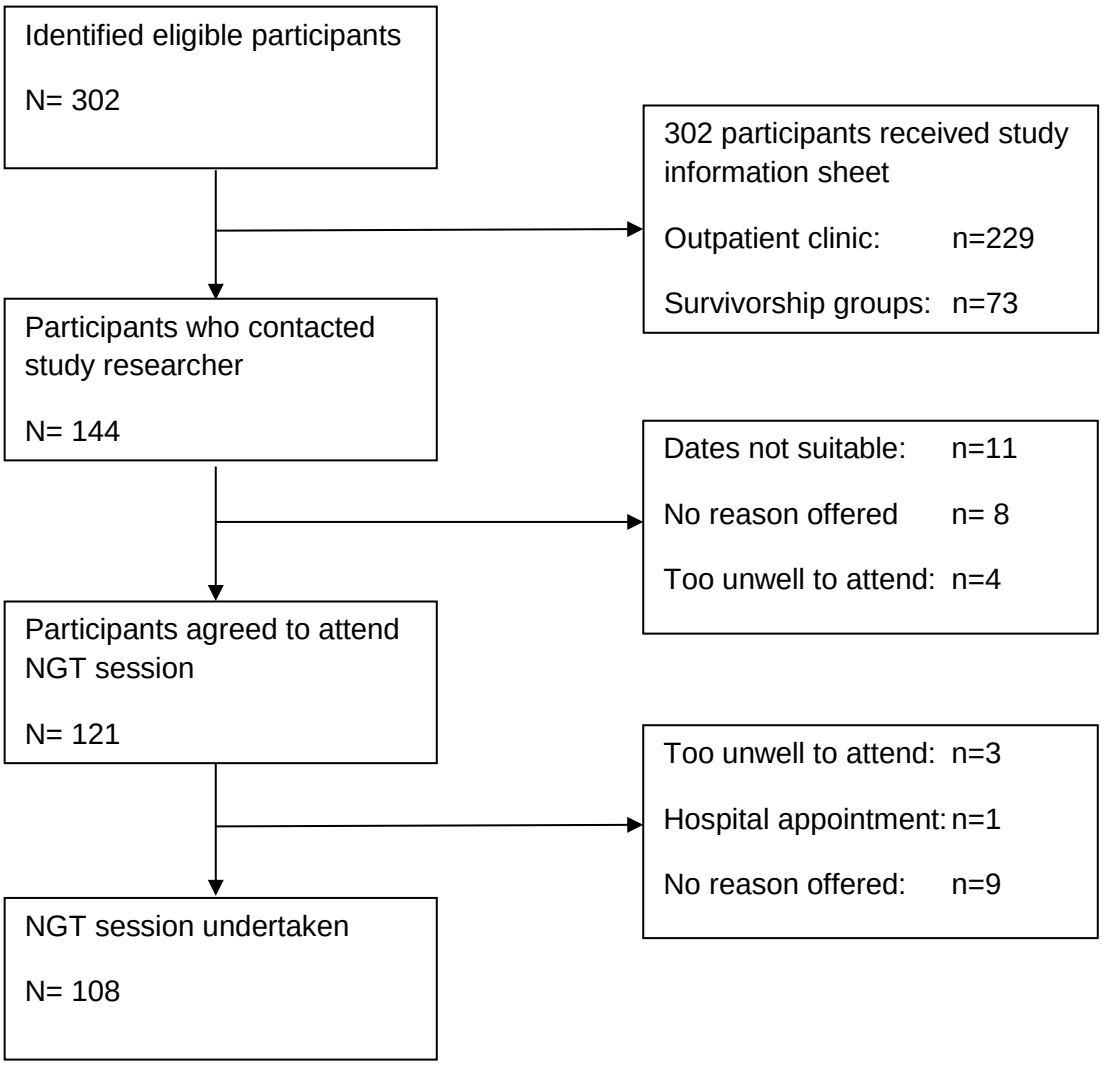
These four stages were used in this study. Contrary to most nominal group questions which are problem-focused (Tully & Cantrill, 2002), the primary question in this investigation asked participants to think about concepts of PCM, with which most patients had very little personal experience. The phrasing of the research questions were built on

an appreciative inquiry approach (Gonzales & Leroy, 2011), used when participants find it challenging to articulate preferences due to lack of technical knowledge. This approach directs participants to adopt a positive outlook, think beyond fixing problems and into theoretical clinical entities, thereby promoting greater engagement and creativity.

4.3.1. Participant selection and group composition

Patients attending cancer survivorship groups and outpatient department at the Beatson West of Scotland Cancer Centre, Scotland were invited to participate in the NGT. Patients were eligible for the study if they were over 18 years of age, had a personal diagnosis of cancer and received treatment including surgery, chemotherapy, endocrine/targeted/biological therapy, radiotherapy or combination of multi-modality therapies. There was no stipulation for patients to have personal experience or awareness of precision cancer medicine prior to involvement in this study. Patients were offered a participant information sheet (Appendix 6) when they attended either the outpatient department or cancer survivorship groups, prior to participation and could contact the study chief investigator if they wished to participate. *Figure 3* demonstrates the participant flow diagram throughout the NGT study. Patients were included only after they had given written consent at least 24 hours after receiving the study participant information sheet.

Figure 3. Flow diagram of participant recruitment to NGT.



4.3.2. Introduction to the Nominal Group process

All groups involved two facilitators who adopted distinct roles; the primary moderator lead and provided directions to the group, as well as writing participant ideas on a whiteboard, whilst the second providing supportive care to participants throughout each group session (Carney, McIntosh, & Worth, 1996). The first stage of each group entailed providing an overview of the study and objectives (Delbecq, Van de Ven, & Gustafson, 1975). Some authors (Claxton, Ritchie, & Zaichowsky, 1980; Sink, 1983) advocate an introductory step prior to starting the nominal group. This study provided a brief synopsis of the study

overview then clarified the procedure as each group progressed throughout the relevant stages.

In general for NGT, one (Dening et al., 2012), (McMillan et al., 2014), (Tully & Cantrill, 2002) or two (Hutchings, Rapport, Wright, Doel, & Jones, 2012; Potter, Gordon, & Hamer, 2004) questions are posed per group, with each question usually considered as a separate nominal group process. This study included two main questions. These were:

1 - What are the features of a genomic test that are important to you?

2 - For each of the features highlighted in question 1, are you able to rank them in order from most to least important to you?

4.3.3. Silent generation of ideas

The next step of the NGT design involved participants being given a pre-defined time period in order to consider the research question. There is wide variety in the literature around the optimal time for this, with some authors advocating 5 (Aspinal, Hughes, Dunckley, & Addington-Hall, 2006), 10 (Carney et al., 1996), 15 (Gallacher, Hares, Spencer, Bradshaw, & Webb, 1993) or 20 (Claxton et al., 1980) minutes for this aspect. During this time, participants were asked to individually record, in silence, as many answers as possible. In this study, participants were allowed a maximum of 15 minutes for this stage. Any discussion was avoided. Delbecq et al (Delbecq et al., 1975) recommend the facilitator models participant behaviour, including writing down and sharing their thoughts. Many other authors (Tuffrey-Wijne, Bernal, Butler, Hollins, & Curfs, 2007) recommend facilitators simply maintain silence throughout this phase of the process. In this study, the facilitators remained silent throughout and assisted participants if they required help with writing.

4.3.4. Round robin

This phase can last from 15 (Dening et al., 2012) to 30 minutes (Potter et al., 2004), providing participants opportunity to contribute one idea at a time until all ideas are exhausted. Delbecq et al (Delbecq et al., 1975) advised facilitators encourage participants to add new ideas after listening to other comments, but only when it is their individual turn. Discussing during idea presentation was not permitted in this study. There is consensus in the literature that ideas should be recorded verbatim on a whiteboard or flipchart for participants to see (McMillan et al., 2014). However, there are differences of opinion with respect to the facilitator's role at this stage. For instance, Delbecq (Delbecq et al., 1975) suggests the facilitator contribute ideas in the same was as participants. In this study, the facilitator avoided contributing ideas, fearing that it may bias participant responses. Preference attribute themes identified by participants and collated on the white board during the round robin stage, are shown in *Appendix 4*.

4.3.5. Clarification

This phase ensured participants understand the meaning of each idea, thus enabling individuals to make informed decisions during priority rating at the next stage. The ambiguity about this phase relates to whether ideas can be grouped or eliminated. Some papers advocate the grouping of duplicate (Carney et al., 1996) or similar ideas (Potter et al., 2004; Sink, 1983) or deletion of items (Claxton et al., 1980). According to Delbecq (Delbecq et al., 1975), the facilitators' role in this stage should be to pace the group, avoid argument and ensure that all ideas are discussed. In this phase, amalgamation of ideas will be dependent on individual group consensus.

In the NGT study, all preference attributes from the round robin stage were collated on a whiteboard and participants were allowed to amalgamate them into attribute themes if

there was consensus on grouping. If consensus was not be reached on theme grouping then the preference attributes remained disparate. The preference attributes themes selected by participants at the end of the clarification stage are shown in *Appendix 4*.

4.3.6. Rating of preference attribute themes

There are different methods to conduct the attribute rating phase of NGT. For example, participants could rate a number of ideas in terms of importance (Carney et al., 1996; Dening et al., 2012; Sink, 1983; Tully & Cantrill, 2002) or could use two-step process comprising secondary ranking (Allen, Dyas, & Jones, 2004; Gallacher et al., 1993) (Jones & Hunter, 1995). Delbecq (Delbecq et al., 1975) suggested public voting could instigate social pressure to conform to the norm, so proposed a more private voting process. Due to time constraints and high cognitive burden of questioning in this study, it was decided that secondary ranking process by participants was not feasible.

Participants in this phase were asked to select and rate preference attributes themes, which can range from 5 (Carney et al., 1996; Dening et al., 2012), 8 (Claxton et al., 1980) and 10 or more options (Gallacher et al., 1993; Hiligsmann et al., 2013). This phase lasted up to 10 minutes (Dening et al., 2012). Participants were allowed to rank 9 items. This was done by first asking participants to individually select their top 9 themed preference attributes from the entire set generated at the end of clarification phase. Participants were asked to rank themed preference attributes, with 9 points allocated to their top priority, 8 points for their second priority, continuing down to zero points for their lowest priority. If participants felt there are less than 9 themed preference attributes they valued then they started at 9 points for their highest themed attribute and stopped when they reached their lowest rated attribute. To avoid errors, participants were provided with a rating sheet for

recording votes. The entire rating process was completed individually, without group discussion.

4.3.7. Data management

As this study involved a large number of participants, data management involved a streamlined analysis process across multiples groups. Microsoft Office Excel version 16.0 was used to record scores allocated by each participant and ratings of the themed preference attributes for each group. The sum scores for each attribute were then calculated. This allowed for immediate reporting back of results to participants.

4.3.8. Data analysis

Initial review of the raw data from each focus group identified any anomalies or nuances within the data. The raw data was used to construct attribute rating scores within each group and participants were offered feedback on individual group results at this time if they wished.

Summing the votes allocated to each attribute is the most common way to analyse nominal group data (McMillan et al., 2014),(Dening et al., 2012; Hiligsmann et al., 2013),(Tully & Cantrill, 2002). Given the number of groups and group sizes, analysis also considered the mean attribute rating (Gastelurrutia et al., 2009) of each preference attribute across all groups. The mean attribute rating reflects the proportion (%) of all scores in the top nine ranking, calculated using the following equation:

(Score achieved for the attribute across all groups) / (maximum possible score) x 100

For this method of analysis, the overall rating score for each themed preference attribute was calculated, the top order attribute received 9 points, the second receives 8 points, etc. The voting frequency of the top 9 attributes was then calculated to determine how many times a particular attribute was voted for, and subsequently, how popular it was amongst participants. This style of analysis accommodated the fact one participant could have voted for two different attributes which were coded into the same higher order theme. The mean and standard deviation of mean attribute rating (Kristofco, Shewchuk, Casebeer, Bellande, & Bennett, 2005) was calculated for each group.

4.4. Conclusions

This chapter outlined employed methodology and design considerations for this thesis study, which identified and rated patient preference attributes of genomic testing. One of the major considerations within the methodology design was the high cognitive burden genomic testing placed on patients and their lack of prior experience of the modality. The breadth of fields encompassed within genomic testing, including screening, diagnostics and therapeutics, means the study required methodology which, based on an appreciative enquiry approach, supports participants articulating preferences in areas of high complexity or lack of experience. NGT provides a framework to support participants in consensus decision making addresses the high complexity and lack of participant experience. The NGT also allows face-to-face interaction with group participants and moderator. Given these considerations, as outlined throughout this Chapter, the research study employed a mixed methods research design using consensus research technique, namely NGT.

Chapter 5 presents results of the NGT sessions which employed methodology described throughout Chapter 4.

Chapter 5. Results

5.1. Pilot study

5.1.1. Participant demographics for pilot group

Six participants attended the single pilot nominal group session which assessed and described feasibility, alongside predicted strengths/weaknesses of the methodology, materials and research hypothesis. Demographic details for each patient were collected at introductory meeting with group moderators. The demographic details of the six pilot group participants are shown in *Table 5*.

Table 5. Demographics of pilot study participants.

	Total
No of participants (n)	6
Gender	
Male	1
Female	5
Mean Age (years)	71.4
Age range (years)	52-80
Relationship status	
Never married	0
Married	4
Living with partner	0
Separated/divorced	1
Widowed	1
Highest education	
Secondary/high school	3
College/university	2
Postgraduate degree	1
Employment status	
Employed	2
Unemployed	0
Retired	4
Cancer diagnosis (number of participants)	
Breast cancer	3
Colorectal cancer	1
Prostate cancer	1
CNS tumour	1

5.1.2. Preference attribute themes and ratings for pilot group

The results of the pilot study highlighted six unique preference attribute themes of genomic testing in PCM. The attributes and mean importance rating scores are shown in *Table 6*. Participants in the pilot group rated three attribute themes as highest order rating (score of nine).

Table 6. Results of preference attribute rating for pilot nominal group.

Attribute	Importance Ratings (n=6)										
	1	2	3	4	5	6	7	8	9	Mean	S.D.
Sensitivity/true positive	0	0	0	1	1	1	1	2	0	6.33	1.63
Specificity/true negative	0	0	0	2	1	1	0	2	0	5.83	1.83
Test turnaround time	0	0	0	0	2	1	1	0	2	6.83	1.82
Invasiveness of testing	0	0	0	2	0	2	2	0	0	5.67	1.36
Physician approval	0	0	0	0	1	1	0	2	2	7.50	1.64
Regulatory/NHS approval	0	0	0	1	1	0	2	0	2	6.83	2.04

5.1.3. Lessons learned from pilot study

The primary objective of the pilot study was to descriptively assess the pilot nominal group guide v1.0 (*Appendix 5*) along with materials and methods employed in the NGT. This pilot study demonstrated little direct participant experience of PCM and therefore importance that, in the initial synopsis of each session, this was fully explored prior to discussion. This prepared participants for discussion around a topic to which they had little or no personal experience. The location and facilities employed in this nominal group

session have been employed in similar group sessions, to which some of the current participants have previously attended. The setup of the pilot study reflected that which was familiar to some of the participants and researchers, requiring no substantial adaptation for the main study. The adapted nominal group guide (v2.0), amended after feedback from the pilot study, and employed in the main study, is included in *Appendix 6*.

The pilot group assessed methodology identifying and rating preference attributes of genomic testing in PCM. Similar NGT methodology has been employed in previous group sessions and there was minimal adaptation required. One factor highlighted during the pilot group was participant's prior cancer therapeutic/diagnostic experience. This became apparent throughout the pilot group session, so a decision was made to collect participant data on prior cancer therapies and personal experience of PCM for the main thesis study. This had not been prospectively collected for the pilot group participant sample and was included in the adapted NGT group guide v2.0.

5.1.4. Discussion

This pilot study allowed practical assessment of the research methodology and provisional estimation of feasibility. The outcomes of the pilot group were reflected in the iterative changes in the nominal group guides (*Appendix 5* and *6*). Further demographic data on prior cancer treatments were collected in nominal group sessions of the main study. The research questions, as anticipated throughout the pilot session, reflected high cognitive burden for patients.

5.2. Main study Participant demographics

All participants within the main study met with eligibility criteria. The summary demographics across all participants in the main study are shown in *Table 7*. Total of 102 patients enrolled in the main nominal group study. Fifty-five participants were female (54%) and forty-seven (46%) were male. The mean age across study participants was 64.2 years with range 27-84, and inter-quartile range (IQR) 20.87 years.

Participants in the study all had personal experience of cancer treatment and included fourteen anatomical cancer subtypes (breast, prostate, colo-rectal, sarcoma, gynaecological, head and neck, neuro-oncology, lung, renal, oesophageal, gastric, neuroendocrine, bladder and pancreatic cancers). The top five commonest tumour subtypes by participant recruitment were breast cancer (19.6%), prostate cancer and colo-rectal cancer (both 17.7%), gynaecological cancers (12.8%) and neuro-oncology (7.9%).

Participants in the study all had personal experience of cancer therapies including surgery (53.9%), chemotherapy (63.7%), radiotherapy (55.9%), endocrine therapy (29.4%) and immunotherapy (15.7%). Eight participants (7.8%) had personal experience of precision cancer medicine. Characteristics of cancer treatment intent were participant-reported.

Table 7. Summary participant demographics across all main study nominal groups.

	Total (%)
No of participants (n)	102
Gender	
Male	47 (46.1)
Female	55 (53.9)
Mean Age (years)	64.2
Age range (years)	27-84
Age standard deviation	12.13
Age IQR (years)	20.87
Relationship status	
Never married	7 (6.9)
Married	47 (46.1)
Living with partner	8 (7.8)
Separated/divorced	20 (19.6)
Widowed	20 (19.6)
Highest education	
Secondary/high school	58 (56.9)
College/university	33 (32.4)
Postgraduate degree	11 (10.7)
Employment status	
Employed	29 (28.5)
Unemployed	14 (13.7)
Retired	59 (57.8)

	Total (%)
Cancer diagnosis (number of participants)	
Breast cancer	20 (19.6)
Colorectal cancer	18 (17.7)
Prostate cancer	18 (17.7)
Sarcoma	1 (0.9)
Lung cancer	6 (5.9)
Head&neck cancer	5 (4.9)
CNS tumour	8 (7.9)
Gynaecological cancer	13 (12.8)
Renal cancer	4 (3.9)
Pancreatic cancer	1 (0.9)
Gastric cancer	2 (2.0)
Oesophageal cancer	2 (2.0)
Neuroendocrine carcinoma	3 (2.9)
Bladder cancer	1 (0.9)
Previous forms of treatment	
Surgery	55 (53.9)
Chemotherapy	65 (63.7)
Radiotherapy	57 (55.9)
Endocrine therapy	30 (29.4)
Immunotherapy	16 (15.7)
PCM testing	8 (7.8)

5.3. Nominal group A (radical treatment completed within 2 years) Results

5.3.1. Participant demographics

All participants recruited to group A met study eligibility criteria and had received radical cancer therapy completing within 2 years of entering the nominal group study. Five nominal groups were conducted within group A, for which demographic details are shown in *Table 8*.

Table 8. Group A participant demographics

	Nominal Group					
	A1	A2	A3	A4	A5	Total (%)
No of participants (n)	7	6	8	6	5	32
Gender						
Male	3	3	5	2	2	15 (47)
Female	4	3	3	4	3	17 (53)
Mean Age (years)	65.0	60.6	65.1	62.2	67.4	64.1
Age range (years)	44-80	38-78	49-76	47-78	52-82	38-82
Age standard deviation						11.85
Age IQR						21.75
Relationship status						
Never married	1	0	2	0	0	3 (9.4)
Married	4	3	3	4	3	17 (53.1)
Living with partner	0	1	0	1	1	3 (9.4)
Separated/divorced	1	0	2	1	0	4 (12.5)
Widowed	1	2	1	0	1	5 (15.6)

	Nominal Group					
	A1	A2	A3	A4	A5	Total (%)
Highest education						
Secondary/high school	4	3	5	3	2	17 (53.1)
College/university	2	3	2	3	2	12 (37.5)
Postgraduate degree	1	0	1	0	1	3 (9.4)
Employment status						
Employed	2	3	3	2	1	11 (34.4)
Unemployed	1	0	0	1	0	2 (6.3)
Retired	4	3	5	3	4	19 (59.3)
Cancer diagnosis (number of participants)						
Breast cancer	2	1	1	0	1	5 (15.6)
Colorectal cancer	1	2	2	0	1	6 (18.7)
Prostate cancer	1	0	1	2	1	5 (15.6)
Sarcoma	0	1	0	0	0	1 (3.1)
Lung cancer	0	1	1	1	1	4 (12.5)
Head&neck cancer	0	0	1	1	0	2 (6.3)
CNS tumour	1	1	0	0	0	2 (6.3)
Gynaecological cancer	1	0	1	1	1	4 (12.5)
Renal cancer	1	0	0	1	0	2 (6.3)
Pancreatic cancer	0	0	1	0	0	1 (3.1)
Mean duration since treatment (months)	17.4	19.8	16.3	21.1	16.5	18.2
Range of duration since treatment (months)	3-22	5-23	4-24	7-24	6-19	3-24

	Nominal group					
	A1	A2	A3	A4	A5	Total (%)
Previous forms of treatment						
Surgery	4	4	6	3	3	20 (62.5)
Chemotherapy	5	3	4	2	2	16 (50.0)
Radiotherapy	5	3	5	2	3	18 (56.3)
Endocrine therapy	3	1	1	1	2	8 (25)
Immunotherapy	0	0	0	0	0	0
PCM testing	0	0	0	0	0	0

Participants within group A (n=32) had mean age of 64.1 years (s.d. 11.85) with range 38-82 years. Fifty-three percent were female and forty-seven percent were male. Participants within group A included those with previous diagnosis across ten cancer subtypes. These included breast (15.6%), prostate (15.6%), colo-rectal (18.7%), lung (12.5%), gynaecological (12.5%), sarcoma (3.1%), neuro-oncology (6.3%), renal (6.3%), head and neck (6.3%) as well as pancreatic cancer (3.1%). Participants had personal experience of cancer treatments including surgery (62.5%), chemotherapy (50.0%), radiotherapy (56.3%) and endocrine therapy (25%). There were no participants included in group A with personal experience of cancer therapy utilising either immunotherapy or precision cancer medicine. The mean duration since completing therapy across group A was 18.2 months (range 3-24).

5.3.2. Preference attribute themes

Nine themed preference attributes emerged from the data generated by the five group A nominal groups. The attribute themes for group A are shown in *Table 9* and preference attribute theme summary tables are shown in *Appendix 4*.

Table 9. Preference attribute themes for each group A subgroup.

	Nominal Group				
Attribute	A1	A2	A3	A4	A5
Sensitivity/true positive	X	X	X	X	X
Specificity/true negative	X	X	X	X	X
Prevalence of variant	X	X	X	X	
Invasiveness of testing	X	X	X	X	X
Physician approval	X	X	X	X	X
Implications for family	X	X			X
Regulatory/NHS approval	X	X	X	X	X
Test turnaround time	X	X	X	X	X
Distance to travel	X				X

The 9 themes generated (percentage of groups selecting theme) by group A were sensitivity/true positive (100%), specificity/true negative (100%), prevalence of variant (80%), invasiveness of testing (100%), physician approval of test (100%), implications for family (60%), regulatory/NHS approval for testing (100%), test turnaround time (100%) and distance to travel for testing (40%).

5.3.3. Preference attribute theme ratings

The group A preference attribute theme ratings are shown in *Table 10*, including mean importance rating and standard deviation.

Table 10. Group A preference attribute theme ratings.

Attribute	Importance Ratings (n=32)										
	1	2	3	4	*5*	6	7	8	9	Mean	S.D.
Physician approval	2	3	1	2	5	1	9	5	7	6.75	2.49
Sensitivity/true positive	0	2	0	5	4	5	4	5	7	6.40	2.11
Specificity/true negative	0	0	2	7	0	8	3	7	5	6.38	1.95
Regulatory/NHS approval	1	2	2	3	9	2	4	5	5	6.03	2.27
Prevalence of variant	0	0	3	4	4	4	4	5	3	5.12	1.94
Invasiveness of testing	2	3	7	5	3	2	5	3	3	5.06	2.42
Test turnaround time	4	5	4	3	4	8	2	1	2	4.56	2.33
Implications for family	2	3	5	3	2	2	0	1	0	2.03	1.85
Distance to travel	5	3	1	0	1	0	1	0	0	0.81	1.96

The preference attribute theme giving rise to the highest attribute rating score in group A was physician approval, with mean importance rating of 6.75 (s.d. 2.49). It was selected as

highest order attribute by 7 participants (21.9% of total participants). The preference attribute theme with second highest rating was test sensitivity/true positive, with mean importance rating of 6.40 (s.d. 2.11). It was selected as the highest order attribute theme by 7 participants (21.9% of total participants). The third highest preference attribute rating was test specificity/true negative, with mean importance rating of 6.38 (s.d. 1.95). Test specificity/true negative was selected as the highest order attribute theme by 5 participants (15.6% of total). The fourth highest attribute rating score was regulatory/NHS approval, with mean importance rating of 6.03 (s.d. 2.27). It was selected as the highest order attribute theme by 5 (15.6% of total) participants. The fifth highest attribute rating was for prevalence of variant, with mean importance rating of 5.12 (s.d. 1.94). It was selected as the highest order attribute theme by 3 participants (9.4% of total).

The sixth highest attribute theme for group A was invasiveness of testing, with mean importance rating of 5.06 (s.d. 2.42). It was selected as highest order by 3 participants (9.4% of total participants). The next highest rating preference attribute was turnaround time, with mean importance rating of 4.56 (s.d. 2.33). This attribute theme was rated highest order by 2 participants (6.3% of total). The eighth highest attribute was implications for family, with mean importance rating of 2.03 (s.d. 1.85). It was rated highest order attribute by zero participants in group A. The final preference attribute theme for group A was distance to travel for testing, with mean importance rating of 0.81 (s.d. 1.96). This was not selected as a highest order attribute theme by any participants in this group.

5.4. Nominal group B (radical treatment completed more than 2 years prior) Results

5.4.1. Participant demographics

All participants recruited to group B met study eligibility criteria and received radical intent cancer therapy completing more than 2 years prior to entering the nominal group study. There were five nominal groups conducted within group B, for which demographic details are shown in *Table 11*.

Table 11. Group B participant demographics

	Nominal Group					
	B1	B2	B3	B4	B5	Total (%)
No of participants (n)	7	6	6	7	7	33
Gender						
Male	3	4	3	3	2	15 (45.5)
Female	4	2	3	4	5	18 (54.5)
Mean Age (years)	66.4	66.8	61.6	68.4	63.4	65.5
Age range (years)	34-84	50-76	41-76	51-82	27-83	27-84
Age standard deviation						13.39
Age IQR						18.5
Relationship status						
Never married	1	0	0	1	0	2 (6.1)
Married	4	2	3	2	3	14 (42.4)
Living with partner	1	1	0	1	0	3 (9.1)
Separated/divorced	1	1	2	1	2	7 (21.2)
Widowed	0	2	1	2	2	7 (21.2)
Highest education						
Secondary/high school	3	4	4	3	4	18 (54.5)
College/university	2	2	2	2	2	10 (30.3)
Postgraduate degree	2	0	0	2	1	5 (15.2)
Employment status						
Employed	1	1	2	2	2	8 (24.2)
Unemployed	1	0	1	1	1	4 (12.2)
Retired	5	5	3	4	4	21 (63.6)

	Nominal Group					
	B1	B2	B3	B4	B5	Total (%)
Cancer diagnosis (n)						
Breast cancer	1	0	2	1	1	5 (15.1)
Colorectal cancer	2	2	0	2	1	7 (21.2)
Prostate cancer	1	2	1	1	1	6 (18.2)
Oesophageal cancer	0	0	1	0	1	2 (6.1)
Head&neck cancer	1	1	0	1	0	3 (9.1)
CNS tumour	1	0	1	1	1	4 (12.1)
Gynaecological cancer	1	0	1	0	2	4 (12.1)
Renal cancer	0	1	0	1	0	2 (6.1)
Mean time since treatment (months)	44.2	51.1	39.6	60.1	59.4	51.2
Range of time since treatment (months)	28-88	30-84	30-68	41-94	29-71	28-84
Previous forms of treatment (number)						
Surgery	4	3	4	5	5	21 (63.6)
Chemotherapy	4	1	4	3	4	16 (48.5)
Radiotherapy	4	2	5	3	4	18 (54.5)
Endocrine therapy	2	1	2	1	1	7 (21.2)
Immunotherapy	0	0	1	0	0	1 (3.0)
PCM testing	0	0	0	0	0	0

Participants in group B (n=33) had mean age of 65.5 years (s.d. 13.39) with range 27-84 years. Fifty-four percent of participants were female and forty-seven percent were male. Participants had diagnosis across eight cancer subtypes. These included breast (15.1%), colorectal (21.2%), prostate (18.2%), oesophageal (6.1%), head and neck (9.1%), neuro-oncology (12.1%), gynaecological (12.1%) and renal (6.1%) cancer. Participants had personal experience of cancer therapies including surgery (63.6% of group B participants), chemotherapy (48.5%), radiotherapy (54.5%), endocrine therapy (21.2%) and immunotherapy (3.0%). No participants included in group B had personal experience of cancer therapy utilising precision cancer medicine. The mean duration since completing therapy was 52.1 months (range 28-84).

5.4.2. Preference attribute themes

Ten preference attribute themes emerged from the data generated by the five group B nominal groups. The attribute themes for group B are shown in *Table 12* and preference attribute theme summary tables are shown in *Appendix 4*.

Table 12. Preference attribute themes for group B subgroups.

Attribute	B1	B2	B3	B4	B5
Sensitivity/true positive	X	X	X	X	X
Specificity/true negative	X		X	X	X
Prevalence of variant	X	X		X	
Invasiveness of testing		X	X	X	X
Physician approval	X		X		X
Implications for family	X				
Regulatory/NHS approval	X	X	X	X	X
Test turnaround time	X	X	X	X	X
Distance to travel		X		X	X
Family approval				X	

Ten preference attribute themes were generated (percentage of groups selecting theme) by Group B: sensitivity/true positive (100%), specificity/true negative (80%), prevalence of variant (60%), invasiveness of testing (80%), physician approval of testing (60%), implications for family (20%), regulatory/NHS approval for testing (100%), test turnaround time (100%), distance to travel (60%) and family approval of testing (20%).

5.4.3. Preference attribute theme ratings

The group B preference attribute theme ratings are shown in *Table 13*, including mean importance rating and standard deviation.

Table 13. Group B preference attribute theme ratings.

Attribute	Importance Ratings (n=33)										
	1	2	3	4	5	6	7	8	9	Mean	S.D.
Regulatory/NHS approval	0	0	2	2	5	4	5	6	9	6.88	1.89
Sensitivity/true positive	0	0	1	5	6	6	4	5	6	6.39	1.84
Test turnaround time	0	1	1	3	7	5	7	5	4	6.27	1.81
Specificity/true negative	0	0	1	4	5	5	3	5	4	5.18	1.82
Invasiveness of testing	0	0	0	7	2	4	6	4	3	4.94	1.76
Physician approval	0	0	1	3	0	3	5	4	4	4.12	1.85
Prevalence of variant	0	0	1	4	4	4	2	3	2	3.61	1.79
Distance to travel	0	2	8	5	1	0	1	0	1	2.09	1.72
Implications for family	0	0	2	0	2	2	0	1	0	1.09	0.77
Family approval	0	5	2	0	0	0	0	0	0	0.48	0.47

The attribute theme for group B (n=33) giving rise to the highest rating score is regulatory/NHS approval, with mean importance rating of 6.88 (s.d. 1.89). It was selected as highest order attribute by 9 participants (27.3% of total). The preference attribute with second highest mean importance rating was test sensitivity/true positive, with mean importance rating of 6.39 (s.d. 1.84). It was selected as the highest order attribute theme by 6 participants (18.2% of total). The third highest attribute rating score was test turnaround time, with mean importance rating of 6.27 (s.d. 1.81). It was selected as the highest order attribute theme by 4 participants (12.1% of total). The fourth highest preference attribute theme rating score was test specificity/true negative, with mean

importance rating of 5.18 (s.d. 1.82). Test specificity/true negative was selected as the highest order attribute theme by 4 (12.1% of total) participants. The fifth highest preference attribute theme rating score was invasiveness of testing, with mean importance rating of 4.94 (s.d. 1.76). It was selected as highest order attribute by 3 participants (9.1% of total).

The sixth highest preference attribute theme for group B was physician approval, with mean importance rating of 4.12 (s.d. 1.85). This was selected as highest order by 4 participants (12.1% of total participants). The next highest attribute theme was prevalence of variant, with mean importance rating of 3.61 (s.d. 1.79). This attribute theme was rated highest order by 2 participants (6.1% of total). The eighth highest preference attribute was distance to travel for testing, with mean importance rating of 2.09 (s.d. 1.72). It was rated as highest order by 1 participant (3.0% of total) in group B. The ninth highest preference attribute was implications of testing for family, with mean importance rating of 1.09 (s.d. 0.77). This was not selected as a highest order attribute theme by any of the participants in Group B. The final attribute theme from group B was family approval for testing, with mean importance rating of 0.48 (s.d. 0.47). This was not rated highest order by any participants in group B.

5.5. Nominal group C (palliative treatment intent) Results

5.5.1. Participant demographics

All participants recruited to group C met study eligibility criteria and received, or were still receiving, palliative intent therapy prior to entering the nominal group study. Six nominal groups were conducted within group C, for which demographic details are shown in *Table 14*.

Table 14. Group C participant demographics.

	Nominal Group						
	C1	C2	C3	C4	C5	C6	Total (%)
No of participants (n)	5	6	6	7	6	7	37
Gender							
Male	3	2	3	3	3	3	17 (45.9)
Female	2	4	3	4	3	4	20 (54.1)
Mean Age (years)	54.1	62.0	68.7	65.3	58.7	67.3	63.1
Age range (years)	31-75	41-79	48-81	48-79	42-76	46-79	31-81
Age standard deviation							12.47
Age IQR							23.1
Relationship status							
Never married	0	1	0	0	1	0	2 (5.4)
Married	3	2	3	4	2	3	17 (45.9)
Living with partner	0	1	0	0	1	0	2 (5.4)
Separated/divorced	1	1	2	1	2	2	9 (24.4)
Widowed	2	1	1	2	0	2	7 (18.9)
Highest education							
Secondary/high	3	4	3	3	5	5	23 (62.2)
school	2	1	2	3	1	2	11 (29.7)
College/university	0	1	1	1	0	0	3 (8.1)
Postgraduate degree							
Employment status							
Employed	2	1	2	1	2	2	10 (27.0)
Unemployed	1	2	0	2	2	1	8 (21.6)
Retired	2	3	4	4	2	4	19 (51.4)

	Nominal Group						
	C1	C2	C3	C4	C5	C6	Total (%)
Cancer diagnosis (n)							
Breast cancer	2	1	1	2	2	2	10 (27.0)
Colorectal cancer	1	1	0	2	0	1	5 (13.5)
Prostate cancer	0	2	1	1	1	2	7 (18.9)
Gastric cancer	0	1	0	0	1	0	2 (5.4)
Lung cancer	0	1	1	0	0	0	2 (5.4)
CNS tumour	0	0	1	0	1	0	2 (5.4)
Gynaecological cancer	1	0	1	1	1	1	5 (13.5)
Neuro-endocrine cancer	1	0	0	1	0	1	3 (8.1)
Bladder cancer	0	0	1	0	0	0	1 (2.8)
Previous forms of treatment (number)							
Surgery	3	2	1	3	3	2	14 (37.8)
Chemotherapy	5	6	5	7	5	5	33 (89.2)
Radiotherapy	4	4	3	4	3	3	21 (56.8)
Endocrine therapy	2	3	1	3	3	3	15 (40.5)
Immunotherapy	3	2	2	3	3	2	15 (40.5)
PCM testing	2	1	0	2	1	2	8 (21.6)

Participants within group C (n=37) had mean age of 63.1 years (s.d. 12.47) with range 31-81 years. Fifty-four percent of participants were female and forty-six percent were male. Participants included previous diagnoses across nine cancer subtypes: breast (27.0%), prostate (18.9%), colo-rectal (13.5%), gastric (5.4%), lung (5.4%), neuro-oncology (5.4%), gynaecological (13.5%), neuroendocrine (8.1%) and bladder cancer (2.8%).

Participants experienced cancer therapies including surgery (37.8% of Group C participants), chemotherapy (89.2%), radiotherapy (56.8%), endocrine therapy (40.5%), and immunotherapy (40.5%). Eight participants (21.6% of total) in group C had personal experience of cancer therapy utilising precision cancer medicine.

5.5.2. Preference attribute themes

Ten preference attribute themes emerged from data generated by the five group C nominal groups. The attribute themes for group C are shown in *Table 15* and preference attribute theme summary is shown in *Appendix 4*.

Table 15. Preference attribute themes for each group C subgroup.

Attribute	C1	C2	C3	C4	C5	C6
Sensitivity/true positive	X	X	X		X	
Specificity/true negative		X			X	
Prevalence of variant	X				X	X
Invasiveness of testing	X	X	X	X	X	X
Physician approval	X	X	X	X	X	X
Implications for family			X	X		X
Regulatory/NHS approval	X	X	X		X	X
Test turnaround time	X	X	X	X	X	X
Distance to travel	X	X	X	X		X
Family approval	X		X			

Ten preference attribute themes were generated by group C (percentage of groups selecting theme): sensitivity/true positive (66%), specificity/true negative (33%), prevalence of variant (50%), invasiveness of testing (100%), physician approval for testing (100%), implications for family (50%), regulatory/NHS approval for testing (83%), test turnaround time (100%), distance to travel for testing (83%) and family approval of testing (33%).

5.5.3. Preference attribute theme ratings

Group C preference attribute theme ratings are shown in *Table 16*, including mean importance rating and standard deviation.

Table 16. Group C preference attribute theme ratings.

Attribute	Importance Ratings (n=37)										
	1	2	3	4	5	6	7	8	9	Mean	S.D.
Invasiveness of testing	0	1	1	0	5	6	9	9	7	7.14	1.68
Test turnaround time	0	0	0	4	2	10	5	8	8	6.95	1.61
Physician approval	0	0	0	0	3	5	8	7	8	6.19	1.31
Regulatory/NHS approval	0	1	0	2	5	7	6	6	4	5.49	1.69
Distance to travel	0	1	0	4	7	5	6	4	5	5.46	1.82
Prevalence of variant	0	1	3	6	2	2	0	1	3	2.49	2.11
Sensitivity/true positive	0	5	9	5	1	1	1	0	0	2.03	1.29
Implications for family	0	0	9	1	7	1	0	0	0	1.95	1.08
Specificity/true negative	0	0	4	5	2	0	1	0	0	1.32	1.16
Family approval	0	1	4	3	2	0	0	0	0	0.97	0.91

The preference attribute giving rise to the highest rating score in group C (n=37) was invasiveness of testing, with mean importance rating of 7.14 (s.d. 1.68). It was selected as highest order attribute by 7 participants (18.9% of total). The preference attribute with second highest rating was test turnaround time, with mean importance rating of 6.95 (s.d. 1.61). This attribute was selected as the highest order by 8 participants (21.6% of total).

The third highest preference attribute rating score was physician approval, with mean importance rating of 6.19 (s.d. 1.31). It was selected as highest order attribute theme by 8 participants (21.6% of total). The fourth highest preference attribute rating for group C was Regulatory/NHS approval, with mean importance rating of 5.49 (s.d. 1.69). It was selected highest order attribute theme by 4 (10.8% of total) participants. The fifth highest attribute theme rating score was distance to travel, with mean importance rating of 5.46 (s.d. 1.82). This attribute theme was selected as the highest order by 5 participants (13.5% of total).

The sixth highest preference attribute for group C was prevalence of variant, with mean importance rating of 2.49 (s.d. 2.11). It was selected as highest order by 3 participants (8.1% of total participants). The next highest preference attribute was sensitivity/true positive, with mean importance rating of 2.03 (s.d. 1.29). There were zero participants who rated test sensitivity/true positive as the highest order attribute. The eighth highest attribute theme was implications of testing for family, with mean importance rating of 1.95 (s.d. 1.08). It was not rated as the highest order priority by any of the participants in group C. The ninth highest preference attribute was specificity/true negative, with mean importance rating of 1.32 (s.d. 1.16). Test specificity/true negative was not selected as the highest order preference attribute by any participants in group C. The final preference attribute was family approval for testing, with mean importance rating of 0.97 (s.d. 0.91). This attribute theme was not rated as highest order by any participants in this group.

5.6. Summary of Nominal Group Results

The summary preference attribute theme ratings across all nominal groups are shown in *Table 17*, including mean importance rating and standard deviation for each attribute theme.

Table 17. Summary preference attribute theme ratings across all nominal groups.

Attribute	Importance Ratings (n=102)										
	1	2	3	4	5	6	7	8	9	Mean	S.D.
Regulatory/NHS approval	1	3	4	7	19	13	15	17	18	6.11	1.99
Test turnaround time	4	6	5	10	13	23	14	14	14	5.98	2.19
Invasiveness of testing	2	4	8	12	10	12	20	16	13	5.77	2.15
Physician approval	2	3	2	5	8	9	22	16	19	5.71	2.03
Sensitivity/true positive	0	7	10	15	11	12	9	10	13	4.81	2.23
Specificity/true negative	0	0	7	16	7	13	7	12	9	4.16	2.92
Prevalence of variant	0	1	7	14	10	10	6	9	8	3.68	1.99
Distance to travel	5	6	9	9	9	5	8	4	6	2.91	2.37
Implications for family	2	3	16	4	11	5	0	2	0	1.69	1.61
Family approval	0	6	6	3	2	0	0	0	0	0.51	0.45

The preference attribute across all nominal groups (n=102) giving rise to the highest rating score is regulatory/NHS approval of testing, with mean importance rating of 6.11 (s.d. 1.99). It was selected as highest order by 18 participants (17.6% of total). The attribute theme with the second highest mean importance rating was test turnaround time, with mean importance rating of 5.98 (s.d. 2.19). This was selected as highest order attribute by 14 participants (13.7% of total). The third highest preference attribute rating was invasiveness of testing, with mean importance rating of 5.77 (s.d. 2.15). It was selected as the highest order attribute theme by 13 participants (12.7% of total). The fourth highest attribute rating score across all groups was physician approval of testing, with mean importance rating of 5.71 (s.d. 2.03). It was selected as the highest order attribute theme by 19 (18.6% of total) participants. The fifth highest attribute rating score was test

sensitivity/true positive, with mean importance rating of 4.81 (s.d. 2.23). This was selected as highest order attribute by 13 participants (12.7% of total).

The sixth highest attribute theme rating across all groups was test specificity/true negative, with mean importance rating of 4.16 (s.d. 2.92). It was selected as highest order rating by 9 participants (8.8% of total participants). The next highest attribute was prevalence of variant, with mean importance rating of 3.68 (s.d. 1.99). This preference attribute theme was rated highest order by 8 participants (7.8% of total). The eighth highest attribute theme was distance to travel for testing, with mean importance rating of 2.91 (s.d. 2.37). This was rated highest order by 6 participants (5.9% of total). The ninth highest preference attribute theme was implications of testing for family, with mean importance rating of 1.69 (s.d. 1.61). It was not selected as a highest order attribute theme by any of the participants across the groups. The final attribute theme across all groups was family approval for testing, with mean importance rating of 0.51 (s.d. 0.45). It was not rated highest order by any participants across the nominal groups.

5.7. Discussion of results

5.7.1. Introduction

The aim of this thesis was to add to current knowledge by exploring how, using mixed methods research techniques, patient preference attributes of genomic testing in precision cancer medicine can be identified and rated. Building on the work of previous studies, identified by the systematic review in Chapter 3, the aim of this thesis chapter was to:

1 – Identify patient preference attribute themes of genomic testing in PCM.

2 – Identify rating scores for patient preference attribute themes of genomic testing.

3 – Examine the effect of clinical cancer treatment intent and time since completing treatment on identified patient preference attribute themes and ratings.

5.7.2. Defining preference attribute themes of genomic testing in PCM

This thesis study identified patient preference attributes themes of genomic testing including regulatory/NHS approval, test turnaround time, invasiveness of testing, physician approval, sensitivity/true positive, specificity/true negative, prevalence of genomic variant, distance to travel for testing, implications of testing on other family members and family approval of testing.

Regulatory/NHS approval for testing

The UK provides a uniform package of healthcare irrespective of income. In the UK, fiscal sustainability of health care financing remains a key public policy concern (Aggarwal & Sullivan, 2013). Attempts to control the provision of medicines not deemed cost effective by health technology assessment (HTA) agencies such as NICE and SMC have been met with patient and public discontent (Dyer, 2002; Mayor, 2009). Such HTA agencies are designed to ensure all patients receive equitable healthcare in the UK, basing their value judgements on a thorough consultation and health economic impact modelling. In a previous survey of societal preferences for NHS funding, respondents agreed with the premise of value based-pricing, but the majority did not believe that extra value should be placed on specific groups such as children, cancer patients or those with reduced life expectancy (Linley & Hughes, 2013).

Across all participants (n=102) in this study, the highest preference attribute rating score was regulatory/NHS approval for testing. All participants within this study received cancer therapy within the National Health Service (NHS) universal healthcare system in the UK. This attribute had the highest mean importance rating across all groups in the

study. It was also selected as highest order preference attribute theme the second most times.

This is the first study in the UK identifying and rating patient preferences of genomic testing in PCM. This attribute theme was not readily identified in other studies, performed within different healthcare systems in the world. This may reflect the different healthcare priorities between these populations. This study demonstrated cancer patients readily identify regulatory approval within the NHS and role it may play in approval and uptake of genomic testing in PCM. This was demonstrated by the high mean attribute rating and frequency of highest order prioritisation. Many patients reported the robust and peer-reviewed regulatory processes provided confidence around the utilisation of genomic testing and appropriate use of NHS resources.

Test turnaround time

The preference attribute theme with second highest mean importance rating across all groups was test turnaround time. This attribute theme was rated highest order by 14 participants (13.7% of total). This demonstrated patients identify and highly rate the importance of test turnaround time within clinically appropriate timelines. The previous study by Cuffe et al (Cuffe et al., 2014) highlighted that cancer patients were willing to undergo pharmaco-genomic testing and willing to pay for it, waiting several weeks for results.

The results of this NGT study demonstrate turnaround time for test results remained a readily identified and highly rated patient preference attribute theme of genomic testing. This transcended all groups within the study, reflected by the second highest mean attribute rating. Patients within clinical treatment paradigms are acutely aware of treatment

timelines, audited within the UK by cancer waiting times. Patients in this study identified short turnaround time for results as highly rated preference attribute theme of genomic testing. The complexity of genomic testing and plethora of datasets produced does challenge this turnaround timeframes. The increasing advent of multi-professional molecular tumour board meetings helps augment the rapid turnaround of genomic data and its interpretation. This study demonstrated doing so within truncated timelines remains important for patients.

Invasiveness of testing

The third highest preference attribute theme rating score across all nominal groups was invasiveness of testing. Participants had personal history of cancer testing, diagnosis and treatment. This study identified patient preference attribute themes across a breadth of fourteen cancer subtypes, though this did highlight many participants had heterogeneous experience of invasive diagnostic procedures. Prior experiences of invasive biopsy did weight significantly on preference ratings for this attribute theme. The high mean attribute rating reflects patient preference for less invasive genomic tests where possible.

Participants in the study were increasingly aware of circulating tumour cell assays and many participants expressed interest in these novel minimally-invasive techniques for genomic testing. There remains academic interest in minimally invasive PCM, with a small number of tests in clinical practice, such as circulating T790M resistance mutation analysis in EGFR mutated non-small cell lung cancer (Luo J, Shen L, et al, 2014). High mean attribute rating scores in this study reflect patient preference for further minimally-invasive techniques in clinical trials and practice.

Physician approval for testing

The fourth highest preference attribute theme rating was physician approval of genomic testing. It was rated by the highest number of participants as first order attribute theme throughout the study. Hillen et al (Hillen, de Haes, & Smets, 2011) explored published empirical literature assessing cancer patients' trust in their physician. This demonstrated trust in physicians, facilitating communication and shared medical decision-making, resulting in decreased patient fear and better treatment adherence. The authors appreciated the need for further empirical studies to understand the nature and impact of cancer patients' trust in their physician.

This thesis study demonstrated high rating patients placed on patient-physician relationship and influence on preference attributes of genomic testing. Only 7.8% of patients had experience of PCM. Patients, therefore, reported not to retain full confidence in their personal ability to determine suitability of genomic testing, subsequent reliance on physician advice and informed discussion. Individual merits of genomic testing and balance of preference attributes in clinical practice will be guided by balanced patient-physician consultation. The high mean rating for this identified preference attribute reinforces the value patients place on this relationship.

Test sensitivity/true positive

The fifth highest preference mean attribute rating score was test sensitivity/true positive. This demonstrated patient preferences for genomic tests correctly identifying patients who may or may not benefit from therapeutic intervention. Patients had an appreciation that test sensitivity/true positive could potentially lead to either over- or under-treatment.

This study demonstrated patient preference for high genomic test sensitivity, with concern reduction in sensitivity could lead to either under or over-treatment, depending on an individual genomic test. The research aims of this thesis were to identify and rate preferences of genomic testing, rather than focusing on the potential therapies resulting from the test result. Many patients found it difficult to tease these two elements out within NGT discussion of this preference attribute theme. In clinical practice, the two often have significant overlap.

Test specificity/true negative

The sixth highest preference attribute rating was test specificity/true negative. This had lower mean importance rating and selected less times as highest order attribute compared to sensitivity/true positive of testing. Participants in this study identified specificity of testing could impact on potential over- or under-treatment, a consistent concern of genomic testing amongst participants. Patients' had higher preference rating for a genomic test to correctly identify individuals with specific genomic mutation. This study demonstrated high cognitive burden of the sensitivity/specificity preference attribute discussions for patients. Patients' identified these preference attributes, thus the medical and scientific community need to ensure they are presented and addressed in a manner which patient and family members can comprehend within the clinical arena.

Prevalence of genomic variant

The seventh highest preference attribute theme was prevalence of genomic variant. Participants identified frequency of genomic variant as preference attribute with seventh highest mean attribute rating score. It was rated as highest order attribute by 8 participants in total. Participants identified rarity of genomic variants would affect preferences of testing. The study identified this attribute theme, though it had lower preference rating

compared to others. Patients initially considered genomic tests providing a single result, aligned with their previous experiences of clinical practice. Patients were very engaged with platform approaches to genomic testing, though appreciated overall prevalence would still need to be high enough meet the preference attribute theme.

Distance to travel for testing

Distance to travel for testing received the eighth highest mean preference attribute rating. It was rated highest order preference attribute by 6 participants. All participants within the study received cancer treatment within the West of Scotland, but included a wide range of geographical locations due regional and national cancer services. Participants identified distance to travel as an attribute theme, but with low preference rating. Participants considered travel to a regional cancer as entirely appropriate for testing, but travel out with Scotland as an adverse preference attribute.

Implications for family members of testing

The penultimate preference attribute theme rating was implications of testing for family members. A small number of participants identified potential implications for family due to unveiling germline mutations, but with low preference rating scores. The low number of groups identifying this theme demonstrated low awareness around this preference attribute of genomic testing. The low frequency of identification in this study may also disproportionately affect mean attribute rating.

The study highlighted implications for family members can have both positive and negative influence on preferences of genomic testing. Some participants expressed feel more positive towards genomic testing facilitating family members diagnosed at an earlier stage or entering an appropriate cancer screening program based on the result. Other

participants identified negative connotations with this preference attribute, reporting feeling burdened telling family members. One participant identified feeling degree of responsibility if their offspring were to have an inherited germline mutation. This remains a complex area for patients and this study demonstrated there not widespread awareness amongst patients of this attribute theme. The low rates of attribute identification may reflect that only 7.8% of participants had experience of genomic testing. The design of this study did not allow for more comprehensive assessment of the wider implications of this single attribute theme amongst patients.

Family approval for testing

The final preference attribute theme was family approval of genomic testing. It was not rated highest order by any participants within the study. This study demonstrated participants identified preferences of genomic testing are influenced by approval of family members. Some participants identified they could be convinced to undergo testing by a persuasive relative, where others felt family support would reinforce their personal decision-making processes.

5.7.3. Effect of clinical treatment intent on preference attribute themes and ratings

This thesis identified patient preference attribute themes and ratings of genomic testing in PCM. It also aimed to define effect of clinical treatment intent on identified preference attributes and rating scores. As discussed in Chapter 2, previous studies demonstrated therapeutic decision-making is influenced by clinical treatment intent. This thesis explored the effect of cancer treatment intent, between patients who received radical versus palliative cancer treatment, on identified preference attributes and mean rating scores.

Patients treated with radical intent (groups A and B combined, n=65), identified the following preference attribute themes: physician approval, regulatory/NHS approval, sensitivity/true positive of test, specificity/true negative of test, prevalence of genomic variant, invasiveness of testing, test turnaround time, implications for family members, family approval for testing and distance to travel.

Patients treated with palliative intent (n=37), identified the following preference attribute themes: invasiveness of testing, test turnaround time, physician approval, regulatory/NHS approval, distance to travel, prevalence of genomic variant, sensitivity/true positive of test, implications for family members, specificity/true negative of test and family approval for testing.

Regulatory/NHS approval of genomic testing

The highest preference attribute theme rating in the radical treatment group (groups A and B) was regulatory/NHS approval of genomic testing. It had mean attribute rating score of 6.39 and was selected as the highest order preference attribute by 14/65 participants. Regulatory/NHS approval received fourth highest mean attribute rating score amongst participants treated with palliative intent (n=37). In this group, the mean attribute rating was 5.49 and rated highest order attribute theme by 4 participants.

Regulatory/NHS approval received the highest mean attribute scores across both radical and palliative intent treatment groups, though rated higher for patients' treated with radical intent. It was identified across all groups within the NGT study. This reflected high identification and overall rating of regulatory/NHS approval amongst patients. Individuals treated with radical intent rate this attribute slightly higher than those treated with palliative intent.

Sensitivity/true positive of genomic testing

Sensitivity of genomic testing was received the second highest rating in the radical treatment group, with mean attribute rating of 6.39. There were 13/65 participants in the radical treatment groups who rated this as highest order preference attribute theme. In the participant group treated with palliative intent, sensitivity of testing received 7th highest mean attribute rating (2.03) and not rated highest order by any participants.

This highlighted differing preferences between individuals treated with radical versus palliative intent. Patients treated with radical intent demonstrated higher preference rating for sensitivity of genomic testing compared to those treated with palliative intent. This included risks of both under- and over-treatment depending on the genomic test.

Physician approval for testing

Physician approval for testing was rated fourth highest preference attribute theme for patients treated with radical intent, demonstrating mean attribute rating of 5.43. It was selected by 11/65 participants as highest order preference attribute theme. In patients' treated with palliative intent, physician approval of testing received the third highest mean attribute rating of 6.19, with 8/37 participants selecting it as highest order attribute.

Patients receiving radical and palliative cancer treatment identified doctor-patient relationship as a highly rated preference attribute of genomic testing. This demonstrated importance patients placed on physician-patient relationship, regardless of cancer treatment intent.

Test turnaround time

Test turnaround time received the fifth highest mean attribute rating (5.42) amongst participants treated with radical intent. It was selected highest order preference attribute by 6/65 participants in the radical treatment intent group. This contrasts with the palliative treatment group, where test turnaround time received the second highest mean attribute rating of 6.95 and highest order attribute by 8/37 participants.

Patients treated with palliative intent placed greater importance on genomic test results being delivered in an appropriate timeframe. The high rates of attribute identification across the study demonstrated all patients remain acutely aware of timelines for testing across both radical and palliative intent groups. Patients with a life-limiting cancer diagnosis, though, had higher preference rating for test turnaround time compared to those treated with radical intent.

Specificity/true negative of genomic testing

The specificity/true negative of genomic testing received the third highest mean attribute rating (5.78) and ranked highest order preference attribute by 9/65 participants within the radical treatment groups. This contrasted significantly with patients treated with palliative intent, for whom specificity/true negative of testing received the ninth highest mean attribute rating at 1.32 and not rated as highest order attribute by any participants.

Patients treated with radical intent demonstrated higher preference rating for specificity of genomic testing compared to those treated with palliative intent. Patients treated with radical intent demonstrated significant concern about both over- or under-treatment by placing high preference rating on specificity of genomic testing. Patients treated with palliative intent prioritised other preference attribute themes over specificity of testing and

displayed lower priority rating for over- or under-treatment compared to those receiving radical therapy.

Invasiveness of testing

Invasiveness of testing was identified across both radical and palliative treatment intent groups. In participants treated with radical intent, it received sixth highest mean attribute rating (5.00) and rated highest order preference attribute by 13/65 participants. This contrasted participants treated with palliative intent, where invasiveness of testing received the highest mean attribute rating at 7.14 and rated highest order attribute by 7/37 participants. This shows a stark contrast in how participants view preference attributes of invasiveness of testing between radical and palliative treatment intent.

Participants in the study had personal experience of wide-ranging cancer diagnostics and testing, which influenced their preferences of invasive testing within the PCM arena. Patients treated with palliative intent demonstrated higher preference rating on less invasive testing compared to those treated with radical intent. This suggested patients treated with radical intent are more prepared to accept short-term morbidity from more invasive biopsy for genomic testing. Patients treated with palliative intent, on the other hand, placed greater preference on factors affecting quality of life.

Prevalence of genomic variant

This preference attribute theme received the seventh highest mean attribute rating across participants treated with radical intent. It received mean attribute rating of 4.37 and ranked highest order attribute by 5 participants within the radical treatment group. The prevalence of genomic variant attribute received the sixth highest mean attribute rating (2.49) amongst

participants treated with palliative intent. It was rated highest order preference attribute by 3 participants in this group.

This demonstrated both radical and palliative treatment intent groups, had similar identification rates of prevalence of genomic variant but it retains relatively low mean attribute rating scores.

Implications of testing for family members

This preference attribute theme was identified by both radical and palliative participant groups. Implications of testing for family members received the eighth highest mean attribute rating (1.56) across the radical treatment groups. It received mean attribute rating of 1.95 amongst the palliative treatment intent group, making it the eighth highest preference attribute rating. It was not rated as the highest order preference attribute theme by any participants.

These results are consistent across both treatment intent groups. Patients identified implications of testing for family members as a preference attribute theme, but it retains relatively priority across all participants in the study. Treatment intent does not appear to have a significant impact on its mean attribute ratings.

Distance to travel for testing

This attribute received the ninth highest rating across participants treated with radical intent, with mean attribute rating of 1.45. Distance to travel for testing was highest order preference attribute for 1/65 participants within the radical intent group. It received the fifth highest mean attribute rating across the palliative intent group at 5.46. Distance to

travel was the highest order preference attribute theme for 5/37 participants treated with palliative intent.

Patients treated with radical intent identified distance to travel, but assigned lower preference attribute rating compared to patients treated with palliative intent. The reasons under-pinning this were multi-factorial. Participants treated with palliative intent may be less physically able to travel or place greater significance on spending time nearer family and home. Distance to travel had low preference attribute rating for genomic testing in patients treated with radical intent.

Family approval of testing

Family approval of genomic testing was identified as a preference attribute theme by 1/10 groups treated with radical and two out of six groups treated with palliative intent. Within the radical intent participants, family approval for testing received mean preference attribute rating of 0.24 and was not ranked as highest order attribute by any participants. Within the palliative treatment intent groups, it received a mean preference attribute rating of 0.97 and was not ranked order attribute by any participants.

The family approval for genomic testing was identified as a preference attribute theme by three out of sixteen participant groups in this study. Within those groups, it received the lowest mean attribute rating and was not rated highest order attribute by any participants. This demonstrated family approval for genomic testing is identified by some patients but had lower preference rating in both radical and palliative intent treatment groups compared to other attribute themes.

5.7.4. Effect of time since completing treatment on preference attribute themes and ratings

This thesis identified patient preference attribute themes and associate ratings for genomic testing. It also investigated the novel hypothesis that time since completing treatment may influence identified preference attribute themes or ratings. As discussed in Chapter 3, previous studies demonstrated patients therapeutic decisions were influenced by intent of cancer treatment. It was hypothesized that increasing time from therapeutic equipoise and reflective thinking after completing cancer therapy may influence identified preference themes and ratings of genomic testing.

Patients treated with radical intent (groups A and B, n=65) identified the following preference attribute themes: physician approval, regulatory/NHS approval, sensitivity/true positive of test, specificity/true negative of test, prevalence of genomic variant, invasiveness of testing, test turnaround time, implications for family members, family approval and distance to travel for genomic testing.

Regulatory/NHS approval

Regulatory/NHS approval received the fourth highest mean attribute preference rating (6.03) for participants treated with radical intent within the past 2 years (group A) and was highest order attribute theme for 5/32 participants. It received the highest mean attribute rating (6.88) amongst participants treated with radical intent more than 2 years prior (group B). It was rated highest order preference attribute by 9/33 participants in this group.

These results demonstrated similar preference attribute theme ratings of regulatory/NHS approval for patients completing treatment within and longer than 2 years prior. It received high mean attribute rating across both groups, reflecting its preference rating

amongst patients receiving cancer therapy with radical intent, regardless of time since completion.

Physician approval

Physician approval received the highest mean attribute rating for group A participants (6.75). It was highest order preference attribute for 7/32 participants treated with radical intent within the preceding 2 years. Participants in group B, who completed cancer treatment more than 2 years prior to the study, assigned physician approval the sixth highest mean attribute rating (4.12). It was rated highest order preference attribute by 4/33 participants in this group.

Patients treated within 2 years demonstrated higher preference rating for physician approval, compared to those treated more than 2 years prior. Patients having completed treatment within two years were closer to time of therapeutic equipoise, having made clinical treatment decisions based on available information and often with support of their physician. This data demonstrate patients placed greater preference rating on physician approval closer to the time of therapeutic equipoise.

Sensitivity/true positive of testing

Sensitivity/true positive of testing received the second highest mean attribute rating across patients from both group A and B (6.40 and 6.39 respectively). It was rated highest order preference attribute by 7/32 patients in Group A and 6/33 patients in group B.

Sensitivity/true positive of testing was a highly rated preference attribute theme across all patients treated with radical intent. These results demonstrated duration since radical therapy did not affect preference attribute identification or rating of test sensitivity. There

remained awareness of the importance of genomic test sensitivity/true positive in reducing either over- or under treatment, reflected by the high mean attribute rating and frequency of highest order rating.

Specificity/true negative of testing

Specificity of genomic testing received the third highest mean attribute rating (6.38) across participants in group A, who received radical intent treatment within two years prior to study entry. It was rated highest order preference attribute by 5/32 participants. Participants who received treatment more than 2 years prior (group B) gave specificity of testing/true negative the fourth highest mean attribute rating (5.18). It was rated highest order preference attribute theme by 4 /33 participants in group B.

Patients receiving radical cancer treatment demonstrated similar identification and ratings of specificity/true negative of genomic testing, regardless of duration since completing therapy. Patients treated with radical intent had similar preference rating of specificity/true negative and sensitivity/true positive of genomic testing. This highlighted importance of under- or over-treatment for this patient group, which does not diminish with increasing time since completing cancer therapy.

Prevalence of genomic variant

Prevalence of genomic variant received the fifth highest mean attribute rating across group A (5.12). It was rated highest order preference attribute by 3/32 patients. Patients in group B assigned prevalence of genomic variant the seventh highest mean attribute rating at 3.61. It was rated highest order preference attribute by 2/33 patients in this group.

These results demonstrated the low rating prevalence of genomic variant had on patient preferences of genomic testing. The mean attribute ratings were similar across all radical patients groups, with no demonstrable correlation between duration since completing radical treatment and preference attribute identification or ratings for prevalence of genomic variant.

Invasiveness of testing

Invasiveness of testing received the sixth highest mean attribute rating across group A participants (5.06) and highest order preference attribute for 3/32 participants. Group B participants assigned invasiveness of testing the fifth highest mean attribute ranking (4.94). It was rated highest order preference attribute by 3/33 participants in group B. Patients placed similar preference rating on invasiveness of testing, which was not influenced by time since completing radical cancer therapy.

Test turnaround time

Test turnaround time received the seventh highest mean attribute rating (4.56) amongst group A participants. It was rated highest order preference attribute by 2/32 participants. This contrasts group B participants, for whom test turnaround time received the third highest mean attribute rating (6.27) and rated highest order preference attribute for 4/33 participants.

These results demonstrated patients who received cancer treatment more than 2 years prior assigned higher preference rating to test turnaround time compared to those patients treated within 2 years of study entry. The attribute rating may be disproportionately influenced by the relatively small numbers assigning highest order preference rating to this attribute (2 and 4 participants in group A and B respectively).

Implications of testing for family members

This preference attribute theme was only identified by three nominal groups within group A and one nominal group within group B. Implications of testing for family members received the eighth highest mean attribute rating (2.03) across group A participants and was not rated as highest order preference attribute. It received the ninth highest mean attribute rating in group B (1.09). Implications of testing for family members was not rated highest order attribute in group B.

These results demonstrated some participants identified genomic testing can have wider implications for family members, but with low preference rating. This study showed no correlation between the implications for family preference attribute rating and time since completing treatment.

Distance to travel for testing

The distance to travel preference attribute theme received lowest mean attribute rating (0.81) across group A participants and was not rated highest order preference attribute. Amongst group B participants, distance to travel for testing received the eighth highest mean attribute rating (2.09). It was not rated highest order preference attribute by any participants in group B.

Participants who received radical cancer treatment identified distance to travel for testing as a preference attribute theme, but it retained low mean attribute rating. There is was no correlation between mean attribute rating for distance to travel and time since completing cancer treatment.

Family approval of testing

This preference attribute theme was not identified by any participants in group A. Family approval of testing was identified by a single nominal group of participants greater than two years since receiving radical cancer therapy. Overall across group B, it received the lowest mean attribute rating (0.48) and was not rated highest order preference attribute by any participants.

This demonstrated a single group of participants receiving radical therapy identified family approval of genomic testing as a preference attribute theme. The low mean attribute rating (0.48) demonstrated it is not a highly rated preference attribute for patients considering genomic testing.

5.8. Conclusions

There is increasing recognition around emerging scientific potential of genomic testing providing therapies with durable clinical benefit to patients. There have, in recent years, been a plethora of newly approved PCM therapies including in EGFR-mutated lung cancer, ALK-mutated lung cancer, HER2 testing in breast cancer amongst many others. Such interventions resulted in clinical, psycho-social, health and quality of life benefits to patients. Policy makers in oncology advocate need to involve patients and carers in cancer therapy frameworks to ensure scientific progress retain patient preferences at its epicentre. This led to increasing acknowledgement of the need for further research assessing novel genomic testing in PCM and its adaption to individual patients.

This thesis built on the work of previous studies by identifying and rating patient preference attribute themes of genomic testing, which had not previously been assessed within the UK healthcare setting. This thesis also explored the novel hypothesis that

identified preference attributes and ratings may be influenced by cancer treatment intent and time since completing cancer therapy.

The results from this NGT study support the novel hypothesis that patients' preferences of genomic testing in PCM are not uniform and that heterogeneities can, in part, be explained by cancer treatment intent. Patients who received radical intent cancer treatment placed higher preference rating on attributes such as sensitivity and specificity of testing. This reflected concern amongst this patient group about potential for under- or over-treatment leading to either increased toxicity or increased risk of cancer recurrence. Patients treated with palliative intent demonstrated lower preference rating for test sensitivity or specificity, but instead higher preference rating for factors such as invasiveness of testing or distance to travel.

Patients treated with palliative treatment intent attached higher preference rating to invasiveness of testing and test turnaround time. This may, in part, be explained by the fact that these patients have a life-limiting illness, influencing preferences and perceived benefits of genomic testing. These individuals had a more acute awareness of the balance between therapeutic efficacy from testing and quality of life. In contrast, patients treated with radical intent assigned lower preference rating to invasiveness of testing or distance to travel, demonstrating willingness to tolerate shorter term invasive procedures or travel compared to patients treated with palliative intent.

This NGT study identified some preference attribute themes of genomic testing seen across all patient groups. Patients treated with both radical and palliative intent assigned high preference rating to regulatory/NHS approval and physician approval of testing. Within the NHS universal healthcare system, patients attached importance to genomic testing

receiving regulatory/NHS approval. This reflected trust individual patients place in these independent regulatory systems and also awareness that tests approved by regulatory bodies are more likely to be available to individual patients. Patients across both radical and palliative groups also assigned high preference rating to physician approval of genomic testing. This may be rooted in positive experiences of doctor-patient relationship and element of trust that a patients' doctor will act in their best interests. The study demonstrated this preference attribute rating was uniform across participants.

The other novel hypothesis of this thesis was that patients may identify different preference attribute themes or ratings for genomic testing with increasing duration since completing radical treatment. Patients who completed radical cancer therapy within 2 years assigned higher preference rating to physician approval for testing compared to patients who completed therapy more than two years prior. This reflected persisting doctor-patient trust and relationship in those less than 2 years since treatment, many of whom will still be attending follow-up clinics and have an ongoing clinical relationship with their physician. Patients with longer duration since completing radical treatment assigned lower preference rating to physician approval of genomic testing.

Patients who completed radical intent treatment more than two years prior to entry assigned higher preference attribute ratings to regulatory/NHS approval of testing and test turnaround time. Some attribute themes received consistent preference ratings across radical treatment groups, such as test sensitivity and specificity. Patients treated within and greater than two years prior to study entry assigned high preference ratings to these attribute themes. This demonstrated preference for accuracy genomic testing to reduce potential over- or under-treatment, which persisted in patients having received radical cancer treatment regardless of duration since its completion.

The premise of precision cancer medicine is delivering the right treatment to the right patient at the right time, based on scientific principles of individual genomic tumour assessment. This study also demonstrated the promise of genomic testing also relies on patient-centric factors including as treatment intent and duration since completing therapy. This study was the first to produce empirical evidence that, across a breadth of cancer subtypes and treatment intent, patients' preference attributes of genomic testing can be identified and rated. The scientific advances of precision cancer medicine transcend the breadth of tumour subtypes and cancer stages. The results of this study highlighted we should not consider genomic testing as a single homogeneous scientific entity, but retain factors such as treatment intent when considering its clinical application.

Clinical trials play a key role in innovative cancer therapies and subsequent regulatory approval. As discussed in Chapter 1, the innovations of genomic testing necessitate novel clinical trial designs incorporating the plethora of data provided and allow trials to transcend existing taxonomies of cancer. Having identified and rated patients' preference attribute themes of genomic testing, this thesis will now explore how these attributes were incorporated within a novel PCM clinical trial conducted in the UK.

Chapter 6. Benchmarking patient preferences of genomic testing in the ATLANTIS clinical trial

6.1. Introduction

This thesis identified and rated preference attribute themes of genomic testing for patients. Clinical trials play an important role in oncology. There is relatively sparse evidence about what motivates cancer patients to enrol in a clinical trial. Participation potentially imposes a number of restrictions on individuals and, depending on study design, patients may be asked to comply with assignment randomisation, undergo additional tests and be unaware what treatment they are receiving for the duration of the study. Clinical trialists have, for the most part, addressed mechanics and ethics involved in optimising recruitment, study retention and compliance. Even within this remit, many clinical trials still fail to reach projected targets for recruitment in the UK (McDonald AM, 2005). McDonald et al (2005) demonstrated that only 31% of UK Medical Research Council (MRC) and Health Technology Assessment (HTA) trials achieved their original recruitment target and that 53% were awarded an extension to do so.

Insufficient or untimely patient recruitment into clinical trials has serious consequences, such as extending trial recruitment length leading to increased resource and delaying availability of study outcomes or treatments. The integrity and validity of clinical trial outcomes also rely on sample size calculations, hence studies failing to reach intended patient recruitment potentially increase the chance of a type II error. Patient recruitment is influenced by both patient and investigator factors. A systematic review by Abraham et al (Abraham et al, 2015) highlighted reasons why eligible patients may not wish to participate in real or hypothetical randomised controlled trials. Understanding and addressing potential patient preferences is important when developing a study recruitment strategy.

Activated and engaged patients are empowered to participate in their own health care. Mullins et al (2014) suggest that 'when it comes to research, people generally participate passively in the learning process, being involved in clinical trials as human subjects rather than as engaged stakeholders.' Study design elements of clinical trials, intended for regulatory approval of therapies, traditionally do not align with the patient-centric healthcare approach. Patients increasingly want to be informed, empowered and engaged with their healthcare. Contemporary clinical trial methodologies helped address some issues of participant-related factors (such as medical research mistrust, hard-to-reach groups and lack of resources), contextual factors (such as cultural or language barriers) and research-specific factors (such as risk of receiving placebo, randomisation and risk of harm). Mullins et al (2014) postulated means by which clinical trials can promote patient recruitment and retention in clinical trials by improving patient experience.

Chapter 1 identified challenges facing clinical trials in the era of precision cancer medicine, necessitating innovative designs incorporating genomic testing and targeted therapies. One such example is the ATLANTIS trial (ISRCTN 25859465, Eudract 2015-003249), sponsored jointly by the University of Glasgow and NHS Greater Glasgow and Clyde (Chief Investigators Professor Robert Jones and Professor Thomas Powles). Developing the study protocol and regulatory submissions formed an element of the thesis author's (BF) research fellowship under the guidance of the Chief Investigators and Cancer Research UK Glasgow Clinical Trials Unit. The design of ATLANTIS was confirmed prior to this research identifying and rating preference attributes of genomic testing. The ATLANTIS trial was selected for this study due to its novel adaptive design, exploration of precision medicine novel biomarkers and potential for the outcome to influence adaptations of study design in future, ensuring incorporation of patients' preference factors of genomic testing.

This thesis identified and rated patient preference attribute themes of genomic testing in precision cancer medicine clinical trials. This started by identifying preference attributes themes and associated ratings for genomic testing in PCM. In this chapter, these preference attribute themes were utilised to assess how the ATLANTIS clinical trial incorporated patient preferences of genomic testing into its design and implementation. This work was done in parallel with the ATLANTIS trial protocol development and this analysis is, therefore, retrospective though may have implications for design of future PCM trials. This will provide evidence of how innovative study designs incorporate patient preferences of genomic testing.

6.2. ATLANTIS trial

6.2.1. Aims and objectives of ATLANTIS

Urothelial cancer (UC), incorporating cancers of the bladder, urethra, ureter and renal pelvis, is the eighth most common cause of cancer related death in the United Kingdom (UK). Around 5,600 people died from UC in 2016 (Cancer Research UK CancerStats, 2016). Cytotoxic platinum-based chemotherapy is routinely used as palliative treatment for metastatic or advanced UC in the first-line setting. Although the majority of patients initially derive benefit, relapse is inevitable and occurs, on average, 4 months after completion of chemotherapy. Once patients develop relapsed UC, survival and quality of life are often poor. In recent years, immune checkpoint inhibitors, which can benefit around 20% of patients with durable responses and proven survival benefit, have found a role in second line treatment after failure of platinum-based chemotherapy (Bellmunt, J., Powles, T., Vogelzang, NJ., et al, 2017). Their role in the first-line treatment of patients with UC is currently limited to patients whose tumour shows high PDL-1 expression who are not suitable for platinum-based chemotherapy. Nonetheless there are still a majority of

patients with advanced UC who do not derive significant benefit from immune checkpoint inhibitors and for whom subsequent treatment options are very limited. No consensus exists around the role of optimal systemic therapy in the second-line setting. Chemotherapy agents can be used, but response rates are low and benefits compared to best supportive care are unknown. Therefore, maintaining response after first line chemotherapy may be an attractive way to improve outcomes for patients with advanced UC.

The molecular heterogeneity of UC lends itself to the hypothesis that new treatments may be tailored to an individual's tumour biology and a precision medicine approach. Testing new therapies alongside conventional first-line chemotherapy has proven challenging due to the toxicity profile of such combinations in this patient group. Patients requiring second or subsequent lines of chemotherapy often have limited survival and high symptom burden, meaning conducting clinical trials in this patient group can be challenging. Therefore, maintenance therapy after first line chemotherapy is a potential opportunity for single agent drug development in patients with advanced UC.

The primary research question of the ATLANTIS trial is to determine whether molecularly defined maintenance treatment after first line chemotherapy can delay time to tumour progression in patients with advanced UC. This phase II, signal-searching study may therefore establish clinically relevant initial evidence of activity for the novel agents tested, in order to justify validation in a phase III trial. There will be a number of novel agents tested, each compared to placebo. Treatment will be based on molecularly defined subgroups of patients, where laboratory or clinical evidence to support such enrichment is clear, or in a manner that allows exploration of, or provides initial evidence for, predictive biomarkers.

The primary objective of the ATLANTIS trial is to:

Compare progression-free survival (PFS) on the interventional study arms to that on placebo within each biomarker/novel agent subgroup. PFS has been chosen as it is largely objective, as most patients with advanced urothelial cancer will display progression in accordance with RECIST 1.1 criteria. PFS is also clinically meaningful, as progression after first line therapy reflects transition to the lethal stage of the disease and often requirement for further systemic therapy.

The secondary objectives of the ATLANTIS trial are:

- Compare overall survival (OS) between the intervention arm and placebo for each component subgroup of the trial.
- Evaluate the safety and tolerability of the regimens in this patient population
- Compare the best response rate (BRR) between the intervention arm and placebo for each component subgroup of the trial
- Compare the maximum reduction in size of measurable lesions between the component subgroups of the trial

The exploratory/translational objectives of the ATLANTIS trial are to:

- Investigate the correlation of outcome with different levels of biomarker expression, where possible.
- Collect archival tissue and blood specimens for future biomarker testing.

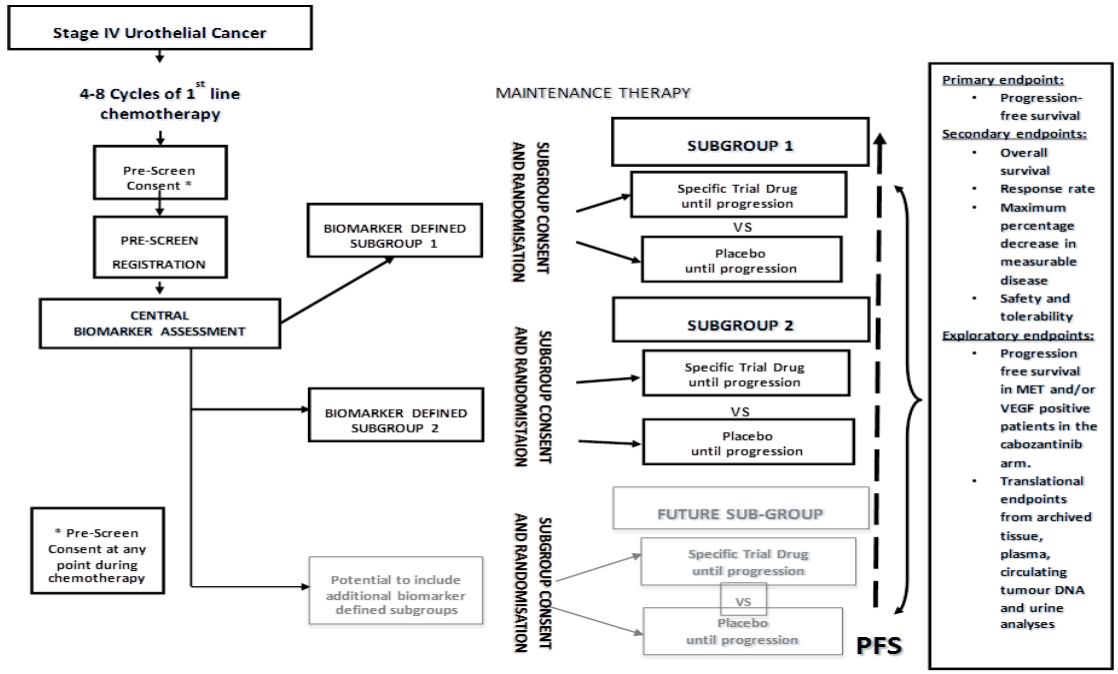
6.2.2. Study design

ATLANTIS is a multi-centre randomised phase II signal-searching trial in biomarker-defined subgroups of patients with advanced UC, using an adaptive design. The study

team considered a Bayesian adaptive approach to biomarker identification, but this design was felt too developmental to include within the proposed trial. Multiple novel agents will be used in parallel and patients will be entered into ATLANTIS subgroup studies dependent on tumour biomarker profile. The SPIRIT diagram of ATLANTIS trial design is shown in *Figure 3*.

The control arm for each comparison will be placebo and comparison will be double-blind, where possible. Biomarker analysis will be performed on archival tissue during the pre-screening trial phase, in order to define study subgroups.

Figure 3. The SPIRIT diagram illustrating ATLANTIS study design.



The design of the ATLANTIS trial allows addition of further biomarker-defined subgroups throughout its lifespan. ATLANTIS is currently exploring three novel drug comparison arms. These include the MET and VEGF inhibitor cabozantinib, androgen receptor (AR) antagonist enzalutamide and rucaparib in patients whose tumour demonstrates DNA repair deficiency phenotypes due to defects in genes including BRCA1/2, BAP1, PALB2,

FANCD2 and ERCC2. In addition to the current novel agents being tested within ATLANTIS, the trial provides a framework allowing new treatments to be introduced by amendment, with prospective stratification based around a molecular target.

The design and implementation of ATLANTIS was undertaken by the study development team, supported by the Cancer Research UK Glasgow Clinical Trials Unit. Patient representatives were involved from the inception stage of study design through to its implementation and study recruitment, via the National Cancer Research Institute bladder cancer Clinical Studies Groups and the Cancer Research UK Glasgow Clinical Trials Unit patient representatives. This thesis explored benchmarking of preference attribute themes in parallel with the study design. The results, therefore, reflect a retrospective analysis of preference attributes of genomic testing with ATLANTIS, but may inform design of future clinical trials. The thesis author (BF) was a member of the study development team for ATLANTIS, involved in regulatory submissions, protocol writing and clinical conduct at site for the trial.

6.2.3. Patient population and eligibility criteria

The target population for ATLANTIS are patients with newly diagnosed metastatic or locally advanced urothelial cancer. Patients must have achieved an objective response or stable disease with at least 4 cycles of first-line chemotherapy (maximum of 8 cycles). Patients are allowed to have received any chemotherapy regimen and does not necessarily need to include cisplatin. Patients must start trial treatment at least 3, but not more than 10 weeks after last dose of chemotherapy infusion. Biomarker analysis will determine ATLANTIS subgroup allocation and can occur any time after the diagnosis of advanced urothelial cancer prior to randomisation, as long as the necessary informed patient consent

has taken place. Archival tissue can be used and all biomarker analysis will occur centrally.

Inclusion criteria for ATLANTIS are as follows:

- Previously diagnosed stage IV urothelial cancer (UC) (T4b, Nany, Many, Tany N1-3 M0, Tany Nany M1).
- Histologically confirmed urothelial cancer. This includes cancers of the urinary bladder, ureter, renal pelvis or urethra of transitional and/or squamous histology. A component of either or both of these histologies is adequate for entry
- Able to commence trial treatment within 10 weeks of completing chemotherapy
- Adequate tissue for biomarker testing. Testing will occur centrally.
- Patients must have received between 4 and 8 cycles of first line chemotherapy for metastatic/advanced UC to be eligible. Previous adjuvant or neo-adjuvant chemotherapy does not count as a line of therapy.
- Adequate organ function as defined in drug-specific appendices
- ECOG performance status 0-2
- Age ≥16 years
- Female patients of childbearing potential must agree to comply with effective contraceptive measures and have negative pregnancy test within one week of trial entry
- Male patients with partners of child bearing potential must agree to take measures not to father children by using one form of highly effective contraception.
- Written informed consent prior to admission of this trial
- Meets all inclusion criteria for the relevant component subgroup listed in appendices

ATLANTIS study exclusion criteria:

- Progression during first line chemotherapy for metastatic disease. This should be based on a radiological comparison between the pre-chemotherapy CT and end of treatment CT (local review). Patients with progression during the final 3 cycles of chemotherapy are potentially eligible if there is at least stable disease compared to baseline. These patients should be discussed with the trial team.
- Patient does not currently require second line chemotherapy in the opinion of the investigator
- More than one line of chemotherapy for metastatic or locally advanced disease. Prior adjuvant/neoadjuvant chemotherapy is permitted in addition
- Patients receiving radical/curative surgery at the end of first line treatment (palliative radiotherapy is allowed)
- Significant co-morbidity or organ dysfunction as defined in the drug specific appendices
- Patients receiving less than 4 or more than 8 cycles of chemotherapy before randomisation and initiation of trial intervention (excluding chemotherapy given with adjuvant or neoadjuvant intent)
- Treatment with any other investigational agent within 28 days prior to the first dose of trial medication within ATLANTIS
- Less than 3 or more than 10 weeks since the last infusion of chemotherapy for advanced disease at the initiation of trial interventions
- History of another malignancy within the preceding 2 years (other than treated squamous/basal cell skin cancer, treated early stage cervical cancer or treated/stable organ confined prostate cancer not requiring on-going androgen deprivation therapy)

- On-going prohibited medication which cannot be discontinued prior to starting trial specific intervention (as defined in drug specific appendices)
- Serious inter-current medical or psychiatric illness, including active infection which, in the opinion of the investigator, would make it inappropriate to enter the trial
- Women who are breastfeeding
- Patient meets any of the exclusion criteria listed in the relevant component subgroup specific appendix

6.2.4. Statistical considerations

Each ATLANTIS component subgroup will be based around a randomised phase II screening design to detect a certain level of improvement in median PFS with the novel agent compared to placebo/observation. This will be with 90% power, at the 20% 1-sided level of statistical significance, or equivalent with 80% power at the 10% level of statistical significance. If the observed PFS in favour of the novel agent is statistically significant at 10%, this will be a clear signal that subsequent phase III trial is warranted. A result that is statistically significant at the 20% level, but not the 10%, will require supportive data, such as reduction in size of measurable disease, before a subsequent phase III trial would be considered.

The study analysis plan will be universal across all subgroups. All analyses will be conducted on an intention-to-treat basis, with progression-free survival compared between the trial arms in the context of a Cox model incorporating baseline minimisation factors. The p-value for the observed hazard ratio will be determined from this model. The maximum percentage decrease in measurable disease will be compared using a Mann-Whitney U test. Progression-free survival will be illustrated using Kaplan-Meier plots and

worst toxicity grades during chemotherapy will be compared using the Mann-Whitney U test.

6.3. Benchmarking patient preferences of genomic testing in ATLANTIS

Adaptive trial designs, such as ATLANTIS, allow features of the trial to be altered as evidence accrues across the study. These include changes such as participant numbers, processes for patient selection and modification of subgroups as participants respond to therapies or not. The adaptive design has the potential to evaluate comparative effectiveness of different treatments during the trial, rather than waiting for its completion. This has relevance for rare disease states, or genomic signatures, where specific subgroups may be under represented in a traditional study design. In the case of an ineffective trial subgroup, newly enrolled participants can also potentially still be randomised into the remaining cohorts where equipoise still exists. In addition, when prior information indicates that a trial population should be more narrowly focused, based on genomic profiling, the improved target enrolment criteria have the potential to motivate participants because the trial more closely mirrors their unique experience. Through the application of such clinical trial methods, it is possible to improve the quality of care for participants.

Multiple advances in quality improvement methodologies have focused on reliability and validity of how clinicians, patients and organisations perform specific functions of healthcare. These are reflected in process-of-care indicators such as cancer treatment waiting times, clinical trial recruitment rates as well as clinical outcomes of efficacy and morbidity from treatment. For each of these processes, identification of a realistic, achievable, ‘gold standard’ performance, or benchmark, should be incorporated. For each process-of-care indicator, there are inherent clinical, organisational and patient-centric factors meaning perfect benchmarks are unlikely to be achievable in the clinical arena. For

example, preferences of patients and healthcare providers means it is unlikely there will be 100% attainment of cancer waiting times initiatives. It is, therefore imperative that established benchmarks of performance are realistic and achievable.

6.3.1. Aims of benchmarking exercise

The aim of this benchmarking exercise was to assess whether the ATLANTIS clinical trial incorporated patients' preference attribute themes of genomic testing identified in this thesis. In order to do this, a descriptive benchmarking exercise was performed, comparing the ATLANTIS trial against the identified 'best practice' benchmark preferences attribute themes of genomic testing.

6.3.2. Methods

Multiple techniques have been developed to evaluate outcomes based on effectiveness research methodologies (Hunsley and Lee 2007, Minami et al 2008). Benchmarking allows researchers to compare results of treatment conducted in natural settings to best practice standards (Hunsley and Lee, 2007). Kiefe et al described benchmarking as 'the identification of industry leaders so that their practices can be understood and emulated.' The definition and classification of benchmarking vary between authors, depending on the time and criteria they focus on. The core aspects of evaluation and improvement by learning are embedded across the different forms of benchmarking (Ball 2000, Buyukozkan and Maire 1998, Carpinetti 2002, Longbottom 2000, Watson 1993).

In order to be effective, benchmarking must ensure performance metrics are correlated with consumer needs and be part of a continual process resulting in effective outcomes. There is no standard system for reporting benchmarking methodology, stemming from differences among industries regarding the nature and complexity of its application. For

example, Maleyeff et al (2001a) reported a system for benchmarking healthcare facilities using metrics related to patient care. The statistical sophistication of these systems range from no statistical analysis to methods such as data envelope analysis (Madu and Kuei, 1998).

Analysis and reporting of benchmarking include both qualitative and quantitative methodologies. The benchmarking framework developed by Hunsley and Lee (2007), involves comparison of variables, participant completion rates and major study outcomes with a 'best practice' benchmark. Other benchmarking healthcare studies (Curtis et al 2009, Minami et al 2007) also incorporate effect sizes for each intervention.

Due to its theoretical nature, this benchmarking study was limited by lack of quantitative measurable study outcomes to assess effect sizes, so outcomes were analysed descriptively. This qualitative research process involved gathering and distilling extensive descriptive data into a few key messages or ideas (Cresswell, 1998). This study descriptively assessed incorporation of preference attributes of genomic testing within the ATLANTIS trial. Previous benchmarking studies employed qualitative descriptive analysis to describe outcomes and provide in-depth analysis (Hubert and Gardner, Webb 2009, Arnold and Zink, Driscoll, Still and Strang 2008).

The implementation of benchmarking methodologies, as described by Hunsley and Lee (2007) incorporate four steps:

1 – Identification of the population and treatment

2 – Selection of a 'best practice' benchmark

3 – Measurement of outcomes against the benchmark

4 – Comparison of outcomes to the benchmark

6.3.3. Identification of patient population

The benchmarking study assessed inclusion of patient preference attributes within the ATLANTIS clinical trial design. The population and treatment under consideration for the benchmarking exercise therefore mirrored the eligibility criteria for the trial.

6.3.4. Selection of 'best practice' benchmark

As demonstrated in Chapter 3, there is very sparse empirical evidence assessing patient preferences of genomic testing in precision cancer medicine trials, such as ATLANTIS, on which to base 'best practice' benchmarking. This thesis identified and rated patient preference attributes of genomic testing. This benchmarking study therefore utilized the identified preference attribute themes as the 'best practice' against which the ATLANTIS trial was compared.

These preference attributes, in order of descending rating score are:

- Regulatory/NHS approval
- Test turnaround time
- Invasiveness of testing
- Physician approval
- Test sensitivity/true positive
- Test specificity/true negative
- Prevalence of variant
- Distance to travel
- Implications for family
- Family approval

6.4. Results

Regulatory/NHS approval

The ATLANTIS trial met the regulatory approval preference attribute benchmark meeting standard UK ethical and clinical trial conduct and governance frameworks. The trial will was conducted in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000, Washington 2002, Tokyo 2004, Seoul 2008). Each participating site required to comply with Good Clinical practice (GCP) and was not activated until local Clinical Trial Agreement is signed between Research and Development office and trial sponsor. The accruing trial data was monitored by an Independent Data Monitoring Committee (IDMC) assessing any safety or efficacy issues that should be brought to participants' attention or reasons for the trial recruitment to cease.

The regulatory approval process enshrined in clinical trials in the UK supported ATLANTIS meeting the regulatory/NHS approval benchmark attribute. Each participating site was required to meet these standards of conduct, supporting participants' confidence on the trial. This attribute was considered universal across UK clinical trials and is not unique to ATLANTIS.

Test turnaround time

The patient pathway in ATLANTIS incorporated genomic and other molecular testing throughout the pre-screening phase. This design minimised the impact of test turnaround time by exploiting the opportunity to test during first line chemotherapy, which is around eighteen weeks for most patients. This relied on early identification of potentially eligible patients to allow biomarker screening. The anticipated test turnaround time in ATLANTIS is 14 days from receipt of sample at the central laboratory. The central laboratory

processing of samples was anticipated to maintain consistency of test turnaround time across all participants in the trial, when compared to local testing. One key strength of the ATLANTIS design is that test turnaround time did not defer treatment starting or randomisation.

When benchmarking ATLANTIS against the best-practice attributes, test turnaround time was anticipated to meet patient preferences. This was reliant on early patient identification throughout first line chemotherapy. The central testing maintains parity of turnaround time across the whole study population, whilst not delaying time until randomisation or starting treatment.

Invasiveness of testing

Patients with UC had initial diagnostic biopsy performed as standard of care prior to commencement of first line chemotherapy. Patients in ATLANTIS did not require additional tumour biopsy nor tissue collection, presuming sufficient archival tissue from diagnostic sample for molecular profiling. Patients with insufficient archival tissue for molecular screening would be required to undergo repeat tissue biopsy if they wish to participate in the trial. It was anticipated this would be a small number of participants. This contrasts some precision medicine trials, which mandate repeat tumour biopsies to determine genomic signature at different time points or for trial eligibility. Patients in ATLANTIS had additional venepuncture tests compared to standard of care, where patients did not have further maintenance therapy. Patients were be informed of this during the consent process and documented within the trial specific patient information sheet prior to embarking on any trial-related interventions.

ATLANTIS incorporated the preference attribute theme for invasiveness of testing, given they were not required to undergo further invasive testing or re-biopsy prior to trial entry. This was balanced against the scientific premise that biomarker expression within an individuals' tumour can change throughout its lifetime, including during cytotoxic chemotherapy. There was therefore, the possibility not repeating biopsy testing may result in errant genomic signatures that may not be truly reflective of the patients' tumour at the screening and initiation of trial therapy. The design in ATLANTIS reduced burden of repeat biopsy for patients and reflected the pragmatic study design. This contrasts to some PCM studies, where repeated biopsy is necessary to meet eligibility criteria.

Physician approval

Investigators at each site were responsible for identifying potentially eligible patients, discussing the trial and screening processes. This involved local research nurses and other clinical staff, including the patients' own physician. Patients were able to discuss the trial in detail with their physician and the merits of study enrolment prior to proceeding with molecular testing or entry into the main study. It was therefore envisaged that participation in ATLANTIS will augment the patient-doctor relationship already in place at local centres, supporting decision-making around study entry. This would lend itself to ATLANTIS having incorporated this preference attribute for testing.

Test sensitivity/specificity

The statistical design of ATLANTIS acknowledged test sensitivity and specificity need to be high to maintain scientific as well as patient-centric validity. The test sensitivity/specificity is unique to each molecular subgroup within the study. For patients enrolled in the trial, sensitivity or specificity of each molecular test will likely not be known at point of trial pre-screening. This information may be discovered throughout the

lifetime of the trial. Some arms of the study, such as the HRD biomarker arm, utilised pre-existing data to inform on likely sensitivity/specificity based on experience from other disease settings but this was not be uniform across all subgroups.

The ATLANTIS trial incorporated large volume molecular tumour profiling for patients entering the pre-screening stage. The study aimed to determine predictive biomarkers of response, with data published as the study matures. There was potential to align data produced in ATLANTIS with other biomarker studies in the UK. It cannot be assumed this would provide information on test sensitivity or specificity for all patients enrolling in the study.

Prevalence of genomic variant

The adaptive design of ATLANTIS incorporated patients with molecularly defined subgroups of UC, alongside the cabozantinib arm for patients whose tumour profiling does not identify a novel agent-specific subgroup. It was therefore anticipated all patients meeting study eligibility criteria, having provided informed consent, will potentially be eligible to enter a component sub-study. The multi-arm design of the study allowed screening for multiple molecular signatures simultaneously. The novel design meant patients were screened for multiple molecular variants, potentially with low individual prevalence, within the single adaptive design. This leads to more efficient design for patients, including for low prevalence genomic variants. Patient's whose tumour do not meet pre-defined molecular subgroups, will still be eligible for inclusion in the cabozantinib component subgroup and were potentially be allowed to cross over if they meet eligibility for further molecular subgroups added in future.

The design of ATLANTIS favoured molecular signatures with low prevalence, tested simultaneously during the single pre-screening phase. This aligned with the identified benchmarking preference attribute, which ATLANTIS incorporates. This led to more efficient study design for patients, providing a platform for molecular testing rather than screening for discrete clinical trials of low prevalence molecular profiles.

Distance to travel

The ATLANTIS trial was conducted across more than 30 centres in the UK. This allowed most patients access to study enrolment via their existing cancer centre. Molecular screening for central biomarker analysis could be done on archival tissue and avoided complex specimen transfer for participating sites. The study used drugs with an established safety profile, so participating sites did not require a centre specialising in early phase trials or comprehensive critical care facilities. In the setting where a patients local cancer centre is not participating in ATLANTIS, patients may be required to travel to the nearest participating site. This could lead to financial and time implications for patients participating in the study, although the anticipated number of patients for whom this would apply were small.

ATLANTIS incorporated this benchmarking attribute by facilitating central testing of archival tissue retrieved from local pathology departments, removing the need for patients to travel for testing. ATLANTIS was supported across multiple UK sites, facilitating patient recruitment across wide geographical section of the country. This allowed representative national patient sample as well as reducing travel commitments for patients who wish to enrol in the study.

Implications for family

There is an increasing awareness of potential for genomic testing to unmask molecular signatures reflecting germline mutations in an individual, which could have genetic implications for other family members. Patients in ATLANTIS were tested for DNA repair deficit phenotype, resulting in defects in a variety of genes including BRCA1/2, BAP1, PALB2, FANCD2 and ERC2. These DNA repair gene defects predict switching to maintenance therapy with PARP inhibitor in a BRCA-like patient subgroup may be beneficial. Evidence supports the development of PARP (poly(ADP-ribose) polymerase) inhibitors in patients with either germline or somatic BRCA-like mutations and also a wider group of patients with evidence of homologous recombination deficiency (HRD) associated tumours (Farmer, H., McCabe, N., Lord, CJ., et al, 2005). All patients in ATLANTIS had archival tumour tested for a composite HRD biomarker. This may lead suggestion of germline mutation in BRCA genes in some patients, with associated implications for other family members. This facilitates family members being appropriately screened for BRCA germline mutations, alongside therapeutic implications of prophylactic therapy or cancer screening. The information also posed ethical challenges for patients and investigators around confidentiality and disclosure of such information to family members. This was dealt with throughout the informed consent process for ATLANTIS, where patients were asked to opt in or out from discovering information which may pertain to possible inheritable cancer syndromes.

Genomic testing across multiple clinical trials has potential to reveal germline mutations with potential wider implications for patients and family members. Patients in ATLANTIS were tested for composite HRD biomarker, with potential implications for BRCA-type phenotype. During the study screening phase, all patients were be informed of this prior to pre-screening via the study specific patient information sheet and asked to provide

informed consent. Patients were offered the chance to opt in or out of receiving such information, though there is an appreciation this uncertainty still had potential to cause distress for patients.

Family approval of testing

Potential study participants were given time to consider the patient information sheet for ATLANTIS and sign informed consent prior to any trial-related activity. It was anticipated this allowed individuals time to personally consider trial enrolment, as well as discussion with family members. This preference attribute was not captured or recorded formally throughout the study, but may be reflected in the trial screening log of patient enrolment.

The design of ATLANTIS allows prolonged pre-screening period during first line chemotherapy. This allows participants time to consider the trial, discuss options with clinical staff and family members. This reduced time pressure and allowed time to reflect on biomarker testing with family members. It is not possible to empirically predict whether family members would endorsed the molecular testing within ATLANTIS. This would require validation with further qualitative analysis in parallel with the study design.

6.5. Discussion

The aim of this benchmarking exercise was to assess and describe the benchmarking of patients' preference attribute themes of genomic testing and how they are incorporated within the ATLANTIS trial. ATLANTIS is a flagship UK study in patients with advanced UC and represents an opportunity for the UK to innovate in development of precision targeted therapies. The novel adaptive design of ATLANTIS lends itself to incorporating multiple patient-centric factors laced throughout its architecture. The ten preference

attribute themes demonstrated throughout this thesis were benchmarked against the ATLANTIS trial.

The ATLANTIS trial incorporated many preference attribute themes. The adaptive study design allowed features to evolve as evidence accrued throughout the study. The study design and molecular testing lent itself to favourable benchmarking for test turnaround time. It incorporated molecular screening during first line chemotherapy, reducing delay in potentially commencing study screening and maintenance treatment. The adaptive umbrella design also favoured genomic variants with low prevalence, where patients were screened within the framework of a single study, reflecting an efficient design for patients. Within conventional study designs, patients with low prevalence genomic variants may have necessitated screening across multiple clinical trials, representing low yield of clinical trial entry and potential need for repeated tissue biopsy.

The molecular testing in ATLANTIS was performed on archival tissue, reducing the need for invasive testing, particularly re-biopsy for patients. This reduced number of screening tests performed compared screening for multiple targeted therapy trials. ATLANTIS also compared favourably to the benchmark attributes for regulatory approval, as it has regulatory and NHS approval throughout the UK alongside local approval at participating sites. This supported patient confidence the study is being conducted within regulatory governance frameworks within the UK and peer-reviewed throughout funding and regulatory processes.

The ATLANTIS study minimised distance to travel for participants by opening at over 30 centres with wide geographical distribution across the UK. There remains potential some patients may have to travel greater distances to a participating site than their local cancer

centre, but it was anticipate these would be small numbers. This attribute benchmark may be appreciated by assessment of the patient screening logs at participating sites and individual site feedback on recruitment.

The benchmarking attribute of physician approval for the study was difficult to quantify. Local site investigators were expected to offer study screening to potential patients in whom they feel it would be appropriate, reflecting an element of physician approval. It remains challenging quantifying this nor the impact it may have on patients suitable for the study. Local investigators discuss study screening procedures and would be anticipated to have an established pre-existing patient-clinician relationship.

Patients entering the ATLANTIS trial are unlikely to know the either sensitivity or specificity of testing, though it was possible in some subgroups. This information is one of the primary research questions in conducting such trials. The novel nature of the scientific and translational elements embedded within the study meant information would not necessarily be available to participants considering study enrolment. It may be possible for some subgroups to extrapolate from previous studies where data for enrichment exists or availability of sensitivity/specificity data if agents with positive efficacy signal in the trial are transferred to standard of care paradigms.

Molecular biomarker screening entailed HRD composite marker, with potential to select patients whose tumour displays a BRCA-like phenotype. In some individuals, this suggested, but not specifically test, potential germline mutations in BRCA genes. This has implications for other family members, with both positive and negative preference factors. Knowledge of germline BRCA mutations may allow other family members to be tested and potentially undergo prophylactic treatment or enhanced cancer screening. It did,

though, have potential psychological and emotional burden for patients and families at a time when they are dealing with their own life-changing cancer diagnosis. ATLANTIS biomarkers in future may highlight inheritable mutations pre-disposing to cancer or health conditions for which there are no therapeutic interventions available. This is a challenging field across the breadth of genomic testing and not unique to the ATLANTIS trial. This complex issue cannot be fully appreciated within the remits of this benchmarking exercise, but it is important it remains within the ATLANTIS informed consent process so that patients and family members can consider its implications prior to study screening.

The long interval during first line chemotherapy for screening in ATLANTIS facilitated patient discussion with clinicians as well as other family members. It is difficult to predict how family members perceived the ATLANTIS trial. Some inferences can be made from site screening logs and anecdotal consultations with individual patients, but robust assessment of this attribute would require validation via parallel qualitative research alongside the trial.

6.6. Conclusions

This thesis identified and rated patient preference attribute themes of genomic testing in precision cancer medicine, also demonstrating preferences were influenced by cancer treatment intent. The identified preference attribute themes were then utilised in a benchmarking exercise against the current ATLANTIS clinical trial, assessing patients' preferences were incorporated by a novel clinical trial design.

This benchmarking exercise demonstrated the novel design and research questions ATLANTIS incorporated many preference attributes of genomic testing in PCM. The three preference attributes with the highest mean attribute rating were regulatory/NHS

approval, test turnaround time and invasiveness of testing. The pragmatic adaptive study design incorporate these attributes, which reflected positively on the study design.

The ATLANTIS trial failed to fully incorporate some preference factors of genomic testing. These included attributes that were not fully predicted at the time of testing, such as test sensitivity/specificity or family implications of testing. This in part reflected the innovative approach of molecular stratification for patients. This information may become apparent throughout the lifetime of ATLANTIS, though the average life-expectancy of participants with advanced urothelial cancer means these individuals may never be aware of these results. The role of genomic profiling and discussion of its implications remains a challenge for the wider precision medicine community in ATLANTIS as well as other precision medicine studies.

Chapter 7. Discussion and Conclusions

7.1. Introduction

This thesis added to current knowledge by exploring how, through mixed methods research, patients' preferences of genomic testing in PCM were identified, rated and benchmarked against a current UK clinical trial. This thesis explored the novel hypothesis that preference attributes and ratings were influenced by clinical treatment intent and time since completing therapy.

This thesis demonstrated feasibility of identifying and rating preference attribute themes and benchmarked these against a current PCM clinical trial, providing empirical evidence for patient preferences of genomic testing in PCM clinical trials. This thesis commenced by outlining the existing landscape of UK clinical trials, genomic testing and precision cancer medicine, then latterly defined primary thesis research questions (Chapter 1). Chapter 2 considered methodological approaches to answer the research questions of the thesis. Following on from this, a systematic review of the literature (Chapter 3) was conducted, to identify and rate patient preference attributes of genomic testing in PCM.

Throughout Chapter 4 and into Chapter 5, the thesis outlined employed methodology alongside results which identified and rated preference attribute themes of genomic testing. Chapter 6 benchmarked the identified preference attribute themes of genomic testing against a current PCM clinical trial.

This concluding chapter will revisit the thesis research questions and summarise the key findings of each. The links to wider literature and context will be discussed in parallel with strengths and limitations of the work. Finally, this chapter will consider anticipated policy and clinical trial design implications of the work.

7.2. Revisiting the thesis research questions

7.2.1. How are patient preferences of genomic testing in PCM defined and rated?

This was the first empirical research identifying and rating patient preference attributes of genomic testing in the UK across a breadth of cancer subtypes. The concepts underpinning genomic testing transcend the breadth of diagnostics and therapeutics with intertwined physician, policy-maker and patient preferences. The systematic review in chapter 3 illustrated lack of empirical evidence assessing patient preferences of genomic testing in the era of PCM. The study by Issa et al demonstrated patient-centric attributes of genomic testing in specific clinical settings such as Oncotype DX in breast cancer and KRAS/UGT1A1 in colo-rectal cancer, though these may not be fully applicable to the wider cancer patient population out with these two tests. The study by Najafzadeh was confounded by the fact that it only incorporated 38 patients and had 1,058 healthy volunteers from the population. The employed hypothetical clinical scenarios were also aligned with treatment paradigms in treatment of patients with lymphoma, which may not be applicable to the wider cancer patient population.

The study by Cuffe et al explored patient preferences of chemotherapy treatment but without consideration of genomic testing. This study also considered the novel hypothesis that patient preferences were influenced by cancer treatment intent. Patients who received adjuvant therapy put greater significance on cure rate and efficacy, whereas patients with metastatic cancer had higher preference for predicting response and test turnaround time. These identified studies were performed within North American participant groups and may, therefore, not be fully applicable to the UK cancer patient population.

Through collating and presenting the existing evidence identifying and rating patient preference attributes of genomic testing, chapter 3 identified that prior to assessing how current UK Clinical trials incorporate patient preferences of PCM, key patient preference attributes needed to be identified and rated. The current evidence provided a clear directive that assessing patient preferences must also consider individual patient context such as clinical treatment intent influencing preference attributes and ratings. This supported design of the mixed methods research study used throughout this thesis.

Given these considerations and in order to answer the research questions of this thesis, an empirical study was required which identified and rated patient preference attributes of genomic testing in PCM. Chapter 4 discussed the methodological considerations in order to answer these research questions. The mixed methods research design employed Nominal Group Technique (NGT). The complexity of genomic testing, paired with low patient experience of PCM, led to high cognitive burden for participants. NGT methodology helped support participants through appropriate moderation and study design.

Chapter 5 presented results of the NGT study and identified ten preference attribute themes with associated mean ratings. The attribute ratings demonstrated patient preferences of genomic testing are influenced by clinical treatment intent. Patients who received treatment with radical intent rated regulatory/NHS approval, test sensitivity and test specificity as the first, second and third highest order preference attribute themes, respectively. Patients having received treatment with palliative intent rated invasiveness of testing, test turnaround time and physician approval as first, second and third highest order preference attribute themes, respectively.

This research provided empirical evidence the promise of genomic testing in PCM is not uniform across patient groups. Clinical treatment intent should be considered when assessing its impact in the clinical arena. This thesis added weight to existing evidence patients facing a life-limiting incurable illness have different preferences of genomic testing to those facing therapeutic decisions on radical cancer treatment. Whilst acknowledging these results are subject to limitations, this provides an indication that, in answer to the thesis research questions, patient preferences of genomic testing are influenced by clinical treatment intent.

7.2.2. Do current clinical trial designs incorporate patient preference attributes of genomic testing in PCM?

Clinical trials remain the method for investigating and validating novel therapies and genomic tests prior to regulatory approval. Having established evidence of key patient preference attributes of genomic testing, chapter 6 explored how these attributes were incorporated within a UK PCM clinical trial. This thesis ran chronologically in parallel with design of the ATLANTIS clinical trial, so results did not directly inform the study design, but may inform future clinical trial design or amendments.

The ATLANTIS trial is a flagship UK study for patients with advanced urothelial cancer and represented an opportunity for the UK to innovate in development of precision targeted therapies in this patient group. The novel adaptive design of ATLANTIS lent itself to incorporating multiple patient preference attribute themes of genomic testing. This thesis research ran in parallel with implementation of ATLANTIS, so its results were a retrospective narrative rather than informing study design. The study benchmarked the ATLANTIS trial against the ‘gold standard’ preference attribute themes identified throughout this thesis.

The benchmarking exercise demonstrated the novel design of ATLANTIS incorporated many patient preference attribute themes of genomic testing. The first, second and third highest order preference attribute themes were regulatory/NHS approval, test turnaround time and invasiveness of testing, respectively. The pragmatic design of the trial, with genomic screening based on archival tissue, did not necessitate further invasive testing and minimised concerns of test turnaround time, given testing was performed during first line chemotherapy. The highest order preference attribute, regulatory/NHS approval, was supported within a national clinical trial endorsed by the robust standards of clinical trial conduct and Good Clinical Practice (GCP) in the UK.

The ATLANTIS trial did not fully incorporate the preference attributes of test sensitivity/specificity or family implications of testing. This in part reflected these are primary research questions the study aimed to answer. This evidence may become apparent throughout the lifespan of the trial, but such data would not always be known at the point of genomic testing for a patient entering the study. The role of genomic profiling and its potential to confer germline or inheritable genomic profiles is a challenge for the wider precision cancer medicine community. It may not be possible to identify presence or clinical relevance of all germline genomic genomic signatures at trial entry, with the potential uncertainty this could cause patients. This was dealt with in ATLANTIS via the informed consent process. Patients were offered the opportunity to opt in or out of discussions about potential inheritable or clinically significant genomic signatures identified by study pre-screening.

7.3. Implications for policy and clinical practice

This thesis was the first in the UK to empirically identify and rate patient preferences of genomic testing across a spectrum of cancer subtypes and assess its incorporation in clinical trials. This research identified ten patient preference attribute themes of genomic testing, along with providing evidence these attributes and preference ratings were context-specific, being influenced by factors such as cancer treatment intent. As a result, clinicians, clinical trialists and policy makers need to ensure they have a clear understanding of how individual patient context influences preferences of genomic testing. This thesis demonstrated patients receiving treatment with radical clinical intent identified different preference attributes themes and ratings compared to patients treated with palliative intent.

This research demonstrated the identified preference attribute themes were all valued by patients, and thus, future provision of genomic testing supporting patient preferences should not exclude one attribute for another. The number of identified attribute themes, paired with number of patients rating multiple, reflects the complex interaction between many preference attributes.

As discussed in Chapter 1, PCM challenges existing clinical trial designs addressing large populations of patients. This thesis outlined the sparse empirical evidence assessing patient preferences of genomic testing within PCM clinical trials. The novel adaptive design of a single clinical trial design incorporated many preference attribute themes, whilst providing evidence of the challenges incorporating attributes including implications of inheritable mutations. This thesis provided the first empirical evidence that novel pragmatic clinical trial designs can address many patient preference attributes of genomic testing.

7.4. Study strengths and limitations

7.4.1. Study strengths

This thesis was the first to study patient preferences of genomic testing within the UK healthcare setting and its incorporation within a PCM clinical trial. This drew on qualitative identification of preference attribute themes followed by quantification of attribute ratings. This built on existing literature assessing patient preferences of genomic testing and supported the hypothesis patient preferences are context-specific with regard to clinical treatment intent. Using NGT allowed a realistic decision-making format for patients in order to identify preference attribute themes and ratings. The use of mixed methods research incorporated both qualitative identification and quantitative rating of preference themes.

This research involved patients across a wide spectrum of fourteen solid cancer subtypes including patients having received, or still receiving, an array of cancer treatment including surgery, radiotherapy, chemotherapy, immunotherapy, endocrine therapy, but the participant group had limited personal experience of precision cancer medicine. Previous studies incorporated large numbers of healthy volunteers, which can lack robust application to cancer patient preferences. This thesis recruited 102 patients, all of whom had personal experience of cancer diagnosis and therapy, making results more applicable to this population.

Previous studies, conducted in North America, demonstrated preferences for specific tests such as Oncotype DX in breast cancer or KRAS in colo-rectal cancer, though these cannot readily be extrapolated to the wider cancer population, as preference attribute themes and

prioritisation may be unique to this subgroup or genomic test. These attributes are also not directly comparable to the patient population within the UK healthcare system.

This work further informs policy and clinical trial design by demonstrating patient preference attribute themes of genomic testing and benchmarked these against a current PCM clinical trial. The clinical trial favourably incorporated many of these patient preference attributes, whilst also highlighting the challenges still facing novel clinical trial designs incorporating some others.

7.4.2. Study limitations

This thesis explored the current literature identifying patient preference attribute themes of genomic testing. As discussed in Chapter 3, there were sparse empirical studies assessing patient preferences of genomic testing and none within the UK. There were also no previous studies assessing incorporation of preference attributes within PCM clinical trials.

The study sampling strategy included participants having received cancer therapy within a single centre in the West of Scotland. The identified preference attributes and ratings were applicable to this patient population, but may not be fully representative of patients from out with this geographical region or healthcare setting. Participants were also recruited to this study having either attended previous patient support groups or attending oncology follow-up clinics within the Beatson West of Scotland Cancer Centre. This had potential to add patient selection bias, since participants were very motivated to attend and participate in the research project. This had potential to recruit patients of higher socio-economic group and those out with full-time employment. These participants, having attended prior survivorship groups, may also have prior experience and greater understanding around clinical paradigms of PCM than the wider cancer patient population,

leading to bias. The participants in this study, therefore, may not be fully representative of the wider cancer patient population across the UK.

Allocation to subgroups within the study were based on participant-reported perception of cancer treatment intent. This was done to reduce potential upset to participants of revisiting their cancer medical records and history, which may alter the relationship they have with the group moderator. Given this study examined patient preferences, their perceptions of events have equal weight to the clinician-perceived outcomes of an individuals' cancer care. This, though, does not confirm the clinical validity of individual cancer treatment intent.

This thesis explored patient preferences of genomic testing across a wide range of tumour subtypes, given the promise of PCM transcends tumour histologies. This, therefore, does not focus on one specific genomic test, so may lack applicability for individual patients facing therapeutic decisions around a single genomic test in clinical practice. This thesis did, though, add to existing literature by identifying transferrable preference attribute themes which could be considered when applying principles to a specific genomic test.

This study employed mixed methods research design to identify and rate patient preference attribute themes of genomic testing in PCM. One limitation of this design is that it did not allow exploration of potential interactions or trade-offs between different attributes. The design was selected due to high cognitive burden of preferences within the infancy of the PCM paradigm for patients. This allowed moderator involvement and support for participants addressing these complex issues, whilst ensuring the research questions were addressed throughout the Nominal Groups. This did, though, lead to possibility of introducing further bias, by having a cancer clinician acting as group moderator. It is

possible participant responses may have been influenced by the presence of a clinician. The study design attempted to mitigate this effect by always having a second moderator, who was a non-clinical member. This study mirrored decision-making for patients around genomic testing in real-life, which would be performed in a clinical arena. The design of this study reflected this paradigm.

This thesis used a benchmarking exercise of the ATLANTIS trial. The limitation of using this solitary study is that it involved a single tumour type and only incorporated patients' treatment with palliative intent. The use of ATLANTIS, a trial in which the thesis author is readily involved, had potential to introduce bias as non-independent assessment. The author had involvement with the implementation of the trial, which may have altered perceptions of the applied benchmarking exercise. The benchmarking exercise may, therefore, not be entirely applicable to other clinical trials. One outcome of the benchmarking exercise, though, was to demonstrate the application of the 'benchmark' preference attributes identified throughout this thesis and how they could be applied to a single study. This benchmarking exercise could, therefore, be applied to other clinical trials within the PCM arena, as was demonstrated by this thesis.

7.5. Future research

This thesis identified and rated patient preferences of genomic testing, then assessed how these were incorporated within a novel PCM clinical trial design. The timeframes for clinical trial approval and conduct meant the thesis study could not be engrained within the trial or influence design. It would be interesting to empirically examine whether preference attributes could be assessed in conjunction with a clinical trial, linking cohort data to the attributes identified in this thesis. Such work may be suited to qualitative

methodology such as focus groups, structured interviews or longitudinal patient questionnaire.

Following on from the work in this thesis, it would be interesting to research preferences of genomic testing by both funders and the general population. This would give a comparator with patient preferences and potentially balance the priorities of different stake holders. The current study did not allow assessment of interaction and trade-offs between multiple inter-related attributes. Future studies could consider this in defining trade-off thresholds for preference attribute themes.

7.6. Conclusions

This thesis contributed to the understanding of how patient preferences of genomic testing can be identified and rated in their own right as well as incorporation within a novel adaptive clinical trial design. Involvement of patient preferences is seen as a barometer for high quality comprehensive clinical care, promoting empowerment and engagement. This thesis identified the limitations of previous empirical evidence assessing patient preferences of genomic testing and incorporation in clinical trials. Throughout the NGT and benchmarking studies, this thesis identified and rated preference attributes which can be used by clinical trialists and policy makers in order to ensure PCM retains patient-centred values at its core and engrained throughout clinical trial design.

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Appendix 1 – PRISMA CHECK LIST

Appendix 1. PRISMA Checklist for studies included in systematic review

Section/topic	*#*	*Checklist item*	*Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	55
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	55
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	56
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	58
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A

Section/topic	*#*	*Checklist item*	*Reported on page #*
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	58
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	56
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	57
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	57
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	59
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	56
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	59
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	61
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	*#*	*Checklist item*	*Reported on page #*
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	61
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	61
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	62
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A

Section/topic	*#*	*Checklist item*	*Reported on page #*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	69
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	73
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	74
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Appendix 2 – Data extraction tables of studies included in systematic review

Study	Country	Methodology	Participant characteristics	Attributes assessed	Attribute levels	Reported outcomes
Najafzadeh et al 2013	Canada	Discrete choice experiment of theoretical scenarios (aggressive curable versus non-aggressive incurable cancer)	Total of 588 participants 550 healthy volunteer participants 38 patient participants	Invasiveness of testing	Mouth swab, blood test, tumour, bone marrow or liver biopsy.	Factors with greatest impact on patient decision-making were: Severity and likelihood of toxicity, sensitivity/specificity of testing, invasiveness of testing. Type and prognosis of cancer also affected preferences for genomically-guided treatment.
				Genomic test sensitivity	5, 20, 35 and 50%	
				Genomic test specificity	5, 20, 35 and 50%	
				Side-effects	Mild, moderate or severe	
				Test turnaround time	2, 7 or 12 days	
				Cost of testing	Can$50, $500, $1000 or $1500	
				Privacy of results	Patient and doctor, PD and insurance company, PDI and employer.	

Study	Country	Methodology	Participant characteristics	Attributes assessed	Attribute levels	Reported outcomes
Cuffe et al. 2014	Canada	Hypothetical trade-off clinical scenario questionnaire (either metastatic or adjuvant setting). Utilised probability trade-off testing.	244 patient participants	Primary attribute: Efficacy of therapy (adjuvant group)	5-50%	Factors with greatest impact on patient preferences were: Adjuvant group: efficacy of therapy Metastatic group: toxicity of therapy Median Willingness To Pay (WTP) across the study was CAD$1000-2000.
				Primary attribute: Toxicity of therapy (metastatic group).	2.5-40%	
				Both groups: cost of testing, waiting time and prevalence of genomic signal		

Study	Country	Methodology	Participant characteristics	Attributes assessed	Attribute levels	Reported outcomes
Issa et al 2015	USA	Discrete choice experiment utilising genomic testing scenarios in breast and colorectal cancer	300 patient participants (previous history of breast or colorectal cancer)	Cost of genomic testing	US$25, $100, $500, $1000, $2000, $4000	Factors with the greatest impact on patient preferences were: Probability of efficacy Predictive value of testing High willingness to pay for genomic testing
				Privacy of results	Patient and doctor, PD and insurance company, PDI and employer.	
				How test is used	Doctor decides, patient decides or patient and doctor decide. Insurance company use to determine coverage	
				Predictive value of testing	Positively predict response 55%, 70%, 80%, 90%, 96% or 99%.	
				What information will test provide	Recurrence risk, recurrence/likelihood of benefit from chemotherapy, recurrence risk/likelihood of toxicity from chemotherapy, benefit from chemotherapy and likelihood of toxicity.	

Appendix 3 – Mixed Methods Appraisal Tool (MMAT) methodological quality criteria

Category of study design	Methodological quality criteria. Study: Genomic testing to determine drug response: measuring preferences of public and patients using a DCE (Najafzadeh).	Responses		
		Yes	No	Can't tell
Screening questions	S1. Are there clear research questions?	X		
	S2. So the collected data allow to address the research questions?	X		
	Further appraisal may not be feasible or appropriate if answer is no to both questions			
Qualitative	1.1. Is the qualitative approach appropriate to answer research questions?			
	1.2. Are the qualitative data collection methods adequate to address research questions?			
	1.3. Are findings adequately derived from data?			
	1.4. Is the interpretation of results sufficiently substantiated by data			
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?			
Quantitative randomised controlled trials	2.1. Is randomisation appropriately performed?			
	2.2. Are the groups comparable at baseline?			
	2.3. Are there complete outcome data?			
	2.4. Are outcome assessors blinded to the intervention provided?			
	2.5. Did the participants adhere to assigned intervention?			

Category of study design	Methodological quality criteria. Study: Genomic testing to determine drug response: measuring preferences of public and patients using a DCE (Najafzadeh).	Responses		
		Yes	No	Can't tell
Quantitative non-randomised	3.1. Are the participant's representative of the target population?			
	3.2. Are the measurements appropriate regarding both the outcome and intervention (or exposure)?			
	3.3. Are there complete outcome data?			
	3.4. Are the confounders accounted for in the design and analysis?			
	3.5. During the study period, is there intervention administered (or exposure occurred) as intended?			
Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research questions?	X		
	4.2. Is the sampling representative of the target population?		X	
	4.3. Are the measurements appropriate?	X		
	4.4. Is the risk of non-response bias low?	X		
	4.5. Is the statistical analysis appropriate to answer the research question?	X		
Mixed methods	5.1. Is there adequate rationale for using mixed methods design to address the research question?			
	5.2. Are the different components of the study effectively integrated to answer the research question?			
	5.3. Are outputs of integration of qualitative and quantitative components adequately interpreted?			
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?			
	5.5. Do the different study components adhere to the quality criteria of each tradition of methods involved?			

Category of study design	Methodological quality criteria. Study: A national study of breast and colorectal cancer patient's decision-making for novel personalised medicine genomic diagnostics (Issa, Tufail, et al).	Responses		
		Yes	No	Can't tell
Screening questions	S1. Are there clear research questions?	X		
	S2. So the collected data allow to address the research questions?	X		
	Further appraisal may not be feasible or appropriate if answer is no to both questions			
Qualitative	1.1. Is the qualitative approach appropriate to answer research questions?	X		
	1.2. Are the qualitative data collection methods adequate to address research questions?	X		
	1.3. Are findings adequately derived from data?	X		
	1.4. Is the interpretation of results sufficiently substantiated by data	X		
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?	X		
Quantitative randomised controlled trials	2.1. Is randomisation appropriately performed?			
	2.2. Are the groups comparable at baseline?			
	2.3. Are there complete outcome data?			
	2.4. Are outcome assessors blinded to the intervention provided?			
	2.5. Did the participants adhere to assigned intervention?			

Category of study design	Methodological quality criteria. Study: A national study of breast and colorectal cancer patient's decision-making for novel personalised medicine genomic diagnostics (Issa and Tufail, et al).	Responses		
		Yes	No	Can't tell
Quantitative non-randomised	3.1. Are the participant's representative of the target population?			
	3.2. Are the measurements appropriate regarding both the outcome and intervention (or exposure)?			
	3.3. Are there complete outcome data?			
	3.4. Are the confounders accounted for in the design and analysis?			
	3.5. During the study period, is there intervention administered (or exposure occurred) as intended?			
Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research questions?	X		
	4.2. Is the sampling representative of the target population?	X		
	4.3. Are the measurements appropriate?	X		
	4.4. Is the risk of non-response bias low?		X	
	4.5. Is the statistical analysis appropriate to answer the research question?	X		
Mixed methods	5.1. Is there adequate rationale for using mixed methods design to address the research question?	X		
	5.2. Are the different components of the study effectively integrated to answer the research question?	X		
	5.3. Are outputs of integration of qualitative and quantitative components adequately interpreted?	X		
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	X		
	5.5. Do the different study components adhere to the quality criteria of each tradition of methods involved?	X		

Category of study design	Methodological quality criteria. Study: Cancer patients' acceptance, understanding and willingness-to-pay for pharmacogenomics testing (Cuffe et al).	Responses		
		Yes	No	Can't tell
Screening questions	S1. Are there clear research questions?	X		
	S2. So the collected data allow to address the research questions?	X		
	Further appraisal may not be feasible or appropriate if answer is no to both questions			
Qualitative	1.1. Is the qualitative approach appropriate to answer research questions?	X		
	1.2. Are the qualitative data collection methods adequate to address research questions?	X		
	1.3. Are findings adequately derived from data?	X		
	1.4. Is the interpretation of results sufficiently substantiated by data	X		
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?	X		
Quantitative randomised controlled trials	2.1. Is randomisation appropriately performed?			
	2.2. Are the groups comparable at baseline?			
	2.3. Are there complete outcome data?			
	2.4. Are outcome assessors blinded to the intervention provided?			
	2.5. Did the participants adhere to assigned intervention?			

Category of study design	Methodological quality criteria. Study: Cancer patients' acceptance, understanding and willingness-to-pay for pharmacogenomics testing (Cuffe et al).	Responses		
		Yes	No	Can't tell
Quantitative non-randomised	3.1. Are the participant's representative of the target population?			
	3.2. Are the measurements appropriate regarding both the outcome and intervention (or exposure)?			
	3.3. Are there complete outcome data?			
	3.4. Are the confounders accounted for in the design and analysis?			
	3.5. During the study period, is there intervention administered (or exposure occurred) as intended?			
Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research questions?	X		
	4.2. Is the sampling representative of the target population?	X		
	4.3. Are the measurements appropriate?	X		
	4.4. Is the risk of non-response bias low?	X		
	4.5. Is the statistical analysis appropriate to answer the research question?	X		
Mixed methods	5.1. Is there adequate rationale for using mixed methods design to address the research question?	X		
	5.2. Are the different components of the study effectively integrated to answer the research question?	X		
	5.3. Are outputs of integration of qualitative and quantitative components adequately interpreted?	X		
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	X		
	5.5. Do the different study components adhere to the quality criteria of each tradition of methods involved?	X		

Appendix 4 – Patient preference attribute summary tables

Ten preference attribute themes emerged from the data generated in the nominal groups after the clarification stage. There were thirty four attributes identified at the end of the round robin, which were taken into the clarification stage. These preference attribute themes are shown below.

Identified preference attributes theme after NGT clarification stage	**Preference attributes identified on whiteboard after round robin stage**
Invasiveness of testing	1 – 'Soreness of test' 2 – 'Whether biopsy or blood test' 3 – 'Test to be simple and not intrusive' 4 – 'The least painful test'
Regulatory/NHS approval	5 – 'The test approved so my doctor can authorise it' 6 – 'I know tests need NHS approval' 7 – 'If a test is really good enough then I have faith the NHS would approve it, so I would feel more confident in it'
Test sensitivity/true positive	8 – 'If I had the genetic thing being tested then I would want the test to find it' 9 – 'I would want the test to pick up the variant almost all the time and not miss an opportunity that could benefit me' 10 – 'The test should be accurate in showing me the problem'
Test specificity/true negative	11 – 'I would want to know if I don't have the thing being tested, rather than waste time with treatment that may not help me' 12 – 'I would want to correctly know if I don't have the variant, rather than waste anyone's time'

Physician approval	13 – ‘I trust my doctor and if they feel it’s a good idea then I’d probably go for it’ 14 – ‘My doctor knows me and my case best, so if she agreed then I’d try it’ 15 – ‘If my consultant wanted to put me forward’ 16 – ‘I trust my doctor to know what’s best for me.’
Family approval	17 – ‘I would not want to upset my family and if they pushed me then I would probably do it’ 18 – ‘I know they care so I would think about it, my wife helps me with all the difficult decisions in my life’ 19 – ‘My family go through everything with me, so I would need their support for this too.’
Distance to travel for testing	20 – ‘They can’t do some tests in my local hospital, another patient I knew had to travel to England and he found it hard’ 21 – ‘I would like it to be near home if possible’ 22 – ‘I would struggle to travel, that would make me anxious.’ 23 – ‘I wouldn’t want to travel somewhere the medical team don’t know me.’
Test turnaround time	24 – I remember so much worry at that time and the days went so slowly waiting for results’ 25 – I wouldn’t want to wait for results’ 26 – Don’t want it slowing down my treatment starting’ 27 – ‘Time is precious to me and I don’t want to waste it waiting for results’

Implications for family members of testing	28 – ‘This may help my daughter being diagnosed sooner than I was’ 29 – ‘I would feel so much guilt to know I may have passed something onto my children’ 30 – ‘I do not know how I would tell my family, but would prefer to know’ 31 – ‘As a parent, I would want to protect my children’
Prevalence of variant	32 – ‘How commonly is the result positive’ 33 – ‘How many people the test has a result that would help them’ 34 – ‘The chance of actually having the genomic thing if it’s very rare’

Appendix 5 – Pilot Nominal Group Study guide (v1.0)

General Introduction

Each nominal group will have the same set of interview questions and will be conducted by two moderators. Demographic questionnaires will be collected prior to the beginning of the nominal groups.

'Welcome to our session. We wish to thank you for taking the time to join us in talking about genomic testing in precision cancer medicine. Introduce self (names of moderators). We would like to develop effective genomic tests that are valued by cancer patients. In order to develop such tests, we need firstly to understand the attitudes of patients regarding cancer testing. These nominal groups we are holding are a first step in this proceed. We are going to have further similar discussions with groups of patients over the coming weeks.

You have been invited to attend because you have each previously been diagnosed with cancer and received cancer treatment here in the West of Scotland. In our discussions today, there are no right or wrong answers, but rather differing points of view. Our hope is to gather all of these points of view, so please feel free to share yours, even if it is different to what has been suggested by the rest of the group. Although you may not necessarily agree with the views of others, we would be grateful if you would listen respectfully as others share their views and that only one person talks at a time. We would be very grateful if the discussions we have today remain in this room, in order to respect the confidentiality of everyone participating.

We have placed name cards on the table in front of you, so please let us start by finding out some more about each other by going around the table. Moderator to start and introduce

self, name and what you hope to achieve form today's session. Then invite next participant to follow suit until all participants have done so.

Stage 1 - Silent generation of ideas

Now we would like to ask some questions about your experiences of cancer, diagnosis, testing and treatment. We would like you to take some time on your own to think about your personal experiences of cancer testing. What were the main features/attribute of a genomic cancer test that you feel would have either a positive or negative effect on your preference towards having that test? Please take a few minutes to think about this yourself and write down your answers.

Stage 2 – Round robin

After everyone has written down their answers and is ready, we will go around the table in turn and ask people to share one from their list until all the items have been heard. As you read out the items, we will write them on the whiteboard as a record for us all to see.

Stage 3 – Clarification

Once all items have been shared, we will discuss each of them in turn and why they were selected. Then we will have one long list of responses. It is possible that different people may use similar terms to describe the same response, so we will discuss these with the whole group to come up with a final list and can combine some if they refer to the same response/attribute. As a group, you will decide this.

Stage 4 – Rating of preference attribute themes

The group will have a full list from Stage 3 of the responses regarding the attributes of a genomic test from and at this point we will ask you each individually to rate each item by

writing these on the printed paper which we will provide for you. This is done by giving a score of 9 to the item which you feel is most important to you, 8 to the item you feel next most important and so on. You do not have to give a score to every item on the list if you do not feel it applies to you. For this part, you do the rating on your own and can consider any of the information you have heard during the prior discussions.

We will then collect the individual rating paper sheet from each of you and will collate all the information. If you wish, then you can wait and we will discuss preliminary results of this with you, or you can attend a further update session at a later date if you wish more detailed summary of the group results.

Conclusion

We have come to the end of our nominal group session for today. We would like to sincerely thank each of you for participating today and those who helped bring you to this group session. Does anyone have any final questions?

Appendix 6 – Main Nominal Group Study Guide (v2.0)

General Introduction

Each nominal group will have the same set of interview questions and will be conducted by two moderators. Demographic questionnaires will be collected prior to the beginning of the nominal groups.

'Welcome to our session. We wish to thank you for taking the time to join us in talking about genomic testing in precision cancer medicine. Introduce self (names of moderators). You have been invited to attend because you have each previously been diagnosed with cancer and received cancer treatment here in the West of Scotland and so have personal experience of cancer tests and treatment. We appreciate that many patients will not have personal experience or possibly much awareness of precision cancer medicine. Precision cancer medicine is an approach to patient care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their cancer. This idea is not new, but recent scientific advances have helped speed up the pace of this area of research. In the past, when a patient is diagnosed with cancer, they usually receive similar treatment as others who have the same type and stage of cancer. Even so, different people may respond differently and until recently doctors did not know why. With emerging scientific discovery, doctors now understand that patients' tumours have genetic changes that cause cancer to grow and spread. These changes may occur in one individual but no another.

If there is a targeted treatment that is approved for your type of cancer, you will likely be tested to see if the genetic change targeted by the treatment is present in your tumour. This test can be done in many different ways. We would like to develop these effective genetic tests that are valued by cancer patients. In order to develop such tests, we need firstly to

understand the attitudes of patients regarding cancer testing. These nominal groups discussions we are holding are a first step in this proceed. We are going to have further similar discussions with groups of patients over the coming weeks.

In our discussions today, there are no right or wrong answers, but rather differing points of view. Our hope is to gather all of these points of view, so please feel free to share yours, even if it is different to what has been suggested by the rest of the group. Although you may not necessarily agree with the views of others, we would be grateful if you would listen respectfully as others share their views and that only one person talks at a time. We would be very grateful if the discussions we have today remain in this room, in order to respect the confidentiality of everyone participating.

We have placed name cards on the table in front of you, so please let us start by finding out some more about each other by going around the table. Moderator to start and introduce self, name and what you hope to achieve form today's session. Then invite next participant to follow suit until all participants have done so.

Stage 1 - Silent generation of ideas

Now we would like to ask some questions about your experiences of cancer, diagnosis, testing and treatment. We would like you to take some time on your own to think about your personal experiences of cancer testing. What were the main features/attribute of a genomic cancer test that you feel would have either a positive or negative effect on your attitude towards that test? Please take a few minutes to think about this yourself and write down your answers.

Stage 2 – Round robin

After everyone has written down your answers and is ready, we will go around the table in turn and ask people to share one from their list until all the items have been heard. As you read out the items, we will write them on the whiteboard as a record for us all to see.

Stage 3 – Clarification

Once all items have been shared, we will discuss each of them in turn and why they were identified. Then we will have one long list of responses. It is possible that different people may use similar terms to describe the same idea, so we will discuss these with the whole group to come up with a final list and can combine some if the group feel they refer to the same response/attribute.

Stage 4 – Rating of preference attribute themes

The group will have a full list from Stage 3 of the responses regarding the attributes of a genomic test from and at this point we will ask you each individually to rate each item by writing these on the printed paper which we will provide for you. This is done by giving a score of 9 to the item which you feel is most important to you, 8 to the item you feel next most important and so on. You do not have to give a score to every item on the list if you do not feel it applies to you. For this part, you do the rating on your own and can consider any of the information you have heard during the prior discussions.

We will then collect the individual rating paper sheet from each of you and will collate all the information. If you wish, then you can wait and we will discuss preliminary results of this with you, or you can attend a further update session at a later date if you wish more detailed summary of the group results.

Conclusion

We have come to the end of our nominal group session for today. We would like to sincerely thank each of you for participating today and those who helped bring you to this group session. Does anyone have any final questions?

Appendix 7 – Ethics Approval

NHS
Health Research Authority
London - Bromley Research Ethics Committee
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 104 8049

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 September 2016

Dr Ben Fulton
Level 4
Beatson West of Scotland Cancer Centre
1053 Great Western Road, Glasgow
G12 0YN

Dear Dr Fulton

Study title:	**Focus groups to determine patient preference factors and attitudes towards precision cancer medicine.**
REC reference:	**16/LO/1665**
Protocol number:	**N/A**
IRAS project ID:	**203595**

The Proportionate Review Sub-committee of the London - Bromley Research Ethics Committee reviewed the above application on 06 September 2016.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Maeve Ip Groot Bluemink, nrescommittee.london-bromley@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Appendix 8 – Participant Consent form

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDY

Title of Project:

Nominal group research to determine patient preferences for genomic testing in precision cancer medicine.

Please initial box

1. I confirm that I have read and understand the information sheet dated 23/05/2016 (v2.0) for the above research study, that I fully understand what is involved in taking part in this research study, and that I have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my information may be looked at by representatives of the study Sponsor (NHS Greater Glasgow and Clyde) for audit purposes. ☐

4. I understand that the focus groups sessions will be audio-recorded. ☐

5. I agree to take part in the above research study. ☐

Please sign and date below:

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed, 1 original for participant; 1 original for researcher;