

A clinical and ethical evaluation of secondary findings in the era of clinical whole-genome sequencing



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A thesis submitted for the degree of

Doctor of Philosophy

Trinity 2017



Incidental Findings, Jane Pearce, 2016

This piece was produced through a collaboration between the Wellcome Trust Centre for Human Genetics and the Oxford Printmakers Cooperative. The artist, Jane, developed the image through discussions with me about the work in this thesis.

The following was provided by the artist: '*Incidental Findings* was printed in oil based ink on Fabriano paper from two metal plates using a Rochat intaglio press. The chromosomes were etched on a copper plate (chosen because of this particular metal's ability to take deep, but clear edged, biting of the lines in acid). This plate is printed in green and yellow, with added chine collé (fine Japanese paper pieces applied with bookbinders glue), to emphasise the downward movement. The spiral of children, unexpected finding and figure with jar (suggesting Mendel, or perhaps Pandora's box) was etched on a zinc plate for a softer, delicate appearance. This plate is printed in burnt umber.'

Acknowledgements

This piece of work would not have been possible without the support of so many people. First, I want to thank my supervisors: Professor Hugh Watkins, for providing me the opportunity to explore my own curiosities, and for his unwavering support and guidance throughout the process; Professor Michael Parker, for providing an invaluable counterbalance to the clinical side of my project, and for his wisdom throughout the writing process; and, Dr Liz Ormondroyd, for being a sounding board and a oft-needed reality check, for helping me learn to navigate academia and qualitative research, and for her provision of the constant support that a wayward graduate student so desperately needed.

I would also like to thank the wider genetics community in Oxford—I have learned so much from their allowing me to come along to meetings, and attend various clinics. Thank you, in particular, to the Oxford Molecular Genetics Laboratory for their insights and the analysis that contributed to this thesis. I would also like to thank the Watkins Group, and the Division of Cardiovascular Medicine, for the invaluable discussions and for giving a home to a diehard geneticist. A special thanks to Kate Thomson, for her friendship and invaluable technical guidance. Finally, I would like to thank Professor Andrew Wilkie and the whole Wilkie lab for their confidence, warm welcome, and for helping me find my feet.

I would not have had this opportunity without generous financial support. First, I would like to thank the Rhodes Trust and everyone at Rhodes House—Mary Eaton, Warden Charles Conn, and all of the staff (especially the porters)—for the care and friendship they have shown me throughout my time in Oxford. To the Radcliffe Department of Medicine, for providing me license to pursue my interests and supporting me at every turn in the road. Finally, to St John's College, for putting a roof over my head, and for allowing me to take my work around the world.

To my flatmates and friends, thank you for the laughs, the adventures, and for putting up with all of my 'beans'. You have left an indelible mark on my life, and I am a better person for having known you. A special thanks to those who provided research, editorial, or technical support (Dylan, Courtney, Mahesh, and others). To my friends, mentors, and family in Canada—especially Mom, Dad, Melissa, Michelle, Jerry, the Stevensons, and the whole clan—thank you for your unending faith and support, I hope I have made you proud.

Lastly, to Julianne: thank you for your relentless belief in me, surpassing my own in myself. Thank you for following me around the world in pursuit of that belief, and for being there at the end of each day—in person or over FaceTime—with unwavering love and support. I admire your fierce defence of what you believe in, and only hope to capture a glimmer of that in what I do. Also, thanks for telling me when not to use a semi-colon.

Abstract

With transformative initiatives like the UK's 100,000 Genomes Project underway, vast amounts of data from genome sequencing are being generated. Genomic results are being actively returned to participants, although policies around their management remain inconsistent and a subject of debate. Secondary findings (SF) have been of particular concern—variants associated with health conditions other than the indication for sequencing, which may or may not be medically actionable. I have conducted a mixed methods study to explore the current transitional period and the issue of secondary findings, and inform future management. Following a narrative review of the literature around SF in genome sequencing and a focused systematic review of primary studies on stakeholder views towards the subject (*Part I*), gaps in the current literature were identified. These were, chiefly: (1) the need for diverse stakeholder views based on experience making actual decisions around SF; and, (2) empirical data—phenotypic, psychological, behavioural—on actual returned SF. Thus, taking advantage of the local programme of translational genome sequencing, I conducted qualitative studies involving genomic healthcare professionals and genome sequencing participants, to explore their views towards genomic medicine and SF (*Part II*). Following this, I detail a case study illustrating the process and challenges of returning an SF, as well as outline a study designed to collect empirical data on actual returned SF and present preliminary data to this end (*Part III*). I illustrate that secondary findings will be a part of tomorrow's genomic medicine: cautious optional screening of actionable SF (including treatable conditions and carrier status information) appears favourable. However, if SF are to be a part of the genomic medicine paradigm, several barriers must be considered: insufficient connectivity between specialties, variant interpretation, clinical interpretation and management, and overpromise and expectations (including recontact in light of new information). In order to overcome these challenges, individuals in unselected populations must be prospectively phenotyped to derive more accurate estimates of population-level penetrance and better understand the full phenotypic spectrum, and we must explore the downstream impact of disclosure. As genome sequencing is mainstreamed, clear evidence-based guidelines for SF in genome sequencing will be essential if harms are to be minimised and benefits are to be maximised, both for participants and the healthcare system at large. At this point, albeit cautiously, we must 'learn by doing'.

List of publications

Manuscripts contributing to thesis

Mackley MP, Blair E, Parker M, Taylor JC, Watkins H, and Ormondroyd E. Views of rare disease participants in UK whole-genome sequencing study towards secondary findings: a qualitative study. *Accepted*.

Ormondroyd E, **Mackley MP**, Blair E, Craft J, Knight JC, Taylor JC, Taylor J, and Watkins H. (2017). 'Not pathogenic until proven otherwise': Perspectives of UK clinical genomics professionals towards secondary findings in the context of a Genomic Medicine Multidisciplinary Team and the 100,000 Genomes Project. *Genetics in Medicine*. epub 26 Oct 2017.

Mackley MP, Capps B. (2017). Expect the unexpected: screening for secondary findings in clinical genomics research. *British Medical Bulletin*. 122(1): 109-22.

Ormondroyd E, **Mackley MP**, Blair E, Craft J, Knight JC, Taylor J, Taylor JC, Wilkie AOM, and Watkins H. (2017). Insights from early experience of a Rare Disease Genomic Medicine Multidisciplinary Team: a qualitative study. *European Journal of Human Genetics*. 25(6): 680-86.

Mackley MP, Fletcher B, Parker M, Watkins H Ormondroyd E. (2017). Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: a systematic review of quantitative and qualitative studies. *Genetics in Medicine*. 19(3): 283-93.

Conference abstracts during DPhil

Mackley MP, Parker M, Watkins H, Ormondroyd E. Careful deliberations and limited desire to know: insights from whole-genome sequencing providers and recipients on secondary findings. *ELSI Congress 2017: Genomics & Society*. June 2017. The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut. Poster.

Mackley MP, Fletcher B, Parker M, Watkins H, Ormondroyd E. Factors influencing decision-making around secondary findings in whole-genome and whole-exome sequencing: a systematic review of qualitative and quantitative studies exploring the views of diverse stakeholders. *Association of Inherited Cardiac Conditions Conference*. December 2016. London, UK. Poster.

Mackley MP, Parker M, Watkins H, Ormondroyd E. Decision-making around secondary findings in genomics: insights from whole-genome and whole-exome sequencing recipients. *American Society for Human Genetics Conference*. October 2016. Vancouver, Canada. Poster.

Mackley MP, Fletcher B, Parker M, Watkins H, Ormondroyd E. Rights and responsibility in genomic decision-making: exploring stakeholder views on secondary findings in genomic sequencing. *European Human Genetics Conference*. May 2016. Barcelona, Spain. Poster.

Mackley MP, Ormondroyd E, Fletcher B, Parker M, Watkins H. Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: a systematic review. *International Congress on Human Genetics*. April 2016. Kyoto, Japan. Poster.

Statement of Contributions

I confirm that this thesis is wholly my own work. Certain elements of the chapters have been necessarily assisted by other individuals—where this is the case, initials are used. The contributions of others are as follows:

- **Elizabeth Ormondroyd** (EO) acted as an additional reviewer for the systematic review (*Chapter 3*). She also provided interview training, conducted the interviews with GM-MDT members (*Chapter 4*), which I observed, and supported my analysis of all interviews (*Chapters 4-6*). Dr Ormondroyd also guided the methodological development of the clinical study (*Chapter 7*).
- **Benjamin Fletcher** (BF) provided methodological support for the systematic review (*Chapter 3*) and acted as an additional reviewer, supporting data extraction and the critical appraisal of included studies.
- **Kate Thomson** (KT) conducted some of the preliminary computational work in the SCARFE study, including the initial variant filtering, and supported the subsequent variant analysis (*Chapter 7*).

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List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
ACMG56	original ACMG minimum gene list [1]
ACMG59	updated ACMG minimum gene list [2]
AMP	Association for Molecular Pathology
ARVC	arrhythmogenic right ventricular cardiomyopathy
BRRD	Cambridge Bioresource for Rare Disease
CCMG	Canadian College of Medical Genetics
ECG	electrocardiogram
EHR	electronic health records
ESHG	European Society of Human Genetics
ETT	exercise tolerance test
ExAC	Exome Aggregation Consortium [3]
GDR	genotype-driven recruitment
GM-MDT	Oxford Genomic Medicine Multidisciplinary Team
gnomAD	Genome Aggregation Database [3]
HCM	hypertrophic cardiomyopathy
HICF2	Health Innovation Challenge Fund WGS programme
HCP	healthcare professional
ICC	inherited cardiac condition
ICD	implantable cardioverter-defibrillator
IRB	institutional review board
LMM	Partners Laboratory for Molecular Medicine (Boston, USA)
LOF	loss of function
LQTS	long QT syndrome
MAF	minor allele frequency

MGAC	‘Molecular Genetic Analysis and Clinical Studies of Individuals and Families at Risk for Genetic Disease’
MRI	magnetic resonance imaging
NHS	National Health Service
NIHR	National Institute for Health Research
OMGL	Oxford Medical Genetics Laboratory (Oxford, UK)
OUHFT	Oxford University Hospitals NHS Foundation Trust
SCARFE	‘Secondary Cardiac Findings Evaluation’
SCD	sudden cardiac death
SF	secondary finding
VUS	variant of unknown significance
WGS	whole-exome and whole-genome sequencing, collectively

'The power of genomics is that it provides a broad view of the landscape of heritability—it is wasteful to discard variants in all genes other than primary causative variant.'

— Leslie Biesecker [4]

1

Thesis overview and introduction

Alex¹ is a three-year-old boy who has been diagnosed with hereditary spastic paraplegia, a rare inherited disease that causes weakness and spasticity in the lower limbs [5]. With time, walking will become increasingly difficult for Alex and he could eventually require a wheelchair. The disease is usually caused by a genetic variant causes nerve deterioration in the spine. In order to provide a genetic explanation for the diagnosis, and counsel Alex's parents on the probability of having another affected child affected, Alex's clinical team carried out genetic testing.

Unfortunately, routine genetic testing—where genes known to be associated with the primary condition are sequenced, in single gene tests or in multi-gene panels—yielded no results. At the time, however, there were several whole-exome and whole-genome sequencing projects underway. In patients or families with a suspected genetic disorder where single gene or panel testing fails to provide a genetic explanation, like Alex, genome sequencing is becoming widely available. In contrast to more targeted testing, genome sequencing involves the analysis of a significantly larger set of genetic information—the protein-coding parts of the genome, in the case of whole-exome sequencing, or an individual's entire genetic makeup, in the case of whole-genome sequencing (collectively, for this thesis, 'WGS'). With costs dropping dramatically, and our ability to interpret results

¹Alex and his family are real patients who underwent whole-genome sequencing in Oxford, but pseudonyms have been used throughout the thesis.

improving quickly, it is possible that WGS could completely replace panel tests in the foreseeable future. Having not found a result thus far, and desperate for an answer, Alex's clinical care team turned to WGS. As a trio strategy permits more sensitive identification of variants where de novo or compound heterozygote variants are expected [6], patients and both of their parents are often recruited. However, in this case, Alex was born from an egg donor, so a sample from his biological mother was not available. Thus, in order to find the cause of Alex's primary condition, both he and his father—David—were recruited into an Oxford-based WGS project.

While WGS provides a valuable opportunity to learn about genomic contributions to Alex's condition ('primary findings'), it also has the potential to reveal genetic information that may not pertain to hereditary spastic paraplegia—including variants associated with other health conditions, which may or may not be medically actionable. Such unrelated results, called 'secondary findings' (SF), are not unique to genetics or even new to medicine, but are becoming a more frequent concern due to the newfound feasibility of exploring the entire genome. With each human genome expected to contain around 100 genuine loss of function variants [7], SF in WGS are not exceptional, but inevitable.

1.1 Thesis aims and objectives

As genome sequencing is mainstreamed and moves from the realm of research and difficult-to-solve clinical cases into routine clinical care, so do the wider implications of the technology. Broadly, the primary aim of this thesis is to examine the issue of secondary findings in the era of diagnostic whole-exome and whole-genome sequencing. The main objectives are as follows:

1. To explore whether or not secondary findings should be sought and returned to individuals who undergo diagnostic WGS, as well as the various factors underlying reasoning as to whether or not different types of secondary findings should be sought and returned;
2. To investigate the extent to which there is sufficient empirical evidence on which to base decisions around the management of secondary findings in WGS; and,

3. To determine whether secondary findings, if sought and returned, will pose challenges and barriers to the translation of WGS into clinical practice.

1.2 Research methodology

To complement the quantitative and qualitative nature of the research objectives, a mixed methods study design will be employed. To achieve the above, literature-reviewing methods will be used in conjunction with qualitative methods (semi-structured interviews) and clinical study. As the methods are diverse, relevant details will be provided in each chapter. Additionally, a recurring narrative detailing a single case (Alex and his family) is used to connect the different studies. This serves to highlight challenges, embed the work in practice, and reinforce the collective importance of the separate components to the experience of WGS participants—the individuals who serve to benefit from, or be harmed by, the return of SF.

1.3 Context and setting

The large WGS programmes currently underway in Oxford are operating at the interface of research and clinical contexts: participants are recruited in clinical settings for clinical purposes, but the projects also carry research aims. This blurring of the boundary between research and clinical contexts is representative of the current state of genomics (and will be revisited in *Chapter 2*). Thus, this thesis explores SF in WGS in both research and clinical domains, with a focus to applications in a translational or clinical context.

Within these domains, however, WGS can be used in different ways. My thesis will focus on the use of WGS in diagnostic sequencing for hereditary rare diseases. Thus, SF in WGS in the context of somatic cancer sequencing (where a tumour-matched normal strategy is employed) or screening without a primary indication (such as with direct-to-consumer testing) will not be explored in any detail. These situations lack a hereditary primary condition, and are not the focus of the Oxford WGS programmes that form the basis of my empirical dataset.

1.4 Structure of thesis

The thesis will be divided into three parts, as follows:

Part I provides a critical review of the current state of affairs around secondary findings in WGS based on a systematic search of the current literature. *Part I* serves to set the stage for *Parts II* and *III* by identifying gaps in current evidence.

- **Chapter 2** presents a narrative review of ethical commentaries, guidelines and recommendations, policy statements, legal commentaries, and empirical evidence on SF in WGS.
- **Chapter 3** presents a systematic review of quantitative and qualitative studies exploring stakeholder views on secondary findings in WGS.

Part II builds on the results of *Part I*, providing an in-depth exploration of local stakeholder views on secondary findings in WGS by collecting primary data through interviews.

- **Chapter 4** presents a semi-structured interview study, with genomics healthcare professionals in Oxford, exploring their views and experiences of genomic medicine and SF.
- **Chapter 5** presents a second semi-structured interview study, with rare disease patients and family members enrolled in a local WGS programme, exploring their views on SF.

Part III also builds on the results of *Part I*, and provides a preliminary exploration of the clinical utility of SF in WGS.

- **Chapter 6** presents an in-depth case study of a cardiac SF returned to a participant enrolled locally in WGS. This chapter serves to explore the utility and impact of returning such variants, as well as illustrate the challenges of doing so.
- **Chapter 7** outlines a study designed to assess the clinical utility of cardiac SF in WGS, aiming to provide some of the much-needed evidence as identified in *Part I*. The chapter focuses on participant ascertainment and variant interpretation, presenting these preliminary results.

At the beginning of each part, background information and methods relevant to the included chapters will be provided. The three parts will be followed by a broad discussion (**Chapter 8**) that seeks to synthesise the findings of each part, explore the barriers SF pose to the mainstreaming of WGS, as well as what is required to overcome these challenges.

PART I
The current state of the field

Despite a seemingly recent interest in the subject, secondary findings (SF) are not new to genetics, or even medicine at large. The issue of SF in imaging diagnostic tests is well described [8, 9]. Ranging from x-rays to modern magnetic resonance imaging (MRI), it is possible that imaging for one diagnostic purpose could reveal a previously unknown abnormality—such as neoplasms, cysts, or microbleeds. In radiology, such findings would likely lead to more precise imaging and pathological analysis [10]. This has the benefit of initiating treatment pre-symptomatically, but risks causing psychological harm by causing unnecessary distress, or medical harm from complications of unneeded procedures, if a false positive is returned [10]. Consensus in medical imaging is that such findings are unavoidable, and in cases of clinical urgency warrant return [11]. As imaging technologies improve, the incidence of SF has increased [9].

Secondary findings in genetics

The same phenomenon has been observed in clinical genetics—as the capabilities of these technologies increase, so does the incidence of SF. Early forms of genome-wide testing, such as karyotypes and chromosomal microarrays, have well-documented cases of SF [12, 13]. Such technologies can yield additional findings, ranging from gene deletions to chromosome abnormalities. However, since the advent and newly widespread use of WGS, the issue of SF in genetics has dramatically increased. These technologies produce vast amounts of data, and provide very fine resolution—allowing for potentially lethal single base pair variants to be detected ‘incidentally’.

Despite the common use of diagnostic imaging by WGS providers to help describe SF in genomics, this analogy requires careful scrutiny. Unlike imaging technologies, the downstream process following an SF in genetics is much less clear and straightforward [10]. Interpreting genomic SF is complicated by our limited knowledge of the effect of individual variants, the inability to detect clinical features for variants that are only predictive or conditions that are late-onset, and the range of possible indications [10]. There are two further critical areas where SF differ in genomics from radiology: the implications for family members, and the issue of recontact [14]. Unlike lesions on an MRI, genetic variants are shared within families—this could result in additional family members needing to be screened, raising a unique set of practical issues. Our changing knowledge of genetic variation raises questions as to whether individuals should be recontacted in light of new evidence—a practice that would be logistically complex and resource-intensive [15]. Furthermore, rather paradoxically, unlike in diagnostic imaging, many SF in genomics have to be intentionally sought [16]; the process of searching for, and analysing, such variants amongst the other thousands generated during WGS is an active one.

Despite these challenges, such findings may be validated and might be clinically useful; early discovery could lead to better clinical outcomes such as through knowledge of response to specific drugs, or the opportunistic detection of a variant that could lead to treatment or informed reproductive choices. Other findings, however, may point to predispositions for which there are no interventions available—‘utility’, if any, is limited to behavioural changes and life planning. Others findings will be benign, and if it were not for their chance discovery, they would unlikely ever be known. This raises the question as to whether such findings should be returned, or even sought in the first place. It is this question that has been the source of significant debate, and the focus of this part of my thesis.

Defining ‘secondary findings’ in WGS

In order to explore the debate around secondary findings in WGS it is important to provide a definition. When the use of genome-wide analysis was mostly limited to a research setting, Wolf et al. [17] defined SF as ‘a finding concerning an individual research

participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study'. As the clinical use of WGS became more of a reality, a distinction between its use in screening asymptomatic individuals and its use as a diagnostic tool for a specific set of symptoms arose [18]. This is apparent in the definition provided by the American College of Medical Genetics and Genomics (ACMG): 'Pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing was ordered' [1]. While this thesis will explore SF in both research and clinical contexts, the distinction between screening and diagnosis is important: in this thesis I focus on SF discovered during WGS for a specific indication, and not the testing of healthy individuals (unless in the case of trio sequencing or cascade screening). Thus, I will employ the following definition for 'secondary findings':

Potentially disease-causing variants in genes that do not pertain to the participant or family member's presenting condition—including variants associated with other health conditions, which may or may not be medically actionable.

I also acknowledge the variability in terminologies around such variants in the context of WGS. Differences in the use of terms—'incidental', 'additional', 'secondary'—range from unintentional to deliberate. Thus, a detailed discussion of the language around SF, and a rationale for my own use of terminologies will be undertaken later (Section 2.6).

Section outline and objectives

It is clear that while secondary findings in WGS have the potential to improve health outcomes, but they also present novel challenges for healthcare professionals (HCP) and are a source of significant debate in the genomics community. As more individuals are subjected to WGS, it is valuable to collect and review data that might inform this debate, so that WGS initiatives maximise clinical utility and contribute to ethical healthcare delivery. The overall aim of *Part I* of this thesis is, therefore, to present a critical review of the current state of research and literature around SF in WGS. In addition to summarising the literature, and highlighting areas of disagreement, I aim to identify gaps in the existing literature to highlight areas for further research. This is achieved in two distinct reviews:

- **Chapter 2** employs a narrative approach to summarise and synthesise the existing literature around SF in WGS—including policies, guidelines and recommendations, legal literature, ethical commentaries, and empirical data.
- **Chapter 3** presents a rigorous systematic review and synthesis of studies that have explored stakeholder views towards SF in WGS, including both qualitative and quantitative studies.

2

Background: a narrative review of secondary findings in whole-exome and whole-genome sequencing

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As large WGS initiatives get underway around the globe, the likelihood of—and opportunity to—generate secondary findings (SF) in genomic sequencing data grows. It is therefore timely to collect and review data that might inform the debate around secondary findings in WGS. Such a review is also essential to identify gaps in current knowledge and inform the research I will undertake in the rest of this thesis. In particular, existing guidelines and recommendations, ethical commentaries and legal literature from other countries will serve to inform my exploration of views and practices around SF

in Oxford (*Part II*). Furthermore, a summary and assessment of the current empirical evidence on SF from WGS will inform my work on the clinical utility of such findings in practice (*Part III*).

In order to illustrate the current state of research around SF in WGS and inform my own primary data collection, I have conducted a narrative review of existing literature on the topic. I highlight, in particular, areas of disagreement and controversy. Additionally, I highlight gaps in the current evidence base as a means of guiding the work in the subsequent chapters of this thesis. I have published features of this review in the *British Medical Bulletin* as first author [19].

2.1 Chapter aims and objectives

The overall aim of this chapter was to explore the current landscape around secondary findings in the era of whole-exome and whole-genome sequencing. As per the wider thesis, this aim was addressed in both the clinical and research settings. The specific objectives were to:

- Provide a critical review of the literature around secondary findings in WGS;
- Highlight areas of controversy and disagreement around SF in WGS;
- Provide a summary of existing data on the incidence and impact of SF in WGS; and
- Identify gaps in the literature, highlighting areas for further research.

2.2 Literature search methods

It was decided that in order to comprehensively identify literature around secondary findings in WGS that a systematic search would be undertaken. Such a search strategy ensures that the widest range of literature is captured, in a rigorous and reproducible manner. An information specialist from the Bodleian Libraries was consulted in the development of the search strategy, which then formed the basis of this review, as well as the review presented in *Chapter 3*.

A systematic search of the following six databases was conducted: PubMed, Web of Science, SCOPUS, MEDLINE, PsychINFO, and Philosopher's Index. These searches

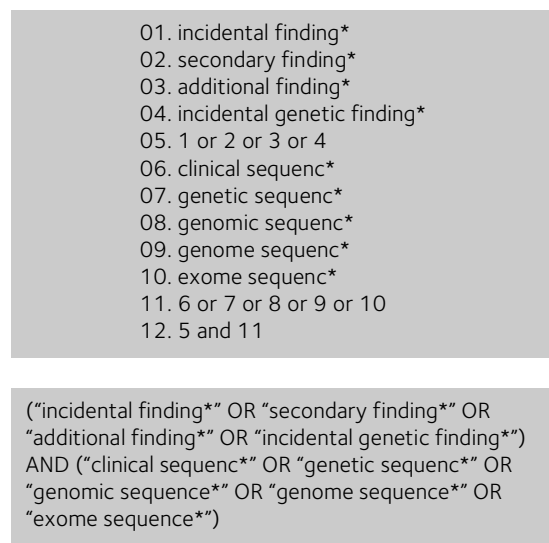


Figure 2.1: Systematic literature search strategy.

were conducted in January 2015, and included all literature in the searched databases from their date of inception. Searches were comprehensively updated in May 2016, and electronic updates from PubMed were included through December 2016. Additional papers, published since the conclusion of the review, have been integrated where relevant. The search included 'incidental findings' as well as its synonyms ('secondary findings', 'additional findings') and terms for 'clinical sequencing' ('genetic sequencing', 'genomic sequencing', 'genome sequencing', 'exome sequencing') (Figure 2.1). The results of each of the searches were exported to Endnote X7 [20], where duplicates were discarded.

After the initial search, exclusion and inclusion criteria were applied to the articles, by reading their titles and abstracts, and in some cases their full text. Initially, articles were excluded if they were non-human, did not discuss WGS, or if they included no (or only superficial) discussion of SF. Publications were ultimately included if they presented detailed or insightful discussions or data pertaining to SF in a human context. Secondary findings specifically for minors are not discussed at length in this review or thesis at large, as I acknowledge that SF in this context raises additional issues and could warrant their own review. Thus, in consultation with my supervisors, I decided to limit the scope of this review (and the wider thesis) to SF in adults.

Due to the recent nature of most of the research, many articles on this topic were difficult to capture. The initial search and screening was followed by reference scanning and

snowballing, where the bibliographies of the papers that met the eligibility criteria were searched by hand to find additional articles that are relevant to the review. In an effort to capture literature not published in an academic journal, such as organisational guidelines and meeting reports, I conducted additional searches outside of these databases while snowballing. I searched databases for governmental reports (PAIS International), grey literature sites (www.greylit.org, www.opengrey.edu), the websites of key organisations (ACMG, ESHG, CCMG, etc.), and conducted focused searches through Google. These searches, however, returned no results that were not captured by the database searches.

2.3 Systematic search results

In order to generate a broader library on the concept of secondary findings in diagnostic sequencing, articles were binned into six categories based on field or methodology: (1) ethical commentaries, (2) legal commentaries, (3) guidelines and recommendations, (4) theory and review papers, (5) empirical clinical studies, and (6) studies reporting on the views of stakeholders. The results of the search from January 2015, in which the conception of this entire piece of work is situated, are shown in Figure 2.2.

It was decided that the ‘bin’ containing papers about stakeholder views warranted its own independent review, as there were a large number of similar studies and no up-to-date reviews. Therefore, these papers were subjected to further methods and formed the basis of a systematic review (presented in *Chapter 3*), and their content will not be reviewed in detail in this chapter. The other categories (1-5) formed the basis of this review.

2.4 Ethical considerations around SF

With each human genome expected to contain around 100 genuine loss of function variants [7], SF in WGS are inevitable. This has necessarily resulted in discussion around the disclosure of SF, both in research and clinical contexts—including the increasingly blurred area in between. Here, I present a brief review of arguments identified in the systematic search offered in support and opposition of disclosing SF generated

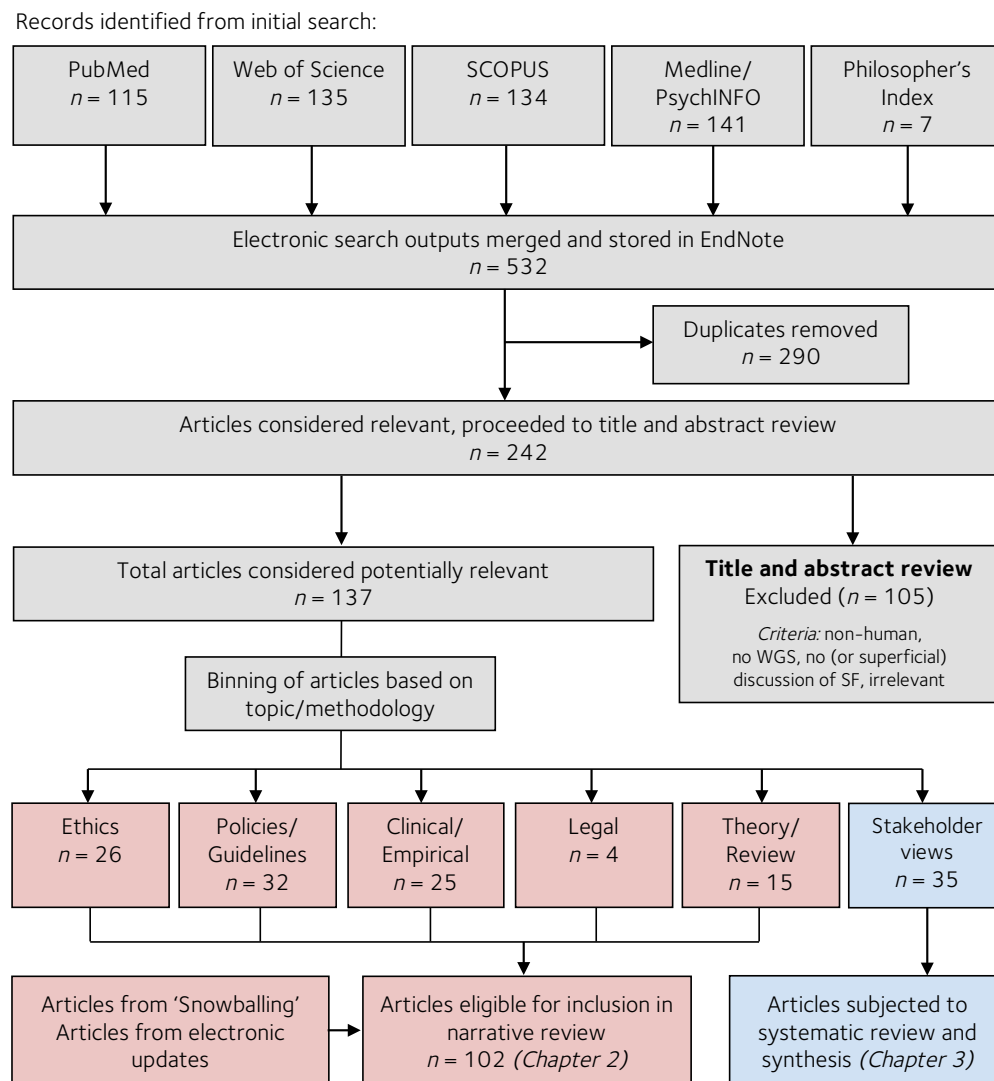


Figure 2.2: Results of electronic database search in January 2015

during WGS—only distinguishing between research and clinical contexts when this is critical to the argument offered.

2.4.1 Published arguments against disclosure of SF in WGS

The most commonly cited argument against the disclosure of SF is that, in the absence of clinical utility, or even in cases where knowledge of a predisposition might allow for behaviour modification to minimise risk, it is possible for findings to cause anxiety and psychological harm in participants [17, 21–23]. Similarly, some commentators raise the potential for harm by overloading participants with information [23–25], or through discrimination or stigmatisation [21, 26]. Some also argue that disclosing SF in a non-

clinical context promotes ‘therapeutic misconception’ [22–24, 27], leading participants to harmfully assume research will benefit them clinically [17]. These harms are not limited to the individual subjected to WGS, as SF could have implications for family members [24, 28, 29]. Furthermore, some argue that these family members, as well as the proband, all have a right not to know that needs to be respected [30]. Other arguments against SF disclosure largely revolve around feasibility: our developing of knowledge of the utility of certain findings [23, 31], lack of expertise in certain contexts [22–24] and justice issues around the added burden on resources and research infrastructure [22, 23].

2.4.2 Published arguments in support of disclosure of SF in WGS

While the arguments for non-disclosure are diverse, support for disclosure of SF in WGS is dominated by the promotion of wellbeing, and best interest of the participant. SF with clinical utility¹ have the potential to inform treatment or aid in disease prevention, and are thus valuable to the wellbeing of the participant [17, 23, 24, 27–31, 34–37]. Such is the case in medical imaging, where consensus is that secondary findings are unavoidable, and in cases of clinical urgency warrant return [11]. Furthermore, in the case of genetic SF, this benefit potentially extends to family members [29]. Other arguments have included that participants have a ‘right to know’ such information [38], and that reciprocity in research—wherein participants are not completely altruistic and expect to derive some benefit—necessitates disclosure [22].

2.4.3 Autonomy and informed consent

Participant autonomy is neither an argument in support of, nor in opposition to, disclosure of SF, but a critical consideration in the return of such results. Commentators widely hold that, regardless of the approach to disclosure taken, informed participant consent—and the resulting choices around SF disclosure—is central to the process. In a widely cited analysis of the ethical issues around SF, Wolf et al. [17] concluded that there is an obligation to explicitly address the possibility of SF in consent documents and in communication with participants at the outset. It is essential that participants are informed

¹Broadly, **clinical utility** is the ability of an intervention or test (here, WGS) to prevent or improve health outcomes through the adoption of screening or treatments based on the results of the test [32, 33].

of the potential for SF, their implications, whether such findings will be returned, and asked which they would want returned (if any). This serves to maximise their autonomy, regardless of the range and nature of results on offer—respecting both their ‘right to know’ and their ‘right not to know’. However, some commentators highlight challenges associated with respecting participant autonomy. This might include when the patient has not been asked about such findings and a life-threatening SF is detected [39]. In certain circumstances, some argue that an SF that is life-threatening and treatable might be cause to override a participant's decision not to receive SF [27]. Such findings not only have implications for the participant who made the decision, but also their relatives [29].

2.4.4 To disclose or not to disclose?

In a systematic review of ethical arguments around SF disclosure, Christenhusz et al. [39] found beneficence to be the strongest guide for disclosure. Accordingly, Lohn et al. [18] demonstrated that many authors have concluded that the benefits of disclosure outweigh the risks, and that full non-disclosure is ethically indefensible. Equally, many concede that complete disclosure is impractical [18]. While pressure is mounting to offer participants raw sequence data, Wright et al. [40] have shown that there are significant challenges to doing so, and argue that such policies have the potential to do more harm than good. Thus, in practice, the extreme positions of full disclosure and non-disclosure are seldom supported [11, 22]. Many of the aforementioned arguments opposing disclosure more accurately reflect support of a very restricted disclosure, and arguments supporting disclosure more accurately reflect support of a wider qualified disclosure policy—one which respects participant autonomy. Precisely where consensus, if any, will sit between these lesser extremes is not yet clear.

2.5 Guidelines and recommendations

With full disclosure of SF being economically and logistically unfeasible, and complete non-disclosure being unethical due to the potential benefits of some SF, a middle ground must be found [18]. Since the publication of many of the aforementioned ethical arguments, various sets of guidelines and recommendations specific to WGS have begun to emerge

from professional organisations, research groups and foundations aiming to guide the management of SF. An early well-cited strategy, proposed by Berg et al. [34], involved a system of ‘binning’, whereby SF were categorised for return based on ‘utility’. In this system, the most clinically actionable SF were always returned, while those that were valid—but not necessarily actionable—were reported based on participant preference.

2.5.1 ACMG guidelines

In 2013, the American College of Medical Genetics and Genomics (ACMG) published an influential set of guidelines concerning SF in clinical WGS [1]. They recommended active screening of a defined list of 57 genes, in which variants could imply risk of potentially life-threatening disease, where intervention is available, and in which a long asymptomatic phase may conceal disease expression. The ACMG policy statement suggested that in all individuals undergoing clinical WGS, there is an obligation to seek and report variants of known (or in some cases expected) pathogenicity and to interpret them in the context of the participant’s personal and family history. The genes on the list are, for the most part, associated with cancer syndromes and inherited cardiac conditions—highly penetrant Mendelian disorders, that are potentially life-limiting and treatable. Although these mostly include adult-onset disorders, the ACMG recommends that reporting SF not be limited by age—they conclude that findings in children could benefit adult family members. In the initial set of guidelines, the ACMG also recommended that SF are reported ‘without reference to patient preferences’ [1]. They argued that honouring preferences requires highly involved counselling for a long list of conditions and regular interaction from the laboratory, and will thus become unfeasible as WGS becomes more common—autonomy is maintained in that participants can decline WGS if they do not want SF. They concluded by acknowledging that the list will evolve as data are collected on penetrance and impact of these variants. The list was quickly updated to remove one gene from the list on the basis of evidence presented to the working group—resulting in a final ‘minimum gene list’ of 56 genes in which pathogenic variants should be actively sought and returned (heretofore, ‘ACMG56’).

Opposition

The publication of these guidelines was immediately met with criticism from a large part of the genetics community, igniting a significant debate on the subject of SF in WGS. Critiques found in the systematic search primarily highlight three problematic areas: (1) lacking evidence of clinical utility, (2) complexity and resources, and (3) a failure to respect autonomy, including the return of results to minors.

Clinical Utility. Burke et al. [41] and Wolf, Annas, and Elias [42] criticised the ACMG56 for lack of evidence: it cited no technical reports or systematic review. At present, there is no evidence on the predictive value of testing or penetrance in an asymptomatic population. Wolf et al. [42] criticised the criteria for inclusion on the ACMG56 for a lack of stringency. Burke et al. [41] called for further evidence (on the predictive value of testing and efficacy in unselected populations) before promoting such practices, rather than afterwards as encouraged by Green et al. [1].

Complexity and resources. Allyse and Michie [43] highlighted the burden imposed on laboratories obligated to conduct extra analysis, questioning how additional costs will be covered. They also noted the further strain on resources caused by the additional counselling that will be required as a result. Additional costs have the potential to widen the gap between individuals and institutions that can afford such care and those that cannot.

Autonomy. The majority of publications in opposition to the ACMG56 have been most critical of the recommendation to report SF irrespective of participant preferences—citing this as a departure from, not only norms in clinical medicine, but prevailing law [41–43]. Wolf et al. [42] held that informed consent is a pillar of modern medicine, and that situations where testing can be done without consent do not apply in this context. Furthermore, criticism of the analogy to radiology has been offered by the ACMG, citing the deliberate and active nature of the search for SF [41, 42]. Participant choice is essential if their ‘right not to know’ is to be protected—patients have a well-established right to refuse testing, even if their view is in the minority. As Burke et al. [41] explained, denying a patient this right in the case of SF could mean their refusing WGS altogether, which may be a detriment to their care. With respect to children, Wolf et al. [42] argued that the ACMG guidelines depart from a well-established consensus on testing

in minors, contradicting past recommendations from the ACMG. Returning adult-onset conditions to children undermines their autonomy [41, 42]. They argued that the risk of harm to the child by returning SF outweighs the possible benefit to the child gained through benefitting family members.

Counterpoints and clarifications

In response to some of the above criticism, some authors of the ACMG56 contributed to a counterpoint [44], and the ACMG offered an official clarification [45]. In the counterpoint, the authors argued that standards are needed to discourage over-reporting, and the clarification affirmed that only ‘unequivocally pathogenic variants leading to disease’ should be reported. The authors of the counterpoint also affirmed that participants are autonomous in their decision-making as they can refuse sequencing altogether, which is consistent with other diagnostic processes. They held that a mandatory search for actionable SF is ethical because ‘it is justifiably assumed that a reasonable patient would agree to a comprehensive evaluation to identify clinically beneficial information’. They argued that the decision not to disclose SF can be taken at the point of the clinician-participant interaction, and laboratories have a duty to report—i.e. WGS participants cannot opt out of their analysis. Finally, they supported the decision to return of SF in children, explaining that the context is different from previous statements—here, they argued, the interests of the child and family must be balanced. The ACMG argued that their policy on returning results in children was consistent with previous statements as it was driven by the best interests of the child, consistent with a joint report from the American Academy of Paediatrics [46]—even the return of variants indicating adult-onset disorders benefits the child via treatment or preventative measures that can be taken in their parents.

2.5.2 Updates from the ACMG

In 2014, the ACMG released the first significant update to their initial guidelines [47]. Based on the results of a survey of its membership [48], the ACMG altered their initial recommendations to allow participants to *opt out* of the analysis of all genes on the ACMG56 list. The ensuing policy statement affirmed the importance of informed consent,

and the need for a detailed discussion around the possibility of secondary findings, as well as the ramifications of opting out of their analysis [49]. Their stance on testing in minors remained the same—although parents were now given the option to opt out.

After the release of the ACMG56, the ACMG established a working group tasked with updating the genes on the minimum gene list in light of new evidence, taking nominations from the wider ACMG community. In November 2016, true to their word, the ACMG published their first update (ACMG SF v2.0) [2], which saw the minimum gene list increase from 56 to 59, representing 27 unique disorders (heretofore, ‘ACMG59’). As most of the studies discussed in this thesis predate the ACMG59, their design is in light of the ACMG56. Thus, the ACMG56 will be referenced often, despite not being the most up-to-date minimum gene list.

In the update, the ACMG acknowledge that penetrance estimates associated with these genes are based on biased ascertainment—penetrance might be lower than estimates predicted based on assessment exclusively in probands and family members. They call for future research, including the use of large population datasets, to help inform these estimates. Finally, the update stresses the importance of research into the impacts of returning SF both on WGS participants and families, but also on clinicians and the healthcare system.

2.5.3 Other guidelines on SF in WGS

Like the ACMG, many other national organisations and groups have published recommendations that include guidance on the communication of SF. These guidelines vary greatly, largely differing on some of the controversial points outlined above. The range of these guidelines has been comprehensively outlined in several reviews [14, 50]. Illustrative pieces of guidance—selected on the basis of their varying origins and widespread use in the literature identified in the systematic search—will be discussed here in order to highlight differences.

Across the board, guidelines stressed the importance of discussing SF at the time of consent. The possibility of SF, which are available for return, and how they will be disclosed should all be discussed at the outset. Guidelines were also consistent with the

Table 2.1: Key differences between the ACMG, CCMG and ESHG guidelines with respect to SF in WGS

Topic	ACMG [2]	CCMG [51]	ESHG [26]
Informed consent	• Possibility of SF, and which might be returned, must be discussed during informed consent.	• Possibility of SF, and which might be returned, must be discussed during informed consent.	• Possibility of SF, and which might be returned, must be discussed during informed consent.
Opportunistic screening	• Laboratories should screen a list of genes known to be associated with medically important conditions for pathogenic variants.	• Laboratories should take a targeted approach, limiting their search to genes relevant to the primary indication where possible.	• Laboratories should take a targeted approach, limiting their search to genes relevant to the primary indication.
Opt-out	• In latest version of guidelines, participants can opt out of the screening of the list of additional variants.	• Where an additional list of genes are screened, participants can opt out of their screening.	• Where an additional list of genes are screened, participants can opt out of their screening.
Children	• Children should be screened for adult-onset disorders as they are clinically useful to parents.	• Children should not be screened for adult-onset disorders.	• Guidelines need to be established as to which information should be returned in children.

ACMG guidelines in their most recent form, in their allowing participants to opt out of the intentional analysis of a minimum list of additional genes [26, 51–56].

For the most part, guidelines identified in the search differed from the ACMG in their stance on whether or not the opportunistic screening of even life-threatening medically actionable conditions was favourable. Guidelines from the European Society for Human Genetics (ESHG) [26], which were published before the ACMG changed their stance on ‘opting out’, and more recent guidelines from the Canadian College of Medical Genetics (CCMG) [51], both advocate for a much more cautious approach to SF, acknowledging the current lack of empiric knowledge on their utility (Table 2.1). Both groups do not endorse the intentional analysis of genes unrelated to the condition for which sequencing was ordered. Instead, they recommend targeted analysis of WGS, such as by using selective filtering to limit the search space to genes relevant to the primary condition. They acknowledge that, while not endorsed, some laboratories may chose to offer screening of minimum gene lists, and provide guidance on the process (i.e. informed consent, ability to opt out, as discussed above).

In contrast to the guidelines in Table 2.1, joint guidelines from the UK Medical Research Council and the Wellcome Trust [55], as well as the report from the Presidential Commission on Bioethical Issues [56], both provide much less instruction. Both of these

documents stress the importance of investigators having a clear policy in place with regards to screening for SF, however neither advocates a specific policy. This serves to allow diversity across programmes, while ensuring policies can be sensitive to context.

2.5.4 Secondary findings and the law

Compared to the amount of policy guidance around disclosure of SF in WGS my systematic search revealed relatively little legal commentary and legislation. Countries best positioned to return SF and most involved in their debate—including the US, UK, Canada and the Netherlands—currently have no law referencing SF or the return of such results. According to a review by Knoppers, Zawati, and Senecal [50], only four countries have legislative approaches to the return of results in WGS—these include the ability to opt out of SF in Estonia and Spain, and no individual return in Taiwan and Finland (with a right to receive on request).

Nonetheless, some legal discussion of SF has ensued. Clayton and McGuire [57] worried that creating an obligation to return results, even on ethical grounds, that leads to the practice being adopted widely, could be used as evidence for standard of care. This could have the undesired consequence of making professionals, including researchers, liable for negligence if results are not returned to participants. However, Wolf [58] pointed out that despite the seemingly looming legal liability outlined by Clayton and McGuire, no one has yet been found liable—and perhaps professionals are made unduly anxious. In a 2013 review of case law, Clayton et al. [59] found no examples of SF from genetic testing, but did find cases involving medical imaging. Despite some of these plaintiffs being found liable for failing to detect incidental information, the problems associated with this analogy have been previously illustrated, thus the applicability to genetics is unclear. Should liability actually be an issue in genetic testing, Evans [60] outlined the legal consequences of the dynamic created by guidelines and standard of care around SF. Evans explained that there may be liability whether one does or does not actively screen for and return variants on the ACMG list (or some other list of actionable findings). This serves to create a state of ‘lawsuit equipoise’, freeing the investigator to judge what is right [60].

In a purely research context, according to Burke, Evans, and Jarvik [61], participants do not have a legal right to access information about themselves, as they do in a clinical context. However, Pike, Rothenberg, and Berkman [62] argued that some researchers are in a unique position to prevent harm and thus might be found to have a duty to notify if a serious abnormality is detected. Wolf argued against separating research and clinical spheres in law altogether—a continuum between research and clinic has been embraced, and progress around SF requires ‘recognizing that the debate is fundamentally about the translational process’ [58].

Regardless of the extent to which commentators believe investigators could be liable if they do or do not search for and return SF, commentators universally stress the importance of informed consent and transparency, where policies are clearly outlined in consent documents and pre-test discussions.

2.5.5 The research-clinical divide

As the legal commentary around SF is largely shaped by the research-clinical divide, it is worth broadly addressing the distinction—or lack thereof—between clinical and research settings when exploring the management of SF. Unlike Wolf [58], Hallowell et al. [23] stressed the difference between the domains: differentiating between these two sets of activities is crucial as those involved have different responsibilities. In the case of the researcher it is to betterment of their science, and in the case of the clinician it is to protect their patient. Gliwa and Berkman [63] argued that (in 2013) there was no obligation for researchers to search for SF at that time on the basis of three criteria: benefit, uniqueness of access, and burden. Before the clinical translation of genomic medicine, the benefit of returning SF was low as knowledge was developing, the uniqueness of access was high as WGS had not entered the clinic, but the burden was also high as it was resource intensive. They also argued that in the far future, when genomic medicine is commonplace, there will be no obligation to return—in a setting of pure research, despite increased benefit and decreased burden, access will not be unique. However, in the intermediate period of translation, where genetic knowledge has increased and

the resource intensiveness decreased, but access is still largely unique to research, there may be an obligation to return.

With large clinical research sequencing projects underway, it seems that we may be at this point. The discussion around returning SF in research is further complicated by the fact that the distinction between clinical and research domains has become increasingly blurred as WGS is translated into clinical practice [54]—translational sequencing projects in the UK, such as the 100,000 Genomes Project [64] and the Deciphering Developmental Disorders project [65] operate at the interface of these domains. In the United States, the All of Us Research Program is doing the same [66]. While having research aims, participants are being recruited into these studies in clinical settings, often by a clinician with whom they have had contact in a healthcare-providing capacity. In such instances, clinician-researchers must ensure that clinical standards of care continue [67]. Berkman, Hull, and Eckstein [68] stated that the convergence of research and clinical care is inevitable, and understandable, in a translational field. They also argued that the collapse of this distinction is the very reason for the lack of consensus around SF. It serves to expand obligations put on researchers, especially at times when technologies are uniquely available in a research context. This is representative of the field of genomics today.

As a consequence of the blurred boundary between clinical and research domains, many of the aforementioned guidelines, regardless of their explicit clinical or research focus, have relevance across domains and projects. Some recommendations that are research-specific have been put forward, often aiming to clarify responsibilities in the grey area. They largely echoed commonalities between clinical guidelines, such as the importance of informed consent and clearly explaining the possibility of SF and which findings participants have the option of receiving, if any [56, 69].

In 2016, a National Institutes of Health working group explored the issue of returning SF specifically in a research context, concluding that some research studies should return SF, but obligatory return is not universally appropriate [70]. They proceeded to outline four factors that influence whether or not it is appropriate to return SF in a given study: the nature of the clinical relationship, the nature of the study, the nature of the study population, and timeliness. Although not always appropriate in a research context,

they argue that investigators providing clinical care, a clinical research question, a study population likely to find findings useful, and potential findings while the participant is actively involved in the study, are all reasons that argue for seeking and returning SF.

As this blurred distinction between clinical and research domains represents the current state of the field, although challenging, I will necessarily explore these contexts together in my thesis—in fact, the larger project in which this work is embedded sits exactly at this indistinct research-clinical boundary.

2.6 Language

This lack of consensus around the management of secondary findings is directly reflected in the terminology itself: many terms—‘incidental’, ‘secondary’, ‘unexpected’—are used interchangeably. In order to reach a consensus on the management of these types of findings, we need to first agree on what to call them. Here, I discuss the various terms employed through literature identified in the systematic search, the cases made for select terms, and explain why I believe ‘secondary findings’ to be the best—or, least imperfect—term for this thesis, and the field at large.

2.6.1 Terminology around secondary findings

There was significant variation in the terminology applied to SF throughout the literature. This variation complicated the systematic searching undertaken and conduction of this review. While ‘incidental’ was the first label applied to these results, authors have pointed out problems associated with the term [14, 71]. In the case of WGS, the use of the term ‘incidental’ is inaccurate—findings beyond those related to the primary condition are not completely ‘incidental’ to the experimental technique. The term ‘incidental’ is also problematic in that it could minimise the significance of the result, and is often used in cases where the findings are actively sought [71]. It has been argued that flawed terminology can be adequately addressed with participants during the consent process, as all terminology requires explanation [72]. This may be the case in an ideal world, but the reality of today’s genomic medicine is that professionals with a wide range of genetic literacy are becoming increasingly involved, and those seeking consent do not always

have the ability to communicate these nuances. In an area where truly informed consent is already difficult to achieve, complicated, inconsistent and misleading terminologies only further complicate the process. This can only serve to impede progress and threaten the quality of care provided to participants in genome sequencing.

Despite the fact that numerous articles call for a shift and agreement in language around SF in WGS, inconsistencies persist [14, 71, 73]. In order for such a shift to occur, authors must start using conventional terminologies, and journals should be involved in their enforcement. Christenhusz, Devriendt, and Dierickx [71] argued against ‘incidental findings’ and supported the term ‘secondary variants’ as an alternative. They applied the term, as used by Johnston et al. [74], to all variants beyond the primary variant. They argue that the term ‘secondary’ allows individuals to distinguish from those variants related to the primary condition without diminishing the potential weight of unrelated findings. Although fewer, this term is not without its own criticisms—some have argued that it has specific meaning in medicine, and might also rank the importance of such findings relative to the primary findings [75].

In a recent update from the ACMG on their controversial guidelines [49], they endorsed the use of ‘secondary findings’ in the place of ‘incidental findings’, citing the Presidential Commission for the Study of Bioethical Issues [56] as having made a case for the switch. This definitional framework is valuable in that it provides a list of terms, allowing for a wider range of perspectives and situations to be captured—a concern raised by some about catchall terms [72]. Unlike Christenhusz et al., here ‘secondary’ is applied only to non-primary findings that fall *within* the search protocol. They still, however, employ the term ‘incidental’—applying it to all findings that fall outside of the search protocol. These ‘incidental findings’ include those that are ‘anticipatable’ (findings that are known to be associated with the procedure, but not actively sought) and ‘unanticipatable’ (findings that are not known to be associated with the procedure at the time it is conducted). This continued use of ‘incidental’ is problematic for the reasons outlined before, especially in the case where they are known to be associated with the test—‘anticipatable incidental findings’ feels, in itself, somewhat oxymoronic.

The language is confusing for professionals, let alone participants who are meant to provide informed consent.

2.6.2 Proposed terminology framework

For my thesis, I will employ the more simple terminology framework presented in Figure 2.3. I use ‘secondary findings’ to apply to all findings beyond those related to the primary condition—eliminating, as Christenhusz et al. [71] argued, many of the problems associated with the term ‘incidental’. I have chosen to maintain the use of the term ‘findings’, however, as ‘variant’ can apply to normal genetic variation and could be confusing in the description of disease predisposition and serve to minimise importance [71]. In order to capture a wider range of situations, I propose expanding on this terminology by imploring researchers to also employ the term ‘additional findings’. While ‘secondary findings’ applies to all variants discovered that are unrelated to the primary condition, ‘additional findings’ are a subset of secondary findings that are intentionally sought. Thus, both primary findings and additional findings fall within the search protocol. The term ‘additional findings’ would thus apply to the most actionable of secondary findings, such as any on the ACMG minimal-gene list [1], if included in the screening. This is consistent with the use of the term in the materials for the 100,000 Genomes Project [64]. Much like the definitional framework proposed by the Presidential Commission, this allows for the differentiation between non-primary findings actively sought and those that are not—which must be made clear to patients—while avoiding the term ‘incidental’. Furthermore, the term ‘additional’ has no connotations that would lead an individual to minimise the importance of such findings, while also communicating their supplementary nature—consistent with participants’ ability to opt-out of their receipt.

Importantly, the choice of the terms ‘additional’ and ‘secondary’ is consistent with preferences from patients themselves. A recent study by Tan et al. [76] reported results from surveys and focus groups of 88 and 40 WGS recipients, respectively. Tan et al. found that participants consistently ranked the terms ‘additional’ and ‘secondary’ above ‘incidental’ in terms of preference—many cited the non-threatening nature of the two

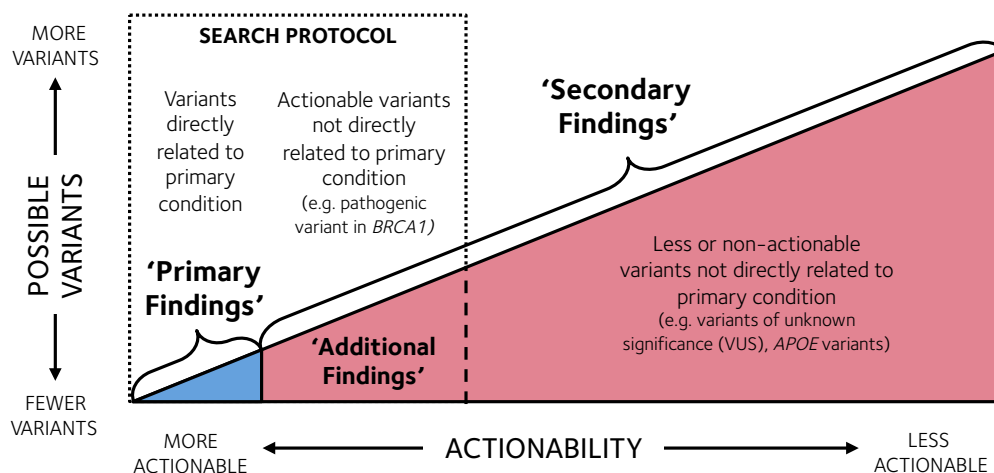


Figure 2.3: Proposed model for language surrounding secondary findings in genome sequencing

terms, and echoed the idea that the latter term demotes the potential importance of such findings.

If the promise of genome sequencing is to be realised, shifting away from flawed terminology cannot itself be secondary; it is important that those involved in WGS and responsible for its promotion—researchers, healthcare professionals, policy makers, journal editors—agree on, and employ, a shared lexicon for genomics.

2.7 Approaches to SF in practice

Since the production of the various sets of guidelines and recommendations, large translational genomics research studies have begun, each having made choices with respect to SF. The ACMG guidelines have certainly influenced the design of many large-scale WGS projects—the extent to which is demonstrated in *Section 2.8.1*. However, many laboratories [77] and research studies have taken different approaches to SF—ranging from avoidance of SF, to offering an even wider range than the ACMG recommends. In a way, these policy decisions represent the views of some key stakeholders and serve to demonstrate how these guidelines are being used in practice. For that reason, I will briefly discuss the policies of selected WGS projects to illustrate the current range of practices around SF, particularly where they differ from the ACMG guidelines.

Here in the United Kingdom, the 100,000 Genomes Project decided to offer optional return of SF based on a shortened version the ACMG56 [64]. At present, the list of SF only

includes genes associated with cancer predisposition and familial hypercholesterolaemia. The 100,000 Genomes Project plans to update this list periodically, increasing the number of genes based on new information and changing evidence. In addition to variants on the ACMG, the Project offers the option of returning recessive and X-linked carrier status to couples and female participants, respectively.

Some studies offer a much wider range of SF than the ACMG56. For example, the large Geisinger-Regeneron ‘DiscovEHR’ Initiative—which aims to combine high throughput DNA sequencing with electronic health records—decided to employ an expanded list relative to the ACMG guidelines, screening for pathogenic variants in 76 additional genes associated with 27 highly penetrant, medically actionable conditions (the ‘Geisinger76’) [78]. They made the decision to not return carrier status to participants. Berg et al. [79] also proposed return of variants from a much longer list of genes, using a binning approach, as per their 2011 paper [34]. In their provisional binning, they placed 161 genes in the bin containing genes in which variants have clinical utility. In order to generate evidence on the benefits and risks of actively searching for and returning SF, the SickKids Genome Clinic [80] decided to screen 2000 genes for SF, based on the NIH Clinical Genomic Database of genetic disorders [81], and will return adult-onset disorders regardless of age.

At the other extreme, some studies have taken the decision to actively avoid the generation of SF altogether. As advocated by Wright et al. [82], interpretable data can be maximised, while minimising unrelated findings, by targeting analysis to pertinent genes or using *in silico* gene panels. The diagnostic laboratory in Nijmegen has employed this strategy, automatically filtering out all genes outside those known to be disease-causing for the relevant condition [83]. This approach, consistent with the guidelines from the ESHG and CCMG, has been taken by a range of studies, most of which are outside the USA [84–86].

One could postulate that the differences observed around SF management are a product of different medical systems, and cultures around healthcare and data-sharing, especially differences between the United States and other countries. Klitzman et al. [87] acknowledged that the USA is much more litigious than other countries, which

influences practices, and that resources are more plentiful—resulting in greater likelihood that a variant is actionable. Knoppers et al. [50] called for ‘greater harmonization of practices and policies across countries’ in order to better facilitate cross-border research collaboration. In order to truly harness the benefits of genomic medicine, which will be driven by large numbers that inform practice, such as more precise penetrance estimates, we need to collate data collected across borders. This process will be complicated, and perhaps impossible, if the methods and actual data collected differ.

2.8 Empirical evidence

Despite the debate around their management, secondary findings are being actively generated by programmes such as those above—and, in some cases, returned to participants. In order to quantify the impact of SF, particularly the ACMG56, several studies identified in the systematic search have attempted to predict their frequency based on modelling [88]. Using an *in silico* model based on the ACMG56, Ding, Burnett, and Chesher [88] predicted that approximately 2.7% of individuals subjected to WGS will have a variant that meets the ACMG criteria for return. As the 100,000 Genomes Project moves towards completion in the UK, and the USA embarks on sequencing 1 million genomes, this represents a large number of SF, and a large number of individuals potentially needing clinical care. The exact clinical implications of such findings will vary according to the specific variant: ranging from differences in clinical evaluation and non-invasive treatments like medications, to the need for long-term follow-up and drastic risk management strategies.

2.8.1 Reported rates of SF in published WGS studies

As policies around their return are fiercely debated, studies that have employed WGS have reported widely variable rates of SF findings in their subjects. From the systematic literature search (Section 2.3), I identified a total of 26 studies that report rates of—what they deem to be—actionable and returnable secondary findings [74, 75, 78, 79, 89–111]. The proportions of subjects with actionable SF reported by the studies (the earliest of which was published in 2012) range from 1.10% [103] to as high as 27.50% [79]. This

dramatic variability can, on one hand, be attributed to different lists of genes—some pre-date the first set of ACMG guidelines [74], and many report SF based on a list different from (or shorter or longer) than the ACMG56 [75, 78, 79, 89, 99–102, 104, 109, 110]. Furthermore, variant classification and interpretation of clinical significance has been shown to be highly discordant across laboratories [112], and change over time, such that there is variability even if the same reporting list is employed (a more detailed description of this variant interpretation process and filtering pipeline will be undertaken in *Chapter 7*). As the authors of one of the studies noted [91], this makes an informative comparison of reported rates of SF very challenging.

Studies reporting rates of SF that have been published since 2014 largely made use of the ACMG56, acknowledging its utility for cross-study comparisons. In many cases where more than the ACMG56 genes are interrogated, studies reported separately both the number of SF in ACMG56 genes and those in genes not on the list [89, 101, 104, 110]. This eliminates the problem of variability in gene lists, allowing for a more informative comparison across studies. Accounting for multiple studies reporting on same populations, and only considering those that report variants based on the ACMG56 (whether exclusively, or as a subset of a larger list), 21 studies can be compared (Table 2.2). While the range of reportable SF does vary, attributable to additional challenges discussed earlier, the range is much narrower (1.10% to 8.33%, $\sigma = 2.49$).

Based on an aggregate percentage (total number of SF found across studies relative to the total number of participants in which SF were sought), 3.66% of WGS participants had SF from the ACMG56 deemed returnable by the respective studies. This is higher than predicted by earlier models [88]. However, as many of these numbers are derived from retrospective analysis with no actual intent to return, it is unclear if this aggregate figure is artificially higher than would be returned in practice. Additionally, many of these calculations do not take into account the primary condition, which may overlap with the ACMG56 list and result in a small enrichment of reportable variants in some studies. Regardless, this illustrates that active search, interpretation, and return of such variants will not be an insignificant task and will have serious resource implications.

Table 2.2: Reported rates of SF in published WGS cohorts based on the ACMG56

Study	Year	Total indiv.	Source	Indiv. w/ SF	%
Amendola et al. [89]	2015	6,503	NHBLI Exome Seq Project	82	1.26
Dewey et al. [90]	2014	12	Stanford Medical Centre	1	8.33
Dorschner et al. [75]	2013	1,000	NHBLI Exome Seq Project	20	2.00
Gambin et al. [91]	2016	11,068	Atherosclerosis Risk in Communities, Baylor	623	5.63
Gierman et al. [92]	2014	17	Stanford Supercentenarians	1	5.88
Green et al. [93]	2016	3,296	CSER Consortium	68	2.06
Jamaur et al. [94]	2016	377	Singapore	6	1.59
Jang et al. [95]	2015	196	Korean Genome and Epidemiology Study	13	6.63
Johnston et al. [96]	2015	591	ClinSeq	23	2.16
Jurgens et al. [97]	2015	232	Baylor-Hopkins Center for Mendelian Genomics	5	2.16
Lawrence et al. [98]	2014	543	NIH Undiagnosed Diseases	27	4.97
Mody et al. [101]	2015	91	University of Michigan	1	1.10
Olfson et al. [103]	2015	1,092	1000 Genomes Project	12	1.10
Parsons et al. [104]	2016	150	BASIC3 Study, Baylor	5	3.33
Retterer et al. [105]	2016	2,091	GeneDx	129	6.17
Shashi et al. [106]	2016	59	Duke Medical Center	2	3.39
Taylor et al. [107]	2015	500	WGS500 Programme, Oxford	6	1.20
Valencia et al. [108]	2015	36	Cincinnati Children's Hospital	3	8.33
Yang et al. [109]	2013	250	Clinical Exomes, Baylor	18	7.20
Yang et al. [110]	2014	2,000	Clinical Exomes, Baylor	59	2.95
Yavarna et al. [111]	2015	149	Hamad Medical Corporation	3	2.01
TOTAL		30,253		1,107	3.66

2.8.2 Reports of returned SF

While many of these studies simply provide calculations of SF prevalence with no intent to return, many of these programmes are returning SF, and some have reported on their return. Of the 26 studies that reported SF prevalence calculations, 16 disclose SF to participants [74, 90, 92, 93, 97, 99–102, 104–106, 108–111]. However, only a subset compared genetic findings with phenotypic data in the article—either data already on file [98], or collected by returning the SF [90, 92, 99, 101, 102, 108].

Some smaller studies, including some of the above, reported details on the return of a single or small number of SF, and their clinical impact, alongside primary results. Some of these do report the detection of a clinical phenotype associated with the SF, such as Valencia et al. [108], which found an *FBN1* variant, resulting in a diagnosis of Marfan Syndrome in the participant. Others discuss false positives, where variants

were found to be polymorphisms following further analysis, or the individuals were found to be asymptomatic where a phenotype could normally be ascertained [92, 113]. In cases where pathogenicity was difficult to ascertain clinically—such as variants in cancer predisposition genes—and there was no family history, studies reported participants entering screening programs or increased surveillance, and cascade screening [74, 90, 100, 101, 108].

2.8.3 Utility of returned SF

Aside from a handful of studies discussing returned SF, there is very little evidence in the literature about the clinical impact of returning such findings. Even amongst those SF returned, many are inconclusive, and their utility is difficult to ascertain without downstream monitoring. Many sources, including the ACMG56 guidelines themselves [1] explain that data on the clinical utility of such findings will be paramount to informing their management. The need for such data can be highlighted by looking closer at the prevalence of the variants detected in any of the studies listed above in Table 2.2—seemingly pathogenic variants are reported at a level higher than the population prevalence of the disease. The Oxford-based WGS500 study [107], for example, found seemingly pathogenic variants in a gene known to cause arrhythmogenic right ventricular cardiomyopathy (ARVC), in the genomes of two individuals (out of 500 participants). This prevalence of 1:250 is dramatically smaller than even the most liberal population estimate for ARVC (1:2000) [114]. This raises the question: while variants may be judged to be pathogenic in an individual with a condition, do the same variants (found as SF) have the same effect in participants who are unaffected? As randomised control trials are not possible with such small numbers, we must therefore employ creative methodologies to inform penetrance estimates of the findings that will be disclosed [115].

A few studies have begun to generate this evidence. Johnston et al. [96] reported on the ClinSeq project [116] where they identified loss-of-function variants where haploinsufficiency was known to cause disease. Of 951 individuals, 23 had variants in genes on the ACMG56 list. Of them, only 7 (30%) showed evidence of the expected phenotype or family history. In order to produce more informative estimates, more recent studies

have employed large phenotyped databases or electronic medical records, in order to match phenotypic data with genome sequences [78, 117, 118]. Two such studies, which will be discussed in greater detail in *Chapter 7*, reported that 35% of the individuals with reportable variants in cardiac genes on the ACMG list had the related clinical features or family history [117, 118]. More recently, Dewey et al. [78] reported results from the DiscovEHR Initiative: of the 49 individuals whose genomes harboured pathogenic or likely pathogenic variants in the 76 genes being screened in the project (the ‘Geisinger76’), 32 (65%) showed disease diagnosis, family history or related clinical features in their electronic health record. These studies, while valuable in their provision of estimates, do not utilise data ascertained for the purpose of diagnosing these conditions, and are unable to mirror the actual process of returning an SF, and the resulting clinical assessment. As large sequencing initiatives are underway, it is critical that they are harnessed to assess the clinical utility of these SF—focused studies must be designed to clinically assess participants with SF. Such studies will need to be creative in their design and generate more evidence than is currently available—either by employing larger datasets or focusing on specific conditions or subsets of the ACMG56.

2.9 Conclusions and chapter summary

In this chapter, I have illustrated the problem of secondary findings in whole-exome and whole-genome sequencing through the various published articles identified in a systematic search of the current literature. Although several sets of guidelines and recommendations have been published regarding SF in WGS—ranging from promoting disclosure of clinically actionable variants, to avoiding their generation altogether, to stressing the importance of a clear policy without advocating for a specific one—there is still a considerable amount of debate around management. There does appear to be consensus around participant ability to opt out of receiving SF, and the importance of discussing SF at the time of consent. However, that is where consensus ends—this is illustrated in the range of management strategies deployed by large-scale genomics projects, as well as the variable language employed.

Important in this debate, and not included in this chapter, are the views of stakeholders—in order to understand whether or not SF should be returned in diagnostic WGS, it is critical to understand the views of the individuals that will have to manage or be impacted by their disclosure. As discussed, the existing literature on stakeholder views is vast, warranting comprehensive review, and will thus form the basis of the next chapter.

The critical review presented here, together with the work in the subsequent chapter, will be valuable in informing my analysis of professional and participant views in *Part II* of my thesis, by affording an understanding of the climate in which decisions around SF are currently being made. Furthermore, this chapter highlights the need for further exploration of the clinical utility of SF in WGS in order to inform their management in the future. I will aim to produce some of this data in *Part III* of my thesis, by identifying individuals with variants in genes associated with inherited cardiac conditions and facilitating clinical evaluation for the associated condition. In *Part III* I will revisit the problem of SF variant interpretation in WGS and also explore the impact of their disclosure.

3

A systematic review and synthesis of stakeholder views on SF in WGS

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The systematic search conducted in *Chapter 2* identified a large number of studies exploring stakeholder views towards secondary findings (SF) in whole-exome and whole-genome sequencing (WGS). In exploring reasoning behind the disclosure of SF in WGS, as per the aims of this thesis, and reaching consensus and developing policy around SF management—filling needs highlighted by the previous chapter—it is critical that the diverse stakeholders¹ affected are considered [120, 121]. It is these individuals who serve to benefit (or be harmed by) such policies, or will be responsible for their implementation. Lemke and Harris-Wai [122] highlight the benefits of engaging stakeholders in genomic policy issues: it helps to identify areas of agreement and disagreement; it helps to

¹Broadly, a **stakeholder** is any individual or group affected by a particular course of action. Although there has been criticism of the term [119], I have found it to be the best term to capture the many parties involved in WGS and is widely used the literature reviewed in this thesis.

align practices with societal needs and expectations; it helps with the execution/uptake of guidelines ultimately produced; and it promotes transparency and increases the quality of the developed policies.

Since the publication of a systematic review on such studies five years ago [123], which urgently called for more research in this area, many empirical studies exploring stakeholder views towards SF in WGS have been conducted. Due to the contemporaneous collection of these empirical data, and lack of comprehensive review, SF management policies in WGS have inevitably been unable to make full use of them.

In order to explore reasoning behind the disclosure of SF in WGS, and to investigate the extent to which there is sufficient evidence on which to base decisions around their management, it is essential that such a review be undertaken before further empirical study is conducted—as will be done in *Part II* of my thesis. I have therefore carried out a systematic review and synthesis, collating these data to evaluate the extent to which they might inform policy on SF, and identify areas for further research. For their rigour and comprehensiveness, systematic reviews are considered one of the highest forms of evidence on which healthcare professionals and policy-makers rely, invaluable in the appraisal and application of existing evidence in practice [124, 125]. Therefore, such an approach is especially valuable in an area where clinical decisions and policy-making desperately need to be informed. In order to capture the full spectrum of views collected on SF in WGS I sought to include both quantitative and qualitative studies. I have published this work in *Genetics in Medicine* as a first author [126].

3.1 Chapter aims and objectives

The overall aim of this chapter was to establish, through the currently available literature, the breadth of stakeholder views on the return of SF in WGS. This aim was addressed in both the clinical and research settings, as in the previous chapter. The specific objectives were to:

- Explore stakeholders' views and experiences towards returning or receiving SF in WGS;

- Determine which SF stakeholders want returned and why;
- Provide a much-needed review of the existing literature on stakeholder views and experiences; and,
- Determine if there is yet a sufficient evidence base for informing policy on SF in WGS.

3.2 Methods

3.2.1 Literature search

Following systematic review guidelines [127], I conducted a systematic search for research studies that examined stakeholder views and preferences towards SF in WGS. Details of the protocol for this review were prospectively registered on PROSPERO [128] in August 2015. Prospective registry of review protocols is important to improve transparency in systematic reviewing, to avoid duplication, and to facilitate the repetition of a review at a later date. The systematic search strategy outlined in *Section 2.2* was employed again for this review, with searches repeated across six databases and included all literature in the databases from their date of inception to April 2015. Electronic updates were included through 1 May 2016 (Figure 3.1). The results of each of the searches were exported to Endnote X7 [20] where duplicates were discarded.

3.2.2 Study selection criteria

Primary research articles employing either qualitative (interview- and focus group-based) or quantitative (survey- and questionnaire-based) methods were included. Studies were included if they explored stakeholder views and experiences around SF in WGS in a healthcare context, in both clinical and research settings. Articles were excluded if they were not published in English, or the citation lacked an abstract. Articles were also excluded if they did not discuss WGS (e.g. discussion limited to chromosomal microarray), or if they did not include (or only included superficial) discussion of secondary findings. Articles that exclusively explored views on return of results in a non-healthcare context, such as direct-to-consumer genetic testing, were also excluded. As discussed in *Chapter*

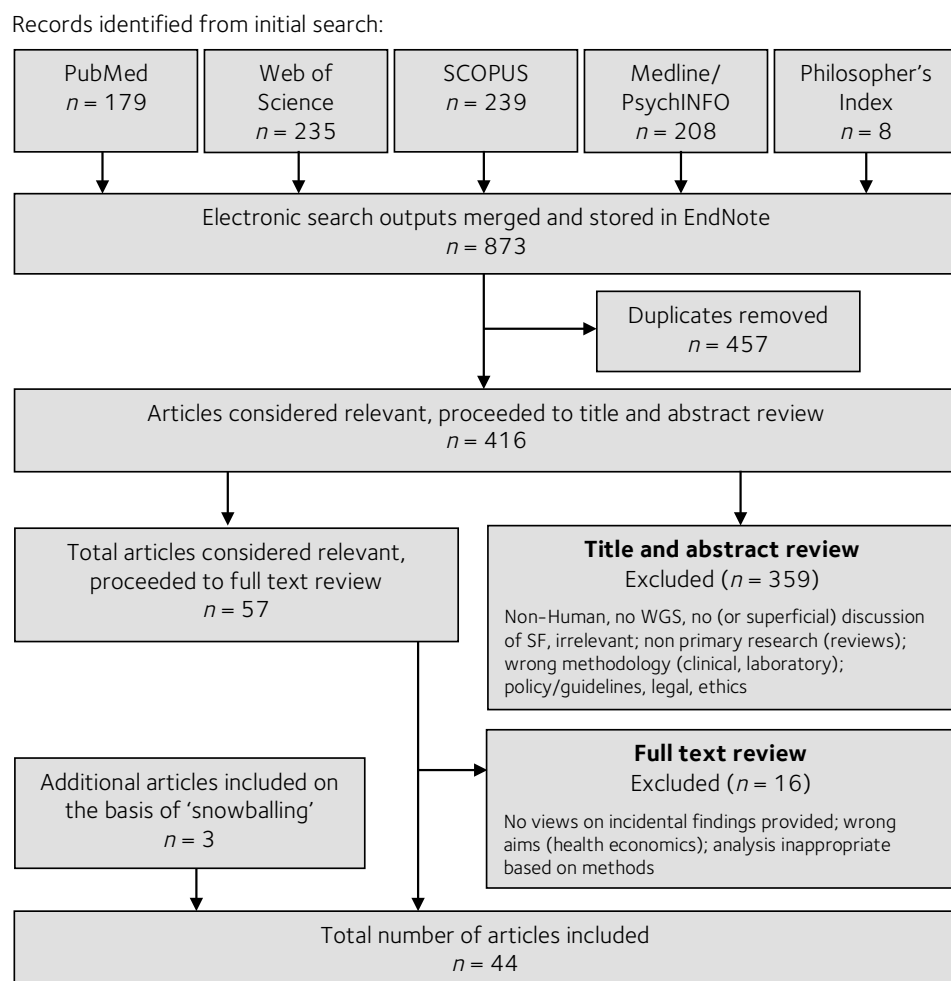


Figure 3.1: Process to select studies for inclusion in review

2, SF specifically in minors are not included, as I acknowledge that this raises additional issues and could warrant its own review.

I screened the titles and abstracts of all articles identified by the searches against the eligibility criteria, using Covidence systematic review management software [129]. A necessary component of rigorous systematic review is screening of articles and extraction of data in duplicate. Therefore, a second researcher additionally carried out some tasks in duplicate (EO or BF). In this case, the screening of articles was repeated independently by EO. In cases of disagreement, inclusion was resolved at a meeting between myself and EO. Both of us then screened full text copies of the selected articles, in order to determine final inclusion in the review. This initial screening was followed by reference scanning and snowballing, in order to capture as many relevant studies as possible.

3.2.3 Data extraction

For both the qualitative and quantitative studies, a general data extraction form was used, which included: bibliographic information, study characteristics, participant characteristics, main findings, and results of the critical appraisal. Both BF and myself independently completed the data extraction form for each study. I then checked the completed forms against each other for accuracy and for completeness of extraction.

3.2.4 Data analysis

In order to analyse the data I employed a framework analysis, where data integration occurred at the point of data extraction. This approach, developed by Ritchie and Spencer [130], is a form of thematic analysis—which will be discussed in greater detail in *Part II*—and is defined by its having a matrix as an output. In the case of my review, this matrix had the individual studies down the rows and the themes across the columns. A framework approach is particularly valuable, and well suited to this review, as it can be easily applied to mixed methods studies and is useful in multi-disciplinary health research teams [131]. Primarily organisational, it is not aligned within any one epistemological viewpoint and therefore relies on the theoretical underpinnings of the particular analysis approach used. It can therefore be dynamic and responsive to novel findings if analysis is meant to be inductive, while affording an organising structure to manage diverse types of data. Although accessible to new qualitative researchers, Gale et al. [131] highlight the importance of not quantifying qualitative data despite the use of a matrix, as might be appealing. An additional limitation of the approach is the resource-intensive nature of a comprehensive matrix, however this was deemed useful and a necessary trade-off in attempting to provide a comprehensive review of literature. While traditionally applied to the analysis of primary data, it was employed here as a review methodology for both qualitative and quantitative papers. This was feasible as both sets of studies investigate the same topics and key issues in a manner that they can be categorised together [131].

Initially, I coded the same six articles (three qualitative studies and three quantitative studies) in a non-restrictive manner. EO independently coded the same articles in the same manner. EO and I then compared our coding of these articles, generating final codes

by consensus. These codes were then grouped together, allowing for the exploration of themes and patterns. The patterns determined through this open coding were then combined with questions asked across the questionnaire and survey studies, in order to produce the initial categories across the framework matrix columns. This framework was then applied to all of the other studies where the 'results' or 'findings' sections of each study were reviewed and coded using NVivo 11 [132], and checked by EO. In cases where the study covered topics beyond SF, only the sections discussing SF were extracted and analysed. Through a process of reading and re-reading, I continued to revise the framework in a manner that more accurately reflected the data present in the studies. For each of the framework matrix column headings I generated a summary document following the 'One Sheet of Paper' method advocated by Ziebland and MacPherson [133]. This ensured that the content of the columns were variable and consistent, with minimal overlap between them. Throughout the process, I allowed for the addition of new codes at any point. The columns of the matrix ultimately formed the final themes, which were further developed with subthemes. Finally I reread the content coded to each theme for illustrative quotations to use in the presentation of my analysis.

3.2.5 Critical appraisal

Studies that met the eligibility criteria were grouped into two categories based on methodology: qualitative studies (interviews and focus groups) and quantitative studies (questionnaires and surveys). Each of the studies was then assessed using an established quality assessment system, with a particular emphasis placed on assessing the explicitness and comprehensiveness of reporting. In the case of the qualitative studies, the COREQ checklist tool (Appendix A, Figure A.2), published by Tong, Sainsbury, and Levinson [134] and adapted using the Critical Appraisal Skills Programme (CASP) checklist [135, 136], was employed. In the case of the quantitative studies, a checklist tool (Appendix A, Figure A.2) adapted from Boynton and Greenhalgh [137] and Greenhalgh et al. [138] was employed. In both cases, BF and I independently scored articles according to the appropriate checklist after piloting three articles by consensus. In each case, checklist items were assigned equal weight. No quality cut-off was used, but a set of initial

screening questions was employed to test against inclusion criteria: if the methodology (qualitative or quantitative, in data collection and analysis) was not deemed appropriate, or if the research was not relevant to the synthesis topic, then the article was omitted from the review. Inter-assessor reliability was measured by calculating κ coefficients using Stata 14 [139] (further details in Appendix A).

3.3 Review results

3.3.1 Systematic search

A total of 44 published research studies met the criteria for inclusion (Appendix B). Of the included articles, 15 employed quantitative methods, 25 employed qualitative methods and four used mixed methods (Table 3.1). The majority of the studies (73%) were from the USA, with the others representing Canadian (14%), European (9%) and multinational (4%) groups of stakeholders.

3.3.2 Study participants

Accounting for studies reporting on the same participants, the viewpoints of 11,566 unique stakeholders are represented (Table 3.2). Stakeholders include patients with genetic disorders or cancer diagnosis, relatives, WGS research participants and members of the public (collectively, 'WGS recipients'); healthcare professionals (HCPs) in genetics or other specialties, both patient-facing and healthcare scientists, primary care physicians, genetics researchers, and institutional review board (IRB) chairs (collectively, 'WGS providers'). Both of these groups include both actual and potential recipients or providers of WGS: participants have a wide range of exposure to genetic disease and genetic testing, from potentially no direct exposure (members of the public) to those who are actively providing or receiving WGS. No studies in the review focused on stakeholder experiences with handling or receipt of genomic SF.

3.3.3 Critical appraisal

Across the studies, quality and comprehensiveness of reporting was highly variable. Between the reviewers, there was substantial agreement on the scores for both quantitative

Table 3.1: Characteristics of included studies ($n = 44$)

Category	n	%
<i>Study Type</i>		
Quantitative	15	57
Qualitative	25	34
Mixed methods	4	9
<i>Study Origin</i>		
United States	32	73
Canada	6	14
Other Countries	4	9
Belgium	1	2
Denmark	1	2
Greece	1	2
Netherlands	1	2
Multi-national	2	4
<i>Topic of investigation*</i>		
Management of secondary findings	28	64
Return of results	11	25
WGS consent process	8	18
WGS, broadly	6	14
<i>Participants have direct experience with WGS</i>		
Yes	19	43
No	10	23
Mixed	15	34

* Total exceeds 100% as some studies were deemed to fall under two primary topics of investigation.

Note: Percentages may not total 100% due to rounding.

papers and qualitative papers. Qualitative studies elicited novel concepts and acted as particularly rich sources of data for the synthesis. Further details, and scoring, can be found in Appendix A.

3.4 Analysis

3.4.1 Themes

From the framework, which was revised iteratively throughout the coding process, I identified 10 major thematic areas (Table 3.3). These themes—some of which are time-specific, pertaining to a particular point in a participant's contact with genomics, whilst others are more longitudinal in nature—are summarised in Figure 3.2. The 10 themes

Table 3.2: Stakeholders represented across the included studies (n = 11,566)

Stakeholder group	n	%
<i>Quantitative and mixed methods studies</i>		
Genetics health professionals	2,789	25.9
Non-genetics health professionals	1,128	10.5
Researchers	681	6.3
Patients*	367	3.4
Research participants*	858	8.0
Members of the public	4,961	46.0
Total	10,784	
<i>Qualitative studies</i>		
Genetics health professionals	204	26.2
Non-genetics health professionals	34	4.3
Researchers	55	7.0
Patients*	152	19.4
Research participants*	129	16.5
IRB chairs	34	4.3
Members of the public	174	22.2
Total	782	

* Parents/relatives of patients and research participants included within those groups.

are presented below, together with illustrative quotations from the participants in the included primary studies.

Preferences and motivations for secondary findings

An overwhelming majority of stakeholders believe that some form of SF should be returned if identified [142, 143, 145–147, 149–152, 154, 158, 162, 163, 166, 168–172, 174, 178, 179]. When measured quantitatively, studies report high desire (95–100%) to receive or return clinically actionable SF [142, 146, 147, 149–151, 154, 168, 169]—notably, this includes surveys of genetics HCPs [149, 151]. The most commonly cited reason for wanting SF was to have the opportunity to act on findings, although the definition of ‘actionability’ varied. It included the availability of treatment [148, 151, 160, 161, 163, 165, 166, 174, 180] and prevention [143, 145, 162, 163], but others endorsed or raised issues such as the ability to plan or alter lifestyle [145, 150, 160, 162, 163, 166, 168, 172, 177] or influence reproductive decision-making [143, 148, 150–152, 156, 160, 164, 169, 170]. Members of both groups acknowledged the potential importance to family members as motivation

Table 3.3: Themes discussed in each study

	Preferences, motivations	Impacts and implications	Literacy	Pre-test processes	Post-test processes	Family	Rights	Responsibility	Time	Policies and Practices
<i>Quantitative and Mixed Methods Studies</i>										
Avoria et al. [140]	■		■	■	■	■	■			■
Barajas and Ross [141]	■				■	■				
Bur et al. [142]	■		■			■				
Facio et al. [143]	■					■				
Fernandez et al. [144]	■			■	■	■		■	■	■
Fernandez et al. [145]	■			■	■	■	■			
Gray et al. [146]	■	■	■		■					
Jeisig et al. [147]	■		■		■	■	■	■		■
Klitzman et al. [148]	■									
Lenke et al. [149]	■			■			■			
Lohn et al. [150]	■	■	■				■	■	■	■
Middleton et al. [151]	■			■						
Scheuner et al. [148]	■	■			■		■			
Shahmirzadi et al. [152]	■									
Smith et al. [153]	■	■								■
Strong et al. [154]	■									
Wynn et al. [155]	■				■		■	■		■
Yu et al. [156]	■	■								
<i>Qualitative Studies</i>										
Appelbaum et al. [157]	■	■		■		■		■	■	■
Bergner et al. [158]	■	■		■	■	■				■
Bernhardt et al. [159]	■	■	■	■	■	■				■
Brandt et al. [160]	■	■			■	■	■			■
Christenhusz et al. [161]	■	■					■	■	■	■
Christensen et al. [115]	■	■	■		■	■	■	■		
Clift et al. [162]	■	■					■	■	■	
Daack-Hirsch et al. [163]	■	■	■	■	■		■	■		
Downing et al. [164]	■	■		■	■		■	■	■	■
Gourna et al. [165]	■	■	■	■	■	■	■	■	■	■
Gourna et al. [166]	■	■		■		■	■	■	■	■
Grove et al. [167]	■	■				■	■	■	■	■
Hitch et al. [168]	■	■	■		■	■	■	■		
Kaphingst et al. [169]	■	■				■	■	■	■	■
Kleiderman et al. [170]	■	■		■		■	■	■	■	■
Klitzman et al. [87]	■	■					■	■		
Levenseller et al. [150]	■	■				■		■		■
Miller et al. [171]	■	■		■		■				
Oberg et al. [172]	■	■	■				■	■	■	■
Rigter et al. [173]		■	■	■			■	■	■	
Sapp et al. [174]	■	■	■	■			■	■	■	■
Simon et al. [175]		■	■	■			■	■	■	■
Tomlinson et al. [176]	■	■			■		■	■	■	■
Townsend et al. [177]	■	■				■	■			
Yu et al. [178]	■	■				■	■		■	■
Yu et al. [179]	■	■				■	■		■	■

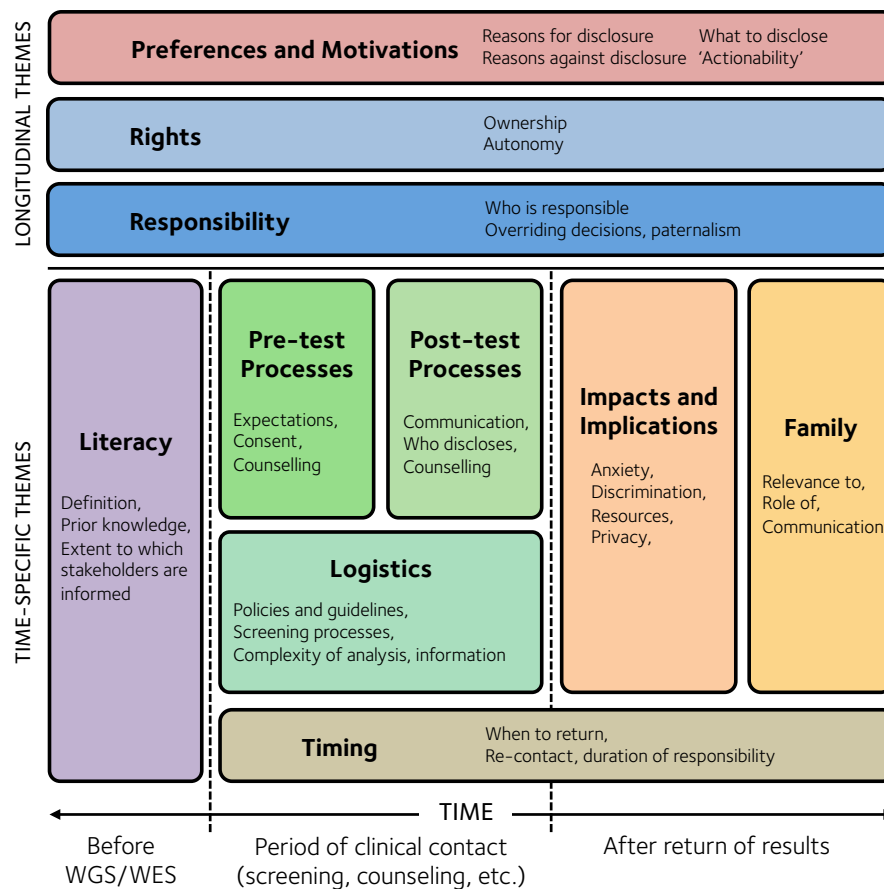


Figure 3.2: Themes identified from included studies around secondary findings in WGS

to disclose or receive SF [87, 143, 165, 171, 172].

Affected adult research participant: 'And then as far as discovering other things, I mean, if there's something else going on, I'd like to know now so that if there's treatment or things that I'm doing that I need to stop doing, I'd definitely like to know that.' [158]

Oncology patient: 'Yeah, I would want to know because I would take up dancing or whatever you can do for Alzheimer's. I would study Alzheimer's and find out what the heck I could do, eat or exercise - I'd take up bridge if I had to! I would like to know if I'm gonna have breast cancer, for instance, because I would try to do whatever I could do to avoid it.' [168]

More than half of the stakeholders, of whom the question was asked, desired to receive or return 'all' secondary findings, regardless of actionability (52-100%) [143, 145-147, 151, 154, 168, 179]. Some expressed the belief that knowledge is empowering [143, 150, 162], and many felt a sense of entitlement to this information (detailed further under 'Rights and Responsibility' below).

Oncology patient: 'I think that information is power [...] It affects your family, home, your children; I mean, it affects everything [...] The more you know, the better off you're going to be.' [162]

Of note, while some studies reported that 'all' participants were interested in receiving some form of SF [143, 158, 169], many reported a small proportion of recipients who only wanted results relating to their primary condition (i.e. no SF) [142, 147, 149, 151, 154, 162, 168].

WGS providers did support the return of some SF, particularly those that point to serious and treatable conditions. However, comparative studies found slightly less support for returning SF among providers with more clinical training [155, 166], and among genetics HCPs compared to non-genetics HCPs [151]—professionals who interact directly with WGS participants, handle genomic data, and might have disclosed, or be in a position to disclose, SF.

In terms of which SF should actually be returned beyond those that are serious and treatable, stakeholders were divided. Although some wanted late-onset conditions [174], support was much lower than for other types of SF [150, 151, 165, 168, 170]. Support for return of SF with less certainty (including variants of unknown significance; VUS) was lower than unambiguously pathogenic variants, but still present [145, 148, 162–164, 168, 169, 180]. There was also no consensus on returning pharmacogenetic results [148, 167] or reproductive information, such as carrier status [143, 148, 150–152, 156, 160, 164, 169, 170].

Medical genetics specialist: 'Personal utility has never been the purpose of medicine... I think the idea of actionability, as the idea to change treatment, the medical actionability, is the way to go on with this. This is the way we think in medicine.' [166]

Impacts and implications

Discussions of reasons to disclose SF invariably led to considerations of the implications of SF and reasons *not* to disclose. Inevitably due to the emergent use of WGS, discussions of impacts of disclosure were largely hypothetical. This theme was widely raised in qualitative studies (Table 3.3): semi-structured interview and, especially, focus group designs elicited interactive and qualified opinions, and provided greater insights into how SF might be construed [150, 161, 162, 164, 166, 170, 177–179]. In some of these

articles, study participants acknowledged becoming less inclined to desire all SF during the course of the interview or focus group [158, 161, 179].

The most commonly cited reason against disclosure was the potential to cause anxiety or psychological harm [146, 153, 160–164, 169, 171, 172, 174, 177]. Although recognised by both WGS providers [146, 153, 156, 157, 164, 171, 175, 177] and recipients [145, 161, 162, 177, 179], potential psychological harms of SF were more frequently of concern to providers:

Medical genetics specialist: '[W]hen these incidental findings come up in a prenatal setting, the anxiety, the turmoil, that I see out of this is tremendous...' [164]

WGS recipients called information about SF 'scary' or 'bad news' [168, 178]—they discussed the burden of knowing, particularly about disease risk that may not affect them for some years, the potential for SF adversely to change the way they lived their lives, and incompatibility with religious beliefs [161, 162, 170, 172, 178].

Adolescent patient: 'I'd rather be surprised than know it's coming, because that's worse, to me... because if I can't cure it, the anxiety of when it will come would make me sick.' [150]

One study found that nearly three quarters of participants factored potential distress arising from SF into their consent choice [145]. However, for most, potential SF-induced anxiety was insufficient for them to decline SF, stating that it was a manageable trade-off or insignificant relative to the utility of findings [163, 171].

Stakeholders also raised concerns about overwhelming WGS recipients with too much information [157], discrimination in insurance and employment [145, 150, 162, 163, 170, 174, 176], and privacy [142, 156–158, 162, 168]. Social impacts were of particular importance in studies examining views on SF in minority groups, or unique cultural or religious contexts [162, 165, 177]. For example, stigmatisation, and its potential to inhibit the sharing of genetic data, was of particular concern in the Greek context:

Medical genetics specialist: 'We are having mothers of teenagers or young adults coming here and they say "... how would we manage to find her a husband if people would know that we have that?" [...] They would do everything to avoid being stigmatised. We face that very often here.' [165]

WGS providers, specifically, raised additional concerns: justice issues related to limited resources [87, 148, 160, 177], complex logistics [87, 173] strains on time and funding [48, 87, 148, 160, 173], lack of participant understanding [148, 167], qualification of HCPs to manage SF [148], and that knowledge around WGS is currently limited and still developing [87, 148, 165].

Researcher: 'The number of potential IFs is essentially infinite. The amount of overhead for identifying and reporting incidental clinical findings would destroy the research enterprise in genetics.' [148]

Providers were also concerned that disclosure of actionable SF would warrant treatment or surveillance that may be harmful in itself, or expensive [160]; it may not always be clear how recommended follow up might be funded, particularly in insurance-based healthcare systems [87, 148].

Literacy

Providers were often concerned that WGS recipients do not always appreciate the implications of SF, and may not be adequately informed to make decisions [148, 160, 165, 167]. Providers raised concerns that WGS recipients might say they want everything, but actually have a difficult time when faced with the results and downstream implications:

Researcher: 'Most people don't think hard about the implications. The casual comment "I want everything" is usually not so reflective of what people want once they've really thought and been educated about it.' [148]

WGS providers who have consented participants to WGS considered that participants' lack of experience with the conditions related to SF complicates decision-making [159]. Providers felt that recipients' apparent enthusiasm for a wide range of SF—often wider than most programmes currently offer—may result from incomplete understanding of the implications of SF, and may not represent fully informed responses [165]. Studies did report highly variable knowledge of WGS among both potential and actual WGS recipients [142, 145, 146, 151, 168, 172, 176]. Providers' own understanding of WGS was shown to be highly variable and sometimes insecure [115, 140, 164, 173, 175, 180], with definitions of SF even varying among participants:

Genetic counsellor: 'I don't think of incidental findings as things like variants of uncertain significance, but that's a different issue altogether, but they sort of get jumbled in my head.' [164]

Genetic counsellor: '[an SF] is a DNA change that we're unable to interpret.' [164]

Stakeholders understandably raised concerns that some HCPs might not have the literacy required to counsel WGS participants, with obvious implications for informed consent.

Pre-test processes

All stakeholder groups, across many studies, stressed the importance of informed consent for SF. Stakeholders felt strongly that disclosure of SF must be guided by what was decided at the time of consent [48, 141, 144, 160, 163, 167, 171].

Genetics healthcare professional: 'I think one of the most important factors is the pre-test consent. Patients have the right to choose if they would like to obtain information about themselves above and beyond information about the pertinent clinical question. The types of results should be explained to the patient who can then decide what they want or don't want to know.' [180]

To optimise informed decision-making, stakeholders in both groups felt that pre-test discussions should supplement written information [141, 163, 177]. Most providers felt that these discussions should include SF, while others variably included which SF would be reported, false negative or positive results, the changing interpretation of variants, family, and the potential for anxiety [140, 157, 159]. Stakeholders felt that discussions are very context-dependent, and should be flexible and tailored to the recipient [157, 159, 160, 165, 176].

Researcher: 'The problem with the consent process is whether to be as detailed as you want. I'm always very fearful that a subject is just going to turn off and just sign, or just say, "Forget it", because we come up with these well-intentioned, but terribly long consent documents.' [157]

More recent studies of HCPs' experiences providing WGS genetic counselling highlighted often-unrealistic recipient expectations and the need to counteract this [146, 159, 176]. The length of time required to achieve informed consent was seen as burdensome for providers and recipients, and providers felt these discussions need to be kept as short as possible in order to keep the participant engaged [157–159, 164, 176]. Some practitioners described increasing confidence in achieving this with experience [159, 160].

Genetic counsellor: 'When I first started, I stuck to the consent form more. Now I've developed my own way to explain it in an easier way to understand. It depends on the participant; I kind of change the way I speak based on how informed they are on the topic.' [159]

Participants in WGS, and HCPs who have obtained consented for WGS from them, acknowledged the difficulty for recipients in thinking about SF during pre-test discussions when they are preoccupied by their primary health condition [158, 159]. Despite this, one qualitative study involving WGS participants found little support among WGS recipients for a second consent process after the report of primary findings [158].

Post-test processes

Members of all stakeholder groups also highlighted the importance of genetic counselling at the point of SF disclosure. Face-to-face meetings with a professional who has knowledge about genetics and the implications of SF was seen as essential by WGS recipients [150, 168, 177] and providers [156, 165, 173, 177].

Parent of affected child: 'Absolutely verbal. [...] It would almost seem uncaring just to receive it on a piece of paper.' [170]

WGS providers felt that disclosure discussions should be tailored to the participant, both in content and timing [140, 157, 160], and should take into account disease burden [171].

Medical genetics specialist: 'I think [it depends on] what the patient is ready to hear...if you've got eight things to discuss you don't have to throw all eight at a patient or a family immediately in the first 10 min of a counselling session and then clean up the mess. I think you can deal with it over time...To prioritize...in a manner that allows the patient or the family to adapt...gain knowledge and then be able to handle something new.' [160]

One study reported stakeholders considering counselling before SF disclosure to be more important than before enrolment [144]. WGS recipients believed that a plan of action for clinical follow-up should be discussed at the point of disclosure [163, 170], and some envisaged a need for ongoing support [170]. Some HCPs felt they would not be able to provide psychosocial support at SF disclosure themselves and would also require support from specialists specific to the SF disclosed [115, 146].

Family

Relatives are considered important in the management of SF and a crucial component of informed consent and SF disclosure [87, 143, 165, 166, 171, 172]. Providers highlighted difficulties with family-based recruitment and consenting, echoing issues well described in genetics around confidentiality and the right not to know [141, 144, 150, 157, 165, 166, 176, 177]. One WGS provider even noted that it was family that differentiated SF in genomics from those in other areas of medicine [165].

Member of the public: ‘...the biggest thing...is... physicians having a problem: “Do I disclose to other family members?” That’s where the confidentiality issues arise. If you find something that’s definitely inheritable...do you tell everyone?...What if they don’t want to know?’ [177]

Stakeholders across all groups are, in principle, willing to share their personal WGS results [142, 144, 145, 150, 157, 160, 161, 168, 170–172, 178]. However, despite wanting to receive SF found in family members themselves, some recipients might filter SF information: passing on only actionable findings [144, 145, 168, 177], making decisions about impact on individual relatives [168], waiting until asked about results [160], or being selective about which relatives to tell [145].

Recipients often cited family as motivation to receive SF, and, particularly for healthy individuals, for initial participation in WGS [143, 161, 162, 171, 178]. In some cases, this was even if they did not want the information themselves [142, 178]. Of note, the role of family as central to decision-making around WGS and SF was especially clear in a qualitative study with African Americans. Members of this group viewed engaging with results as a means of empowering family members to better manage their health, and considered their wider communities as crucial in understanding potential results:

Member of the public: ‘That’s a community and my people dialogue. So the relationship, it wouldn’t just be just with my individual to ask about the research we’re having, but it would be about the collective wisdom and brilliance of my community to think about all those ramifications and then moving forward in that way.’ [178]

Rights

The concepts of both ‘rights’ and ‘responsibility’ (below) are strongly represented across the included studies. Potential WGS recipients stressed the importance of autonomy and the right to choose which SF (if any) they should receive [145, 150, 161–163, 168, 170, 177, 179]. These stakeholders also expressed a strong sense of ownership, and desire for control of their genetic information [145, 148, 161–163, 168, 170, 174, 177].

Patient: ‘I’m wondering why is it even an issue of the doctor having a say? I mean it’s your genome. It’s your body...’ [177]

This sense of proprietorship even extended to family genetic data, with some stakeholders expressing a perceived right to be informed about genetic findings present in relatives [145, 165, 166]. Indeed, perceived rights to ‘their’ information appeared to be an important driver for potential recipients’ desire for a wide range of SF: there were strong objections to paternalism, or WGS providers withholding or interpreting information on recipients’ behalf in an effort to decide what is in their best interest [163, 177, 180]. Widely, WGS recipients’ right to information was echoed by WGS providers [148, 165, 180].

Genetics healthcare professional: ‘It is not our role to withhold information but instead to make this information accessible and understandable to our patients. Once reported, it becomes part of those patients’ medical records and therefore information they are entitled to have.’ [180]

Responsibility

The concept of ‘responsibility’ in SF management was closely linked to the idea of rights—discussions of one topic led to the other in many of the studies. WGS providers agreed that participant autonomy was important, and most believed they would respect informed consent decisions around SF [48, 141, 156, 157, 160, 164–168, 170, 173, 175, 177, 180].

Paediatric genetics healthcare professional: ‘This is the nanny state rearing her goat head again! No one should be forced to undergo testing and receive information that they don’t want.’ [141]

However, providers also perceived a strong sense of responsibility to recipients and believe that fulfilling this responsibility requires careful consideration of the utility of

SF before disclosure, often supporting a multi-disciplinary approach to reach optimally informed decisions [165–167, 173]. In cases where WGS recipients might choose not to receive SF, some providers foresaw a possible conflict between their professional responsibility, in the duty to warn, and respecting participant autonomy [164, 167, 173].

Genetic counsellor: ‘It is absolutely their right to choose...but I think it would be really difficult if we knew something that was medically important, possibly treatable...’ [164]

Some providers did consider overriding a decision not to receive SF if a clinically significant SF were found. [148, 157, 164–166, 180]

Responsibility was also discussed with respect to SF management in general, with most groups agreeing that responsibility should not lie entirely with the healthcare professional—it should be shared [87, 115, 144, 145, 163, 164, 167, 173, 177]. In addition to HCPs, stakeholders discussed the inclusion of WGS recipients [87, 148, 163, 167], parents [71, 145, 150, 174, 177], and laboratory professionals [164, 173]. While a shared responsibility paradigm in the management SF was seen as ideal, there is no consensus on what form such a model would take.

Timing

The idea of ‘duration of responsibility’ recurred in various studies and stakeholder groups. Most WGS providers supported consenting for re-contact and interrogating data as new interpretations become available or results become more relevant [150, 157, 167, 180]. Potential recipients also felt that they should be re-contacted as interpretation changes or information becomes relevant to the individual, such as approaching the age at which a screening program might begin [150, 161, 169, 179].

Patient with breast cancer: ‘They still don’t fully understand it, but at some point, hopefully they will...They would be able to go back and say okay, now we have something we can use with this information.’ [169]

However, there was no consensus as to who should initiate this contact. As genomic knowledge expands, there will be insufficient resources for HCPs to track all genomic developments. There was a sense that responsibility should not fall entirely

on the healthcare system—some felt WGS recipients should share responsibility with providers [167, 177].

Genetics healthcare professional: 'You can certainly put the onus on the patient... but I don't think that you can put the onus on the lab or the physician's office to retroactively review all of their cases where "X" variant was found because now there is this new information on "X" variant.' [177]

While the distinction between research and clinical domains is becoming increasingly blurred, as discussed in *Chapter 2*, time was an area in which stakeholders felt they still differed. WGS providers did consider that the duration of responsibility might differ depending on whether the program had a research or clinical focus: researchers felt that their responsibility would have to be restricted to the duration for which the study was funded [144], and clearly communicated during the consent process [175]. Some providers had concerns that the loss of connection after the completion of a research study would complicate re-contact in a research setting [157].

Researcher: 'What happens if we find something 10 or 20 years from now? I don't know. We'd definitely contact our clinician, but is our clinician still there? Would we even have contact with the patient anymore? I've never seen that in the protocol.' [157]

Policies and practices

Stakeholders in some studies appreciated the logistic complexity of SF management, and that it is further complicated by incomplete understanding of significance for current and/or future health [158, 165]. Some raised concerns about the quality and accuracy of current sequencing technologies and analysis [87, 148, 175, 179], and worried that there are currently insufficient resources to accurately analyse the data and return it in a meaningful way [177].

IRB Chair: 'The dilemma, of course, is whatever incidental finding has been discovered... it's never clear how accurate that information is, how correct it is, and whether it is meaningful to the subject.' [175]

Many WGS providers were unaware of definitive local procedures or policies in place around WGS and SF [87, 115, 144, 153, 164, 165]. Providers discussed various options for SF management: there was support for the ACMG 'minimal gene list' [48, 156, 173], 'binning'

or categorising of variants [148, 167], an advisory board or multidisciplinary team [167, 173], as well as minimising the generation of SF at the present time [141, 144, 165, 177]. However, there was no consensus on the best approach and other study participants voiced arguments against each of these options: some felt a minimal gene list can never be complete, that ‘binning’ was unmanageable, and that multidisciplinary teams are not going to be efficient in the longterm [48, 148, 165, 167, 173].

Clinical molecular geneticist: ‘[An advisory board] is of course something that in the long run will be unmanageable. At a certain point in time, we will have to report our findings within two weeks and if every incidental finding has to pass a committee, that will never work.’ [173]

Further, some researchers expressed concerns about being asked to restrict their analysis:

Laboratory professional: ‘As a person from a lab, I feel trouble not putting in their reports something that I saw. Okay? Parents don’t want to know, but it is there. So I’m not gonna tell anybody, I’m the only one who’s gonna know that?... I have trouble with that.’

Moderator: ‘Is it your own distress that you would feel or is it an ethical, legal concern?’

Laboratory professional: ‘I think it’s both. I mean I think it’s our obligation to spell out everything that we see.’ [150]

There was agreement that guidelines should be flexible, allowing for varying levels of expertise in a highly dynamic field. [161, 164–166]

3.4.2 Synthesis

While there does appear to be agreement that clearly pathogenic SF should be made available to participants in a clinical setting, all other aspects of SF management seem to be void of consensus. There exists a spectrum of views about SF, ranging from those that advocate generating and disclosing a wide range of SF to those that advocate the intentional minimisation of their occurrence. Figure 3.3 offers a theoretical framework that illustrates the balancing of factors that influence stakeholder preferences around SF disclosure in WGS.

Potential WGS recipients’ views frequently fall to the less cautious end of the spectrum, favouring disclosure of a wide range of SF. This often includes non-medical findings as well as findings that have health implications but are for which no treatment is available.

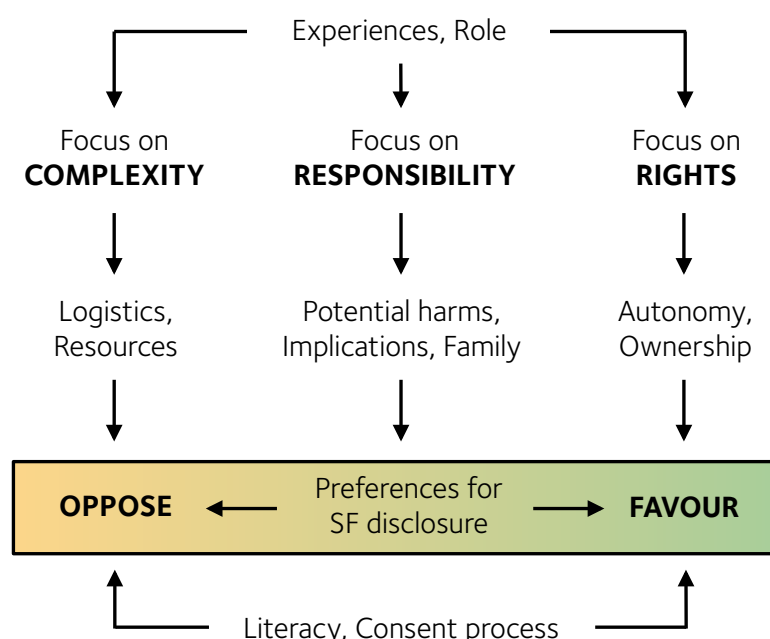


Figure 3.3: Theoretical framework illustrating factors influencing stakeholder preferences around the generation and disclosure of secondary findings in WGS

This prompts questions about recipients' understanding of genomic complexity and difficulties distinguishing 'normal' variation from that which may be clinically significant. Preference for SF among WGS recipients appears to be strongly associated with a sense of rights: ownership, the right to their personal information; and, autonomy, the right to choose what information they receive. Widely, potential recipients feel that they are entitled to access their genetic results, including SF, if they choose to receive them. It seems that there is an element of control involved—sequencing participants want to be the one in control of their own data [161, 163, 170, 174, 177]. As a consequence, WGS recipients can perceive healthcare professionals' deliberations and report of limited SF as paternalistic—sometimes leading them to blindly seek all possible results as if to affirm their autonomy and maintain control. However, this review highlights evidence from qualitative studies that recipients' stated preference for SF may be an initial response that might be subject to change with discussion and reflection on the possible implications.

Providers' views appear more likely to sit towards the other end of the spectrum, and are largely informed by their professional responsibility to WGS recipients. This sense of responsibility manifests in considered views about SF, aimed at minimising harm caused to recipients. Providers were aware of the complexity of offering WGS,

and expressed concerns about the analysis process and the interpretation of variants. Often unsure of how to handle uncertain results, and sometimes untrusting of the information, providers feared causing anxiety or psychological harm to recipients by returning SF. Some studies involving HCPs contain quotes suggesting that they have personal anxieties about disclosing findings of potentially high impact [87, 167] or are concerned about the range of possible SF [115], raising a possible need for further training and support for HCPs actively disclosing SF.

Of note, studies involving parents highlighted distinct and instructive views [145, 150, 170, 172, 174]. As with other potential recipients, parents wish to receive a wide range of SF, but demonstrate intentions to filter the information they tell their children, even when they are no longer minors. This suggests that parents balance a perceived right to their (child's) genomic information and desire to know about potential health conditions, with a responsibility to protect their children from any potential harm—analogous to the balancing of benefits and harms exhibited by HCPs. In recent interviews with parents of children undergoing WGS, Anderson et al. [181] reported greater desire for learning SF in children than themselves, illustrating a perceived parental 'duty to know' with respect to SF. Together, these views highlight the distinct and intermediate views of parents towards SF in themselves that result from the balancing of competing rights and responsibilities.

Some authors of the included studies postulate that greater or lesser knowledge of WGS might account for the differing views. However, those sequencing participants that did appear the most informed, providing the most thoughtful responses, often reported low 'knowledge' of WGS. These individuals, instead, drew on their experience with genetic disease and the healthcare system [162, 168, 169]. For instance, in Hitch et al. [168], which probed views of patients with lynch syndrome, only one participant had ever heard of WGS. However, many interviewees demonstrated a very nuanced appreciation of findings from WGS. Across the studies, for participants who had experience with genetic counselling, genetic illness and longstanding contact with the healthcare system, this informed their understanding of possible outcomes of genetic testing and they expressed tolerance for uncertainty in results. Members of these groups were more likely to make distinctions between the kinds of SF they wish to receive—they were more

likely to decline many results, preferring to receive only ‘actionable’ findings. Individuals with experience informed by genetic disease also demonstrated an appreciation that the relevance of SF is *time- and circumstance-dependent*. This view was reported by genetics HCPs, and by WGS recipients with experience, sometimes extensive, with genetic testing for rare disease or cancer [162, 168, 169].

3.5 Discussion

This systematic literature review and synthesis provides a critical review of the range of perspectives on secondary findings in WGS. The review finds that there is agreement across stakeholders on the importance of participant autonomy in the management of SF. There is less agreement, however, about which results should be generated and made available. Study participants most commonly supported the return of ‘actionable’ findings, however the definition of ‘actionability’ varied. Stakeholders generally agreed that SF that point to life-threatening diseases for which treatment or surveillance is available were classified as actionable, and thus should be returned. However, study participants variously included management, lifestyle modifications and personal utility as aspects of SF ‘actionability’. Although stronger in the case of rare penetrant variants, recent reviews have shown mixed evidence as to whether genetic risk estimates motivate behavioural changes [182, 183]. Christensen and Green [184], however, postulate that SF disclosure may be more effective in prompting behavioural changes in that they provoke a different psychological response. Nonetheless, this variability highlights the context-dependency of ‘actionability’ in SF, poses a challenge to reaching a clear consensus on SF disclosure and management, and highlights the importance of participant choice with respect to SF. Since the conclusion of this review, further studies on stakeholder views have been published, which further diversified the views represented in terms of stakeholder groups [181, 185–187]. The results of these studies largely echo those captured in the review period, with qualitative work demonstrating qualified and considered views among participants.

Despite differing views on what to disclose, stakeholders in the included studies agreed on the concept of shared responsibility around SF management. While standard in

today's patient-centred medical field, the variable understanding of the parties involved, and the perceived paternalism that can result, means that 'shared responsibility' is an ideal we have yet to reach in genomics. It seems ironic that such an innovative field of medicine would need to regress to such old practices. Since there is widespread agreement that SF decisions at the time of consent should determine which results are disclosed, it is incumbent upon providers to ensure that WGS recipients are prepared for results, including their implications and limitations. Education and greater understanding of the potential and limitations of WGS and SF would support informed decision-making and narrow the gap between recipients' expectations and the current situation—where providers consider which SF are useful to generate, based on existing knowledge and resources. This remains a subject of debate [188], and is likely to remain so for the foreseeable future as data accumulate on variant pathogenicity.

Exactly what is required to reach a sufficient level of understanding about SF is not yet clear. It appears that genetic literacy does inform stakeholder decisions and that greater understanding often results in greater circumspection about SF. This 'literacy', however, appears to be less a technical knowledge of WGS, and more a qualitative understanding of its implications and limitations. Tulusso et al. [189], in a survey assessing understanding among parents about WGS, found confusion about SF despite sound knowledge of WGS. In two recent studies which explore HCP experiences consenting WGS recipients, providers acknowledged a shift in the content of their pre-test discussions with experience: moving away from discussing fine details of WGS to focusing on the potential results and implications [159, 166]. Consent sessions should focus on educating participants about the implications of their decisions, rather than the technical details of the field. It will be important for future studies to find ways of measuring what is important to understand in WGS in order to make informed decisions about SF.

It is worth considering the methodologies employed by the primary studies. Much of our idea that WGS recipients want all their results is informed by survey studies—presented with a 'tick-box', recipients elect to receive all SF offered (and may express desire for more than are offered) [143, 151]. However, qualitative studies highlight how recipients might alter these initial thoughts later, or when provided the chance to reflect on and

discuss possible implications. Some studies reported WGS recipients who admitted to changing views on SF during the course of the interview or focus group [158, 161, 179]. This is consistent with a recent study (not captured within the inclusion period) by Ryan et al. [186], which showed that members of the public, through small group deliberations, showed increased willingness to support restrictive SF disclosure policies through consideration of the potential risks. Much like the delivery of the survey studies themselves, the information exchange in informing sequencing participants about the scientific details of WGS is unidirectional. If informed consent mirrors survey studies in the sense that the imparting of information is followed by a 'tick box' answer, most can be expected to elect in favour of receiving SF. The inclusion of qualitative and quantitative studies in this review allows informative comparison: helping participants reach a holistic understanding of the implications of WGS and SF is inherently bidirectional, requiring dialogue much like qualitative methodologies. This suggests that bidirectional interaction akin to qualitative methodologies is more likely to facilitate informed decision-making. This is consistent with findings by Dheensa et al. [190], who concluded that 'tick-box' consent forms with many options do not enhance autonomy and actually weaken the consent process. Included studies suggest that participant reflection and discussion can result in greater appreciation of the potential implications and consequences of SF. This is consistent with the fact that fewer people participate in predictive genetic testing, even for conditions for which intervention is available, than express a hypothetical intent [191]. It is likely that a one-time decision about SF may not represent WGS recipients' changing views and circumstances, and more dynamic forms of consent [192] should be considered.

Stakeholder preference is by no means the only factor requiring consideration in deciding policy on SF; further empirical research collecting data on returned SF is essential to inform stakeholder views. Data is desperately needed on both on clinical utility and impacts in the broadest sense—on WGS recipients, healthcare systems and society. Impacts on resources, for informed consent and genetic counselling in WGS, for analysis and validation, and clinical screening and management downstream of disclosure, need to be assessed as part of overall priority setting.

3.5.1 Strength and limitations

As with SF management, there is no consensus on terminology—some studies employ the term ‘incidental’, others ‘secondary’. Furthermore, discussions of return of results generally often include SF without always referencing them explicitly. Broad search terms and a thorough screening process have been used to capture as many views that relate to SF as possible. However, due to excluding non-English studies, articles without full-text, and this variability in language, some relevant studies may have been missed.

In order to capture the greatest range of stakeholder views, quantitative and qualitative studies were both included. The qualitative studies, however, provided a much richer description of views, and brought out themes and perspectives that were not directly interrogated in the quantitative studies (Table 3.3). As a consequence, these studies tend to come through more strongly in the analysis. In general, the qualitative studies scored higher in critical appraisal—however this is likely a reflection on the checklists employed during the quality assessment, as agreement was higher for qualitative studies than quantitative studies.

The included studies present a predominantly white American perspective, with few studies presenting views of stakeholders from other countries or cultural contexts. Three studies that interrogated stakeholders from unique populations, those of Greek [165, 166] and African American [178] groups, illustrated divergent views. In these studies, there was an emphasis on family that was not present in the other studies. These participants considered family, and even their broader community, as central to the entire process. This illustrates the importance of diverse views, which are noticeably lacking from the current literature. As such, findings from the review might not be comprehensive and representative of diverse stakeholder groups. Further research into the views of non-American groups, as well as cultural and ethnic minorities, is therefore essential.

3.5.2 Implications of findings

This review has implications both for future research and clinical practice:

- Significant gaps exist in the current literature:

1. Understanding of the impacts of SF when returned, in terms of both clinical utility and impacts in the broadest sense—on WGS recipients, healthcare systems and society.
 2. Stakeholders' appreciation for the implications of WGS and SF, what knowledge is required to make informed decisions about SF, and how to assess.
 3. Wider perspectives on SF and WGS, particularly among non-Americans and cultural and ethnic minorities, and individuals undergoing WGS including parents.
- Evidence-based training and education for HCPs providing informed consent is needed.
 - Training and support for HCPs returning high impact SF from WGS is required if SF are to be sought and returned.
 - The communication and apportioning of responsibility between those involved in WGS—HCPs, laboratory professionals, and WGS recipients—needs to be improved.

3.6 Conclusions and chapter summary

In this chapter, I have shown that the views of both WGS providers and recipients with respect to returning SF exist on a spectrum. It appears that a nuanced understanding of the implications of WGS and potential findings—rather than technical knowledge—might better inform decision-making in the management of SF. Rather than the technical details of genetics, counselling should focus on educating participants about the implications of their decisions. Views and preferences of providers and recipients are not fixed; they are continually informed by experience, discussion, time and circumstance. Pre-test discussions with trained practitioners are therefore essential to inform participant decisions. This chapter also highlights the value of qualitative studies, which demonstrated more nuanced and considered views that have been missed in many large quantitative studies exploring such views.

While this chapter demonstrates a significant amount of existing research into stakeholder views on WGS, it is clear that further research into more diverse perspectives is essential to inform the international debate around SF and develop policy. This includes views based on experience actively engaging with SF and SF policies, as well as views from stakeholders beyond those in the USA. This need is particularly urgent as WGS is being rolled out in settings outside the USA, where these views may not be generalisable or representative of actual experiences. Whether this is the case remains unclear until such perspectives are collected. I will aim to help fill this gap in *Part II* of my thesis, through qualitative interview studies with WGS providers (*Chapter 4*) and recipients (*Chapter 5*) in Oxford.

PART II
Views and experiences

Case: Alex and David

The whole-genome sequencing project in which Alex and his family enrolled—called HICF2 (funded by the Health Challenge Innovation Fund)—is an Oxford-based programme that provides clinical diagnostic genome sequencing for children and adults with diverse rare diseases. To enrol, Alex’s parents—David and Cait—met with a genetic counsellor to discuss the programme and signed a consent form (Appendix D). During this counselling session, David and Cait discussed the issue of secondary findings with the counsellor and made a decision as to which findings, if any, they wished to receive. As part of the study protocol, David was offered two groups of secondary findings: (1) those which are discovered unintentionally during the analysis, but not directly sought; and (2) a list of ‘additional findings’ (based on the ACMG56 guidelines). David, after discussion with Cait and the genetic counsellor, elected to receive findings in both categories. After completing the rest of the consent form, blood samples were taken from Alex and David and sent to the Oxford Medical Genetics Laboratory (OMGL) for sequencing and analysis.

Gathering stakeholder views

As illustrated in Alex’s case, and in Chapter 3, there are many stakeholders involved in the process of screening for SF in WGS: the investigators who decide which genes should be screened; clinical scientists in the diagnostic laboratory who undertake the analysis; clinicians who enrol participants in WGS, and may be in a position to disclose SF; genetic counsellors who counsel participants on the potential impact of such findings; and, participants who could potentially receive SF themselves. As highlighted in the

previous chapter, when developing policy around SF it is therefore critical that the various stakeholders affected are considered [120–122]. Much of the current literature on views around SF in WGS predominantly involves white American stakeholders and depicts largely hypothetical views—they do not yet capture stakeholders with actual experience around SF and SF policies. As healthcare systems and cultures vary dramatically around the world, and studies with minority groups highlight diverse views [165, 178], it is critical that the views of more diverse stakeholders are investigated. Additionally, these views may not be generalisable to other healthcare contexts, such as the publicly funded systems common elsewhere. In particular, as large sequencing initiatives are underway here in the UK, it is critical the views of UK stakeholders are considered. With multiple translational WGS projects currently ongoing in Oxford, some established long before counterparts elsewhere in the country, I aim to take advantage of this setting and investigate the views of stakeholders not currently represented in the literature. Such views will be especially valuable and novel as they are made in the context of actual diagnostic WGS and are in response to screening and management policies around SF that have been formed in light of the debate detailed in *Chapter 2*. These individuals have managed and made decisions around actual SF from WGS in practice. As WGS is translated clinically in the UK and abroad, such views will be valuable in the development of ethical policy around WGS and SF.

Setting: genome sequencing in Oxford

Beginning in 2011, investigators in Oxford embarked on a project called ‘WGS500’, a landmark initiative to sequence 500 genomes from patients and family members with diverse rare diseases [107]. This project kick-started an environment of collaborative clinical WGS research in Oxford and laid the groundwork for the projects that have followed. This affords a valuable setting in which to investigate the views of stakeholders who have been engaged with WGS for several years: ranging from clinicians experienced in genomic decision-making, to participants who have made decisions about receiving SF.

MGAC

The protocol under which many of the local whole-exome and whole-genome sequencing programmes fall is called ‘Molecular Genetic Analysis and Clinical Studies of Individuals and Families at Risk of Genetic Disease’ (MGAC). Incorporating research and clinical objectives, individuals and families with rare disease are ascertained through diverse medical specialties after routine clinical assessment and first line diagnostic genetic testing (gene panel and/or chromosomal microarray). MGAC provides a single umbrella consent process and protocol for two sequencing funding streams: an NIHR Oxford Biomedical Research Centre-funded (BRC) ‘Clinical Exomes’ sequencing programme and a separate WGS programme funded by the Health Innovation Challenge Fund (HICF2). The initial protocol for MGAC closely followed guidelines from the Medical Research Council UK and the Wellcome Trust [55] which encouraged WGS programmes to have a clear policy on secondary findings communicated at the time of consent, and took into account the policies of programmes in similar contexts that were already underway [83, 193]. In the initial protocol, individuals were given the option of receiving findings discovered unintentionally during targeted analysis relating to the primary condition (and thus of limited likelihood). No intentional screening was offered (consistent with later guidelines issued by the ESHG [26]). Later, however, the protocol was amended to include the option of screening for ‘additional findings’ based on the ACMG56 minimum gene list.

The 100,000 Genomes Project

Beyond Oxford, current rare disease practice in the UK is being transformed by the 100,000 Genomes Project [64], which also incorporates clinical and research objectives and has been recruiting through patients to WGS through thirteen designated Genomic Medicine Centres in the National Health Service since 2015. The project—which, in Oxford, runs in parallel with MGAC—recruits individuals and families with diverse rare diseases, as well as somatic cancers (where tumour-normal sequencing is undertaken). Oxford is one of these centres, thus affording another WGS stream for rare disease patients and their relatives.

Oxford Genomic Medicine Multi-disciplinary Team

In order to maximise local investment into WGS, and to promote the effective utilisation of these diverse programmes, a Genomic Medicine Multidisciplinary Team (GM-MDT) was established in April of 2014 in Oxford. In addition to verifying eligibility and approving cases for WGS, the GM-MDT determines into which funding stream cases are entered: initially whole-exome sequencing through the NIHR Oxford Biomedical Research Centre 'Clinical Exomes' or WGS through HICF2; but more recently, whole-genome sequencing through HICF2 or the 100,000 Genomes Project. Additionally, the GM-MDT reviews findings, including secondary findings, and promotes genomic education and outreach within the University of Oxford and the Oxford University Hospitals Trust. The GM-MDT, however, does not assume responsibility for patient care—this remains with the referring clinician.

Qualitative methods

This part of my thesis will harness both the views of participants enrolled in WGS through MGAC, as well as members of the GM-MDT, using qualitative methods. Broadly, qualitative methods are interpretive techniques, which seek to describe, decode and translate the meaning of phenomena and behaviours from the perspective of an informant [194]. Unlike quantitative research methods, qualitative research largely uses text and discourse as data. Through their inherent open-endedness, qualitative methods afford insights beyond the prior knowledge and agenda of the investigators and are sensitive to topics that would not arise in more prescribed methods. Thus, they are particularly beneficial in generating theory and directing future work. The main aim of the research is to provide insight into participant perspectives and experiences. In healthcare research, such methods are especially valuable in their ability to complement more quantitative techniques: qualitative studies can help us understand how interventions will work (or not work) in practice, they can help explore the ways clinicians and patients think, feel and interact with the healthcare system [195]. Thus, in an exploration of the various factors underlying reasoning as to whether or not SF should be sought and returned in WGS, qualitative methods are well-positioned to help elucidate the views of stakeholders

involved. This is made especially clear through the high proportion of qualitative studies represented in the systematic review in *Chapter 3*.

Interviewing methods

In my work, I employed semi-structured interviews as my primary method of data collection. Although a range of qualitative methods are available (observational methods, focus groups) I used interviews as they are best suited to understanding participant experience, but can also help in understanding perceptions and influencing factors [196].

To conduct my own interviews, I first spent significant time reading similar interview studies through my systematic review (*Chapter 3*). By analysing and critically appraising these studies, I was able to learn what makes quality qualitative research. I also attended a respected Qualitative Research Methods course offered by the Nuffield Department of Primary Care Health Sciences. The first set of interviews presented (with health-care professionals; *Chapter 4*) was conducted by an experienced qualitative researcher (EO)—a subset of which I observed. I then carried out my own independent analysis of these interviews, affording me the opportunity to analyse properly collected qualitative data. Finally, to complete the training process, I conducted my own set of interviews independently (with WGS participants; *Chapter 5*).

The interviews were semi-structured. This approach employs an interview guide, where a list of open-ended questions and topics to be covered are determined in advance. This strategy affords some level of consistency across interviews, yielding reliable and comparable data. However, the method also allows the interviewer to follow topical trajectories when they arise—allowing data beyond those anticipated by the interview guide to be generated. In both of the included interview studies, the interviews were audio-recorded and transcribed verbatim.

Thematic analysis

In both *Chapter 4* and *Chapter 5*, interviews were subjected to thematic analysis, as outlined by Braun and Clarke [196, 197]. Thematic analysis, which has been a widely used analysis method in this subject area [165, 169, 170, 177, 198], is not tied to any theoretical underpinnings, and was selected for the flexibility this affords. As compared

with other popular qualitative methodologies—such as Grounded Theory or Interpretive Phenomenological Analysis—this facilitates the exploration of experiences as well as understanding, practices and influencing factors [196, 197]. Thus, it is well suited to the research aims of this project. Furthermore, a pure Grounded Theory analysis, or Interpretive Phenomenological Analysis, ideally requires a naïve researcher—this is not possible in my case, and is also not suited to the very specific and technical research aims of my thesis. Importantly, thematic analysis was also selected for pragmatic reasons: it is known to be accessible to new qualitative researchers, and works well in diverse team settings with diverse types of data. Specific details of the coding and analysis process will be discussed in *Chapters 4* and *Chapter 5* where relevant. As much as possible, results are reported following the quality checklist for qualitative studies employed in *Chapter 3* (Appendix A).

As thematic analysis is theoretically flexible, it is worth briefly outlining the methodological orientation of my own approach to thematic analysis. First, my methodology is *experiential*, rather than critical. Such an approach is descriptive and exploratory, prioritising participant interpretation, views, and perspectives. My analysis aims to provide a *rich description* of the entire dataset, rather than a detailed account of one aspect. Although some depth may be lost necessarily, this allows for broad exploration and interpretation of the topic—which is particularly important in a developing subject area, and thus useful in achieving my research aims. The themes derived are mostly *semantic* in nature, rather than latent, focusing on describing what interviewees say, rather than over-interpreting what they think beyond what is discussed. Finally, my analytical approach is as *inductive* as possible, where the analysis is highly data-driven and built from the bottom up. I acknowledge the inherent subjectivity in qualitative methods, and do not claim to separate my own views from the analysis: I have a degree in human genetics and am acquainted with the HCP interviewees. However, I was not part of the clinical team caring for patients and not a contributing member of the GM-MDT myself, and could thus remain somewhat of an ‘outsider’ [199]. These are important considerations as reflexivity is a critical component to quality qualitative research [199]. So, while remaining aware of my own views on the subject, I aim to

conduct the thematic analysis without imposing any preconceptions on the data—thus allowing novel themes and ideas to be generated.

Section outline and objectives

As a means of exploring the broader question of whether or not secondary findings in WGS should be sought and disclosed, and the various factors underlying reasoning as to which SF should be sought and returned, the overall aim of *Part II* of my thesis is to explore the views and experiences of individuals involved in WGS in Oxford towards SF in genomics using the above-described methods. This will be achieved through two distinct interview studies:

- **Chapter 4** combines observations of GM-MDT meetings with semi-structured interviews with GM-MDT members to explore the views and experiences of WGS providers on decision-making in WGS around SF.
- **Chapter 5** presents an analysis of semi-structured interviews with participants enrolled in WGS through MGAC, about their experiences as WGS recipients and their views towards SF.

4

Views of genomics professionals towards secondary findings in WGS: an interview study

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Of the many stakeholders involved in WGS, the views of genomics professionals are important and unique—these are the individuals variously faced with the task of analysing data, gaining consent, and ultimately returning SF to participants. In *Chapter 3*, while views were diverse, I found that many healthcare professionals largely agree that SF should be returned to WGS recipients, with the strongest support for SF that point to conditions that are serious and treatable. Furthermore, the systematic review showed that views of WGS providers were largely informed by their sense of responsibility, which manifests in considered views about SF, in order to minimise harm caused to the recipient. Some studies hinted at potential anxiety on the part of professionals returning such

results, highlighting the need for further training and support.

Few of the views captured in the systematic review are in response to the implementation and utilisation of policies around SF—few stakeholders have handled such results in practice. Additionally, despite being well-represented, current literature on healthcare professional views towards SF is largely American. With a unique healthcare system and culture, it is possible that these views are specific to that setting—as evidenced by minority (ethnic, nationality) views from other stakeholder groups highlighted in *Chapter 3* [165, 178]. Thus, here I present an analysis of the views and deliberations of healthcare professionals based in Oxford around SF in genomics—individuals working in a programme that is actively returning such results. By observing the monthly Genomic Medicine Multi-disciplinary Team (GM-MDT), and analysing interviews conducted with a subset of its members, I explored the early experiences with the genomic decision-making process and views towards SF. Features of this chapter have been accepted for publication in *Genetics in Medicine*. Analysis of the decision-making process in the GM-MDT, of which the distinct work I undertook comprises some of this chapter, has been published in the *European Journal of Human Genetics* [200].

4.1 Chapter aims and objectives

The overall aim of the research reported in this chapter was to explore the views of both clinical and research professionals involved in WGS towards secondary findings in a UK context. This was achieved through: (1) an analysis of the GM-MDT meetings, including notes and meeting minutes; and, (2) interviews with a subset of GM-MDT members on the meeting themselves, as well as secondary findings and genomic medicine more broadly. The specific objectives were to:

- Understand the views of clinical and research professionals towards, and understanding of, WGS and SF;
- Understand which types of SF WGS providers think should be generated and returned, and why; and,

- Explore how decisions around WGS and SF are reached, and how this process changes over time.

4.2 Methods

4.2.1 Setting

As discussed, a Genomic Medicine Multi-disciplinary Team (GM-MDT) meets monthly in Oxford to make decisions around case selection, strategy and results (including SF) in WGS. GM-MDT meetings are held on an Oxford University Hospitals NHS Foundation Trust (OUHFT) site and scheduled to last two hours. Members represent a diverse range of specialties and roles. Meetings were quorate when the Chair or deputy, at least four clinical members, and at least one laboratory member were present. For WGS case consideration, the referring clinician must submit a short application form summarising clinical information relating to the proband and their relatives, along with a pedigree. Cases must be submitted in advance of the meeting and are sent for internal peer review by one reviewer with clinical expertise relevant to the case. Cases for review are circulated ahead of the meeting to the GM-MDT, and briefly presented to the group by the reviewer or applicant (if present). The applicant is informed in writing of the decision, with any recommendations for further action before acceptance, shortly after the meeting. The approval process is shown in Appendix C (Figure C.1).

4.2.2 GM-MDT observations

With members' consent, EO or myself took observational notes at 24 meetings of the GM-MDT between June 2014 and June 2016 (one was missed). In this chapter, these data were used to inform understanding of the GM-MDT and the decision-making process, as illustrated by similar process studies of GM-MDTs [201, 202]. This served to provide context for the interviews, and highlight issues that prompted discussion or differences of opinion. Additionally, observational data from the meetings, as well as minutes circulated after the meetings, were subjected to analysis where they discussed SF. Discussions of SF specifically were open-coded and analysed in a descriptive manner in order to depict

GM-MDT policies towards SF and present vignettes of specific SF discussed in the GM-MDT—it is valuable to outline experiences of the GM-MDT with SF as they inform the views articulated in the interviews. Additionally, the meeting minutes were analysed to determine the total number of cases approved, and through which sequencing stream.

4.2.3 Interviewees

Members of the GM-MDT were contacted by email by EO and asked if they would be willing to participate in an interview. Recruitment continued until data saturation was reached (no new themes emerged from the analysis of subsequent interviews).

4.2.4 Interview guide

A semi-structured interview guide was developed, based on review of the literature and the observational data collected in the GM-MDT. A list of the topics covered in the interview guide (Appendix E.1) is found in Table 4.1.

Table 4.1: Topics covered in semi-structured interview guide with GM-MDT members

-
- Experience with the GM-MDT.
 - Experience and opinions of the consent process for WGS.
 - Views towards SF in WGS, and screening for additional findings.
 - Views on responsibility in SF management.
-

4.2.5 Data collection

Interviews were conducted by EO between August 2015 and April 2016, and observed by MM. Interviews took place on an OUHFT site. The interviewer explained that the interview would be recorded and de-identified, such that participants could not be identified. Participants were given the opportunity to ask questions of the interviewer and written consent was taken before the interview commenced (Appendix C). Interviews lasted from 40-120 minutes, and were audio-recorded and transcribed verbatim.

4.2.6 Data analysis

Anonymised interview transcripts were checked against the original audio-recording by the interviewer (EO) for accuracy. A thematic analysis was then undertaken, as discussed

in the introduction to *Part II*. To start, I engaged in a process of reading and re-reading the transcripts to familiarise myself with the data, taking note of initial ideas. Then, I selected three transcripts to be coded in a non-restricted manner. EO independently coded the same three transcripts, and coding disagreements were resolved at a meeting by consensus. I then imported all of the transcripts, including the first three, into NVivo 11 [132], a computer-based qualitative data analysis software package, where I reviewed and thoroughly coded the data in a systematic manner. For these interviews, I undertook two independent analyses: responses to questions on the general functioning of the GM-MDT were coded and analysed separately from the other responses, including those on SF.

Throughout the coding process for both analyses, codes were grouped together where possible, allowing for the exploration of themes and patterns. Through a process of reading and re-reading, I continued to revise the coding structure in a manner that more accurately reflected the data present in the interviews, grouping and renaming codes where appropriate. Based on the grouping of codes, I ultimately arrived at higher-level themes and associated subthemes. While working towards a final thematic structure, I generated ‘thematic maps’ [197] of the analysis—helping to situate the themes relative to one another. For each working theme I generated a summary document following the ‘One Sheet of Paper’ method [133]. This process helped ensure that the content of the themes were distinct, with minimal overlap between them. I also ensured that the themes worked relative to each of the individual interviews, as well as the entire dataset. At this point, I also refined the specific details of the theme and settled on a title and clear definition. Throughout the process, I allowed for the addition of new codes at any point. Finally, I re-read the content coded to each theme for illustrative quotations to use in the presentation of my analysis. EO checked the final coding for accuracy and completeness, as well as the final thematic structure.

4.3 Results

4.3.1 GM-MDT member demographics

During the study period membership of the GM-MDT comprised 40 individuals (although the membership varied at any one time). The characteristics of the interviewees are

Table 4.2: Demographics of GM-MDT members ($n = 40$)

Category	n	%
<i>Member roles</i>		
Clinical scientist	4	10
Genetic counsellor	1	2
Genetic counsellor-researcher	1	2
Physician	12	30
Physician-researcher	16	40
Researcher (non-clinical)	5	12
Project manager	1	2
<i>Patient-facing</i>		
Yes	30	75
No	10	25
<i>Specialty (and sub-specialty)</i>		
Administrative	1	2
Bioinformatics, statistical genetics	3	8
Cardiovascular medicine	4	10
Clinical genetics	14	35
General	5	12
Cancer	5	12
Cardiovascular	1	2
Craniofacial	1	2
Foetal/neonatal	1	2
Neurology	1	2
Clinical science	3	7
Endocrinology	2	5
Gastroenterology	1	2
Haematology	2	5
Immunology	3	7
Infectious disease	1	2
Neurology	2	5
Oncology	1	2
Renal medicine	1	2
Rheumatology	1	2

Note: Percentages may not total 100% due to rounding.

shown in Table 4.2. Members represent diverse roles, with 75% of those being patient-facing. A wide range of specialisms was represented (14), and the most represented specialism was clinical genetics (35%). However, the sub-specialisms within clinical genetics were diverse.

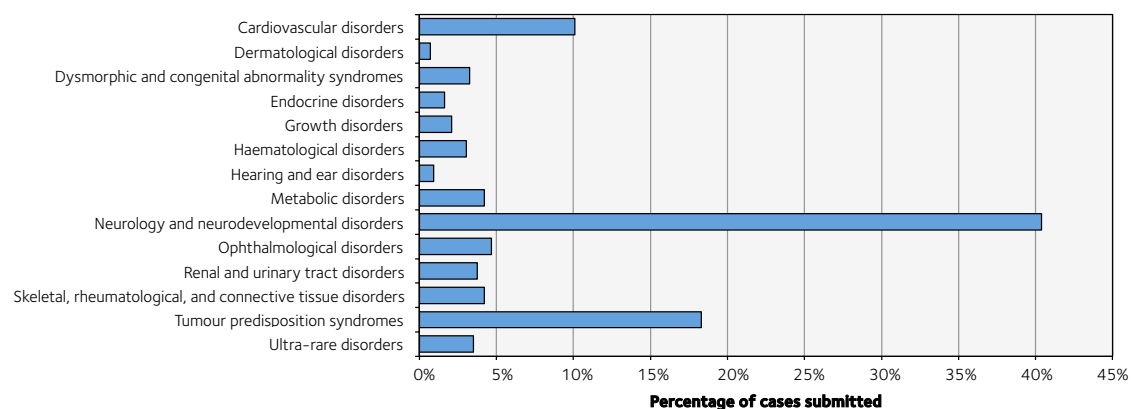


Figure 4.1: Cases submitted to the GM-MDT by specialty (n = 467)

4.3.2 GM-MDT meetings

All meetings in the study period were quorate; the average attendance was 14 members. Meetings were chaired and followed a written agenda. Policy and project updates, and any additional proposed research were presented at the start of the meeting. Results and other business at the end. Case discussion formed the main component of meetings during the study period: between 5 and 34 applications were considered per meeting. A total of 467 cases (single individuals, more than one affected family member, or trios including the patient and unaffected parents) were considered across the meetings, from a range of specialties (Figure 4.1). The number of cases considered each month—including the number accepted and rejected—is shown in Figure 4.2. As a new avenue for sequencing became available—the 100,000 Genomes Project—the number of submitted and approved cases rose dramatically.

4.3.3 Secondary findings in the GM-MDT

From observations and meeting minutes, SF were largely a topic of discussion in early meetings, when protocols and pipelines were being devised. These discussions highlighted the importance of reaching a consistent policy on how—where participants consented to receive them—SF would be managed. Some members commented that the wider field of genomics was moving towards actively screening for ‘actionable’ SF. However, many others noted that there was no existing infrastructure for the systematic return of SF, and that the data needed to inform interpretation was lacking. The

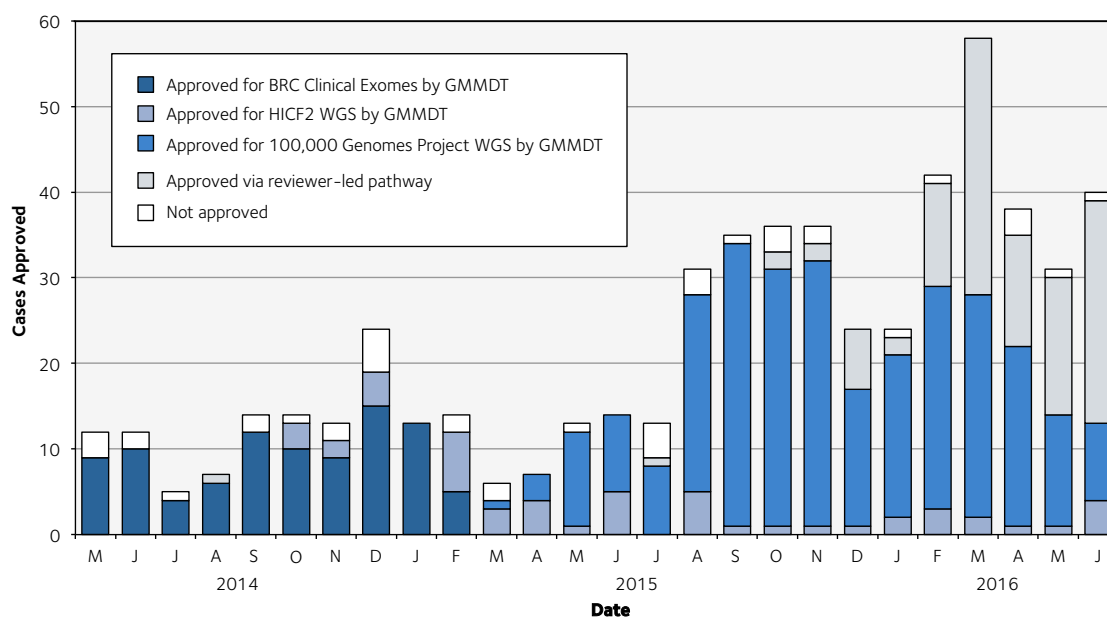


Figure 4.2: Sequencing stream of cases approved by GM-MDT over time. BRC: NIHR Biomedical Research Centre; HICF2: Health Innovation Challenge Fund

importance of seeking external expertise recurred in discussions of SF in the GM-MDT: members sought external expert input, including the authors of the ACMG56 guidelines, and looked to consent forms from similar studies to inform the development of the consent process for SF in MGAC. It was ultimately agreed that GM-MDT members would play a central role in the interpretation and feedback of SF, and a management pathway (Figure 4.3) and pro forma structure (Appendix C) were developed by a subgroup of the GM-MDT to guide this SF management. Initially analysis was limited to genes pertaining to the primary condition—a minimum gene list would only help guide the return of truly ‘incidental’ SF and no additional genes would be actively screened. It was agreed, however, that the process for managing SF should be kept under regular review.

Midway through the study period (March 2015) an amendment to MGAC was approved allowing for the *active screening* of genes on the ACMG56 list in samples for which consent is given. Following this amendment, adult MGAC participants were given the option to opt in to receive: (1) ‘additional findings’ based on active screening of the ACMG56 list; and, separately, (2) incidental secondary findings (also based on the list, but not actively screened). This represents a significant shift from the initial protocol, in line with a general trend in the field (e.g. the 100,000 Genomes Project was planning to

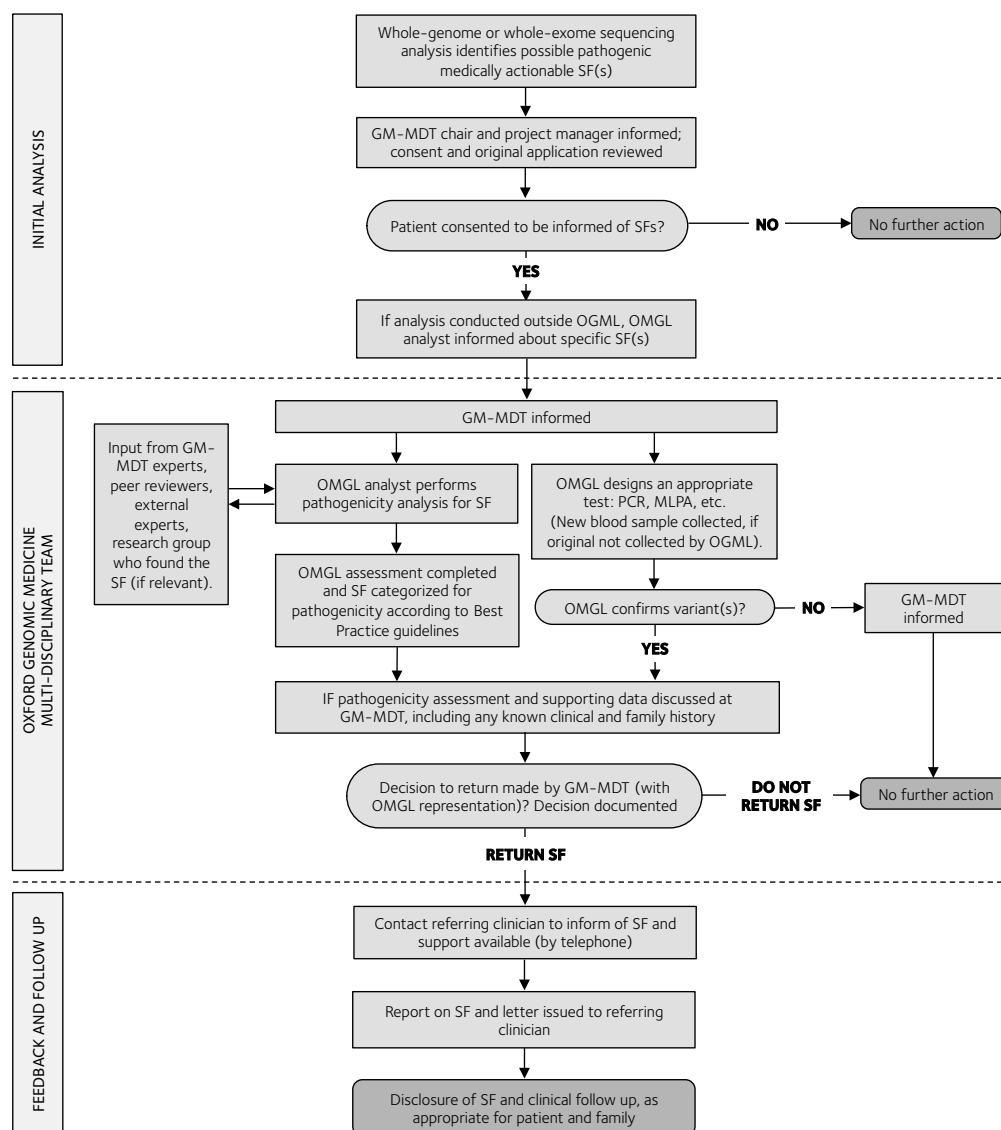


Figure 4.3: Pathway for management of SF as agreed upon by the GM-MDT. *Note:* molecular confirmation of WGS findings is to be reported within three months of activation or sample receipt.

offer SF). The decision was additionally influenced by the local expertise with inherited cardiac conditions (ICCs): participants in whom pathogenic cardiac SF were identified could benefit from local resources, expertise, and existing infrastructure.

Following early discussions about policy and pipelines around SF, the topic did not recur until later in the study period, when members had to make decisions around the return of specific variants. The details of these SF, which inform the views articulated in the interviews discussed later, are outlined below. These cases serve to illustrate important challenges and provide useful examples—affording discussion of SF beyond

the hypothetical.

A secondary finding in *RYR1*

One SF presented to the GM-MDT was a variant in the gene for ryanodine receptor 1 (*RYR1*). *RYR1* encodes the skeletal muscle ryanodine receptor, the calcium release channel of the sarcoplasmic reticulum, and hence plays a critical role in skeletal muscle function. Variants in *RYR1* have been shown to cause malignant hyperthermia, a condition in which affected individuals can die when exposed to general anaesthesia due to an excessive release of calcium ions in muscle cells leading to uncontrolled contraction [203]. It was a significant cause of anaesthesia-related death in healthy individuals, however mortality rates have decreased dramatically since the genetic predisposition was discovered and treatment became available [204]. As these risks can be mitigated if detected pre-symptomatically, *RYR1* is on the ACMG56 list, and was thus included in the MGAC protocol.

The variant in question, c.5036G>A, p.Arg1679His (NM_000540.2), was found in a 16 year-old male referred for an unrelated craniofacial condition. As presented to the GM-MDT, the variant had been previously detected in an individual with a diagnosis of malignant hyperthermia diagnosis, which was confirmed by functional analysis [205]. However, it was also present at higher than expected levels in population-based cohorts (0.2%-0.3%) [75, 206, 207]. The OMGL reported the variant as a 'variant of uncertain significance' (VUS) and noted that confirmation of a diagnosis would require functional studies (in vitro contraction testing).

In the discussion of whether or not to return this variant, one GM-MDT member noted that the patient had previously had two major surgical procedures without any complications. Another member commented, however, that such information would not be particularly anxiety-inducing and that intervention would be minimal—simply warning an anaesthetist would mitigate risk. Based on the population-based evidence, however, most felt that the probability that this variant would cause disease was low. This was corroborated by the variant not being on current European guidelines as a causative variant for malignant hyperthermia. Further input from an external expert presented by a GM-MDT member was of the opinion that the variant should not be

reported. Thus, despite the potentially straightforward actionability, the GM-MDT did not recommend feedback of this variant—on the basis of its prevalence in the wider population, the expert advice, and the unproblematic previous surgeries.

A secondary finding in *BRCA2*

Another SF presented to the GM-MDT was a variant in *BRCA2*, a tumour suppressor gene, which encodes breast cancer type 2 susceptibility protein, and is critical in the regulation of cell growth. Variants in the gene can cause a loss of tumour suppressing activity, resulting in uncontrolled cell growth and the formation of cancers. Variants in *BRCA2* increase lifetime risk of developing breast cancer or ovarian cancer. Together with *BRCA1*, a related tumour suppressor gene, variants in these genes account for a quarter of all hereditary breast and ovarian cancers [208]. Approximately 45% of women who have pathogenic variants in *BRCA2* will develop breast cancer by the age of 70, and up to 17% will develop ovarian cancer (as opposed to 12% and 1.3%, respectively, in the general population) [209, 210]. As risk-reducing measures are available to mitigate risks if pathogenic variants are detected pre-symptomatically, *BRCA2* (as well as *BRCA1*) is on the ACMG56 minimum gene list.

The variant presented to the GM-MDT, c.7556C>T, p.Arg2520* (NM_000059.3), was found in a 21-year-old female patient referred for an unrelated craniofacial condition. The nonsense variant was predicted to produce a truncated protein that is subjected to nonsense-mediated RNA decay, resulting in a single functional copy. As described above, haploinsufficiency¹ of *BRCA2*, as is caused by such a truncating variant, is strongly associated with a predisposition to breast cancer. For this reason, the OMGL reported the variant as ‘highly likely to be pathogenic’.

The ensuing discussion of the variant was very brief. Some members raised concerns: questioning whether there could be other variants acting to render this variant benign, noting the lack of family history. Many others, however, felt that such an explanation was unlikely, and that a lack of family history did not guarantee reduced risk. The GM-MDT quickly agreed that the variant warranted feedback and clinical referral. The referring

¹**Haploinsufficiency** occurs when only one functional copy of gene is present, and an insufficient amount of gene product is produced to ensure the normal phenotype [211].

clinician, a GM-MDT member, noted the difficulty of contacting the patient as the family were not local to Oxford and had been discharged from his care, but would attempt to make contact nonetheless. Additionally, the decision was taken to discuss the case with a local cancer genetics team, such that the patient could see a relevant specialist as soon as possible to minimise any potential anxiety.

The clinician reported back to the GM-MDT that the SF actually fit with an unrecorded positive family history. As a consequence of the disclosure, the participant began discussing screening and treatment options with the relevant specialist.

A secondary finding in *KCNQ1*

A third secondary finding, a variant in the gene *KCNQ1*, was presented at the GM-MDT after the interviews were concluded. This variant is discussed in detail in *Chapter 6*.

4.3.4 Interviewee demographics

A total of 19 GM-MDT members (48%) were interviewed. Interviewee demographics are shown in Table 4.3. All interviews were conducted in person at the place of work of the interviewee. The interviewees represent the full range of roles present on the GM-MDT. All physicians interviewed are also involved in research (i.e. physician-researchers).

4.4 Thematic analysis

The interviews covered two main topic areas: the first (presented in *Section 4.4.1*) focused on the functioning of, and decision-making process in, the GM-MDT; the second (presented in *Section 4.4.2*) focused on views around secondary findings and genomic medicine more broadly. As analyses were conducted independently, the themes for each are presented separately. Illustrative quotations are presented with anonymised codes for each interviewee: the codes and relevant details for each interviewee are in Appendix F ('P' is used here to denote 'WGS provider,' in order to distinguish from 'R' for 'WGS recipient' used in *Chapter 5*). The recording of one interview was lost, and therefore not included in the analysis.

Table 4.3: Demographics of GM-MDT member interviewees (*n* = 19)

Category	n	%
<i>Gender</i>		
Male	12	63
Female	7	37
<i>Member roles</i>		
Clinical scientist	3	16
Genetic counsellor	1	5
Physician (genetics)	4	21
Physician (non-genetics)	8	42
Researcher	3	16
<i>Consented patients to WGS</i>		
Yes	7	37
No	12	63
<i>Years experience</i>		
5 or less	1	5
6 to 10	3	16
11 to 15	3	16
16 to 20	6	32
Over 20	5	32

Note: Percentages may not total 100% due to rounding.

4.4.1 Decision-making in the GM-MDT

Four main themes were identified from the interviews that were central to understanding the functioning of, and decision-making process in, the GM-MDT: (i) the idea that the GM-MDT, and the resulting decision-making, benefits from the number and diversity of its members; (ii) group dynamics, especially the variation in an individual's participation depending on their role and level of experience; (iii) the shifts in decision-making that occur with changing resources and available sequencing programmes; and, (iv) tension between meeting quotas and selecting quality cases for inclusion. Detailed descriptions of these four themes are presented below.

Strength in numbers and diversity

All interviewees demonstrated a positive overall impression of the GM-MDT meetings and their role in decision-making around WGS. First, interviewees felt that shared decision-making between many individuals resulted in better decisions. One interviewee noted

that this has the benefit of allowing responsibility to be shared between those involved. Second, interviewees felt that the range of disciplines represented was also an asset, as wide representation was needed to make decisions in different disease areas.

‘So the reasons I like it are firstly, that it’s multidisciplinary and it brings neurology together with lots of other specialities, which can be difficult in other contexts. Secondly, it brings together people who have a genuine interest in genetics, as well as people who are geneticists. There are a lot of people who are interested in trying to refine genetic diagnoses for patients.’ (P12)

‘I think they’re a unique asset and they have the capacity to nucleate a bunch of people from different specialities with a generic interest but with also detailed speciality, which is unique worldwide.’ (P7)

Efforts to encourage representation from across disciplines and specialties allowed the GM-MDT to act as a means of informing the wider medical community in Oxford about genomics—both its advantages and its local availability.

‘My overall impression is that it’s been a success and that’s it’s attracted interest from elsewhere so may or may not be a model that other people take up but I think in terms of bringing together a diverse range of people from different disciplines then that really helps with the idea of trying spread genomics more broadly.’ (P9)

The diverse representation and outreach fostered learning and growth amongst members, which interviewees noted as a particular benefit of participating in the GM-MDT. Members who were less familiar with genetics and genomics felt that they had learned about the benefits of using WGS after attending. More experienced members expressed greater confidence in using genomics in clinical practice as a result of their engaging with other professionals on the GM-MDT.

‘I really enjoy going to them because often I learn from other people, their way of thinking about solving problems or things that I wouldn’t have thought about, about family structure or a particular dilemma.’ (P4)

Group dynamics and decision-making

While most members viewed the composition of the GM-MDT as its greatest strength, many interviewees noted the group dynamics when discussing the decision-making process. Some interviewees felt that the more senior members of the group, particularly those with extensive clinical experience, had the highest participation and were most

involved in decision-making. Furthermore, those with experience in a certain disease areas were often deferred to during decision-making around related cases. Some felt that the presence of experts created a somewhat intimidating environment for new and more junior members.

‘People don’t always contribute as fully as perhaps they might because there is very senior people, and I think some of the younger people find it a quite intimidating environment, and certainly I know that some people that I’ve had along as guests were like, “Oh my goodness, there are many important people in that meeting”, but it’s good that it’s got buy-in at that level as well...’ (P11)

As senior members were most involved in decisions, and their attendance was variable, this was seen to cause inconsistencies in the decisions made.

‘When there’s uncertainty, you need the expertise and if the expertise isn’t in the room in that disease area you may get different feedback than if it is in a disease area.’ (P15)

However, not all members felt this was the case: ‘it’s a very professional atmosphere, collegial’ (P10). And, even amongst members who agreed that a power dynamic existed, interviewees did not necessarily think it was to the detriment of the GM-MDT—in fact, many highlighted the participation of these senior members as an asset.

‘[The GM-MDT is] a fairly open forum for discussion. I don’t think they are inhibiting and I don’t get the sense that people, most of the time, feel they have to hold back because they’re in a fairly large group of people, many of whom they don’t know. So I think that they can be direct, straightforward and honest.’ (P2)

Shifts in decision-making with changing resources and programmes

Changes in available resources had a substantial effect on decision-making in the GM-MDT. Consistent with the meeting content, interviewees noted a shift in decision-making with the introduction of the 100,000 Genomes Project. While the meetings initially funnelled cases into resource-limited WGS programmes, the introduction of 100,000 Genomes Project required recruitment to increase. This resulted in a shift from focusing on case prioritisation to meeting inclusion criteria.

‘There’s probably such a drive to use up the resources that there are available to complete this work that people are, to some extent, turning a blind eye to the lack of additional phenotypic data which would help the decision-making, and that what’s being done is pragmatic.’ (P2)

Interviewees noted that, with increasing sample numbers (Figure 4.2), the meetings became increasingly pressurised. The relaxed stringency in case selection resulted in a shift in the limiting resource from funding and availability of sequencing to GM-MDT members' time. Interviewees felt that debating all cases through the GM-MDT was unsustainable if the available resources were to be used most effectively: 'I think it's a luxury that we can't necessarily afford to keep applying.' (P13) In order for the GM-MDT to be used to its full potential, interviewees felt that the pipeline needed to be reconsidered. In times of increased capacity for WGS, where members' time is the limiting resource, straightforward cases should be reviewed outside of the meetings—allowing for the more complex cases to be discussed.

'I think some are very straightforward and now the idea of not everything having to go through the meeting but just to say, well this clearly meets criteria and a smaller group sanctioning that; I think that's fine, to enable a discussion of those more complex cases.' (P12)

Ideally, in the long-term, this should become more feasible as genomics itself (and understanding of genomics) becomes more widespread, as is the intention of the 100,000 Genomes Project itself. As referring clinicians become better acquainted with inclusion criteria, and are able to ensure their cases meet the necessary criteria, only the complex cases will need to be reviewed by teams of experienced professionals, such as the GM-MDT.

Tension between quotas and good science

Throughout the interviews it became clear that there was a tension between meeting recruitment targets and avoiding conducting 'rubbish science' (P4): choosing cases that are most likely to yield a positive result. This appeared to be a product of the aforementioned shift in the funding programme, and the membership of the GM-MDT, some of whom are proven experts who appreciate the criteria required for obtaining genetic diagnoses by WGS in their respective fields.

'So there's always this tension, isn't there, between this fits the criteria for example with the GEL stuff now, there's a tension between well, it fits the criteria, it ticks all the boxes that we should submit this and actually, this is rubbish science; this

is probably not going to give us a result. I think that's a tension within the group. I'm not sure we always get that right. I probably lean more towards doing the right experiment being purist about it but that's probably not realistic always.' (P4)

Some members of the GM-MDT expressed concerns that quotas were being met at the expense of only selecting cases likely to be solvable by WGS. However, with time, the interviewees felt that the group had reached a consensus, and maintained quality over quantity in their decision-making.

'There was a period a few months ago when I felt there was a kind of state of panic amongst the leadership and that actually basic good genetics had slightly gone out of the window in the quest just for sample numbers. But that does seem to have improved, the atmosphere seems to have improved of late, so there's more of a recognition that quality is more important than quantity.' (P8)

Some interviewees also raised the role of research ownership on decision-making. In submitting samples to a larger national project, members feared losing local control over the project and not benefitting from publishing results themselves. One interviewee noted that the need for members to publish might affect sequencing decisions, and questioned whether such cases are brought to the GM-MDT altogether.

'The risk that's come out of it really has been a case of I might be putting something in that I'll never hear anything else back about or get any useful information from. That's kind of the only risk that I've come across with that or there could be a paranoid part which comes out that says, "I'm risking somebody else getting a fantastic paper because they get access to results and data that I've not been told about".' (P14)

4.4.2 Genomic medicine and secondary findings

During the analysis of the part of the interview pertaining to secondary findings and genomic medicine, five main themes were identified. A list of the main themes and secondary themes are shown in Table 4.4. Detailed descriptions of these five themes are presented below, with illustrative quotes and references to anonymised interviewee codes.

A. Screening for secondary findings: rationale and responsibilities

Positions on screening and return of SF. For the most part, at the time of interviewing, GM-MDT members felt that the capacity to return *limited* secondary findings for WGS

Table 4.4: Primary and secondary themes in GM-MDT member interviews around genomic medicine and secondary findings

A. Screening for SF: rationale and responsibilities
• Positions on screening and return of SF • Concerns and perceived challenges • The need for a cautious approach
B. Feasibility of informed consent: paramount, but challenging
• Respecting informed decisions • Barriers to informed consent • Consent process and practicalities
C. Actionability and pathogenicity: determining which SF to return
• What is 'actionable'? • The importance of pathogenicity • Considering context • Group decision-making and shared responsibility
D. Returning SF in practice: disclosure and duties to family members
• The need for a plan • The importance of expertise and specialist input • Sharing results and responsibilities to family members
E. Evolving science, evolving practice: a field in flux
• The need for stronger evidence • The need for standards and guidelines • The future of secondary findings and genomic medicine

should be enabled. While some benefits were raised, including an 'economic benefit to the NHS—if they can catch these things early it will reduce the cost of treatment downstream' (P6), for most, providing potentially helpful information to participants justified the active search and disclosure of some SF:

'So, very much so, I feel that where there's a clear evidence base to say knowledge of this is something that is going to influence medical management [...] and that that medical management will be beneficial, then it's a very important thing to have the capacity to return that.' (P8)

For many, this appeared to be rooted in a sense of responsibility to act in the participants' best interests and a 'duty of care'. Some, however, additionally described the heavy 'burden' (P4, P11) they might feel as healthcare providers by having additional information—or even the ability to obtain additional information—but not being able to act on it:

'I certainly know from a laboratory perspective that we do not want to have information that is not going back to the patients.' (P13)

'I'd be very uncomfortable, for example, if I knew that but wasn't in a position to discuss [an SF] with a patient. I would not want to be in that situation. That is analogous to noticing that someone's got a breast lump and then not referring them on or seeing some shadow on an X-ray and not ordering up further tests, and physicians will be very uncomfortable with that.' (P16)

While still enthusiastic about the potential for WGS to transform healthcare, some interviewees were less convinced about screening for SF in WGS, suggesting that they 'make it messy' (P15). Some articulated that healthcare professionals (HCPs) should 'stick to areas of familiarity' (P5) and that screening for SF was too far removed from the aims of WGS:

'It feels to me like it's getting too complicated and too far from the original reason for which the person actually entered into the whole genomic sequencing.' (P13)

Others raised justice issues in providing SF to WGS participants when others do not have the opportunity to derive the same benefits:

'Why should we feel so bad about people who happen to have one condition and therefore by proxy are getting some access to genomic sequencing, why are we going to wring our hands in anguish about them if we don't find something, when they wouldn't have been in in the first place, other than with their initial condition?' (P5)

Concerns and perceived challenges. Many of those who voiced opposition to screening for SF cited the challenges that would present themselves: 'I just think there are too many issues that need to be worked out. I think there could be too many complications.' (P6). Interviewees raised concerns widely described in the literature, including: unnecessary medicalisation of participants, insurance problems and risk of discrimination, potential to cause 'undue anxiety' (P15), and psychological harm.

'For me, the bigger question... is with what confidence you can convey this interpretation? Because a worse scenario is if you harm a patient psychologically, for a variant that doesn't actually confer harm.' (P7)

Of particular concern for interviewees, however, was the challenge of interpretation. Interviewees demonstrated a growing fear that we are underestimating the challenge of interpreting SF, and that there is a serious risk of over-interpreting the data that is generated. They felt that this problem would only be exacerbated by the current lack of evidence and expertise.

'I remain strongly influenced by the evidence we have that suggests that we will find interpretation difficult. I'm just guessing that [...] the proportion of variants that are possibly relevant but really hard to tie down will be high and there then will be another even bigger number of variants which I will be very minded to dismiss. So that is likely to make all of this hard, and if there's been any change in my thinking it's probably in the direction of thinking that's more of a hurdle than we think.' (P16)

In particular, interviewees highlighted the difference between interpreting findings when there is a phenotype or family history of disease (as is the case with 'primary findings') and the relatively uncharted territory of interpreting variants in their absence (as with SF):

'I've become more convinced that we understand very little about how to interpret the vast majority of variants that we see in the absence of a diagnosis. I think the problem of interpreting variants that are potentially relevant to a diagnosis is an easier one than prediction that comes with a secondary finding.' (P17)

'I think we're used to dealing with these mutations when we know the family history [...] but suddenly they're going to move this into the realm where there's no family history. You don't know what you're dealing with. You don't know that they mean the same thing.' (P18)

The need for a cautious approach. Despite the challenges, even for those wary of current ability to interpret SF, the potential benefits of screening for some SF—where potentially life-saving—outweighed the risks:

'I think there's always the potential for harm. The counter-argument is that there is that benefit, there is that potential life-saving or increasing someone's life expectancy based on the treatment they're going to receive.' (P6)

Thus, it was felt by interviewees that screening and disclosure of SF should be enabled within WGS protocols. In order to maximise the benefits of this disclosure, interviewees felt that local factors and infrastructure must be considered: resources, including costs and counselling; local culture and practice; availability of necessary care.

'I think it's hard to not give people the option [to be screened for SF] but then you have to try and make sure that what you're doing is responsible and that you have resources with which to counsel patients about that in your programme and then the resources if they actually need to be seen by other clinicians in other specialities.' (P13)

Interviewees ultimately agreed that if screening SF were to be offered, HCPs cannot 'go in gung ho' (13). Instead, they advocated for a cautious approach that is thoughtful and limited: doing good and minimising harm need to be carefully balanced.

'We might find better treatments, we might find better screening, we might have a very different concept about health and the elderly and all sorts of stuff. I mean, that's if we don't all blow ourselves up.' (P5)

Such an approach requires careful consideration of the local factors discussed, as well as the risks and concerns—including careful interpretation and ensuring a sufficient evidence base exists to be sure a result is worth returning. Interviewees felt that such an approach needs to be consensus-driven and requires a sharing of responsibility across the wider healthcare system:

'The very broad discussion about secondary findings, and how we do them, [...] should be everybody's responsibility to take that thought forward and develop the ideas and the ethical framework that goes into that, because otherwise it's a very big burden on the one person who is sitting there, on their shoulders.' (P11)

B. Feasibility of informed consent: paramount, but challenging

Respecting informed decisions. Across all of the interviews—regardless of role, experience of the consent process, or views on other issues—interviewees universally stressed the importance of informed participant choice, and the consent process. Many considered it to be the most critical part of the entire genomic medicine pipeline: 'It all boils down to the consent, the counselling and how it's delivered' (P2). Interviewees widely expressed an assumed need to respect informed decisions made by WGS recipients at the time of consent—interviewees expressly articulated a perceived participant 'right to know', as well as a 'right not to know', that should be respected.

'People have got the right to know the information if they want to know it' (P1)

'I think the right to not know has just as much sway as the right to know.' (P6)

Despite its perceived importance, some interviewees did raise the possibility of overriding a participant's decision with regards to SF. This appeared to be founded in a sense of discomfort and anxiety that some interviewees expressed at the idea that they would have potentially life-saving information that a participant opted not to receive—for them or their families:

'[...] there might be a therapy or a treatment for something it does seem uncomfortable for us to not tell them because they didn't want to know. Then we're sitting on the information; the burden's on us.' (P4)

For the most part, however, interviewees felt that—if properly informed—participant decisions were never to be overridden: 'So I guess that's what it comes down to really, patient choice. It's not clinician choice; it's patient choice' (P3). Interviewees variably feared being paternalistic; felt their views were immaterial compared to the patients; or felt that the genomic professional-participant relationship was one of privilege that must be respected in order to advance the field:

'I don't really believe in hiding anything from patients about their care or their management or what's happening to them [...] I think that's the way healthcare should be. It's very much a partnership. We're privileged to try to be able to help them and that will enable better engagement [...] Otherwise we run the risk of actually undermining the consent, not just for that patient but for everybody.' (P12)

Barriers to informed consent. While there was agreement that informed decisions should be respected, interviewees were not optimistic about the extent to which patient decisions around SF are actually informed:

'There's absolutely no informed consent. It's like saying to a patient, "Do you want a bag of chips?" They're going to say, "Oh yes, please. I'd like a big bag of chips", but they don't actually sit down and think, "well, what's that going to do to my cholesterol and what sort of impression am I going to give to the kids sitting here stuffing my face with a bag of chips". They don't think about it.' (P18)

Interviewees cited numerous barriers to obtaining truly informed consent: the need for a complex discussion of risk, lack of time, lack of professional understanding, and length and complexity of documents. Of particular concern was the difficulty capturing the range of possible SF in an informative manner—the gene list was long, requiring varying expertise, and regularly changing.

As a consequence of these barriers, interviewees expressed concern about participant understanding of SF. Coupled with mismatched expectations for WGS—‘they probably overestimate the yield of sequencing’ (P15)—and a focus on finding an answer with respect to their primary condition—‘These are not people’s primary concern, they’ve come into this to find out what they’ve got, this rare condition or something, this is not at the front of their minds’ (P4)—interviewees worried that participants did not fully consider the implications of SF, thus impacting their ability to make informed decisions:

‘I think that is a complicated concept to get across to people so making sure it’s truly informed consent is a potential issue [...] I’m not sure that for the public as a whole, there’s really the understanding that can allow truly informed consent. I would say that we do do that in as good a way as best practice would currently allow.’ (P9)

‘I don’t imagine that patients when they consent have a very good mental image of the range of outcomes and likelihood and consequences associated with secondary findings.’ (P17)

Of note, many of the interviewees had no actual experience of obtaining informed consent for SF from WGS participants. However, those with experience described the same difficulties perceived by the wider group. Nonetheless, these interviewees emphasised the attention they devote, and some expressed a growing level of comfort with obtaining informed consent around SF with time and practice: ‘the more you do the more comfortable you are’ (P12).

Consent process and practicalities. In order to maximise the utility of consent sessions, and best inform decision-making, interviewees discussed what they deemed necessary in terms of structure and content. In doing so, interviewees demonstrated a perceived sense of responsibility to equip participants as best possible to make informed decisions: ‘We just try to empower the patient to understand what exactly it means and that there’s no obligation to know if they don’t want to know’ (P12). While the written materials were felt to be helpful by some, most felt that this empowerment required face-to-face discussions. In these consent sessions, interviewees stressed the importance of specifically explaining SF to participants, and ensuring they understand the potential for SF in their own sample:

‘I think if incidental findings for example hadn’t come up in that conversation, I would check with them and make sure they’ve gone through that and that they’ve understood that was something we’re agreeing to and talk through.’ (P4)

For some interviewees, this meant ensuring the participant has thought through the various implications of SF: 'It's only when you start saying well, here are the issues that it might have for you as an individual that you get people sometimes who go oh, okay, I need to think carefully about that' (P16). Others said they use illustrative examples:

'I think the only real way patients could come to understand the implications would be in a case example. So, I've come to think about this a lot. I think the only way to convey it to the patients in a way they'll understand is to say, for example, "Imagine if we found X" [...] It's not to say that they can predict how they're going to react but the only way that they'll understand what is being presented to them, I think is by exemplar rather than theoretical concepts.' (P7)

In light of the changing list of potential SF, interviewees felt that consent needed to be broad, underpinned by a conceptual appreciation of possible SF, rather than specific details, and understanding that any disclosed risk would be actionable.

Regardless of the specific content, interviewees broadly agreed that 'everyone is different' (P6) and stressed the importance of individualising the content of consent sessions: care must be taken to provide 'the right level of information' (P3) to ensure maximum understanding for each participant. In addition to differing from one another, frequent consenters noted that a single individual's views towards genetic information can change over time, and that this was an important consideration during the consent process:

'I can meet somebody and a year later meet them again and they'll make a very different decision. They're in a different place. That year has changed how they viewed things.' (P14)

Additionally, some noted the life-stage-specific relevance of some types of SF, such as carrier status information being more appropriate at reproductive age. Some interviewees noted that, since their own attitudes continue to evolve, it was reasonable that participant attitudes might be subject to similar (or other) influences with developing knowledge. In light of the changing nature of participants' views and contexts, some interviewees felt that tiered or more dynamic forms of consent should be considered, albeit somewhat aspirational and resource intensive.

C. The problems of actionability and pathogenicity: determining which SF to return

Where participants have consented to receive SF, interviewees explored the factors that determine whether a particular finding should be sought and returned. While many factors were discussed—including seriousness or severity; invasiveness of treatment or intervention; age of onset; importance to family members—two determinants dominated discussions: ‘I think we should be sure of what it means and it should be actionable’ (P11).

What is ‘actionable’? Interviewees largely felt that if there was potentially a beneficial action that could be taken as a result of the finding it warranted returning to participants. Consistent with guidelines on SF, for all interviewees this included medical actionability, where there is some form of intervention or change in clinical management available: interviewees largely agreed that SF need to be, ‘treatable, preventable, screenable, that you would do something about it’ (P18). However, for many, ‘actionability’ was not limited to medical intervention or screening—in fact, views on which SF were actionable were extremely variable:

‘So, the filter that people usually apply of course is “actionable”, that’s the term and there’s a logic to that intuitively. But it’s not actually logical because what’s “actionable” in your book or not “actionable” in your book may be “actionable” in mine.’ (P7)

For some, an SF was actionable if it could impact planning or prompt lifestyle changes—even if there was no treatment available. Other interviewees, however, questioned the utility of such results:

‘It makes sense if there is something you can do about it, then it is justifiable if you can get the information back and if there is nothing that can be done, then there is a much bigger question mark about the utility of that.’ (P1)

In cases where a medical intervention was available, some felt that the nature of the action itself impacted the extent to which a finding was actionable and therefore should be returned:

‘The action that you would take if a variant was actionable will strongly drive the extent to which we can manage the situation. So if the action would be really simple [...] I’d think we’d be much more comfortable going there than if the action would be you might need a defibrillator or you might need a prophylactic mastectomy,

whereupon the burden of proof needs to be much higher but the level of anxiety is going to be much higher.' (P16)

Interestingly, almost all interviewees felt that information that could inform reproductive decision-making was actionable and warranted return. This feeling was particularly strong in cases where the condition affects a child and the parents are likely to be planning further children. Despite exclusion from prominent guidelines on SF, including the recent ACMG59, interviewees almost universally felt that carrier status information for serious diseases should be offered:

'So I mean there are often things that can be done around family screening. That would be actionability. You get into the whole screening pregnancies and family planning, so actually that is informing choice.' (P11)

'I think carrier testing is a good one. I would certainly want to know if I was a carrier for things. Because then I could make a decent judgement as to the likely risk of a child actually having a particular syndrome. And I could for example choose, myself and a partner could choose to test the other person to actually see what the realised risk is. So it's actionable. It's useful. It's actionable because there's something I can do...' (P17)

Some felt that this could be limited to couples of reproductive age that enrol in WGS. However, others felt that situations are unfixed and the offering of such findings should be irrespective of relationship status: 'What happens if couples do change? Do you then ask for the other partner to redo the whole thing in order to recalculate the risks, depending on one partner's mutations' (P10).

The importance of pathogenicity. Even more important than actionability as a determinant for interviewees was pathogenicity²:

'I suppose it's not the condition itself. It's just the certainty you have that it's pathogenic.' (P15)

Where the gene harbouring the variant and the nature of the related disease dictate 'actionability,' 'pathogenicity' operates at a variant-level: it is the variant that determines whether the gene product will function (or not function) in such a way to cause disease. HCPs rarely spoke in terms of 'genes', almost exclusively discussing 'variants' during the

²**Pathogenicity:** the *capability* of a variant to cause disease [211].

interviews. While agreeing that there should be a consensus gene list, most interviewees strongly felt that the reporting decisions must be made at the variant level. Drawing on experience of genes relevant to disease for which they had specialist knowledge, interviewees discussed important variant-specific factors that need to be considered: their predicted impact on function; whether the variant has been described previously; prevalence in the wider population.

‘You’re not going to make a judgment on that particular variant if nothing else is known about it. You’re going to try and base it on empirical evidence.’ (P6)

However, interviewees felt this was not straightforward; at present, this evidence is often lacking, which makes determining pathogenicity with any certainty very difficult:

‘The problem is, “is it genuinely pathogenic?”, and I think that’s the problem, we’re not clear about that.’ (P5)

‘The problem, of course, is there is no curated list of definitely pathogenic variants that you can rely on that makes it more automated and more able to undertake this at any level, any scale’ (P13)

Interviewees invariably discussed the penetrance³ of a variant as an important determinant in returning an SF: ‘They’ve got to be quite penetrant’ (P6). Interestingly, while many interviewees considered penetrance and pathogenicity as distinct concepts, ‘so I think that what we know in terms of pathogenicity and disease penetrance is very important’ (P9), many conflated the two:

‘I don’t really see penetrance and pathogenicity as separate concepts.’ (P17)

‘I just don’t think that you can assume because it’s pathogenic in a family with a five-generation history of cancer that it’s pathogenic in a family with a five-generation history of nothing.’ (P18)

Ultimately, actionability was contingent on pathogenicity and (or including) penetrance—interviewees felt an SF could not be actionable if there was uncertainty as to whether the particular variant would cause any problem.

³**Penetrance:** the proportion of individuals of a specified genotype (e.g. variant) that show the expected phenotype (e.g. disease) [211].

'My usual mindset is just to be conservative and if actually we are not sure the penetrance is high to think twice about actually calling it an 'actionable' incidental finding.' (P16)

Considering context. As an added layer to the criteria of actionability and pathogenicity, interviewees regularly raised the importance of context in evaluating SF:

'It is a package: it's not just a genetic variant, it's a genetic variant in that person—there are lots and lots of other factors that are important.' (P3)

Interviewees highlighted numerous patient-specific factors: age; disease susceptibility; timing; burden of primary condition; importance to family.

'I mean there is really no point in if someone is 67 and this was something that was going to affect them at five reporting something that is completely out of context for them, unless it is something that you think actually for their family they should know...' (P11)

'Whether or not you give that information clearly should be modulatable by various things. If someone was dying of a terminal disease you wouldn't go and tell them, "Oh by the way you've also got all these other mutations".' (P17)

Others, however, felt that highly likely pathogenic variants should be reported irrespective of participant-specific factors, often citing the benefit to family members.

'If he's got an increased risk of prostate cancer and he hasn't had anything until he's 70, that's probably okay, but it will be still of value for him to know that: he needs to know that actually you had a 90 per cent risk of prostate cancer, whatever it is, you were in the lucky 10 per cent, but your offspring may not be, take that on board.' (P15)

Group decision-making and shared responsibility. Finally, when considering all of the above—and echoing previously discussed benefits of the GM-MDT—interviewees highlighted the importance of group decision-making. Interviewees felt it important to involve many parties in the final decision as to which variants to return—both for the benefit of diverse views and specialist input, as well as the sharing of responsibility.

'Except for a very small number of variants, our ability to have absolute confidence in those variants is very low [...] When I say, "Do you believe it?" [...] I'm sort of saying, "Help me out here, I'm articulating to you that I'm not confident and I just need someone to push me over the line." I recognise that the person that is pushing me over the line knows no more than I do, it's just a, sort of, brothers in arms phenomenon.' (P7)

D. Returning secondary findings in practice: disclosure and duties to family members

After debating which SF should be disclosed, interviewees discussed how they would be returned in practice. As few have experience returning SF, these discussions were necessarily hypothetical. Interviewees felt it was important that the consent process laid the groundwork for return of SF. Despite this, however, many felt there was no way for WGS recipients to be fully prepared for receiving an SF:

‘I think you can’t prepare yourself fully for something like that because, actually, compared with the reason why you are consenting in the first place, which is related to a very specific condition, even amongst the sort of secondary findings that might be reported back, the range of consequences of those is so broad [...] You can’t really prepare for it but when it comes up you have to deal with it, whatever it is.’
(P8)

In order to minimise the potential anxiety caused by disclosure, interviewees highlighted the importance of several factors: honesty and transparency about uncertainty, face-to-face disclosure, timeliness of return—‘It needs to be quick, it needs to be well managed and as stress free for the family as possible’ (P3). Above all, however, interviewees highlighted the importance of two things: (1) providing a plan; and, (2) specialist input and expertise.

The need for a plan. Interviewees universally felt it was important to provide participants with a plan alongside an SF: ‘I think you need to give the patients some kind of plan. I think that’s really important’ (P4). Interviewees widely agreed that, before any result is disclosed, a potential plan for treatment or screening needed to be determined. This would involve coordinating any follow-up such that a precise course of action can be offered to the participant. One interviewee with actual experience returning an SF (the *BRCA2* variant depicted in Section 4.3.3) reflected on their own experience of devising a plan:

‘[W]hat I did was to phone up the clinical geneticist, who dealt with that particular condition in the particular area the family lived in, and discussed the situation with them. So that when they heard from me that this thing had turned up, there was a pre-existing plan, this wasn’t in a vacuum [...] they knew that there was someone that they could be referred to who, already, was cognisant of the situation and [...] could fit them in and basically deal with it in hopefully a clinically streamlined and

professional way. It's really important with these types of findings that they are handled by people who are used to it and not by just any old jobbing consultant-doctor.' (P8)

The importance of expertise and specialist input. By their secondary nature, SF are likely to pertain to a condition outside the area of expertise of the referring clinician. Thus, as highlighted above, interviewees widely felt that gaining input from a specialist in the relevant disease area was a critical step in the disclosure of SF. For some, as above, this was support that should be made available to SF recipients after disclosure:

'If we've found something in an area that is completely outside of our expertise, we will make sure that [they] get to the right person and yes, you can pull them in and say, "There's a cancer risk, it's really big, I'm going to send you to my cancer colleague".' (P5)

For many, however, this also included having expert support available during the disclosure discussion itself: 'For that clinic, I think there should be a specialist present' (P6). Many interviewees anticipated a lack of personal expertise around potential SF, and felt they would need to rely on others to aid in the communication of such a result, in addition to its clinical management. They demonstrated a sense of responsibility to fill their own shortcomings in order to maximise participant understanding, wanting to provide participants someone qualified to answer their questions at the point of disclosure:

'I think that there may be situations where you're giving very difficult information, where you might want help in delivering the information. If, for example, it was about a condition about which you knew nothing and it had major implications for the family. I don't think you would want to go into it in such a way that you would deliver it and leave such a gap of uncertainty...' (P2)

Sharing results and responsibilities to family members. When discussing the return of SF to WGS recipients, interviewees also discussed the importance of these results to their family members. Interviewees acknowledged that family was an important consideration when disclosing SF: 'My initial responsibility is to this person in front of me but of course then it has implications more widely than that. That is important' (P4). Some interviewees acknowledge a perceived 'responsibility to the wider family' (P9), and some felt they should be able to contact family members if they felt they were at risk:

'I think if the man had a BRCA mutation and two daughters, in their 30s, and he didn't want that information passed to them, I would feel that the information should be passed to them. I'm not quite sure, that's a gut feeling, I'm not quite sure whether we have the right structures in place, in this country, to enable that. But, I think if I know something, I think there is a duty of care.' (P17)

For the most part, however, interviewees felt the issues of family for SF were not significantly different than well-described issues in clinical genetics broadly: despite creating discomfort for healthcare professionals, most interviewees felt that directly sharing data with family members was not their responsibility.

'[T]he responsibility of the clinician is to the patient in front of them, not to the rest of the family.' (P13)

'Well if the sister isn't referred to you, there's nothing you can do about it and that's life and it's not great but that is the way it is, because you can't break confidentiality.' (P5)

Most interviewees felt that encouraging participants to share results themselves, and providing them the resources to do so, best fulfilled their sense of responsibility to family members:

'I think the clinicians should encourage their patients to discuss it with their family members. I don't think it's the clinician's responsibility to do that, but I think it is the clinician's responsibility to encourage them to talk to their family members about it [...]' (P3)

E. Evolving science, evolving practice: a field in flux

The need for stronger evidence. Throughout discussions secondary findings, most interviewees highlighted, in some form or another, that the field was currently in a 'difficult transition phase' (P9) in the translation of genomics into clinical practice. For most, this transition period was challenging, but also enlightening, as professionals were beginning to appreciate challenges and see the way forward.

'There's a core of people that are now beginning to understand stuff and I think when I sit and talk and participate in [GMMDT] meetings I realise the challenges are substantial.' (P7)

To overcome the major challenges of managing SF in WGS—namely that of interpretation—interviewees stressed the importance of generating a stronger evidence base for the variants that are to be returned as SF.

'The fundamental issue is we don't really have enough data to be able to say reliably what the implication of these variants are on the whole.' (P17)

'Give research ten or 15 years to try and sort out all these variants, then we might have an idea.' (P5)

In particular, interviewees highlighted the aforementioned difference between secondary findings and primary findings: current evidence for variants is based on families ascertained through a proband. Thus, little evidence exists about the impact of these variants in the wider population. Many interviewees highlighted this knowledge gap, and called for research into variants in individuals not ascertained via the related condition:

'There is a body of research that's not being done that needs to be done to ask what does a variant that we think we know how to interpret in a family setting mean when it's found in the normal population? Is it the same or is it different because of the prior odds and I think we don't know.' (P16)

In addition to the predictive value of pathogenic variants in the wider population, the required evidence base also variously included information and precedence on the clinical decision-making pathways, as well as understanding the impact on participants after disclosure.

The need for standards and guidelines. With this evidence in hand, clearer guidelines can be produced and best practices can be established. Even without this evidence, in the interim, interviewees highlighted the current lack of guidance and need for clear standards: 'We don't have standard procedures, standard protocols' (P18). Primarily, interviewees felt this complicated local decision-making and could lead to poor decisions:

'There has to be some guidance otherwise you could have some maverick approaches from people who have opinions at both ends of the spectrum of either no information or as much information as the patient wants and then you run the risk of it being unregulated in terms of how much detail.' (P13)

Interviewees also highlighted how the lack of guidance could inhibit the sharing of data between institutions and across borders:

'I think if this were to be rolled out nationally, routinely, then I think there would have to be some considerable debate about what should be done. If not on a national scale, on an international scale because this information is one, important to individuals but it's also important globally to potentially share this information.' (P6)

In terms of available guidance, many interviewees were aware of the minimum gene list produced by the ACMG, with many labelling it as 'a start' (P11), noting that a list provides necessary structure in an otherwise devoid of direction:

'I think it would be quite difficult not to have a list. I think having a list gives you some kind of framework and some kind of consistency across programmes; some kind of starting point really.' (P3)

However, interviewees insisted that the list needs to be dynamic, changing with the generation of new data on SF:

'I think there has to be a consensus list and it will have to evolve [...] I think if you didn't have a list, I don't know where you'd start really.' (P16)

'I think the gene list is a little bit limited and I think it needs exploration and evolution and maybe it is too long or too short and time will tell.' (P1)

The future of secondary findings and genomic medicine. In general, interviewees were hopeful about the future of genomic medicine and the debate around secondary findings. Interviewees noted that enhanced engagement with, and education of, the wider community—both clinical and the public—were required. Such responsibility might extend to promoting realistic concepts of the limitations of genetic testing:

'Where you can say the medical community is at fault is that, within the media, and pushed by some commercial companies, one is constantly bombarded with a sense of genetics being deterministic, predictive and having all these exciting consequences for future health and health management, which I don't believe myself [...] the public are often extremely receptive to these notions and think the quality of information is higher than is actually the case.' (P8)

Perceived lack of appreciation of the complexities of genomic information, particularly among HCPs, led some to suggest that mainstreaming of WGS may be premature. While highlighting the barriers ahead, many interviewees were optimistic about the field's ability to overcome the challenges:

'So I don't think this problem's going to go away actually. I think there's going to carry on being issues about interpretation. Hopefully, we'll get more confident about having the systems to manage it.' (P4)

Ultimately, interviewees who cited the need for more evidence felt the only way to move the field forward was to start actively returning SF: 'I think we can only learn by doing' (P1). They felt that the necessary confidence would come from experience actively returning SF, which would also serve to generate the evidence needed to further inform these discussions.

'Increasingly, worldwide, we will start to get the relevant knowledge of how to be using these secondary findings outside of a direct presentation of a disease phenotype. So I think that we'll be in a very different place in ten years' time.' (P9)

'I think it will be interesting to see what happens. We're all going to have to learn a lot, aren't we?' (P5)

4.5 Discussion

Although diverse, many of the views expressed by healthcare professionals from the Oxford GM-MDT were consistent with those identified in the systematic review in *Chapter 3*. There was broad agreement on the importance of participant autonomy, and general resistance to overriding any participant decisions around SF. Consistent with the framework in *Chapter 3*, the strong consideration of participant rights and potential benefit was accompanied by minimal total opposition to disclosing SF. In fact, cautious limited screening and return of 'actionable' secondary findings in WGS was considered optimal by interviewees, promoting participant choice while restricting disclosure to clearly pathogenic variants, while concentrating on building an evidence base. Although cautiously supportive, these views align closely with early criticisms of opportunistic screening for SF [41, 212], which called for the gathering of further evidence to inform such practices.

Like criteria for 'actionability' outlined by HCPs in the literature identified in *Chapter 3*, the limited range of SF supported by interviewees included those findings that point to serious conditions for which treatment is available. However, for almost all interviewees in this chapter, actionability also included the ability to influence reproductive decision-making: interviewees were widely supportive of returning carrier status information to WGS recipients. Not only is such broad support of returning carrier status information inconsistent with the systematic review, but also with the ACMG59 guidelines, which do

not include such genes. It is, however, consistent with the current policy of the 100,000 Genomes Project. While some felt this should be limited to couples, others felt these findings should be offered to all adult WGS recipients.

An additional area in which interviewees raised views not widely discussed in the existing literature, was with respect to the interpretation of variants. While guidelines tend to focus on which genes should be screened for SF, interviewees were much more concerned about the individual variants within those genes: interviewees were satisfied with current knowledge pertaining the involvement of certain genes in disease, but much less confident in our ability to interpret individual variants in these genes. This was illustrated in the focus on pathogenicity and penetrance by interviewees, and its importance in their decision-making around SF. Of particular concern to interviewees was the difference between interpreting findings when there is evidence of disease supported by a family history (as is the case with ‘primary findings’) and the relatively uncharted territory of interpreting such variants in the absence of a clinical phenotype or family history. As a consequence, interviewees felt that there was a higher threshold of certainty with respect to pathogenicity and high penetrance that needs to be met with secondary findings compared to primary findings. Interviewees felt that greater evidence for these factors is required for individual variants in order to inform decisions and influence future guidelines on SF. Considering the framework outlined in *Chapter 3*, this focus on complexity—through difficulties faced during interpretation—contributes to the the broad recommendation for a cautious approach in screening for SF in WGS.

Of note, while considered of the utmost importance in SF decision-making, interviewees sometimes confused the terms ‘pathogenicity’ and ‘penetrance’. Sometimes the former was used in the place of the latter as a means of articulating the proportion of affected individuals rather than the disease-causing potential of the variant. ‘Penetrance’ in some cases was used to refer to the proportion of individuals affected in a family rather than relative to the population. This highlights the inability of old terminology to keep pace with a fast-moving field. As these variants are studied at a population level, beyond large families presenting with probands in clinic, ‘penetrance’ estimates will begin to genuinely reflect a population-level penetrance. Thus, new terminology may need to be

considered to reflect proportion of affected individuals at the family level. Additionally, with population-level data, the proportion of detected ‘pathogenic’ variants that do not actually lead to disease will increase. Colloquially synonymous with disease-causing (and not just predicted capability to cause disease), this will necessitate a solidification in our use of the term, and might require the development of new terminology.

The concept of ‘responsibility’ appeared across the themes identified in the interviews. Interviewees described different sources of responsibility: to participants, to families, to research agendas, and to the field of genomics at large. In making decisions around SF in genomics—whether to screen for SF, which individual SF to return—healthcare professionals balance these responsibilities. This is illustrated in their discussion of returning variants, where WGS providers sometimes include the benefit to family members as a criterion for return in addition to participant-specific factors. This participant-family member tension in genetics has been well-described in the literature [213], and a study by Klitzman et al. [87, 148] described a similar ‘balancing act’ with respect to responsibilities around SF. The tension between competing responsibilities is also apparent in discussion of the GM-MDT itself. With the introduction of the 100,000 Genomes Project in March 2015 (Figure 4.2), increased funding, coupled with high recruitment targets, allowed for more cases to be sequenced. In response to this shift from limited resources to resource-abundance, interviewees described a conflict between meeting quotas imposed by the project and choosing the most tractable cases. It will be important for these tensions to be resolved and responsibilities delineated as SF are sought and returned.

GM-MDT interviewees reiterated the lack of evidence surrounding SF in WGS, marking evidence-generation as a priority throughout the interviews. This lack of evidence, in combination with the conflicting responsibilities faced by healthcare professionals described above, leads to difficulties for WGS providers around SF. Interviewees expressed a sense of discomfort or unease across the interviews in response to complex SF scenarios: ‘I think I’d find that really hard’ (P11); ‘I’d be very uncomfortable’ (P16); ‘I would be very nervous’ (P17); ‘I’d be very, very uneasy’ (P18); ‘I’d feel uncomfortable living with that [...] that seems difficult’ (P4). In order to ease this discomfort and resolve difficulties,

and fulfil their many conflicting responsibilities, HCPs look to expertise and guidance from a range of sources, both within and outside formal structures. Interviewees were informed by discussions with colleagues and WGS recipients, as well as personal and social interactions. Interviewees discussed the importance of drawing on local expertise: they highlighted the need for having experts and specialists at the GM-MDT, as well as having specialist support during SF disclosure. However, such expertise and judgment—which will be vital if benefit is to be derived from genome sequencing [214]—relies heavily on guidance from expert organisations and requires sufficient evidence on which to base decisions. As highlighted by interviewees, this guidance and evidence is currently lacking, posing a significant obstacle to accurate variant interpretation and responsible disclosure of SF. Thus, in the absence of such guidance and evidence, HCP discomfort is unable to be completely resolved. This creates a self-perpetuating cycle (Figure 4.4), which can manifest in a lack of consensus and can risk poor decision-making. HCPs can be overzealous despite lacking strong evidence on which to base decisions—over-interpretation of findings for new molecular diagnostic tests has been shown to be common [215]. Conversely, HCPs can be overly cautious—surveys of HCPs have shown they often act conservatively even when they know participants would want more information, or they would want more information themselves [216].

In order to break this cycle it is therefore imperative that evidence is gathered and guidelines produced. As articulated in *Chapter 2*, the penetrance of pathogenic variants in the wider population—among ‘healthy’ individuals, those without a clinical phenotype or have not been selected on the basis of family history—remains unknown. Such information would inform a variant list for SF, rather than a gene list, as supported by most interviewees. Although still subjective in their implementation, as acknowledged by some interviewees and as will be explored in *Chapter 7*, recent variant interpretation recommendations from the ACMG and the Association for Molecular Pathology (AMP) [217] will likely facilitate this process by allowing for the collection of more comparable data from different diagnostic laboratories. Furthermore, the wider clinical utility of returned SF—taking into account psychosocial and ethical factors, in addition to downstream clinical and behavioural outcomes—needs to be explored. Thus, in the meantime,

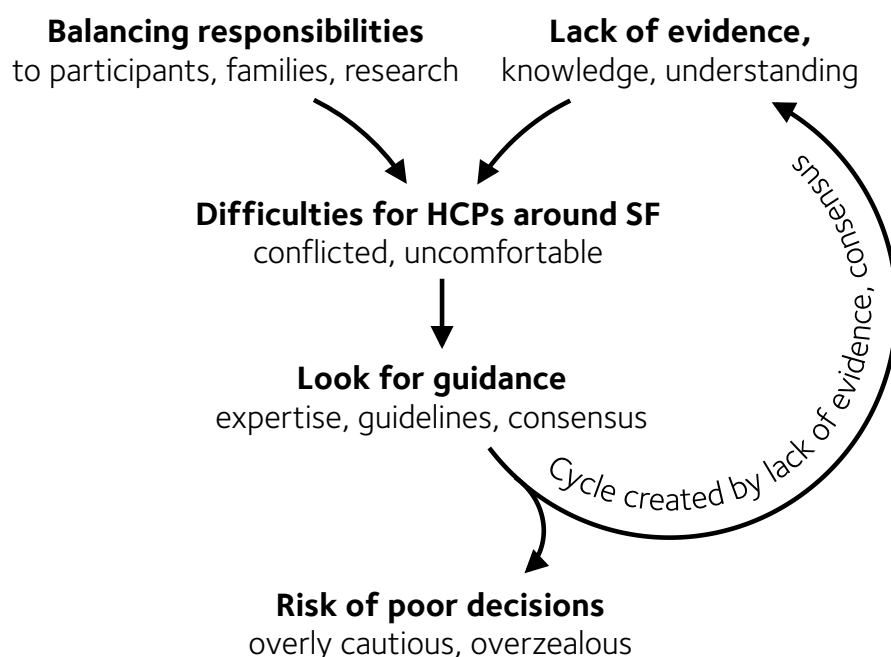


Figure 4.4: Problematic cycle created by lack of evidence around SF in WGS, illustrating factors influencing genomics healthcare professional decision-making around disclosure of secondary findings in WGS

interviewees considered a cautious approach to be optimal—promoting participant choice while restricting screening to limited pathogenic variants, while focusing available resources on building the evidence base required to realise genomic medicine in practice.

4.5.1 Strengths and limitations

Many strengths of the study are afforded by the structure of the GM-MDT. First, by sampling from members of the GM-MDT, which is diverse in specialty by design, the interviews captured a broad range of specialty areas: in addition to capturing views of physicians who specialise in clinical genetics, physicians specialising in cardiology, neurology and many other specialties were included. Additionally, diverse roles were represented across the interviews: clinical scientists, research scientists and genetic counsellors were interviewed alongside consultants with expertise in genetics, as well as those without. The qualitative methodology employed allowed interviewees to articulate nuanced and qualified views.

Another strength of the study is the novelty of the sample. In addition to presenting the views of non-USA stakeholders, filling a gap identified in *Chapter 3*, the context is

unique. Only one qualitative study identified in the systematic review [87, 148] explores the views of HCPs on factors influencing the return of SF in WGS—most qualitative studies with HCPs focused on the informed consent process. Besides operating in a very different healthcare context from the NHS, this previous study was published prior to the ACMG guidelines. Thus, the interviews analysed here are unique in their exploring views towards SF in response to actual policies around SF. Additionally, and importantly, interviewees in this sample have had significant experience with WGS for rare disease, which will have informed and shaped their views.

However, while unique, the sample is limited. Interviewees, despite being diverse in role and area of specialisation, are still somewhat alike: working in Oxford and participating in the GM-MDT means they have similar experiences of WGS. The academic climate in Oxford, means that these views may not be generalisable to hospitals across the UK. Additionally, while most interviewees have experience discussing SF in the GM-MDT and making decisions around their management, most interviewees have still not dealt with SF themselves. While different from the studies in the systematic review in that some experience with SF in WGS is captured, many views articulated with respect to experience returning SF are still hypothetical.

4.5.2 Implications of findings

This study has implications for research and clinical practice:

- While remaining limited to variants about which WGS providers have the utmost confidence of their pathogenicity, consideration should be given to refining or expanding the concept of ‘actionability’ in the development of future protocols and policies: based on this study, disclosing carrier status is favourable.
- HCP use and understanding of terminology (including ‘penetrance’ and ‘pathogenicity’) needs to be explored, and new terminology or clarification is needed to reflect the current population-wide genomics paradigm.

- Variant-specific evidence on the predictive value of ‘pathogenic’ variants is desperately needed to inform decision-making around SF in WGS, along with evidence on the impact of disclosure—including psychological and behavioural outcomes.
- If SF are to be sought and returned, training and support for HCPs returning SF from WGS is required.
- Further research is needed into the views and experiences of HCPs who have actually returned SF to better understand, and overcome, the challenges faced.

4.6 Conclusions and chapter summary

It is clear that views and practices with respect to secondary findings are changing in the era of clinical WGS. In this chapter, using semi-structured interviews, I have explored the views and experiences of members of a rare disease Genomic Medicine Multidisciplinary Team in Oxford. Representing a UK perspective, these views help to fill gaps in the literature identified in *Chapter 3*—both in terms of the novel context but also by providing non-hypothetical views towards SF made in response to actual policies and experience. Consistent with the existing literature synthesised in the systematic review, many interviewees were supportive of providing capacity to screen for limited ‘actionable’ SF, to fulfil their responsibility to act in the participant’s best interest and also build an evidence base to inform future management. Beyond genes that point to treatable conditions, interviewees widely expanded ‘actionability’ to include carrier status information. Additionally, GM-MDT members highlighted the importance—and challenge—of determining pathogenicity: their discussion of SF focused on variants rather than genes, and they perceived the lack of variant-specific evidence as a major flaw in the current guidance and literature. Consistent with the framework developed in *Chapter 3*, interviewees balancing of perceived complexity (through complicated variant interpretation and lack of guidance), their responsibilities (to participants, families, research), as well as their awareness of participant rights, led to intermediate views on SF disclosure: although views were diverse, interviewees were broadly supportive of

screening for 'actionable' SF, but advocated for a cautious approach that is responsive to accumulating evidence.

In order to expand on the views collected in this context, and further contribute non-American views and those made in response to actual policies around SF to the literature, I will explore the views of participants enrolled in WGS in Oxford in the following chapter. Consistent with the wider aims of this thesis, and the challenges facing the management of SF in WGS identified in *Chapter 2*, interviewees in this chapter highlighted the desperate need for empirical data on returned SF: in order to inform the interpretation of SF in WGS, and therefore maximize the benefit to participants, we must 'learn by doing' (P1). The need to provide data on the utility and impact of actual returned SF from WGS, and how this evidence gap could be filled, will be revisited in *Part III*.

5

Views of participants in diagnostic WGS towards secondary findings: an interview study

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As medicine becomes increasingly patient-centred and decision-making becomes increasingly shared [218, 219] it is critical that patient views inform guidelines and policy in healthcare. This is true in the case of whole-exome and whole-genome sequencing (WGS) policy, as is evident from the emphasis placed on informed consent and participant autonomy by healthcare professional (HCP) interviewees in *Chapter 4*—it is patients that serve to benefit (or be harmed) by returning SF. Patient views are additionally valuable in that, in a way, they can serve as ‘expert’ WGS recipients, providing views informed by their experience with disease and interactions with genomics and the healthcare system. In the systematic review presented in *Chapter 3*, I showed that WGS

recipients, including patients, informed by their sense of rights largely express desire for disclosure of secondary findings (SF). While the majority of WGS recipients want to receive ‘actionable’ SF (although, definitions of actionability vary) some individuals, informed by their experience as patients or their parents, expressed more considered and qualified views towards SF [168, 169], indicating that nuanced understanding of the implications of WGS and potential findings—rather than technical knowledge—might better inform decision-making around SF. However, as previously discussed, the data on such views are largely dominated by studies conducted in a distinct context—the USA—and are mostly limited to hypothetical views. As illustrated by divergent views from more diverse stakeholders in the systematic review, as well as the healthcare professionals interviewed in the previous chapter, these views are not entirely generalisable. Furthermore, a recent survey study showed that individuals of different ancestry or culture expressed differing views towards desirability of genetic results [220]. Thus, diverse views are essential to move the debate around secondary findings forward, particularly as WGS are underway in contexts outside the USA.

As discussed in *Chapter 1*, sequencing programmes have made diverse decisions about handling secondary findings—the implementation of specific policies towards SF affords the exploration of perspectives of WGS participants with reference to informed consent and actual decisions made. Recently, survey studies have begun to capture such individuals [220], but I am aware of no such in-depth qualitative analyses conducted to date. Afforded by the climate of WGS in Oxford, I was able to access individuals who have made such decisions around SF. Complementing the views presented in the previous chapter, I conducted semi-structured interviews with participants in a local WGS project, aimed at providing rich data on the views and experiences of rare disease patient and parent participants who have made actual decisions about SF. After having conducted an in-depth analysis and critical appraisal of existing qualitative studies (*Chapter 3*), and having observed interviews and analysed quality secondary interview data (*Chapter 4*), this study provided me the opportunity to conduct interviews independently.

5.1 Chapter aims and objectives

The overall aim of the research reported in this chapter was to explore the views of participants in WGS in Oxford towards secondary findings—helping to contribute diverse views from diverse contexts to the existing literature in an effort to better inform policy. The specific objectives were to:

- Understand the views of WGS participants in Oxford towards, and understanding of, WGS and SF;
- Understand participant reasoning behind the types of SF they want to receive; and,
- Understand participant views on policies and decision-making around SF in WGS.

5.2 Methods

5.2.1 Study participants

At the time of enrolment in MGAC (outlined in the introduction to *Part II*), participants were asked on their consent form whether or not they would be willing to participate in social sciences research (Appendix D). All adult participants (18 years of age or older) who consented to be re-contacted for further research were considered eligible to participate in this interview study. These were individuals that had, therefore, made decisions as to whether or not they wish to be informed of SF. Individuals were considered eligible to participate irrespective of their primary condition and whether or not they were affected themselves.

5.2.2 Recruitment

All eligible participants were recruited via a letter that explained the purpose of the sub-study (Appendix D), together with a questionnaire to elicit demographic data and opinions on the MGAC study as a whole (Appendix D). At the end of the questionnaire participants were asked whether they would be willing to be contacted for an interview. I then contacted all of these individuals by email or telephone to invite them to participate. The recruitment pipeline is outlined in Figure 5.1.

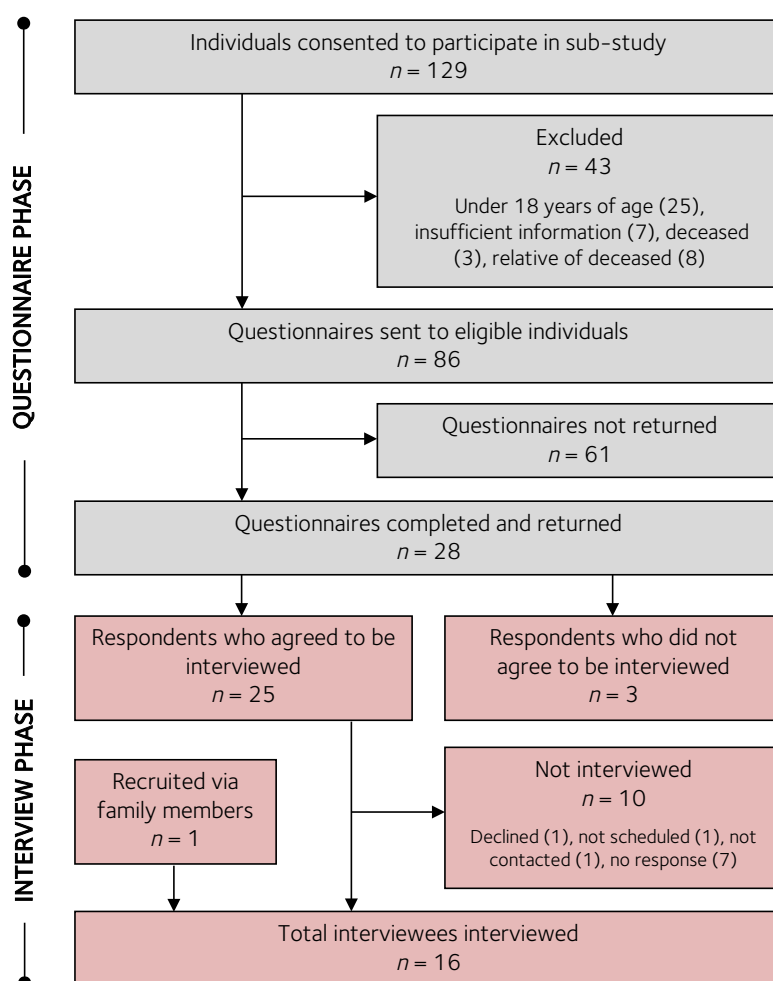


Figure 5.1: Recruitment pipeline for questionnaire and interviews with WGS recipients

5.2.3 Interview guide

A semi-structured interview guide was developed based on a review of the literature and received ethics approval together with the MGAC study. After conducting the first three interviews, the guide was modified by the interviewer to further explore issues arising in the early interviews as well as the findings from the two literature reviews (*Chapters 2 and Chapter 3*). These changes largely involved a restructuring of the guide to refine a hypothetical scenario, as well as added focus on the decision-making process and those involved. The final interview guide (Appendix D) was then used for the remaining interviews. A list of the topics covered in the interviews is found in Table 5.1.

Table 5.1: Topics covered in semi-structured interview guide with patients who received WGS

-
- Participant experience with genetic disease and testing.
 - Motivations for participating in WGS research.
 - Understanding of WGS and implications.
 - Views towards different types of SF (treatable, not treatable, etc.).
 - Views towards policies around SF, including opportunistic screening.
 - Views towards decision-making around SF and who should be involved.
 - Views towards data-sharing and re-contact in light of new information.
 - Hypothetical scenario where an SF is returned.
-

5.2.4 Data collection

I conducted the interviews between March and November 2016, which took place in the residence of the interviewee whenever possible. At the outset of each interview, I explained that I was not involved in the participant's clinical care or the analysis of their genomic data, and that I was blind to their medical record. I then explained that the interview would be recorded and anonymised, such that participants could not be identified. Participants were given the opportunity to ask questions of the interviewer and written consent was taken before the interview commenced (Appendix D). Interviews lasted 30-60 minutes, were audio-recorded and transcribed verbatim by a professional transcription service.

5.2.5 Data analysis

First, I checked anonymised transcripts against the original audio-recording for accuracy and completeness. The same process of thematic analysis outlined in *Chapter 4* (Section 4.2.6) was undertaken during the analysis of these interviews.

5.3 Results

5.3.1 Questionnaire respondent demographics

129 individuals who were consented to WGS through MGAC consented to participate in this sub-study. Of these 25 were under 18 years of age and thus ineligible to participate. A further 7 individuals were excluded as there was insufficient information (no NHS number, means of obtaining their address, or ensuring their information was up to date).

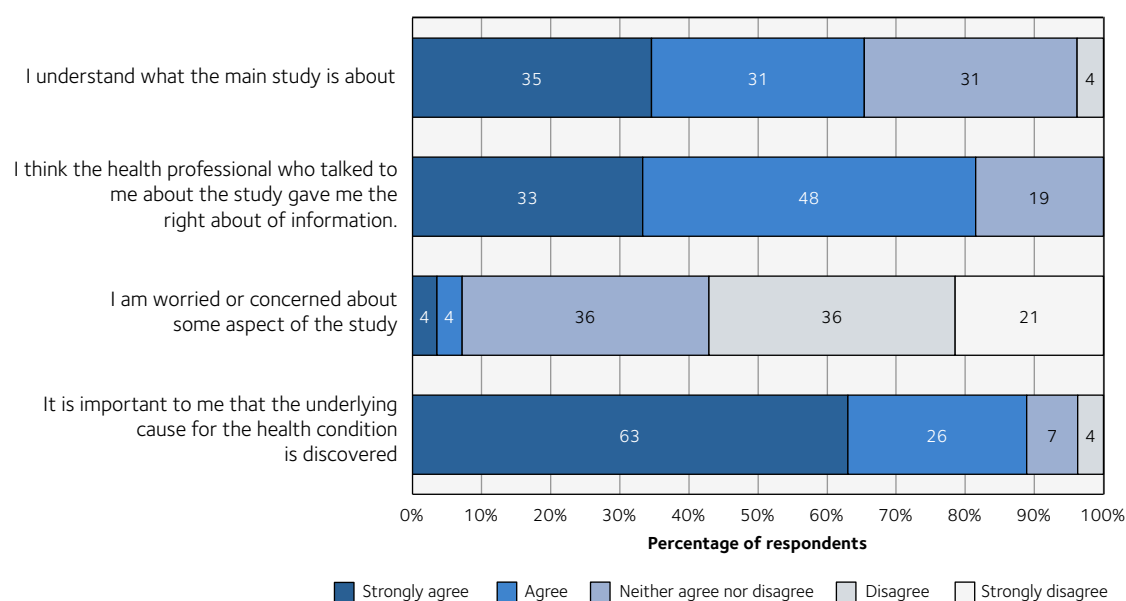


Figure 5.2: Questionnaire respondents confident they understand the original study and express little to no concerns, motivated by discovering underlying cause of the primary condition affecting their family.

A further three individuals were deceased since consenting to MGAC—these individuals, as well as their family members, were excluded. A total of 86 postal questionnaires were sent to the remaining eligible participants. Of these, 28 were returned (response rate 32.6%). The demographics of the questionnaire respondents are shown in Table 5.2.

5.3.2 Questionnaire responses

In addition to providing the demographic information above, questionnaire respondents answered questions about their understanding of, and feelings towards, the WGS study. Figure 5.2 shows participant responses to likert scale questions. The majority of participants stated that they understood the study and most participants stated that the health professional that spoke to them about the study provided the right amount of information. Most participants were not worried or concerned about the study, or were neutral. Two participants did express concerns: in open space following the question one explained that the waiting time between receiving a result and seeing a clinician caused them distress; the other has not received a result and expressed anxiety that no result would be found. Both of these individuals were captured in the subsequent interviews.

Table 5.2: Demographics of questionnaire respondents (*n* = 28)

Category	n	%
<i>Gender</i>		
Male	15	54
Female	13	46
<i>Affected</i>		
Yes	10	36
No	17	61
Not known	1	4
<i>Others affected</i>		
Child(ren)	19	68
Grandchild	1	4
Parent	3	11
Sibling	1	4
No one else	7	26
<i>Ethnicity</i>		
White British	26	93
Asian	1	4
African	1	4
<i>Religion</i>		
Yes	15	54
No	11	40
Not sure	2	7
<i>Education</i>		
to 16 (GCSE or equivalent)	6	21
to 18 (A level or equivalent)	5	18
Degree or equivalent	9	32
Post degree	8	29
<i>Age</i>		
Under 20	1	4
20-50	9	61
50-70	5	25
Over 70	1	11
<i>Children</i>		
Yes, and would like more	6	21
Yes, but not planning more	16	57
No, but would like to	1	4
Unlikely to have children	4	14

Note: Percentages may not total 100% due to rounding.

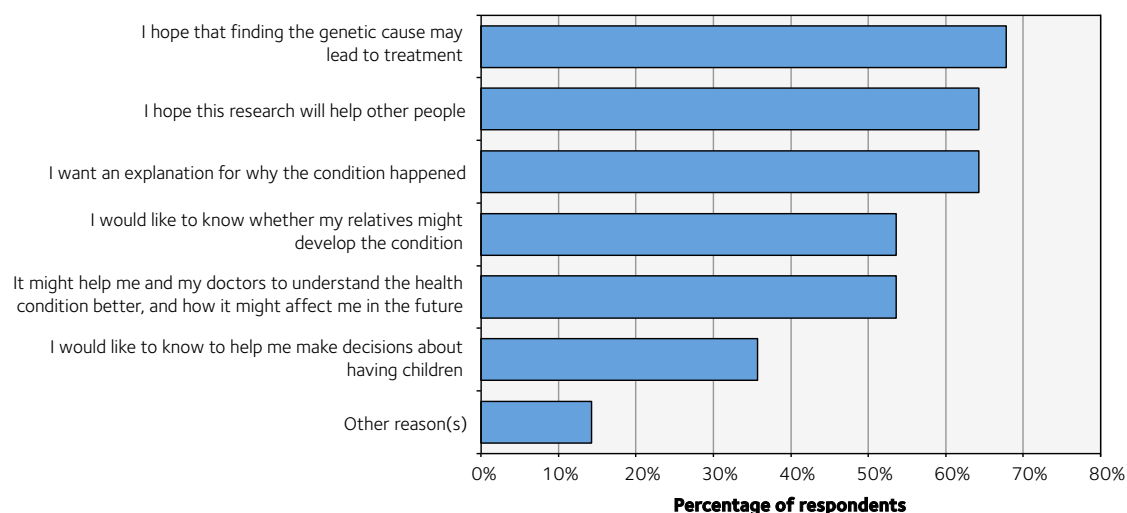


Figure 5.3: Questionnaire respondents cite different reasons for wanting to know underlying cause of their primary condition: commonly motivated by potential for treatment and benefit to others.

Participants felt very strongly that it was important to discover the underlying cause for the health condition affecting their family (Figure 5.2). As illustrated in Figure 5.3, there were various reasons for this. The most common reasons were the potential to inform treatment (68%), followed by an explanation for the condition (64%) and the ability to help other people (64%). Other answers that were provided as free text included: reproductive assistance, directly benefit medical research, and improving knowledge around health.

5.3.3 Interviewee demographics

Of the 28 questionnaires returned, 25 individuals agreed to be contacted for an interview and were invited to do so by telephone or email. Of these, 17 individuals responded. One individual chose not to participate, and 15 interviews were ultimately scheduled (one participant who initially agreed was never able to schedule an interview). A further individual, who did not complete the questionnaire, but met the initial eligibility criteria but did not return their survey, was also recruited and interviewed via a family member.

A total of 16 individuals were interviewed. The characteristics of the interviewees are shown in Table 5.3. Responses were gathered over 15 distinct interviews (in one case two family members were interviewed together). Most interviews were conducted

in the interviewee's home ($n = 11$). However some interviews took place at an OUHFT site ($n = 1$) or over the telephone ($n = 4$). As some interviewees are related, a total of 12 distinct MGAC cases are represented across the interviews.

Table 5.3: Demographics of WGS recipient interviewees ($n = 16$)

Category	n	%
<i>Gender</i>		
Male	7	44
Female	9	56
<i>Affected</i>		
Affected	6	38
Parent	10	62
<i>Ethnicity</i>		
White British	16	100
<i>Education</i>		
to 16 (GCSE or equivalent)	2	13
to 18 (A level or equivalent)	2	13
Degree or equivalent	6	38
Post degree	6	38
<i>Want SF personally</i>		
Yes, all	4	25
Yes, limited	5	31
None	7	44
<i>Age</i>		
Under 20	1	6
20-50	9	56
50-70	5	31
Over 70	1	6
<i>Specialty</i>		
Cardiology	5	31
Neurology	7	44
Clinical genetics	4	25
<i>Primary Result</i>		
Yes, positive	4	25
Yes, negative	3	19
None yet	9	56

Note: Percentages may not total 100% due to rounding.

5.4 Thematic analysis

Through the thematic analysis of the interview transcripts, five main themes were identified. A list of the main themes and secondary themes are shown in Table 5.4. Detailed descriptions of these five themes are presented below, together with illustrative quotations and references to anonymised interviewee codes. The codes and relevant details for each interviewee are listed in Appendix F.

Table 5.4: Primary and secondary themes in WGS recipients interviews around genomic medicine and secondary findings

A. Literacy and understanding: informed by experience
• Primary condition and the diagnostic odyssey • Knowledge and understanding of WGS
B. Why sequence? Decision-making around participation in WGS
• Seeking an answer and desire for control • Altruism as a motivator • Perception of risks associated with WGS, including SF • Clinical testing to research as 'natural progression'
C. 'I won't mind not knowing': Views towards, and decision-making around, SF
• Actionability, and motivations for SF • Desire to receive different types of SF • Focus on primary condition, and motivations against SF • Context-dependent desirability of SF
D. Communication of SF: who, when, how
• Disclosure of SF and the need for a plan • Family and information sharing
E. 'They know what's best': healthcare professionals and the healthcare system
• Faith and confidence in the NHS • Distribution of limited resources • Expectation of re-contact and continuity

A. Literacy and understanding: informed by experience

Primary condition and the diagnostic odyssey. The majority of interviewees demonstrated a high level of literacy and understanding around genomics. As patients or parents of patients with rare disease, their knowledge and understanding was invariably informed

by their experience—both with their primary condition and their resulting interactions with the healthcare system and clinical genetics.

The specialties through which interviewees were recruited to WGS varied, and can be broadly classified into cardiology, neurology or clinical genetics. Even within a specialty, however, interviewees had diverse conditions—and similarly diverse experiences with their primary condition itself. Despite diverse experiences with their diseases, most interviewees described a similar experience with the diagnosis of their primary condition: most recounted the diagnostic odyssey that they experienced prior to enrolling in WGS. Interviewees described the quantity of tests they had had: ‘he’s had numerous tests over the years [...] he’s had everything they could think of’ (R10); ‘He’s hit me with a barrage of different tests’ (R11). These included genetic and non-genetic tests: ‘I have had loads of testing. I’ve got a muscle biopsy, I’ve had various blood testing and brain scans and things.’ (R1); ‘They did all manner of genetic tests on him’ (R3). Almost all described similar periods of uncertainty and unpredictability in the absence of a diagnosis, with little control over its resolution. Many described obtaining a diagnosis as ‘very difficult’ (R14) and some felt it was ‘quite a long process’ (R15). Many describe this period of testing as ‘all a blur’ (R3) and had difficulty recalling specific details:

‘It’s quite a hazy time, there is a lot going on at that time, because that was going on, and I was also seeing a cardiovascular team, and the two overlapped occasionally. And I think I was still seeing a heart rhythm clinic. So there’s a lot that’s kind of muddled and blended.’ (R2)

Some interviewees recounted nearly giving up: ‘I was almost resigned to never finding it really’ (R13). Invariably, it was this exhaustive process that ultimately resulted in their recruitment to WGS:

‘So the initial genetic testing [...] revealed nothing. They were just hitting brick walls at every turn. So we were referred at that stage for more extensive testing again.’ (R5)

At the end of this diagnostic odyssey, in cases where a primary finding was returned, interviewees widely differed in how they responded to them. For some, the primary finding was a relief:

‘Getting the diagnosis is primarily a relief to have something that you know has been wrong for years and is there, so you have an explanation and to give you an idea, what I do now is two main things.’ (R1)

For one parent, who had grown confident in their abilities to manage their son’s condition on a day-to-day basis, a primary finding was something they actually dreaded: ‘we didn’t want to know what was causing them because if they found what was causing them, it wasn’t going to be good news’ (R3). When they ultimately received a result, they wanted more information immediately and found the experience anxiety-inducing:

‘I just felt I want more information, I want it now. I want to know what do you mean by the cause, is this good news or is it bad news and I’d like to know now.’ (R3)

For others, receiving a primary finding made no difference at all: ‘The cause made no difference really. Having a label against him makes no difference for me’ (R13). For interviewees who received no positive result, many expressed a sense that the experience has been tiring and ‘depressing’ (R8) or ‘frustrating’ (R14). Others, however, were more upbeat: ‘I don’t think we’re going to hear anything. But, you know, I’m quite okay with it’ (R6).

Knowledge and understanding of WGS. Interviewees demonstrated a high level of understanding of WGS. This was consistent with the high level of self-reported perceived understanding observed in the questionnaire (Figure 5.2). This reflected the level of education in the sample (Table 5.3), but also their significant experience with the healthcare system due to their rare disease, including genetic counselling. Interviewees were aware of the difference between WGS and other forms of genetic testing, some even demonstrating an appreciation for the nuances—and *limitations*—of genetic information, including variations on complex concepts such as reduced penetrance, variable expressivity, and the role of environmental factors:

‘There’s so many other influencing causes that can exacerbate or minimise the effect of that. Some people say that you can have a genetic disposition for things [...] but actually there’re so many other factors that influence that, that actually you still don’t know what’s going to happen.’ (R13)

For some interviewees understanding was additionally informed by experience with other genetic diseases in their families or friend groups: 'I've had friends who've gone through similar things' (R10). Some drew on their own professional roles or relevant education:

'I think we were helped by the fact that I'm a biologist by degree, and I've always taught biology and kept up to date.' (P8)

A few interviewees demonstrated a lack of understanding: 'No, I didn't know an awful lot' (R12), 'I think they just took some blood and then that was it really' (R6). Some acknowledged minimal understanding at the time of consent, while others remembered little about WGS at the time of interview. This was not true of most interviewees, however—many were sufficiently aware of the complexity of WGS that they even expressed concern about others not being as informed as themselves:

'So we were ahead of the game, I think [...] just an awareness that probably lots of people wouldn't have.' (R9)

'I think the trouble is, there's an awful lot of people, to be honest, in this situation, don't understand, because most people don't have the understanding [...] so consequently, I'm not sure how they make that decision, but that's a reflection on other people, not on myself.' (R8)

This high level of understanding, in some interviewees, resulted in an appreciation for the challenges of the analysis process: 'It's too big a job, isn't it?' (R9), 'I think there's got to be a point of stopping, hasn't there?' (R15).

B. Why sequence? Decision-making around participation in WGS

Seeking an answer and desire for control. Interviewees' conditions were uncertain and unpredictable: for most, their primary motivation for enrolling in WGS was to end the diagnostic speculation and find the cause of their primary condition. This is consistent with the results of the questionnaire (Figure 5.2). After having been through the diagnostic odyssey, interviewees perceived WGS as final chance to find 'an answer [...] to find out what could be wrong' (R16). Some interviewees felt an answer would inform treatment or management:

'I suppose the main reasons I'm looking at are, if we can find a reason, if we can help with the control of his condition and perhaps find medication that is better suited and not as much medication.' (R10)

However, many interviewees were aware that finding a genetic cause for their condition would not have an impact on the treatment of their disorder: 'In terms of an actual cure, or a treatment pathway, I didn't expect that' (R2). For these individuals, there were other motivations for seeking an answer. For some, a genetic result could inform reproductive decision-making. For others, WGS satisfied an element of curiosity. Many interviewees cited the benefit to family members as a motivator for their participation. Some parents highlighted the importance of having a label, regardless of treatment implications, in order to manage fears and educate others about their child's condition:

'The cause made no difference really. Having a label against him makes no difference for me, but it probably would have been much nicer knowing much earlier on, then at least I could have limited the fear of what I thought was going to happen or what I was going to have to deal with.' (R13)

'I understand that even if we do find out a name it still might not have any bearing on treatment or prognosis or anything like that, but [...] from an education funding point of view it's quite difficult to try and get extra support for a child even if they need it because of the fact they haven't got a name.' (R15)

One interviewee described themselves as 'lucky' that GS was available to them, otherwise they would have had to 'throw in the towel' (R13). For many, the desire to find an answer appeared to be a manifestation of a search for control: a welcomed opportunity to help to manage their condition to the benefit of the patient and family, and to limit progression and prevent recurrence.

Altruism as a motivator. Again, mirroring the results of the questionnaire (Figure 5.2), the other significant motivator for participation in WGS was the potential benefit to others. Aware that there was no likely impact on their own treatment, an overwhelming number of interviewees demonstrated altruistic intentions behind their enrolment in WGS: 'I'm obviously keen to participate because, whilst it may not benefit me, it would hopefully benefit others' (R4). For some, this was to specifically benefit others in similar positions or affected by the same conditions:

‘We were happy part of a programme, [...] if they didn’t find any answers for him, and probably they haven’t, then possibly other answers can be found to help others in similar situations.’ (R8)

Others hoped to contribute to science and research more broadly:

‘If we hadn’t thought we would get anything out of it for [our son] we’d still have done it, just for the sake of contributing to the big picture.’ (R3)

Regardless of who or what they were hoping to help by participating in WGS, nearly all of the interviewees cited altruistic motivations of some kind, participating in the study despite knowing they may not derive any benefit themselves:

‘My attitude is generally is if this is in any way useful, at least its useful for maybe for the future, for someone else in 20 years time, or something I don’t know then brilliant. Yeah, that’s my take on it. You’ve got a set of medical conditions—why not try to put them to some good use.’ (R2)

Perception of risks associated with WGS, including SF. Some interviewees did not perceive any risks associated with WGS: ‘No [...] I just carried on’ (R6); ‘Personally, I didn’t have any worries’ (R2). However, well-informed about WGS, many interviewees were also aware of the implications. Before any prompting about SF, interviewees often raised the potential for additional results in WGS:

‘Well, the risk that I’ve got to think through is that you could find more. You’re looking at everything.’ (R13)

‘Yes, I guess the risk with that is, obviously, it could throw up other things.’ (R10)

A few interviewees also raised concerns about discrimination and insurance. For the most part, however, all of these concerns were minimal and did not prevent enrolment in WGS: ‘from our point of view any risks were outweighed by the huge potential benefits’ (R5). This is echoed in the questionnaire responses, where the majority respondents were not worried by the testing.

Participants expressed little to no concerns about data-sharing or privacy around WGS, either. In fact, in line with the strong altruistic motivations described earlier, interviewees often highlighted the importance of data-sharing: ‘I think the wider it goes the better. If it can help with other conditions, or treatments, then that needs to be done’ (R14). Some went as far as to say that policies at the time were too restrictive:

'No, I think that's the biggest point of the study is that that happens and that that data is available for research [...] So, I don't even know the whole anonymous thing, to my mind, in some ways that limits the use' (R3).

Others acknowledged that data-sharing was a necessary component of research, but highlighted the importance of keeping it secure: 'I think that's just the way things are. Of course, keeping the information confidential, it's just the normal challenges of any information' (R15). Some worried about involving commercial entities, in particular:

'So, you'd have to be very careful about commercial organisations. Yes, if you can keep things within the NHS-type environment and partnering perhaps with other research-type organisations, I'd be comfortable. I'm not so comfortable with commercial organisations being involved.' (R1)

Clinical testing to research as 'natural progression'. For the most part, interviewees did not perceive any difference between clinical and research spheres, beyond additional paperwork and greater discussion. While some perceived the two to be equivalent, if anything, some interviewees felt that the research process was *more* thorough than clinical testing and more likely to provide an answer: 'I'd imagine research has, obviously, got a bit more behind it' (R14). For most interviewees, WGS was simply perceived as a 'completely natural next step' (R16) in their diagnostic odyssey: 'it didn't feel any different [...] it felt like a natural progression' (R13); 'that was another day at the office really. Just with a different team of people.' (R2)

C. 'I won't mind not knowing': views towards, and decision-making around, secondary findings

Actionability, and motivations for SF. Many interviewees clearly recalled discussions around SF when consenting to WGS. Although not all could clearly recall their actual decision, many did claim to have opted to receive SF. For most, this decision revolved around the potential usefulness of the results. Additionally, interviewees wanted SF to provide the information to their family members, or for the benefit of the wider community, similar to their altruistic motivations participation. Some interviewees also articulated a right to this information, and one interviewee linked their desire for SF to the importance of reciprocity in research:

'I just think if that data is available, and if that data is about you, yes, I just kind of feel you should be able to have it, if you've agreed to participate in the study.' (R14)

In particular, some felt an information imbalance between WGS providers and recipients was unethical.

'I think it's quite difficult isn't it, because to have that information—to have that information and then not to pass it on to the person is quite, it's quite dodgy isn't it?' (R15)

'But for me, I'd say it's maybe a little bit disappointing to think that somebody could, potentially, hold some data which is quite significant to you, but yet you can't be told.' (R14)

Desire to receive different types of SF. The utility-based motivations behind decisions to receive SF at consent were reflected in views around the desirability of different types of SF. Most interviewees who wanted SF were interested in those where action could be taken to manage the related condition. This utility varied for different interviewees, echoing a well-described variability in individual definitions of 'actionability'—it variously included the potential for SF to inform treatment and prevent disease, the ability to plan or alter lifestyle, and the ability to inform reproductive decision-making.

Some of these interviewees, although few, expressed interest in receiving *all* findings, regardless of actionability or certainty. These individuals, based on their experience, felt they could cope with dire prognoses:

'But even then with conditions that there aren't treatments for there are still ways, positive ways of life and making the most of life. I think it's one of those things that all of a sudden everything can be taken away from you and I think actually having a respect for the fact that life isn't a given.' (R15)

Most interviewees, however, were much less interested in learning these types of results. Consistent with documented concerns about SF [126], many felt that non-actionable results would cause unnecessary anxiety, and that uncertain results would be unhelpful and difficult to process:

'I would just spend 40 or 50 years worrying about it!' (R7)

'I don't think it helps anyone being told, "Well you've got...", I don't know, "...this faulty gene, but we've got no idea what the implications are". That's not beneficial, it's just worrying.' (R3)

Of note, the most commonly desired type of SF among interviewees was carrier status information: 'If it was something I could potentially pass on, I would definitely want to know about it' (R2). In many cases, this was even desired by individuals who declined additional findings at consent. Interviewees perceived information that could inform reproductive decisions to be particularly useful, often questioning the policies of the study itself, which does not return carrier status information:

'I don't agree with that. I think if I was a carrier for cystic fibrosis I would want to know because then I could find out if [my partner] was as well and then if he was we could decide what we were going to do about that.' (R3)

Focus on primary condition, and motivations against SF. Many interviewees, however, said they chose not to receive SF of any kind. Some interviewees expressed concern about the analysis process: 'I think given the situation where we are in terms of our knowledge it's the safest and the best policy' (R9). Most of those who declined SF felt that additional results would cause unnecessary anxiety:

'We just took the decision that we would rather live our lives in blissful ignorance than be perhaps weighed down by the risks of "what if?" or what could happen.' (R5)

In discussions around their motivations to decline SF, interviewees often raised the burden of their primary condition:

'More than anything else, I was worried that [...] they'd find something genetically abnormal, and that our son was carrying a heavy enough load in terms of anxiety and blame and guilt [...] I felt he had enough of a bad hand-out to him, and I was worried that any knowledge that we might learn about ourselves would add to his load.' (R9)

'Yes, but then I've already got epilepsy so [...] it would be really scary knowing that I've got something else as well.' (R6)

Much like broad understanding and literacy around WGS, it became clear that interviewee views towards SF were also widely coloured by their experience with their rare disease and the resulting interactions with the healthcare system. Equipped with this experience of a rare disease, and knowledge of the impact of such a condition, interviewees appreciated the gravity of a potential additional diagnosis. Thus, in order

to minimise additional burden, or remain true to the reason for which they enrolled in WGS, many of the interviewees who declined SF cited a preference to focus on finding an answer for their primary condition:

‘So we took the decision that rather than potentially find out a list of other issues that could affect us, that we would rather focus on the one issue we knew was affecting us.’ (R5)

‘I think we probably concluded that actually if there was something else we wouldn’t want to know it because we were looking for the cause of his physical disabilities and we weren’t looking for anything else.’ (R13)

Context-dependent desirability of SF. In discussing which types of SF they wanted interviewees highlighted the influence of their context on the desirability of SF. Interviewees acknowledged, ‘different people react differently’ (R10), and felt that the impact on the wider family should be considered in decisions to receive SF (the importance of family will be revisited below). Others acknowledge that at different stages in one’s life—such as before or after reaching reproductive age—SF might be more or less relevant:

‘But I’m happy that I don’t necessarily have to know everything about myself, and whether or not it’s relevant to how I live my life, I really feel like at the moment it isn’t.’ (R5)

‘For me now it doesn’t matter, I’ve got three children, I’m not going to have any more, whatever the package is, it’s here already.’ (R3)

Following from this, many interviewees highlighted the impact age would have on the desirability of SF. Some older interviewees felt that their age meant they could handle any sort of result: ‘I’m old enough to take it, I think, now!’ (R12) Conversely, another older interviewee felt that because of their age, SF were no longer of any relevance. They went on to explain that, however, if they were younger they would be more inclined to want SF:

‘No, if I was [my daughter’s] age I’d want to know, you know especially if it’s something treatable, or what have you. Like you say a heart problem or something like that, that I can adjust my lifestyle or what have you, I’d want to know about it. But like at my stage, I’m not that bothered to be quite honest.’ (R7)

D. Communication of secondary findings: who, when, how

Disclosure of SF and the need for a plan. When asked to consider how they would react upon receiving an SF, interviewees were realistic about the difficulty—‘I mean, it would be awful’ (R14)—but largely felt they could cope with the information: ‘Yes, you’d cry but then you’d react positively to being told that news’ (R13). In order to minimise the emotional impact of the disclosure process, interviewees felt that the information should be disclosed face-to-face, in a timely manner, and from someone familiar to the recipient.

Most importantly, interviewees highlighted the need for a plan of action. Regardless of their anticipated reaction to an SF, interviewees universally stressed the importance of being told what to do next. This desired sense of direction and control mirrors that which they sought for their primary condition, which led them to enrol in WGS in the first place. Thus, interviewees felt that the person disclosing the SF needed to have sufficient experience to advise on this desired plan—interviewees wanted to hear about SF from ‘someone who was definitely qualified to speak on that topic, so they could advise me on how to deal with it and what next steps’ (R2). They also wanted access to the appropriate specialty in a timely manner:

‘You’ve got to have something in place to [...] refer them on to the clinician who has the answers [...] because some people could take it very, very badly and you’re bound to have questions and want answers.’ (R10)

‘[I would want] a ticket to the appropriate department in the hospital which would set me up with whatever I needed.’ (R9)

For many, the importance of being provided a plan, and thus gaining control, superseded any other requirements for the disclosure process:

‘Most importantly, actually if it was a complete stranger, fine, most importantly that whoever gives you that information is also equipped to discuss with you the plan of how you manage knowing that.’ (R3)

This is consistent with their overarching desire for control with respect to their primary condition. In light of their experience with their (or their child’s) rare disease, and aware of the workings of the healthcare system (including its limitations; discussed below),

many interviewees would want timely control over any additional diagnoses to minimise any of the anxieties discussed with respect to their diagnostic odyssey.

Of note, despite this need for a plan, some indicated they would struggle to take significant action based on such a finding, particularly in the absence of a family history:

'I would actually find it very hard to have a mastectomy if I didn't actually have a problem or didn't actually have active cancer there to do it as a preventative thing [...] If I'd got two sisters, an aunt who'd all been through it and had it then, yes, I think I might think quite differently.' (R10)

However, many felt they would 'weigh up [their] options' (R16) and then likely follow the instructions that were provided to them by the healthcare professional: 'I would have immediate treatment' (R11).

Family and information sharing. Interviewees widely discussed sharing SF with family members. Interestingly, at first, some interviewees felt they would only share results with their immediate family. On further prompting about the shared nature of genetic results these interviewees said they would share their results with their wider family. Despite a sound understanding of genomics, this seems to indicate that some individuals still instinctually consider these results to be private health information above information of shared familial importance: 'that's my information to share' (R13).

Some interviewees, however, were immediately aware of the potential value of SF to family members. Many felt they would share results widely, with 'anybody else who would find the information useful' (R9). Some even felt that their family members should be involved in the initial decision-making process around SF:

'I discussed it initially with my siblings because of the fact it was something that wasn't just my decision to make because of the fact I would share that information with them because it wouldn't be fair not to.' (R15)

The potential impact of SF on family members influenced interviewee decision-making around SF, particularly among parents. For some, the potential negative impact on children led them decline SF altogether. Others indicated that, despite wanting all SF themselves, they would filter information to family members in order to minimise anxiety among others.

'Knowing [my son] may get a disease which isn't treatable, I think I would be less appreciative of the information. I can't do anything about it, neither can he; so it's really a waste of information [...] Bowel cancer, I'd tell them. Alzheimer's, I probably wouldn't.' (R11)

E. 'They know what's best': healthcare professionals and the healthcare system

Faith and confidence in the NHS. Throughout the interviews, interviewees repeatedly discussed the National Health Service (NHS). The tone of these discussions was particularly respectful: 'I have great faith in the National Health Service' (R4); 'I feel very confident in our NHS' (R5); 'I'd pay a penny more on my tax if it all went to the NHS' (R9). It became apparent that the NHS—as a cultural institution and point of shared investment—informed many of their views around healthcare and research, including the management of SF. For some this faith and confidence was tied to their own experience as a patient in the system: 'My experience of the NHS, particularly in Oxford, has been very positive' (R4). Following from this confidence in the NHS, many interviewees were comfortable allowing healthcare professionals to make decisions around SF:

'I mean, I put faith in that decision-making process, because I think a lot of medicine these days is putting people back on the patient, saying, "What do you want to do? The decision is yours", but the person often doesn't have the right set of information to make that.' (R8)

With awareness of the developing science and acknowledging significant person-to-person variation, several interviewees even expressed comfort allowing professionals make decisions about SF entirely on their behalf:

'They know what's best at the end of the day, and they've studied it. They know what's right, what's wrong [...] so, I trust them enough to make those decisions for me.' (R6)

'Because, I mean I'm not, I have no clinical, no real, nothing beyond, I'm quite happy with them coming to a decision as to whether there is something to inform me about.' (R2)

'I think maybe it is best if that decision is just taken by you.' (R3)

Although not universal, many were comfortable deferring responsibility, feeling that professionals were better equipped to make the decision than themselves: 'I think the

best people to make those decisions are the most senior people with the experience' (R1). Underlying this, for some interviewees, were their own struggles in making decisions around SF. Some interviewees felt it was important caveat, however, that these decision-makers 'honestly genuinely got the patients' best interests at heart' (R3).

Not all interviewees, however, were so willing to cede responsibility in decision-making around SF. Understandably, these interviewees were commonly the same individuals who were more inclined to want all of the different types of SF—regardless of actionability or certainty. For example, one of these interviewees highlighted the expertise she acquired during her own diagnostic odyssey:

'Before that I would have wholeheartedly said, "Oh, yes, you're a doctor, you know absolutely everything", and actually, I suppose, as a parent of two children with a genetic condition, we know far more about that condition than, actually a lot of doctors who specialise in kind of other things. I understand that they can't possibly be the specialist in everything, but yes, I think, ordinarily, you would put your trust in them, and actually that might not be the best thing to do, because they don't necessarily know everything.' (R14)

Much like the interviewees who declined SF as a result of their experience with their primary condition and clinical contact, the considered view articulated by the above interviewee is clearly informed by their experience with their rare disease and interactions with the healthcare system. In light of this, they are aware of the structural limitations of the system in addition to its benefits.

Distribution of limited resources. As discussed previously, the interviewees were largely aware of the complexities of delivering WGS. Many interviewees were additionally aware of the resources required to offer the testing. With an appreciation of the NHS, and awareness that the system is very resource-limited, many interviewees expressed concern over offering unnecessary testing:

'[R]olling it out in the NHS you've got to look from a funding point of view because that's going to involve more analysis and more time [...] I think there's got to be a point of stopping, hasn't there?' (R15)

In the absence of sufficient understanding of the utility of SF, one interviewee questioned the justification of returning of SF when resources are limited:

'So is there a risk that there's a huge amount of money going on treating healthy people who may never get sick? In a time when the NHS is struggling for funding, I would perhaps wonder whether or not that would be a good way of using money.' (R5)

As a result, many interviewees felt that options for SF should be restricted:

'I think it should be decided before it's even offered [...] I think it should be, 'We can also test for this, this and this. Would you like to be tested for it?' Rather than, 'What else would you like?' It's not a sweet shop; it's a medical service.' (R15)

Others, returning to the previously discussed preference to focus on primary findings, articulated that limited resources further justified focusing on the primary condition. Following from the aforementioned faith in the NHS and judgment of healthcare professionals, some interviewees felt WGS providers were best equipped to make decisions around resource allocation and investigating SF:

'I'd put it back in your court with the clinicians and I think it's for them to determine in the study just how much more they can practically do. I've no problems with whatever you do.' (R4)

Expectation of re-contact and continuity. Of note, many interviews demonstrated an expectation that they could be re-contacted later in light of new information. This may be rooted in their confidence in, and experience with, the healthcare system, but many interviewees—even those who declined SF—felt their results would be kept on file should they choose to access them later:

'But we decided not to do that, so we haven't asked to be told any other information that came out from the genome. We've got the information there, it is accessible to us should, at a later date, we change our minds.' (R8)

'I think I'd just keep it on file and if something did come up in the future then you can always deal with it then. I presume anyone who's volunteered for the study, the results are going to be stored and kept.' (R10)

Others who consented to receive actionable SF felt that the non-actionable results should be kept on file should they become actionable. And, among some interviewees, there was a sense that research would continue and their data would be re-interrogated for SF in the future: 'If new things are learned that are relevant, I think then it should be relayed then' (R10).

Some interviewees, however, were aware of the challenges of re-contact in WGS. Some highlighted how difficult it would be to receive information and how WGS recipients' situations can change: 'You're re-contacting but you have no idea what's going on in that person's life right now' (R13). Others highlighted logistical challenges of re-contact, echoing the lack of resources in the NHS. Another interviewee acknowledged the challenge of re-analysis and re-contact when dealing with so many participants: 'But then how can we expect you, on the other hand, to contact us, when there's going to be so many people involved in that study' (R14). This same interviewee, as a solution, wanted to know all of the possible SF so that they could initiate re-contact themselves: 'If you knew all of the results, that's more likely to perhaps trigger to you to make contact in years to come if something was discovered' (R14). Nonetheless, this interviewee still felt perceived an element of continuity long after the actual sequencing and initial disclosure of results.

5.5 Discussion

Informed by their experience in the healthcare system, many interviewees demonstrated carefully considered views towards SF in WGS, and articulated a nuanced understanding of the implications. This is consistent with research that suggests that experience with genetics and contact with the healthcare system can impact understanding and decision-making [150, 158, 172, 174, 189]. In line with the framework in *Chapter 3*, many interviewees favoured limited disclosure of secondary findings—most were only interested in highly actionable SF. This careful consideration was similar to those presented in Hitch et al. [168] and Kaphingst et al. [169], which explored the views of patients who had similarly experienced the diagnostic odyssey or had long experiences living with a rare disease. Amongst the interviewees in the present study there seemed to be even greater circumspection about SF—many expressed comfort not knowing secondary findings. A recent survey study, by Fiallos et al. [220], which takes advantage of the contemporaneous enrolment of participants in large-scale sequencing programme, also reported higher rates of declined results (20%) among participants compared to smaller numbers predicted in studies based on hypothetical participant decisions. Of note, while the underlying factors could not be captured by this survey, declining findings

was associated with ancestry, highlighting the importance of ethnicity and culture in these decisions.

As offered in Figure 5.4, it seems that much of this comfort in not knowing SF among interviewees in this study (as well as the reverse) is rooted in views towards the wider healthcare system—both its benefits, and its limitations. Although not universally, many interviewees demonstrated a high level of confidence in their healthcare providers and a sense of trust and respect towards the NHS. So much so that some of the interviewees were willing to allow healthcare providers to make decisions around SF on their behalf, trusting that they had their best interests at heart. Extensive experience with the healthcare system also made some interviewees aware of its limitations: they were acutely aware of the resource constraints faced by the NHS, as well as the complexity of offering WGS. Preferring to find the cause of their primary condition, this led some interviewees to express comfort not knowing SF. Additionally, perhaps linked to intense contact with the healthcare system resulting from their rare disease, interviewees expressed raised expectations—namely, an expectation of continuity and re-contact in light of new information (and thus re-analysis) with respect to SF, or the potential for SF to remain on their medical files should they choose to access them later. This could likely be tied to their confidence in the wider healthcare system, and experience of being notified when things of significance arise during their time as a patient—such an expectation may be realistic with respect to primary findings, where the length of the analysis process is discussed at the time of consent. Coupled with a desire to gain control over their rare disease and the ensuing preferred focus on their primary condition, this further contributed to interviewee comfort in not knowing SF. Although not true of all interviewees (motivations for those who want all results are mostly consistent with similar viewpoints outlined in the systematic review), this dynamic does illustrate the factors underlying why many expressed comfort not knowing SF, which has not been illustrated—to my knowledge—elsewhere in the existing literature. However, it is quite possible that this dynamic may be specific to publicly funded healthcare systems, or even to the UK, where the NHS is a cultural institution and investment that interviewees appreciate needs to be shared fairly. Nonetheless, as WGS enters routine clinical care

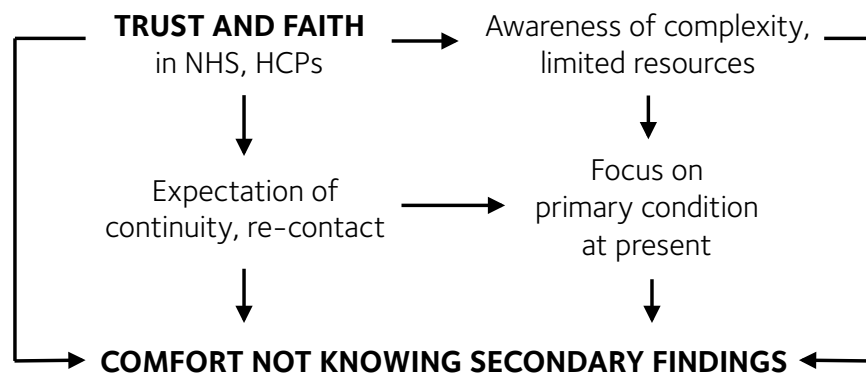


Figure 5.4: Schematic illustrating factors underpinning comfort not knowing secondary findings from WGS expressed by some interviewees

following the completion of the 100,000 Genomes Project, views from participants in similar contexts will be essential to policy development around SF management.

It is worth addressing the widespread assumption held by interviewees that re-contact about SF in light of new information is possible. Although not held by all interviewees—aware of the limitations of the healthcare system, some saw it as idealistic but unfeasible—it seems that, as illustrated above, this expectation contributes to interviewee comfort not knowing SF. However, while ethically desirable, re-contact in genetics has been shown to be practically unfeasible (for even primary findings) [15]. Recent work by Carrieri et al. [198, 221] builds on this by interviewing UK HCPs (including professionals in clinical genetics, other specialties offering WGS, and clinical scientists) on re-contact in clinical genetics. While favourable, interviewees in Carrieri et al. [198] expressed concerns about its feasibility in the NHS, highlighting barriers to its implementation. These barriers were chiefly those of limited resources and a lack of clarity on the responsibilities of different stakeholders. As of yet there are no guidelines for re-contact in light of new information in genetics, however some are working towards this end. Following interviews with WGS participants, who described barriers consistent with those articulated by HCPs, Dheensa et al. [222] proposed a ‘joint venture’ model for re-contact—where responsibility is shared between HCPs and participants. They encourage debate around the allocation of such responsibilities, and further research into the technological infrastructure required. In the absence of such infrastructure and duty to re-contact, interviewees’ idealistic expectations of re-contact about SF are

misplaced. Furthermore, even with a system for re-contact, interviewees who declined SF would not have had additional genes analysed—the idea that they could access results at a later date after declining SF is erroneous as these results will not be on file for never having been generated in the first place. Tulusso et al. [189] reported a similar misconception: survey respondents seemed to think SF were sought by the laboratory in all participants but only reported in those who consented to receive them. Even if SF were generated, it was not made explicit to interviewees in this study that such results would be added to their medical records—and authors have argued that there is no such duty and that placing research results in medical records without consent is actually harmful [223]. This misplaced perception from many interviewees that re-contact is possible has implications for informed consent provision—in order to make decisions around SF it is important that those giving consent understand the distinction between primary findings and SF and the long-term impact of their choices.

Another point of interest is that of carrier testing. Much like the healthcare professionals interviewed in *Chapter 4*, patient interviewees also expressed an overwhelming interest in having access to carrier status information. A majority of interviewees (12 of 16) felt information that could inform reproductive decision-making was desirable, including five individuals who actually declined actionable SF. Again, while being offered by the 100,000 Genomes Project, this is inconsistent with current guidelines from the ACMG [2], and warrants consideration in the development of future guidelines and policies.

During the analysis of the interviews it was striking how many interviewees expressed that they did not wish to receive SF. Based on local experience consenting individuals to the project, as well as my own experience through shadowing consent sessions and reviewing signed consent forms, it was surprising that I would have captured so many SF-decliners in the subset when there were seemingly so uncommon in the study at large. This warranted revisiting the consent forms to confirm decisions taken at the time of enrolment. In a 2015 survey of 154 research participants, Fernandez et al. [224] reported a high degree of stability in attitudes towards SF over time, showing no difference in views towards return of SF over an 18-month period. Interestingly, however, half of the interviewees in our qualitative study who said they would not want SF (and recalled

declining them during the consent process) had actually consented to receive SF. This raises questions as to whether the views of these individuals changed since consenting to receive SF, an important consideration given the potential harms of disclosure [69]. If not, were their decisions at consent actually representative of their feelings? In light of psychosocial research around reactions to other probabilities, Viberg et al. [225] questioned whether WGS recipients could actually express their true preferences towards SF at the time of consent due to various influencing factors (mood, over/underestimation, framing, expectation). In the case of these interviewees, it is certainly possible that their views simply changed—time had passed they enrolled in the project and they may be at a different stage in their lives, which can have different effects on the impact of genetic test results [226]. However, it is worth noting that all three of these individuals had received positive primary results at the time of the interview, having been given the genetic cause of the condition for which they enrolled in WGS. It is possible that, since receiving such a result, these individuals were no longer interested in additional findings. At the time of consent they may not have wanted to close any possible doors—some might have felt that declining any result, even secondary ones, could reduce their chances of finding an answer, and thus consented to receive SF. With a primary finding in hand, their desire for SF may decrease, or they are able to communicate a lack of desire for SF without fear of comprising a diagnosis for their primary condition. While acknowledging the small numbers, this highlights the need for further empirical research exploring the changing views of WGS recipients towards secondary genetic results over time, particularly before and after they have received primary results. This has implications for the consent process: the distinct nature (and analysis) of secondary findings from primary findings must be made clear, and dynamic forms of consent [192] should be considered to account for the changing views of WGS recipients.

5.5.1 Strengths and limitations

The study captured individuals with a diverse range of primary conditions as well as views towards SF. The qualitative methodology employed allowed for the exploration of nuanced and qualified views not afforded by much of the quantitative data currently

available on stakeholder views around SF [126]. Much like the interviews in the previous chapter, an additional strength of the study is the novelty of the sample. By exploring the views of non-USA genetics patients and relatives, which are formed in a very different context than similar studies exploring the views of American counterparts [146, 162, 168, 169], the study helps provide much needed diversity to the viewpoints identified in *Chapter 3*.

However, despite its strengths, the sample is somewhat skewed. Based on the recruitment strategy, interviewees are self-selected. Those who returned questionnaires and agreed to be interviewed saw the value in research, and tended to have higher levels of education. This is highlighted in the increase in education level between questionnaire respondents and interviewees. This likely explains the higher level of understanding about WGS and might account for the importance placed on contributing to research illustrated in both the questionnaire responses and interviews. Additionally, all of the interviewees were White British—individuals of other ethnicities were unable to be recruited. For these reasons, as with most qualitative research, care should be taken in generalising the results.

5.5.2 Implications of findings

This study has implications for research and clinical practice:

- Care must be taken during the consent process to ensure participants understand the long-term implications of decisions around SF including the potential for re-contact (or lack thereof).
- Care must be taken to ensure participants understand that decisions around SF do not impact the probability of primary results.
- Results that inform reproductive decision-making, such as carrier status, should be considered in future updates to minimum gene list policies and guidelines.
- Dynamic forms of consent need to be considered to accommodate changing views of participants towards genomic results.

- Further research into the changing views of WGS recipients towards results over time is needed, particularly exploring the impact of receiving primary results on desire for secondary findings.

5.6 Conclusions and chapter summary

In this chapter, using semi-structured interviews, I have explored the views and experiences of Oxford patients with rare diseases, and family members, towards SF in WGS. Much like the views presented in the previous chapter, these perspectives help to fill gaps identified in *Chapter 3*. Although views were diverse, many interviewees expressed a high level of comfort not knowing secondary findings, to a degree not previously illustrated. It seems that this comfort is underpinned by their experience in the NHS—including an awareness of its benefits and its shortcomings. This may or may not be particular to public healthcare systems or even the UK. Aware of limited resources and preferring to focus on their primary conditions, interviewees were comfortable not knowing secondary findings and, in some cases, allowing healthcare professionals to make decisions on their behalf. To some extent, however, a misplaced expectation for re-contact about SF in light of new information might have contributed to this sentiment. As such practices do not currently exist, it will be important to consider such an infrastructure moving forward or temper such expectations at the point of consent. Additionally, there were indications that interviewees' views may have changed in light of receiving primary results—it will be important to consider dynamic forms of consent to account for views that change over time.

In many ways, the views illustrated by WGS participants in this chapter complement those articulated by providers in the previous chapter. Some participants are willing to defer responsibility to HCPs on the basis that they have the appropriate expertise and have their best interests at heart, and the HCPs demonstrated concern about minimising harm to participants and careful deliberation around decisions. This will be revisited in the final discussion (*Chapter 8*). Similar to the views presented in the previous chapter, the perceived impacts of returned SF discussed in these interviews were entirely hypothetical—no interviewees had actually received SF and had to speculate as

to how they might react to SF. Contrary to the intended utility of SF, however, there were indications that interviewees who received SF might have had difficulty acting on such findings. Thus, it is critical that the actual experience of SF disclosure in recipients be explored. Therefore, to complement these data, I will present actual data—including views and experiences of an individual who received an SF—in *Part III* of this thesis.

PART III
Secondary findings in clinical practice

Case: Alex and David

In his free time, David—Alex’s father—is a competitive cyclist. He trains six days a week, for one to four hours at a time. David regularly participates in high-intensity races and, when training, pushes himself to the point of exhaustion. David appears to be the picture of good health: at the time of enrolment in WGS he had no known health conditions, and—besides Alex’s hereditary spastic paraplegia—knew of none that existed in his family.

During the analysis of David’s sequence data, however, a pathogenic variant was detected in the gene KCNQ1. Although sequencing was undertaken to provide a diagnosis for Alex’s condition, this gene is not known to be associated with that disease. Instead, this gene is on the ‘additional findings’ list used in the MGAC protocol to screen for serious and treatable conditions; screening that David consented to at the time of enrolment. Pathogenic variants in KCNQ1 are known to cause the inherited cardiac condition (ICC) long QT syndrome. ICCs like LQTS are particularly dangerous for individuals who engage in intensive cardiovascular activities—such as high-level athletes like David—as they can result in sudden cardiac death (SCD), and this risk can be increased during exercise. In many cases, SCD is the first symptom that manifests. Thus, pre-symptomatic detection of ICCs can be life-saving.

As highlighted by the healthcare professionals interviewed in Chapter 4, current knowledge of the clinical utility of variants in genes such as this is derived from families with documented cases of the associated condition—to our knowledge, at the time of analysis, David was not known to have any of the related symptoms and he had no family history of long QT syndrome. Thus, with little experience returning secondary genomic

findings, there were concerns: is the clinical team certain the variant is disease-causing; how will we disclose the result to David; although he has consented to receive additional findings, how will he react to this potentially life-altering information?

Closing the loop

In order to mitigate the challenges faced by returning secondary findings to participants like David, it is essential that data be collected from the return of such findings in practice. SF in genes known to be linked to inherited cardiac conditions are a particularly useful place to start. While all SF will provide insight into the processes required to return such results, as well as the impact they will have on recipients, cardiac SF can provide valuable clinical data that are not afforded by currently-sought SF linked to other conditions.

As previously discussed, current additional findings lists, including the ACMG59, generally include genes linked to inherited cardiac conditions alongside many genes associated with cancer predisposition syndromes. Pathogenic variants in cancer predisposition genes indicate an increased lifetime risk for cancer, where the disease could manifest many years into the future. Participants with variants in these genes are offered screening or risk management measures. Due to these genes simply indicating a heightened *risk* for developing the condition, participants can show no symptoms of disease at the time of clinical assessment while the variant itself could still have the potential to cause disease. Where refined penetrance estimates are needed on a population level for variants to be returned as SF, variants in cancer predisposition genes do not afford investigators the opportunity assess whether or not a variant is penetrant in a given individual, as there is no immediate phenotype to measure.

Variants in genes known to cause inherited cardiac conditions (ICC), in contrast, can provide this data. Unlike cancer predisposition syndromes, the risk associated with carrying an ICC-associated variant can be directly assessed by the presence of a detectable phenotype during clinical evaluation. In the absence of any clinical changes in adulthood, the risk of serious complications is very low, perhaps not measurably different from population risk. Thus, variants in genes linked to ICCs allow us to ‘close the

loop’ on secondary findings—providing the phenotypic data necessary to inform refined penetrance estimates, as well as our understanding of the clinical utility of SF broadly.

Inherited cardiac conditions

‘Inherited cardiac conditions’ (ICCs) refers to a variety of inherited disorders that affect the heart. These conditions encompass a range of phenotypes, including cardiomyopathies—disorders of cardiac muscle—and electrophysiological or conduction disorders. In this thesis, I focus on four ICCs: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and long QT syndrome (LQTS). All of these conditions can result in sudden cardiac death (SCD), and are a significant burden to affected families. Fortunately, there are interventions available to mitigate risk. Furthermore, these are conditions for which the genetics are relatively well elucidated, and that are currently included on minimum gene lists, such as the ACMG59, as well as our own. Thus, they are ideal for closer study. Brief descriptions of the four ICCs are detailed here, however the clinical assessment involved in each of these conditions is discussed later (*Section 7.4.4*).

Hypertrophic cardiomyopathy (HCM)

The discovery of variants in sarcomeric genes as causes of HCM signalled the start of an era elucidating the genetic underpinnings of ICCs [227–230]. Of the ICCs, HCM is one of the most common—affecting 1 in 500 individuals—and is the leading cause of SCD in young adults [231]. Clinical diagnosis of HCM is based on unexplained hypertrophy of the left ventricle [232]. The age of onset is commonly during adolescence, but can develop anywhere from infancy to late adulthood [232]. HCM is usually inherited in an autosomal dominant pattern, and is characterised by hypertrophy of the left ventricle [233]. The most common variants causing HCM are in the genes encoding β -myosin heavy chain (*MYH7*) and cardiac myosin binding protein C (*MYBPC3*), which together account for the majority of genotype-positive cases [232, 234]. HCM is very genetically heterogeneous condition, with at least nine additional genes are known to be causative

[235]. Testing of all known HCM genes in an individual with family history yields a diagnosis in up to 60% of cases [236].

Dilated cardiomyopathy (DCM)

DCM is the second most common cardiomyopathy behind HCM, previously estimated to affect 1 in 2700 individuals [237]—but now thought to have an prevalence closer to that of HCM [238]. The diagnostic features of DCM are dilatation of the left ventricle with systolic dysfunction, and myocardial fibrosis is often present [233]. The age of onset of DCM ranges from infancy to late adulthood and, like HCM, the inheritance pattern of DCM is most commonly autosomal dominant [236]. DCM is also caused by variants in sarcomeric genes, thus having significant genetic overlap with HCM. Variants in genes shared between the two conditions, however, cause opposite functional changes in DCM from those causing HCM [233]. Compared to HCM, DCM is even more genetically heterogenous, with causative variants in genes encoding many different cellular components involved in the disease and over 40 implicated genes identified [233]. Mutations in the gene *TTN*, which encodes the striated-muscle protein titin, account for a significant proportion of cases of DCM—Herman et al. [239] found that truncating mutations in *TTN* accounted for 25% of familial cases of DCM, and 18% of sporadic in their cohort of 312 subjects with DCM. This has increased the yield of genetic testing for DCM, which was previously very low [236], but still not to that of HCM.

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Of the three cardiomyopathies discussed, ARVC is the least common: prevalence is commonly estimated at 1 in 5000 [240], with the most liberal population estimates still above 1 in 2000 [114]. ARVC, however, still accounts for a significant proportion of cases of SCD among young athletes (up to 22%) [240, 241]. ARVC is characterised by fibrofatty replacement of the myocardium, primarily in the right ventricle—resulting in an increased susceptibility to arrhythmias [233]. Onset of ARVC is typically during early adulthood—where the presenting symptom is commonly SCD [242]—and is normally inherited in an autosomal dominant pattern [114]. ARVC is primarily caused by variants in genes that encode desmosomal proteins (*PKP2*, *DSC2*, *DSG2*, *DSP*), which serve to

compromise cell-to-cell adhesion and interfere with critical signalling pathways [229]. However, ARVC-implicated variants in non-desmosomal genes have also been identified [243, 244]. The gene most commonly implicated in ARVC is plakophilin 2 (*PKP2*), which accounts for nearly 40% of genotype-positive cases [236]. Variants causative of ARVC are commonly loss of function (LOF) alleles [229], in contrast to those missense variants causing HCM and DCM. Diagnostic yield of genetic testing for ARVC is much higher than that of DCM, and comparable to HCM, with causative variants found in up to 60% of cases [236].

Long QT Syndrome (LQTS)

Unlike the three ICCs discussed above, LQTS is not a cardiomyopathy, but an electrophysiological disorder—affected hearts are structurally normal. The disease is characterised, as the name suggests, by a prolonged QT interval on an electrocardiogram (ECG) [245]. Estimates of the prevalence of LQTS in the population range from 1 in 2000 to 1 in 3000, however—like the cardiomyopathies—these are likely underestimations due to variable disease expression [246]. Also like the cardiomyopathies, LQTS is usually inherited in an autosomal dominant pattern (variants are commonly dominant-negative), and it often manifests as SCD [247]. As the QT interval is representative of the duration of depolarisation and repolarisation of the ventricles, variants in cardiac transmembrane ion channels are causative of LQTS. Although many more genes have been implicated in LQTS, three genes—each encoding a cardiac ion channel—account for the majority of cases: *KCNQ1* (30-35%), *KCNH2* (25-40%), and *SCN5A* (5-10%). Variants in each of these genes produce different phenotypes and thus dictate the classification of inherited LQTS into three subtypes: LQT1, LQT2 and LQT3, respectively [247]. The gene in which the variant is located affects the clinical course of the disease, thus the genetic subtypes are important for risk stratification [248]. While the genes are common between affected individuals, the location of variants within these genes varies significantly, so much so that they are often at positions entirely unique to families ('private' mutations) [249]. Also an issue for HCM, this is likely to complicate the analysis when interpreting such variants as SF. While only a few genes are commonly implicated in LQTS, this within-gene variation

results in significant genetic heterogeneity, as well as variable clinical presentation and prognosis [250]. The diagnostic yield of genetic testing in LQTS the highest of the ICCs discussed—75% for the three main genes, and 80% if all known genes are tested [236].

Treatment of ICCs

Despite being life-threatening, putting affected individuals at high risk for SCD, ICCs are manageable if detected. Although useful for guiding patient care in some instances, genotype-phenotype correlations for ICCs are of limited usefulness at present [233]. Thus, in guiding treatment, clinical assessment remains vital. In particular, variant carriers are risk stratified for SCD, based on available evidence and best practice [251, 252]. For the cardiomyopathies (HCM, DCM, ARVC), when there is sufficient evidence of risk, patients can be given an implantable cardioverter-defibrillator (ICD) [233]. In the case of LQTS, it is managed, first, through the avoidance of QT-prolonging drugs. If risk of sudden death is deemed elevated—based on age and clinical assessment—beta-blockers are the primary therapy. ICDs can also be considered in high risk LQTS patients [247]. The treatability of these conditions is what makes them important candidates for secondary analysis in WGS: if detected pre-symptomatically, and confirmed by clinical assessment, secondary detection of ICC variants could be life-saving. However, there is a potential to cause harm—by causing unnecessary anxiety, interfering with life choices, wasting limited resources, offering inappropriate intervention—if such findings are returned unnecessarily. Thus, ensuring that there is a sufficient evidence base to interpret these results, and policies in place to guide their return, is vital if WGS participants are to benefit from this potentially life-saving information.

Section overview

The overall aim of *Part III* of my thesis is to explore the clinical utility of secondary findings in WGS in clinical practice—by illustrating the challenges faced in returning SF in practice, as well as generating the data needed to mitigate these challenges.

- **Chapter 7** details an in-depth case study of a cardiac secondary finding returned to a participant enrolled in a WGS study in Oxford. This chapter explores the process

and impact of returning this variant to the participant, as well as illustrates the challenges of doing so.

- **Chapter 6** outlines a proposed study designed to explore clinical utility of cardiac SF in WGS, aiming to provide much-needed evidence identified as lacking in *Part I* and demanded by HCP interviewees in *Chapter 4*.

6

Disclosure of a secondary cardiac finding from WGS: a case study

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As illustrated in *Part I* of this thesis, there are few documented actual experiences of returning or receiving secondary findings from whole-exome and whole-genome sequencing (WGS). The challenges posed by this lack of actual experience (and the resulting evidence) are highlighted by the interviewees in *Part II*: WGS participants can only predict how they might react to SF, and healthcare professionals require evidence and exemplars to inform their decision-making. As David (whose case has recurred throughout this thesis) consented to screening and disclosure of additional findings, pursuing the variant in *KCNQ1* respects David's choice at the time of consent and provides a valuable opportunity to illustrate the process of returning SF in practice. Furthermore, variants in *KCNQ1* have well-known cardiac phenotypes: as discussed previously, inher-

ited cardiac conditions (ICCs) have directly measurable clinical features, affording the collection of valuable information as to the clinical utility of returning the SF. A close examination of this case also affords an opportunity to illustrate the challenges that will be faced if the disclosure of such variants is carried out on a systematic scale.

To illustrate the process of returning an SF from WGS, and explore the utility of doing so, in this chapter I provide an in-depth account of the return of this secondary *KCNQ1* variant to David, following case report guidelines [253]. Case reports, such as this, are an essential component of medical literature, as they provide unique information that can contribute to further research and provide useful tools for education [254, 255]. Unlike most case reports, however, the account will borrow from qualitative case study approaches [256, 257], additionally including a semi-structured interview and brief analysis to explore the impact of the SF disclosure on David. The account is divided into three sections: (1) a discussion of molecular features of the case, including the variant and the analysis process undertaken—with particular attention paid to the determination of pathogenicity and the related challenges; (2) a discussion of the clinical features of the case, including the disclosure process as well as the outcome of clinical assessments; and, (3) an exploration of the impact the disclosure has had on David himself.

6.1 Chapter aims and objectives

The overall aim of this chapter was to explore the process of returning a secondary finding from WGS in *practice*. The specific objectives were to:

- Understand the analytical process and clinical pathways involved in returning an SF from WGS;
- Illustrate the challenges of interpreting and disclosing an SF from WGS under the current circumstances; and,
- Explore the impact—both psychological and behavioural—of returning an SF from WGS on the recipient by exploring their views and experience.

6.2 Methods

6.2.1 Whole-genome sequencing

In order to find the genetic cause of Alex's hereditary spastic paraplegia, David and Alex were both enrolled in MGAC (via the HICF2 funding stream). After providing informed consent for himself and his son (to receive both primary and additional findings), blood samples were collected from both individuals. DNA was prepared and sequenced in the Oxford Molecular Genetics Laboratory (OMGL). Samples were prepared for sequencing using an Illumina TruSeq DNA PCR-free library preparation kit and then sequenced on an Illumina HiSeq 4000. Analysis, undertaken by a clinical scientist at the OMGL, was targeted to 74 genes known to be associated with hereditary spastic paraplegia, as well as the 56 genes on the ACMG56 list. Variants were analysed with consideration given to potential patterns of inheritance. Further details of the data analysis process are outlined in Appendix G.

6.2.2 Variant interpretation

No clear candidate variant for Alex's primary condition has yet been identified. However, during the analysis of the 56 additional genes included in the screening protocol a variant was detected in *KCNQ1* (c.573_577del, p.Arg192Cysfs*91, NM_000218.2) in David's sample. According to the pathway devised for the GM-MDT (Figure 4.3), interpretation of this variant, and confirmation of its likely pathogenicity, was carried out sequentially by specialist clinical scientists in cardiac genetics at the OMGL in accordance with the new variant interpretation guidelines from the ACMG and AMP [217]. During this process, the clinical scientist makes a judgement about pathogenicity based on the nature of the variant the frequency of the variant in normal controls (ExAC [3]) as well as the OMGL cohort of patients with inherited cardiac conditions and literature documenting cases with the same variant, with particular emphasis placed on studies reporting segregation or functional data.

6.2.3 Clinical assessment

When the decision was made to return the finding to the participant (as will be detailed below), he was invited to attend Oxford's Inherited Cardiac Condition Service for counselling and clinical assessment. The process mirrored that provided to individuals of unknown status referred to the clinic through cascade screening initiated by an affected family member. At the discretion of the cardiologist, cardiac assessment at this clinic can variably include an electrocardiogram (ECG), an echocardiogram performed to rule out structural heart disease, an exercise tolerance test (ETT) and a 24-hour Holter monitor to record the QT interval during activity, exercise and sleep.

6.2.4 Interview

In order to explore the experience of receiving an SF, the participant (and his wife) was invited to participate in a semi-structured interview. Like the interviewees in *Chapter 5*, the patient had consented to participate in social sciences research when they consented to participate in MGAC. Thus, a modified semi-structured interview guide was developed and received ethics approval through an amendment to the larger MGAC study (Appendix E). Like the interview guides used in *Part II*, the interview guide was informed by psychosocial literature on genetic risk, the literature review undertaken in *Part I*, as well as local clinical experience. Particular attention was given to exploring any changes in David and his wife's experience, understanding, perception and behaviours during the period since disclosure. A list of the topics covered in the interview is found in Table 6.1.

Table 6.1: Topics covered in semi-structured interview guide patient who received SF

-
- Participant experience with genetic disease and testing.
 - Understanding of WGS and implications.
 - Experience of receiving secondary finding.
 - Understanding of, and views towards, secondary finding.
 - Impact of disclosure (psychological and behavioural).
 - Communication with family members after disclosure.
-

I conducted the interview in June of 2017 at the residence of the interviewee, closely following the data collection process employed for the other interviews (*Section 4.2.5*). Acknowledging that it is only a single case, the analysis was largely framed with respect to

the aims of the interview. The interview lasted approximately 90 minutes. David's wife, Caitlin, joined halfway through the interview—both provided written informed consent.

6.2.5 Overall reporting and analysis

The presentation of the molecular and clinical features of the case will follow consensus-based guidelines for case reports [253]. In order to apply the checklist to this case, where the genetic test precedes clinical assessment, the order of components were switched or altered as appropriate. While still a single case report [258], the additional inclusion of qualitative analysis borrows from a qualitative case study approach [256, 257, 259], expanding the 'patient perspective' component [253], aiming to provide an exploration of the impact of SF disclosure. The case study approach is not defined by a method, but by its focus on a case or series of cases—a variety of qualitative analysis methods can be employed [256, 257]. Thus, as in *Part II*, I undertook a brief thematic analysis of the single interview transcript [197]. Guided, in part, by the aims of the interview, I coded the single interview transcript in a non-restricted manner. In this way, the analysis was not as inductive as the studies described in the previous two chapters. EO independently coded the transcript, and coding disagreements were resolved by consensus. Subsequent analysis followed the same process for theme derivation as the interviews analysed in *Part II*. While of intrinsic interest, due to its uniqueness and novelty, this case was also intended to be instrumental, providing insight into a novel phenomenon that is of wide interest and applicability [256]. For this reason, novel findings—such as those specific to actual lived experience of receiving a SF—featured more prominently in the analysis.

6.3 Molecular features: a secondary finding in *KCNQ1*

6.3.1 The gene: *KCNQ1*

David's secondary finding was found in *KCNQ1* (potassium voltage-gated channel subfamily Q member 1), a gene on chromosome 11 that encodes one subunit of a multimeric voltage-gated potassium channel KvLQT1 [260]. The gene contains 19 exons and spans over 400 kb [261], and encodes a 676-amino acid polypeptide (Figure 6.1A) [262]. Four α subunits co-assemble to form the pore and combine with two β subunits (encoded

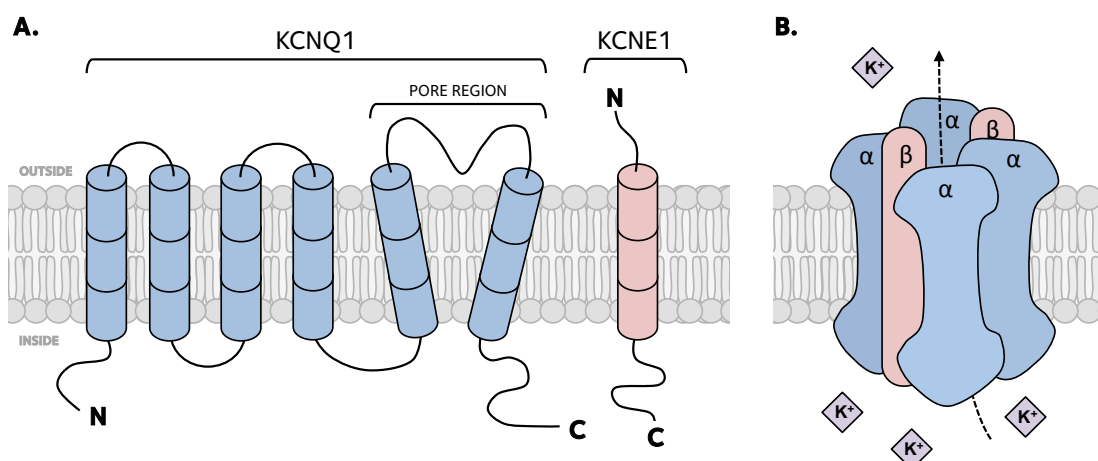


Figure 6.1: Schematic illustration of KvLQT1 protein, encoded by *KCNQ1* and *KCNE1*. **A.** Illustration of a single *KCNQ1*-encoded subunit of the potassium channel in the cell membrane, as well the *KCNE1*-encoded B subunit. **B.** Illustration of the voltage-gated potassium channel (KvLQT1) formed by *KCNQ1* and *KCNE1* subunits.

by the gene *KCNE1*, which is also implicated in LQTS) to form an intact channel (Figure 6.1B) that is needed for the repolarisation phase of the cardiac action potential [263]. The potassium channel is sensitive to catecholamines [264], and thus, when defective, can cause exercise-induced arrhythmia.

When *KCNQ1* was initially identified (by another name, *KVLQT1*) it was found in the critical region for LQTS [265]. This early study found variants in *KCNQ1* in members of 16 different families with LQTS. Since this discovery, many studies have documented variants in *KCNQ1*, including studies describing large affected families and others showing segregation of variants with disease [261, 265–269]. At the time of writing, ClinVar listed 674 variants in *KCNQ1*, with the majority of these implicated in LQTS [270].

The gene has also been linked to several other cardiac phenotypes, with different inheritance patterns—including Jervell and Lange-Nielsen Syndrome 1 [261, 271], atrial fibrillation [272, 273], and short QT syndrome [274, 275]. The gene is also implicated in genomic imprinting—its disruption due to chromosomal rearrangements has been associated with Beckwith-Wiedemann syndrome [276, 277]. Recently, genome-wide associations studies have shown variants in the *KCNQ1* locus to be associated with increased type 2 diabetes susceptibility [278].

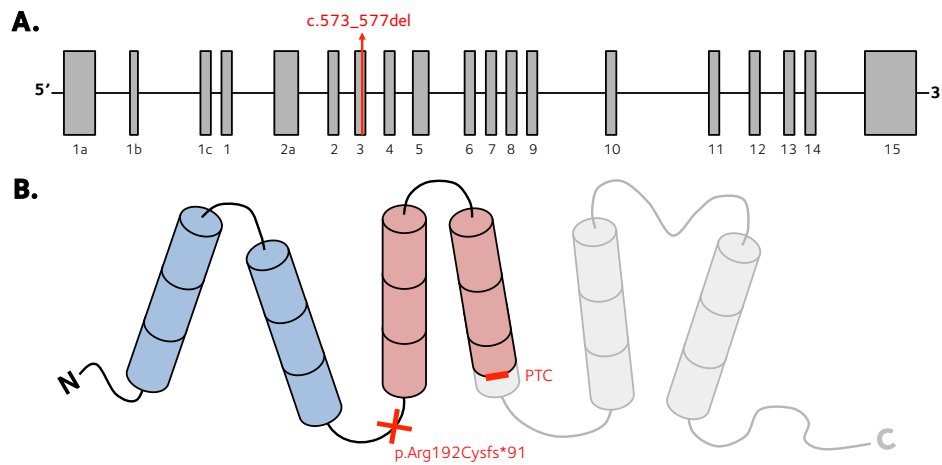


Figure 6.2: Schematic illustration of c.573_577del p.Arg192Cysfs*91 variant in *KCNQ1*. **A.** Diagram of *KCNQ1* gene. Exons are shown as boxes and introns as connecting bars, with both approximately to scale. Exons are numbered, with alternatively spliced exons denoted with lowercase letters. Five basepair deletion occurs in exon three, causing a frameshift. **B.** Location of the deletion (red X) and location of the resulting premature termination codon (PTC; red line) on an illustration of the KvLQT1 protein. Blue indicates normal protein sequence, red indicates altered protein sequence before truncation.

6.3.2 The variant: c.573_577del, p.Arg192Cysfs*91

The variant found in David's sample was a 5-basepair deletion located in the third exon of *KCNQ1*, from basepair 573 through 577 (NM_000218.2). This deletion results in a frameshift and a premature termination codon 91 residues away—ultimately resulting in a completely missing pore and C-terminus of the protein (Figure 6.2). The truncated protein is expected to be subjected to nonsense-mediated RNA decay, resulting in haploinsufficiency.¹

One of clinical scientists responsible for analysing the variant described such LQTS variants as 'difficult' to interpret due to the diverse LQTS phenotypes and inheritance patterns that are often variant-specific. Although truncating variants comprise nearly half of variants implicated in LQTS, evidence has shown that variants with haploinsufficiency result in significantly less risk of adverse cardiac events compared to variants with dominant-negative effects in *KCNQ1* [250]. Local experience has also shown that haploinsufficiency variants such as this one tend to have milder clinical phenotypes and show reduced penetrance (Hugh Watkins, personal communication). Thus, risk of sudden

¹**Haploinsufficiency** occurs when only one functional copy of gene is present, and an insufficient amount of gene product is produced to ensure the normal phenotype [211].

death may not be as high among carriers of such variants compared to others, but is likely to still be significant and a variant carrier would still be at risk from QT-prolonging drugs.

6.3.3 Further evidence of pathogenicity

In addition to the above-described biology, further evidence to support pathogenicity was needed before determining whether the variant warranted return. The clinical scientist responsible for the initial analysis described the process as ‘a steep learning curve’. It was the first time the laboratory had been faced with a secondary cardiac finding from WGS. In current practice, clinical labs interpret variants in light of the affected individual’s phenotype, however that is not the case here—analysing such a variant without any knowledge of clinical features or family history was particularly challenging.

Fortunately, recent advances in sequencing have afforded the generation of vast reference data sets that can provide some additional evidence to support this challenging analysis. At the time of the initial analysis, the largest of these was the Exome Aggregation Consortium (ExAC) [3], a large-scale reference data set of over 60,000 exomes, which has improved our abilities to interpret variants by essentially providing near population frequencies of variants. If the frequency of a particular variant is too high in ExAC the likelihood that it causes a rare disease, such as LQTS, is reduced. As a consequence, the release of data sets like ExAC has resulted in the reclassification of many variants previously thought to be important causes of disease. For example, a recent study by Walsh et al. [279] derived a minor allele frequency (MAF)² threshold of 1×10^{-4} for variants previously reported as important causes of a cardiomyopathy, showing that no known pathogenic variant exceeded this threshold and hence arguing that variants more frequent than this in the general population would not be expected to be highly penetrant pathogenic variants. The authors showed that a significant number of purported disease-causing variants (6.5% to 13.5%, depending on the cardiomyopathy) were present at a frequency incompatible with causation of penetrant disease, and thus warranted reclassification.

²Minor allele frequency is the frequency at which the rare allele occurs in a given population.

Thus, in gathering evidence to support the pathogenicity of the variant, frequency in ‘population’ databases was considered. In ExAC, the *KCNQ1* variant was found in four individuals (of 32,581) of non-Finnish European ancestry (0.012%), and absent in all other populations. Therefore, it has a European MAF of 2.46×10^{-5} . Due to significant experience with clinical cardiac genetic testing in Oxford, a local database of individuals with inherited cardiac disorders (cardiomyopathies and arrhythmias) could also be searched for the variant. Four individuals in the Oxford cohort³ were found to have the same *KCNQ1* variant, and it was not detected in normal controls. Additionally, there was further evidence provided by studies that described the same variant in individuals with LQTS: four cases in a large LQTS cohort [280]; seven Norwegian families with LQTS [281]; an infant with LQTS [282]; and a further family of individuals affected with LQTS that suffered swimming-related incidents [283]. Considering all of this evidence, the clinical lab ultimately classified the variant in *KCNQ1* as ‘highly likely to be pathogenic’.

6.4 Clinical features: decision-making, disclosure and clinical assessment

6.4.1 Decision-making around disclosure

Following the above analysis, the variant and supporting evidence were presented to the GM-MDT. During the discussion of the variant, one GM-MDT member questioned whether, in the absence of a phenotype, it was possible to apply the same variant classification system. However, other members agreed that, in assessing pathogenicity, multiple strands of evidence should be considered in addition to the phenotype. Members of the GM-MDT deliberated and agreed that the variant was worthy of return to the participant on the basis of its predicted pathogenicity (based on the above evidence) and its straightforward actionability, particularly the ease of potential clinical interventions—at a minimum, recommended avoidance of QT-prolonging medications, and possible prescription of beta-blockers. A timeline of the decision-making and disclosure process, as well as clinical follow-up, is shown in Figure 6.3.

³The Oxford ICC cohort has over 10,000 index cases for cardiomyopathies and arrhythmias, of which over 1500 have LQTS.

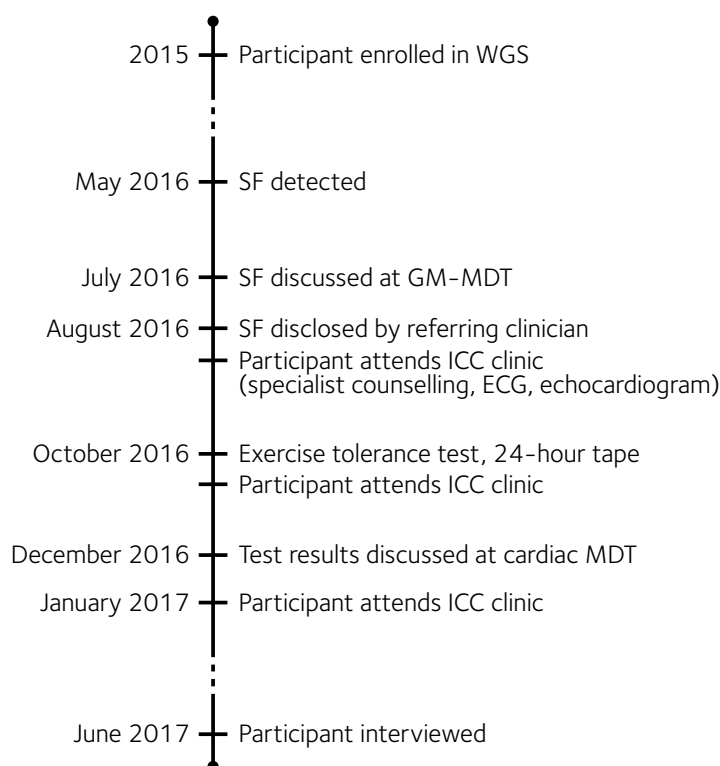


Figure 6.3: Timeline of case study

6.4.2 Disclosure process

It was initially decided by the GM-MDT that the SF would be fed back to the participant together with the primary result by the referring consultant—as this was the primary interest of the family and they did not feel that there was significant medical urgency relating to the SF. It was decided that a clinical letter would be written by a specialist in cardiovascular genetics to accompany the lab report. At the time of the GM-MDT discussion of the SF the analysis for pertinent results had not been concluded, thus it was decided that this analysis should be completed and reported as soon as possible. However, due to having only recruited David and Alex, the analysis for the primary finding proved challenging and time-consuming (compared to a complete trio analysis). Thus, a decision was ultimately made to return the secondary *KCNQ1* variant to the participant without a primary finding.

It was decided that the consultant who enrolled David in the study would disclose the SF to David over a video call, at which point he was immediately referred to the ICC service at the John Radcliffe Hospital. David was promptly scheduled to attend the

next clinic to meet with a cardiologist, a GM-MDT member, specialising in inherited conditions. As when unaffected family members are referred to the ICC service during cascade screening initiated by an affected relative, the clinic appointment began with counselling to discuss the nature of the SF and to determine whether clinical assessment was an avenue the participant was interested in pursuing. Attendance to this clinic provided additional support in the form of counselling specific to ICCs, by a genetic counsellor with specialist experience.

6.4.3 Clinical assessment

The patient

At the time of clinical assessment, David was 39 years old and held a physically demanding job—he was working as an aircraft fitter after having previously spent 12 years in the Royal Air Force. He identified as a competitive track cyclist who trains and competes intensively—he trains six days per week, for one to four hours at a time, year-round. He regularly pushes himself to the point of exhaustion and competes routinely in high intensity races. He had no history of cardiac incidents or unexplained syncope. David also -reported no family history of heart disease, fainting or unexplained accidents. On examination, David was described as having ‘an athletic build’ and was ‘generally well’, with very low resting heart rate of 36 beats per minute. This is consistent with high levels of endurance athletic training, although more extreme than typically observed.

Cardiac phenotyping

During his first ICC clinic appointment (Figure 6.3), David underwent a 12-lead echocardiogram (ECG) to measure his QT interval (further details in Appendix G). The results were reassuring, but the measurement of the QT interval was complicated by a prominent U-wave in the repolarisation pattern, as well as David’s low heart rate. The latter is because the heart rate was far outside the range at which the correction formula has been validated.

To further investigate the QT interval, David was fitted with a QT interval measuring 24-hour Holter monitor and had an ETT at a second appointment. The 24-hour tape

shows QT intervals corrected to within the normal range. The ETT, however, showed the QT interval to be moderately prolonged in recovery (in the abnormal range even when corrected) and showed complete failure of the usual shortening response to the increase of heart rate. Additionally, while David did reach a high level of exercise during the ETT, with good haemodynamic response and no arrhythmias, his peak heart rate was lower than would be expected.

Interpretation and plan

After the first clinic appointment (Figure 6.3), David was advised to avoid QT-prolonging drugs. Following the ETT and 24-hour tape, and after the results were reviewed by a cardiac multi-disciplinary team, it was decided that he did have an overtly abnormal repolarisation pattern that was consistent with LQTS. While David has no QT prolongation at rest, seemingly putting him at low risk, evidence of LQTS manifested during exercise where the QT interval failed to shorten as expected. As a result, David was advised that, while he is likely at lesser risk than someone with QT prolongation at rest, he probably is at some risk of SCD, especially during strenuous exercise. Therefore, David was advised to take a daily low-dose of a non-selective beta-blocker, and told that this would offer substantial protection. At the clinic appointment, David also agreed to moderate the intensity of his training.

6.5 Impact of disclosure: participant experience of receiving SF

Following the aims of the interview, and a brief thematic analysis, four areas of interest were identified: (A) disclosure and understanding; (B) appraisal, behavioural impact and consequences; (C) psychological impact; and, (D) impact on family. Detailed descriptions of these four themes are presented below, with illustrative quotations from the interviewees (quotations are assumed to be attributed to David except where explicitly attributed to Caitlin).

A. Disclosure and understanding

Experience of disclosure. In the interview, David described the moment he was told about the pathogenic variant detected in *KCNQ1*. David described the result as shocking and unexpected: 'it was quite out of the blue'. Reflecting on the decision he made with respect to SF at the time of consent, David recalled considering such findings but having ruled the possibility out in light of his own fitness:

David: 'I thought at the end of the day I probably would want to know but thinking my health, well-being I think I probably didn't think anything would come back, certainly not as drastic as this.'

David: 'I mean I didn't dwell on it too much because I thought well I'm a fit and healthy guy [...] I never even dreamt that something heart-related would come back.'

The shock and disruption caused by the disclosure was heightened by its secondary nature. First, the family was already burdened by the primary condition that lead them to enrol in WGS in the first place:

Caitlin: 'I was like, oh God, not something else because it was like [laughing] we always seem to have bad news.'

Furthermore, David had not considered himself the person in whom they would find a result—it was his son who was the patient.

David: 'Why this, why now or whatever because all our focus has been on [Alex] you see and then all of a sudden it's like, well, yes, no, it's not [Alex], it's [me].'

Understanding. Having no prior knowledge of the condition, and no context in which to situate the information, David described a lack of understanding and an accompanying feeling of dread at the time of disclosure:

David: 'She said "it's pointing towards this condition", which I was totally unaware of, I mean it was just letters and words at that point but she did describe what could and couldn't happen and she didn't pull any punches and basically it was like "oh my God, the next time I'm on my bike I'm going to die" type of thing.'

With time, however, David's understanding increased. During the interview David demonstrated strong recall of the content of each clinical encounter following disclosure, including the evolving clinical interpretation, as well as a nuanced understanding of genetics (including penetrance and expressivity). Personal research informed his understanding of genetics: 'I've since learned [...] that these genes [...] can lay dormant and it's only external triggers, environmental triggers, things can set them off'. Nonetheless, David described the challenge of managing all of the new information, and a demonstrated lack of confidence in his own understanding of the result:

David: 'Yes, the trouble is, it was all kind of a little bit of a mass of information that I needed to let it just all soak in and, you know, he's talking about the way the heart works and what this impacts with regards to the electrical impulses in the heart and I'm like, yes, yes; it's going over my head really. So we didn't have a full understanding of it really, we probably don't now to be fair.'

In terms of his perception of risk, David says aloud that he definitely has long QT syndrome. For David, this statement was based on the genetic finding as well as the clinical interpretation—despite its evolving throughout the process.

David: 'I say, "I've got Long QT", because they've said, "Your genes says or this gene discrepancy or abnormalities points towards Long QT", and the fact that he's actually said, "At 160-odd or high effort, the Q and the T don't compress, which they should do, which is a good indicator that you have got it", because at one point, he was saying, "I really can't see it in your results", but then obviously this guy that he spoke to said, "Well, actually that's looking a bit iffy". So, yes, I say, "Yes, I've got it", yes.'

B. Appraisal, behavioural impact and consequences

Appraisal and information seeking. Despite stating that he has LQTS when asked directly, David's mannerisms and further discussions were inconsistent with this belief. For David, his reaction to the diagnosis—both at the time of disclosure and at the time of interview—was largely characterised by a pervading sense of *disbelief*: 'At the time it was a little bit disbelief'; 'We put the phone down and we were like, "I don't believe this"'. The finding—pointing to a potential problem with his heart—was incompatible with his perception of self: 'It just doesn't add up in my head'. David defined himself by his physical fitness and cycling prowess, and this diagnosis, as he perceived it, was in conflict

with that. Furthermore, the diagnosis was also at odds with his family history—David described his healthy father who continues to cycle into his seventies. Finally, both David and Caitlin reiterated the fact that he had none of the symptoms associated with the disease. In the absence of these symptoms, they were both highly ‘sceptical’ of the diagnosis and his potential risk:

David: ‘That’s the one, the whole symptom thing. If I had symptoms, then I’d realise, well, actually, yes, you’re right.’

Caitlin: ‘[He doesn’t] have all the symptoms. He doesn’t have any of it. I’m sure they got it wrong! It’s just a bit random.’

In light of this scepticism, and to reconcile his sense of disbelief, David has engaged in a significant amount of information seeking. Both David and his wife constantly seek and weigh up information that might inform their own quantification of David’s risk—including their own family history, symptom scanning, and seeking expert opinions. Of particular interest to David was information that is sport-specific—he described making contact with sports scientists at nearby universities, and discussed information he obtained from online sports forums:

David: ‘I’ve been ping emails to various sports science places [...] with a few questions that may seem rubbish to somebody who knows what they’re on about but I just need it explaining to me with regards to how I can be doing what I’m doing and not have any symptoms. Is it unusual?’

In an attempt to explain his lack of symptoms, he seems to think that his fitness level and cycling (he explained that cycling is a ‘non-impact’ sport) might have had a protective effect. He feels that a sports scientist might be able to provide him an answer that a cardiologist cannot.

At the time of interview, David remained sceptical, despite admitting that he knows SCD can occur without symptoms, and knowledge of high-level athletes who died unexpectedly from an ICC: ‘I know but then look at that footballer, he seemed fit’. In the absence of symptoms and family history, and despite his language of certainty around having LQTS itself, David does not feel that his risk of SCD is significant.

David: ‘There’s no evidence really for me apart from the guy pointing out that I’ve got a low max heart and it doesn’t compress.’

David: 'See, to be honest, I always feel a bit wet when I say, "Oh, I've got Long QT", "What's that then?" It's, "Oh well, basically, I could keel over and die at any time", and I'm thinking, no, it's not. I don't feel like that, do you know what I mean? It's like [...] I'm overplaying it a bit.'

David's persistent scepticism, in light of his lack of symptoms and family history, appeared to manifest in a sort of selective acceptance of his diagnosis—he seemed to accept that he has LQTS, but does not consider himself to be at appreciable risk of SCD. He justifies this scepticism by citing the inconsistencies among clinical interpretations: 'it's all their interpretation of it. There's no exact science'. This selective acceptance of his diagnosis has implications for the behaviours that follow, as well as his psychological state.

Compliance with clinical recommendations. David's selective acceptance of his diagnosis manifests in selective compliance to clinical recommendations. First, David was prescribed a low dose of beta blockers. Despite demonstrating initial intentions to take them, David has not taken any of the drugs:

David: 'I said, "Well, I'm not particularly happy but at the end of the day, if that's what's needed then yes." So I then left there with the intention of starting to take beta blockers; I'd get a prescription from your local doctor and get on with it. I never did.'

This decision was additionally influenced by his online research.

David: 'I'd read and heard that beta blockers weren't particularly good for people doing exercise or whatever.'

David: 'On forums, cycling forums and stuff like that and they were like, yes, don't go near them and stuff, it really just made everything so hard!'

Second, David was told to reduce the intensity of his training. Initially, David stopped training completely: 'for the first two months, I didn't touch my bike'. However, with time, David grew more comfortable, and has started training again: 'I suppose I've kind of eased myself probably back into training [...] I've done no real hard sessions but I've been riding'. He justifies his training as a form of treatment: 'Surely, fitness is good for the heart, isn't it?' Although David did not demonstrate many lifestyle changes following disclosure (e.g. diet, other healthy behaviours), he did discuss seeking greater 'peace

of mind' around training—for example, his wife tracks his whereabouts: 'If I go out on my bike now, we've got a tracker on the phone'. Although David has taken the decision to continue training, he has stopped racing completely (i.e. training at max heart rate): 'I haven't raced since the day I was told about this'.

C. Psychological impact

Distress and loss of identity. For David, training decisions and the impact on his ability to race have been the greatest 'psychological hit'. In the interview, he recalled an episode where he felt particularly upset and overwhelmed shortly after the disclosure:

David: 'I had a proper meltdown the following day driving into work [...] I just burst into tears. With the way I felt it kind of upset me and it just all got on top of me and I just started to just - and I was driving thinking "why am I crying here?" But it just got to the point where, yes, you can't do any training again or - at that point I was thinking I can't ride. You know, I was thinking of selling my bikes, I don't need them.'

David discussed thinking about the diagnosis often, and frequency increasing with time: 'I definitely think about it more'. This often occurred while cycling: 'You have lots of time on your bike just think about stuff'.

For David, the incompatibility of the diagnosis with his sense of self and the recommendation for him to moderate his training represented a sort of loss of identity:

David: '[Cycling] defined me almost and I was thinking I was losing that.'

David: 'It's the only hobby I have and it was a real battle in my head when someone then says you can't do that anymore.'

It seemed that David (and his wife) felt that much of his social status and self-worth was tied up in this identity: 'All our friends, "Ask [David], yes, he'll know about training because that's what he does"' (Caitlin). Without cycling, David felt there was little purpose in his life—and thus little to help him cope with the distress and difficult diagnosis.

David: 'Cycling is my kind of thing and it's the only vice I have.'

David: 'What do I do tomorrow when I would usually go out and ride my bike or train or a Thursday night I go and race or a Sunday I go and race or whatever? What am I going to do? Do you know what I mean? It's like that's my thing.'

Fear and inability to control. In addition to the distress caused by the impact on his cycling, David demonstrated a sense of fear due to the lack of warning that comes with SCD:

David: 'That's the thing that really wrecks your head is the fact that it's totally blind.'

David: 'If someone were to say, "[David], you will never have or go into cardiac arrest before you start to have blackouts. You'll have blackouts or you'll have heart palpitations, you'll have blackouts and then you'll go into cardiac arrest", I'd be more than happy with that because I know I've got some warnings. I'm afraid of the lack of warning with this.'

For David, this lack of warning means that he has no ability to control the outcome, making his decision to continue cycling even more difficult.

David: 'You know, I could be run over riding my bike but it's like [...] at least I can see it coming and I can get out the way or can try and get out the way whereas this is just totally blind. If it's going to get you I'm not going to know.'

Regret. Both David and Caitlin discussed whether or not he would have been better off not knowing about the SF at all. After recalling that he had been asked about SF at the time of consent, he scoffed regretfully: 'I had to sign a consent form to say if something's found within me or him that we should be informed, and I signed it!' His wife seemed to agree: 'I think you'd have been better off with the whole not knowing' (Caitlin). However, despite the distress it has caused, David did feel that he would make the same decision again, perceiving some utility in the information:

Caitlin: 'I think he'd have been better off not knowing [...]' *David:* 'But I don't want to just die, that's the thing!'

His wife ultimately reached the same conclusion:

Caitlin: 'In a way, you might not have been better off knowing but on the flip side, the fact that you do know, you can rein it in a bit.'

David highlighted the importance of his age in this decision. He felt that it would have been significantly worse had he learned of the SF in his twenties:

David: 'I think this would have been a million times worse if they'd have turned round to me and said this at 21. I probably wouldn't have even had a career I did because I joined the military [...] but I think at 21, I can even look at it and think, oh my God, I can't cycle from now on or I can't do that but [...] 20 years of it and at least I can say and I'm still alive!'

Ultimately, on reflection, David attempts to find meaning in the information and arrive at a positive outlook, grateful that he had not learned of the result at a younger age:

David: 'If this ultimately results in death, then I'm still alive. Maybe that I should look at it and be thankful that it hasn't actually finished me off rather than thinking, oh my God, it could finish me off, do you know what I mean? So, I think it's the whole glass half-full, half-empty thing. I can either look at it and think, I can't race anymore but I've actually had 20 years racing.'

David was also optimistic about his ability to cope with the information and uncertainty getting easier with time:

David: 'I think the more and more time goes on I really do think it'll just, I will start just forgetting about it, which is maybe a good thing, maybe a bad thing, I don't know.'

D. Impact on family

Family wellbeing. The utility that David derives from the SF, which leads him to not regret to consenting to its disclosure, is principally related to the wellbeing of his family, rather than his own. This was clearly demonstrated in his recollection of the decision to receive SF in the first place—he perceived a 'duty to know', not for himself but for his wife and son.

David: 'I did think, do I? Do I? Do I? Well, I suppose, better had really.'

David: 'I said, well no, I can't really and as well I've got a family and mortgage and I don't want to be leaving them in the [chuckling] lurch.'

The wellbeing of his family largely underpins the psychological impact and behavioural decisions David discussed, and factored into his risk appraisal. In particular, the potential impact on his son is a point of recurring thought: 'I don't want him to be without a dad. I keep on thinking these things'. Despite remaining sceptical of the diagnosis and his risk of SCD, it is because of this sense of responsibility to his family that he stops racing:

Caitlin: 'I think maybe if we didn't have [Alex] and it was just me and you, maybe that would have a different effect on it as well maybe I think.' *David:* 'Yes, no, possibly. I would probably still be racing, to be honest.'

Communication and testing in others. Following disclosure, David described discussing the diagnosis with his wider family. He explained that his family members echoed the

same sense of disbelief described by himself and Caitlin. Both demonstrated understanding of the importance of having family members tested: 'They do really need to get tested because you don't know who's a carrier of it, at the moment' (Caitlin). Despite this, they described a lack of urgency on the part of family members: 'I don't think they're bothered, are they?' (Caitlin).

In the case of their son, Alex, they described an initial sense of resistance to having him tested for the *KCNQ1* variant. This was due to the burden he was already facing from his primary diagnosis and the related diagnostic odyssey.

David: 'They did ask me the last time I was there and I said, at the moment, with the troubles he's having, I'd rather just try and just forget that for now.'

With time, better management of Alex's primary condition, and David's arrival at his own selective acceptance of the diagnosis, David expressed greater interest and perceived utility in having Alex tested for the variant:

David: 'On reflection, I think it probably is maybe worthwhile now he's getting a little bit older with him going to school and [...] I think it might be more beneficial because we take him swimming and [...] he's a bit more active.'

6.6 Discussion

This chapter demonstrates the process of returning a secondary finding, from the point of detection through disclosure, as well as the downstream impact on the recipient. Importantly, this case highlights the many challenges encountered along the way. First was the challenge of deciding to disclose the variant. Consistent with concerns expressed by healthcare professionals in *Chapter 5*, interpreting the variant proved to be extremely challenging. This was due, in part, to the novelty of the case. However, with subsequent SF the challenge of interpreting the variants in the absence of phenotype and/or family history will persist. This demonstrates, in practice, the importance of collecting variant-specific data from affected cases and families, and from unselected populations, to fill the evidence gap identified at the outset of this thesis.

In addition to highlighting the anticipated challenge of variant interpretation, this case illustrated the challenging clinical process that can follow the decision to disclose. First,

despite having a protocol guiding the decision-making process to the point of disclosure, there were no guidelines or experience as to when or how to disclose the SF, or how to refer between specialties. Anxieties were high, and this lack of guidance and precedent resulted in some minor confusion during the disclosure process. Overall, the disclosure went relatively smoothly, but this was more a reflection on the novelty and resulting resources and care that were used to ensure it was carried out effectively. This highlights the importance of documenting such processes and experiences. When the participant was seen in the cardiac clinic (very soon after disclosure), the challenge of interpretation grew beyond that of variant interpretation, to include the interpretation of the clinical features. The difficulty experienced by the clinical team in interpreting the test results can be seen in the evolving interpretation with each clinic visit, as well as consultation with the cardiac MDT: while initially no phenotype was present on the baseline tests, a phenotype was noted on further testing and the extent to which this was interpreted to show an important abnormality changed following the MDT discussion. Although only a single case, this indicates that the genetic finding may have been useful in the pre-symptomatic detection of LQTS in David (and potentially his wider family). Whether this mild phenotype is sufficient for a diagnosis of LQTS under usual circumstances is unclear. Although this could be related to the biology of the variant itself, as discussed earlier in the chapter, the mild phenotype that was detected raises the question of reduced penetrance vs. expressivity. While it was discussed in the literature review in *Chapter 2* that these seemingly disease-causing variants might be present in the population at a much greater prevalence than the related disease—thus calling for refined estimates of *penetrance*—perhaps it is the case that *expressivity*⁴ also varies to a greater degree than anticipated. Other individuals with such variants, who never present clinically with LQTS or other ICCs, may have similarly mild phenotypes that would ordinarily go undetected. Variable expressivity calls into question the risk of such individuals for SCD, and could therefore have implications for risk stratification and yield important avenues for research. Thus, in the collection of variant-specific data from unselected populations it will be important, in addition to simple detection of disease presence (to measure penetrance),

⁴**Expressivity:** the range of phenotypes expressed by a given genotype (e.g. variant) [211].

for fine phenotyping to be conducted, and specific clinical features to be recorded, such that the phenotypic spectrum of these variants can be explored in the wider population.

An important final challenge highlighted by this case study is the impact on the participant. In order for these findings to be clinically useful, by definition, they must positively impact clinical outcomes [32, 33]. In order to improve clinical outcomes, the information needs to positively modify behaviour (including having treatment, screening, following recommendations), with minimum harm. As briefly discussed in *Chapter 3*, literature on the ability of genetic risk information to modify behaviour is mixed, but predicted to be higher in the case of rare seemingly penetrant variants [182, 183]. Christensen and Green [184] hypothesise that SF from WGS may be even more effective in eliciting positive behavioural changes. As literature on the behavioural impact of returned SF is entirely lacking, to my knowledge, this case study provides a valuable opportunity to explore the impact of disclosure.

The Health Belief Model is commonly used to conceptualise health behaviour and compliance with health recommendations [284, 285], and provides a helpful framework with which to consider David's response to his SF. The model holds that health behaviours can be explained by several factors: perceived seriousness, perceived susceptibility, perceived benefits and barriers. Where seriousness and susceptibility are perceived to be great, and the perceived benefits outweigh the barriers, a threat is identified and a force leading to action is generated. In David's case, he perceives the *seriousness* of his diagnosis to be high. David articulates an understanding that the potential outcome is death, and discusses the negative impact this would have on the wellbeing of his family. However, his perceived *susceptibility* is much lower. For David, although he says that he has LQTS, the diagnosis is incompatible with his perception of self and he cites a lack of evidence (symptoms, family history), thus preventing him from reaching complete acceptance of his susceptibility. For David, the *benefits* of complying with clinical recommendations (moderating training, taking beta blockers) are clear: they decrease his probability (or risk) of death, and thus serve to benefit him and his family. However, it seems that the *barriers* outweigh these benefits: David feels that taking beta-blockers and quitting racing strip him of his identity, leaving his life void of purpose.

All of these factors considered (lack of perceived susceptibility, and significant barriers to taking action) lead to David's lack of resolution and confusion, and his selective compliance—he has stopped racing, but is not adhering to his prescribed drug regimen. In the HBM, Rosenstock [285] argues that where resolution does not occur, individuals tend to 'vacillate' between choices or may demonstrate a high degree of fear and anxiety. Both appear to be true of David: his perception of risk is changing; his compliance is selective; he discussed anxiety he has faced since disclosure, particularly when he is on his bicycle; and cited fear about the lack of warning for SCD and his inability to control it. Thus, even with prompt, careful disclosure and highly specialist evaluation and support, it seems that, in the absence of reaching a resolution as to whether or not to act, SF do have the potential to cause psychological harm—a concern raised by critics and stakeholders in *Part I*.

While some of the perceived barriers might be specific to David—not all recipients of cardiac SF will be elite cyclists—his low perceived susceptibility might be a broader issue for the return of SF from WGS. For David, this low perceived susceptibility was largely rooted in a lack of symptoms and family history. Importantly—in the absence of a missed family history of the associated condition at the time of enrolment, effectively rendering the analysis analogous to a primary finding—this will be true of all returned SF. In part, this parallels clinical practice with ICCs where, during pre-symptomatic cascade screening, individuals struggle to conceptualise positive test results in the absence of symptoms [286]. However, these individuals do have a family history—this is the very reason for their screening in the first place. Such personal and family history of disease has been shown to increase the likelihood of behavioural response to genetic risk information [184, 287, 288], but may be entirely lacking for SF. In addition to the lack of symptoms and family history, David struggled to quantify his own susceptibility as the information was in conflict with his perception of self. Harris et al. [289], in a study of YouTube reactions to direct-to-consumer genetic results, noted a similar appraisal of genetic information in light of individuals' own perceived stories of health and illness: result recipients placed greater stock in results consistent with family history, and somewhat discounted those that were inconsistent. This is consistent with psychological literature,

which holds that the likelihood of individuals being persuaded by information is greater if that information is consistent with existing beliefs [184]. Thus, it is possible that the absence of symptoms and family history will not only complicate interpretation of SF, but compliance to recommendations. It is worth briefly noting the simplicity of the recommended intervention in David's case—compared with interventions that would be recommended as a result of other SF on the ACMG59 list, such as ICDs or prophylactic surgery, taking beta-blockers is not particularly invasive. David's response to this clinical recommendation could be unique. Although there could be greater compliance among other SF recipients recommended beta-blockers, more invasive recommendations could lead to similar issues around compliance (and the resulting anxiety). Thus, it will be important for further research to explore the behavioural impact of returned SF to determine whether this low perceived susceptibility is common, and whether (in the absence of the barriers specific to David's situation) it is an obstacle to the clinical utility of returned SF. If perceived susceptibility (and compliance) is low, it will be important for tailored counselling to help recipients reach a resolution and mitigate any resulting anxiety. The collection of variant-specific data from unselected populations, documenting more experiences and instances of individuals without symptoms and family histories receiving these variants, will inform these discussions. Such data will also help individuals (and healthcare professionals) reach a better understanding of susceptibility and, thus, increase the potential to improve clinical outcomes—or determine whether there is any benefit to be derived from the return of SF at all.

6.6.1 Strengths and limitations

This chapter provides an in-depth description and discussion of the return of an SF from WGS—something that is lacking from the current (largely hypothetical) literature. In particular, the qualitative findings provide a nuanced description of the impact of a returned SF on a recipient, and yield important avenues for further research. While some aspects may not be generalisable to all returned SF—such as the cycling-related impacts—the process and challenges described can be valuable, nonetheless, in informing future disclosure processes locally, and at large.

The chapter is limited in that it only depicts a single case. Thus, it is difficult to say whether the impact depicted is specific to David or represents broader issues for the disclosure of secondary findings. Thus, it will be essential for the same process to be replicated in a systematic manner such that the impact of a range of SF on a range of individuals can be studied. This will afford a larger dataset on which a richer and more in-depth qualitative analysis can be undertaken. This will be especially important for the exploration of issues and challenges highlighted in this case that appear applicable to SF broadly, namely the lack of action due to lack of perceived susceptibility.

6.6.2 Implications of findings

This study has implications both for future research and clinical practice:

- If SF are going to be returned to participants in a systematic fashion (as is required to build the necessary evidence base) clearer guidelines on the process of disclosure are required in order to minimise confusion and anxiety, among providers and recipients.
- Variant-specific data on returned SF in unselected individuals are needed to inform interpretation—refined penetrance estimates, but also detailed phenotyping in order to elucidate the full phenotypic spectrum of these variants.
- Further research into the impact of returning SF on WGS recipients is needed—both behavioural and psychological impacts need exploring to ensure SF disclosure is minimally harmful and clinically useful. This is particularly important if a lack of family history (together with a lack of symptoms) biases recipients towards low perceived susceptibility, and thus does not mirror current experience with testing unaffected individuals in cascade screening.
- If disclosure of SF causes anxiety among recipients, particularly because the potential benefit may be lower, extra care must be taken to counsel and support their need for information during the decision-making process following disclosure.

6.7 Conclusions and chapter summary

In this chapter, I have described the process of the disclosure of an SF—from the analysis and decision to disclose, through to the impact on the recipient. Such work begins to fill the evidence gaps identified in the literature review in *Chapter 2*, as well as those identified by WGS providers in *Chapter 4*. In the absence of a strong evidence base and precedence, it appears that the process will be challenging: as predicted by WGS providers, variant interpretation was difficult in the absence of a phenotype and family history and the clinical interpretation was similarly complicated. Despite these challenges, David did present with a mild phenotype deemed consistent with LQTS—potentially valuable information. The mild phenotype creates further impetus to assess these variants on a larger scale—in addition to reduced penetrance, the expressivity of these variants may be more variable than anticipated. To derive value from disclosure of this variant, and others like it, such evidence is needed. The qualitative work, however, calls into question the broader utility of disclosure—David was not entirely compliant with clinical recommendations and demonstrated a high level of distress and anxiety. If benefit is to be provided to WGS recipients through the return of SF, as intended, these obstacles will need to be explored and addressed.

While this chapter illustrates the potential challenges of returning SF to WGS recipients in practice, larger numbers are needed to yield findings that are generalisable, and therefore useful in guiding management of SF from WGS moving forward. The next chapter outlines such a study, which builds on the work in this chapter—replicating the return, clinical assessment, and subsequent psychosocial investigation, but on a more systematic level. This work will provide the phenotypic data, as well as the data on the impact of disclosure, needed to assess the clinical utility of disclosing SF and guide future practice in genomic medicine.

7

Designing a study to investigate the clinical utility of secondary cardiac findings in WGS

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As highlighted in the literature review at the very beginning of this thesis, actual data on returned SF from WGS in clinical practice is desperately lacking. Much of the criticism around the ACMG56 guidelines was based on this lack of relevant evidence—screening for such variants in such genes in individuals not known to be affected by the associated conditions is inconsistent with current practice, and therefore incongruous with currently available evidence [41, 42]. Critics, thus, called for the collection of empirical data on the predictive value of testing in unselected populations before promoting such practices. Even the ACMG56 guidelines conceded that data on the clinical utility of such findings will be absolutely paramount to informing their management [1]. In *Chapter*

4, experienced genomic healthcare professionals, who noted that the thin evidence base complicates decision-making around SF, anticipated the challenges faced by the lack of evidence. Finally, the case study outlined in the previous chapter, perhaps most clearly, illustrates the challenge of disclosing these variants in the absence of a sufficient evidence base—variant interpretation proved to be extremely challenging (a ‘steep learning curve’), and the professionals involved lacked precedent cases on which to model and guide disclosure.

As introduced in *Chapter 2*, some studies have begun to generate the evidence needed to inform penetrance estimates and the assessment of clinical utility of SF [96, 102, 117, 118]. For the advantages discussed previously, many have focused on SF in ICC-associated genes. An early study by Ng et al. [102]—and valuable model—clinically assessed six patients with pathogenic cardiac variants (from a cohort of 870). Of these, three showed evidence of the related clinical features. However, in addition to being a very small sample, expertise in Oxford (KT) disagreed with some variant classifications in light of more recently available population datasets (the OMGL would only have classified one of the variants as ‘highly likely to be pathogenic’, and actually would have classified one of the variants as ‘highly *unlikely* to be pathogenic’). Since then, larger more systematic studies have been conducted, harnessing the power of electronic health records (EHR). A study by Van Driest et al. [118] looked at arrhythmia-associated variants in 2202 individuals. They reported 63 individuals with pathogenic variants in *SCN5A* and *KCNH2*, however, only 22 (35%) of these individuals had the related-clinical features. Similarly, Natarajan et al. [117] reported 17 pathogenic or likely pathogenic cardiac variants (based on ACMG56) in 3513 individuals—but only 6 (35%) had the related features. Most recently, a large study by Haggerty et al. [290], focusing on ARVC-associated genes, found no significant association between loss of function (LOF) variants and ARVC phenotypes in an unselected cohort of over 30,000 participants. Consistent with earlier discussion of studies that found higher numbers of pathogenic variants than would be expected based on the associated disease prevalence [107], this finding indicates that the penetrance of even ‘radical’ variants should be assumed to be low in the wider population and urges caution in their return [290]. However, these studies are not sufficient. While valuable

in their provision of estimates, they do not utilise data ascertained for the purpose of diagnosing these conditions (including family history of SCD), they cannot capture symptom development over time, and they are unable to mirror the actual process of returning an SF and the resulting clinical assessment. For example, the diagnosis of inherited cardiomyopathies commonly involves cardiac imaging with expert analysis highly specific to the diagnostic question—such data is lacking from EHRs. In Haggerty et al. [290] the prevalence of known ARVC was much lower than expected, indicating that the EHR data failed to capture many cases of actual ARVC. Thus, prospective targeted phenotyping is needed [290]—these studies cannot provide the necessary precedent that professionals will use to inform their own interpretation and disclosure pipeline.

In addition to refined estimates of the penetrance of these variants, data on the impact of their return is needed to inform decision-making. As highlighted by the systematic review in *Chapter 3*, little data on actual experience—such as that in the previous chapter—returning or receiving SF currently exists. Available data on the psychological impacts of genetic risk disclosure comes from predictive testing where individuals with an awareness of their risk seek testing based on family history [291–294]. Although these studies show only short-term or no adverse impact on anxiety or quality of life, it is unclear whether their results are transferable to SF—where individuals may not have a family history of the disease and results may be entirely unexpected. Furthermore, the overall clinical utility of SF entirely depends on recipients acting on clinical recommendations made as a result of disclosure. Despite high expectations that genetic information will promote preventative medicine, evidence is mixed on the impact on behaviour among recipients [182, 183]. The impact of a returned SF on David, as outlined in the previous chapter, calls into question the clinical utility of disclosure and warrants further investigation. Thus, it will also be critical for psychosocial research to understand participants' motivation for participation, explore the actions taken after disclosure, and measure the psychological impact.

As randomised control trials require larger numbers than relatively low frequency SF can afford, creative methodologies must be employed to collect these data [115]. In this chapter, I outline such a study—the development of which has been central to

my time in Oxford. This mixed methods study—‘Secondary Cardiac Findings Evaluation’ (SCARFE)—focuses on secondary findings in ICC-associated genes, for the benefits afforded by their detectable phenotypes. The study takes advantage of locally available international expertise in ICCs: both of healthcare professionals affiliated with the Inherited Cardiac Conditions service attended by David in the previous chapter, and of the cardiac team at the Oxford Medical Genetics Laboratory (OMGL) who have conducted over 10,000 such analyses. The study also takes advantage of a large database of sequenced patients—the Cambridge NIHR BioResource for Rare Disease (BRRD)—employing a genotype-driven recruitment (GDR) strategy, in which individuals are ascertained based on genetic information collected during a previous study. The use of GDR in the context of dominantly inherited disease predisposition is relatively uncommon and attention will be paid to relevant ethical issues, including the right not to know and the potential to cause distress by disclosing unexpected genetic risk information [295]. In addition to detailing the study—including future work—the focus of this chapter will be on providing preliminary data on pathogenic variants detected in the BRRD cohort, highlighting the challenges of variant interpretation and detailing the analysis process.

7.1 Chapter aims and objectives

The overall aim of this chapter was to begin to collect the data necessary to fill the gaps identified at the beginning of this thesis, to inform clinical decision-making around SF from WGS. This was achieved through designing a study, which uses genotype-driven recruitment (GDR), to clinically evaluate individuals who have pathogenic variants associated with ICCs. The specific objectives were to:

- Collect preliminary data on the number of eligible participants in a large genomic database (the Cambridge NIHR BioResource for Rare Disease) with pathogenic variants to explore the process of variant interpretation and assess GDR study feasibility; and
- Design a mixed methods clinical study to:

1. Investigate the extent to which pathogenic genomic variants are associated with clinical manifestation of ICC in apparently unaffected individuals; and
2. Explore the psychological and behavioural responses to learning genetic risk information when disclosed as an SF.

7.2 Methods

7.2.1 Study population

The Cambridge NIHR BioResource is a database of approximately 16,000 volunteers—both with and without health conditions—who are willing to be approached to participate in genetic research studies [296]. Participants in the CBR have provided a blood or saliva sample for genetic analysis, and have consented to the storage of clinical and genetic data. Participants have also consented to ‘Stage 2 studies,’ such as this, where they can be recalled by genotype or phenotype. The NIHR BioResource for Rare Disease (BRRD) operates in parallel with the wider CBR, and was originally established to identify genetic causes of a wide range of rare diseases in order to improve diagnostic rates and enable studies to develop treatment. The BRRD has recruited thousands of patients and relatives, and unlike the wider BioResource, these individuals have been subjected to WGS. To take advantage of this valuable cohort, with available WGS data, participants for this study were ascertained from the BRRD.

7.2.2 Dataset

Anonymised WGS data from BRRD participants was analysed to determine the number of individuals who have a putative pathogenic variant in one of the key genes (below) involved in the most common inherited cardiac conditions. For the preliminary analysis, data was taken from the 12.10.2016 release. This included WGS data from a total of 7877 individuals (and some relatives) from non-HCM cohorts in the BRRD. The included cohorts, including the number of individuals in each, are detailed in Appendix H. In this preliminary analysis no individuals were excluded: data on age, relationship status, gender or cohort of origin (besides HCM) was not considered.

7.2.3 Gene list

Genes included in the analysis were those with documented associations with disease, a reliable framework and evidence base for classifying pathogenicity (for primary findings), and where the relevant disorder is one for which a phenotype can be measured that is predictive of disease. Additionally, emphasis was placed on conditions and genes for which there was local expertise: KT, a specialist clinical scientist in cardiovascular genetics, guided the analysis. Thus, the list includes ICC-associated genes on the ACMG59 minimum gene list, but also additional genes for which there is strong evidence for disease causation [279] and local expertise to interpret variants. The genes that were subjected to analysis in the BRRD participants are listed in Table 7.1.

Table 7.1: Genes analysed for putative pathogenic variants in BRRD participants, listed by the associated inherited cardiac condition

Condition	Genes
Hypertrophic cardiomyopathy (HCM)	<i>MYH7</i> , *† <i>MYBPC3</i> , * <i>TNNT2</i> , *† <i>TNNI3</i> , *† <i>TPM1</i> , * <i>MYL2</i> , * <i>MYL3</i> , <i>ACTC1</i> , <i>LAMP2</i> , <i>GLA</i> *
Dilated cardiomyopathy (DCM)	<i>MYH7</i> , *† <i>TNNT2</i> , *† <i>TNNI3</i> , * <i>TPM1</i> , * <i>LMNA</i> , <i>TTN</i> , <i>DSP</i> , *† <i>VCL</i> , <i>DES</i> †
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	<i>DSC2</i> , * <i>DSG2</i> , * <i>DSP</i> , *† <i>PKP2</i> , * <i>DES</i> †
Long QT syndrome (LQTS)	<i>KCNQ1</i> , * <i>KCNH2</i> , * <i>SCN5A</i> *

* Genes also on the ACMG59 minimum gene list

† Genes implicated in multiple ICCs

7.2.4 Extracting variants

Chromosome coordinates for each of the genes in Table 7.1 were obtained from Ensembl [297] and a single file was created to include all genes to be targeted. Using this reference, KT extracted, annotated and filtered the variant data to output all very rare (ExAC MAF less than 1×10^{-4}) protein-coding variants from the relevant genes from BRRD data (further details in Appendix H). This list was further filtered to only include variants that have either been reported by the by two major diagnostic laboratories experienced in inherited cardiac conditions (OMGL: Oxford Medical Genetics Laboratory, Oxford, UK; and,

LMM: Partners Laboratory for Molecular Medicine, Boston, USA), or are loss of function variants (LOF) in genes where haploinsufficiency is known to be a mechanism of disease.

7.2.5 Variant interpretation

The resulting variants were subjected to the the new guidelines from the ACMG and the Association for Molecular Pathology (AMP) for interpreting sequence variants (heretofore, 'ACMG-AMP guidelines') [217]. In order to assess pathogenicity (as 'benign', 'likely benign', 'uncertain significance', 'likely pathogenic', or 'pathogenic') the guidelines employ a framework wherein different pieces of evidence are assigned different weight supporting either benign or pathogenic assertion. The various pieces of evidence supporting pathogenicity include, but are not limited to: supportive functional data, LOF variant where haploinsufficiency is known to be a mechanism of the disease, same amino acid change as well-established disease-causing variant, and absence in population database. Similarly, evidence supporting a benign assertion includes, but is not limited to: silent variant; no impact on splicing; functional studies show no effect; MAF is too high. KT and I applied the ACMG-AMP guidelines to five variants by consensus, taking care to work through each of the potential pieces of evidence. I then classified the remaining variants independently. Manual classification was managed using the ClinGen Pathogenicity Calculator [298], a configurable web-based system that allows the user to enter the relevant evidence according to the ACMG-AMP guidelines. Previous reports of variants were sourced from ClinVar [270], which aggregates genetic data, including documented instances of variant implication in disease, as well as the ARVC mutation database [299], a database specific to variants known to cause ARVC. Population data was obtained from the recently released Genome Aggregation Database (gnomAD) [3]. This significant update includes more than double the number of exomes from ExAC (123,136) as well as over 15,000 whole genome sequences.

In addition to my own manual classification, I input the variants into CardioClassifier [300], an automated web tool that applies the ACMG-AMP guidelines to cardiac sequence variants. The tool accesses various internal resources, including ExAC (not gnomAD), to determine pathogenicity. In order to use the tool, a single VCF file including all of

the filtered variants was uploaded to the CardioClassifier website. Considering my own manual interpretation of the variants, as well as the classifications from CardioClassifier, the OGML and LMM, a final pathogenicity classification for each was determined by consensus between KT and myself. 'Pathogenic' and 'likely pathogenic' variants will be used to recruit participants to the study.

7.3 Preliminary results

64 variants were extracted from the BRRD data and subjected to the ACMG-AMP guidelines. Of these, 39 variants in 57 individuals were considered to have sufficient evidence supporting pathogenicity to be considered in this study. Thus, 0.8% of those eligible (7,877) were deemed to have a potentially life-threatening ICC-associated variant selected according to robust criteria and hence worthy of further investigation. A summary of these variants is presented in Table 7.2

Table 7.2: Putative pathogenic ICC-associated variants (either LOF or previously reported as 'pathogenic' or 'likely pathogenic') to be returned to BRRD participants in the SCARFE study

Condition	Gene	Unique variants	Individuals
HCM	<i>MYBPC3</i>	7	11
	<i>MYH7</i>	1	1
	<i>MYL3</i>	1	2
	<i>GLA</i>	1	1
	<i>TNNI3</i>	2	4
DCM or ARVC	<i>DES</i>	4	4
ARVC	<i>PKP2</i>	8	17
	<i>DSC2</i>	5	5
	<i>DSG2</i>	5	6
LQTS	<i>SCN5A</i>	1	1
	<i>KCNH2</i>	1	1
	<i>KCNQ1</i>	3	4
TOTAL		39	57

7.3.1 Variant details

Details of the individual variants, together with the consensus classification, are presented in Table 7.3. Of note, the majority of the variants deemed 'likely pathogenic' or 'pathogenic' are LOF variants (29 of 39, 74%). In fact, *all* filtered LOF variants were

ultimately deemed worthy of return. Many missense variants—such as those in *KCNH2* and *MYH7*—that were classified by the OMGL or LMM as ‘likely pathogenic’ were classified as variants of unknown significant (VUS) in light of the available evidence using the ACMG-AMP guidelines. In contrast to the LOF variants, of the 33 missense variants subjected to classification, only 10 were deemed worthy of return (30%).

Table 7.3: Details of variants in ICC-associated genes in BRRD participants (after filtering), and the pathogenicity classification for each from the OMGL, LLM, CardioClassifier, manual classification using the ACMG-AMP guidelines, and the consensus classification

Gene	Nucleic acid change	Amino acid change	BRRD Freq.	LOF	OMGL	LLM	CardioClassifier	Manual Classification	Consensus Classification
DES	c.162C>G	p.Tyr54*	1	Yes	Not reported	Not reported	Not included	Path.	PATHOGENIC
	c.226delA	p.Thr76fs	1	Yes	Not reported	Not reported	Not included	Likely Path.	LIKELY PATHOGENIC
	c.948_952delGGCCA	p.Lys318fs	1	Yes	Not reported	Not reported	Not included	Likely Path.	LIKELY PATHOGENIC
	c.1371+1G>A		1	Yes	Not reported	Not reported	Not included	Likely Path.	LIKELY PATHOGENIC
DSC2	c.1123C>T	p.Arg375*	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.959delA	p.Gln320fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.939_942delAGAG	p.Arg313fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.379G>T	p.Glu127*	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2533G>T	p.Glu845*	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
DSG2	c.1038_1040delGAA	p.Lys346del	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.1880-2A>G		1	Yes	Path.	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2434G>A	p.Gly812Ser	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.145C>T	p.Arg49Cys	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.355C>T	p.Arg119*	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.375dupT	p.Leu126fs	2	Yes	Not reported	Not reported	Path.	Path.	PATHOGENIC
	c.603_604delAT	p.Leu203fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2894_2897delAGAG	p.Glu965fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
GLA	c.644A>G	p.Asn215Ser	1	No	Path.	Path.	Likely Path.	Path.	PATHOGENIC
KCNH2	c.1744C>T	p.Arg582Cys	1	No	Path.	Not reported	VUS	Likely Path.	LIKELY PATHOGENIC
	c.2717C>T	p.Ser906Leu	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.2734C>T	p.Arg912Trp	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.865G>A	p.Glu289Lys	2	No	Likely Path.	Not reported	VUS	VUS	VUS
KCNQ1	c.1066C>T	p.Gln356*	2	Yes	Path.	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.1780C>T	p.Arg594*	1	Yes	Path.	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.1781G>A	p.Arg594Gln	1	No	Likely Path.	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.877C>T	p.Arg293Cys	2	No	Likely Path.	Not reported	VUS	VUS	VUS
LMNA	c.949G>A	p.Glu317Lys	1	No	Not reported	Likely Path.	VUS	VUS	VUS
	c.976T>A	p.Ser326Thr	2	No	Not reported	Likely Path.	VUS	VUS	VUS
MYBPC3	c.1504C>T	p.Arg502Trp	3	No	Path.	Path.	Path.	Path.	PATHOGENIC
	c.1624G>C	p.Glu542Gln	1	No	Path.	Likely Path.	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2197C>T	p.Arg733Cys	2	No	Likely Path.	VUS	VUS	VUS	VUS
	c.2249C>T	p.Thr750Met	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.2373dupG	p.Trp792fs	1	Yes	Path.	Path.	Path.	Path.	PATHOGENIC
	c.2909G>A	p.Arg970Gln	1	No	Likely Path.	VUS	VUS	VUS	VUS
	c.3049G>A	p.Glu1017Lys	4	No	Likely Path.	VUS	VUS	VUS	VUS
	c.3192dupC	p.Lys1065fs	1	Yes	Not reported	Not reported	Likely Path.	Path.	PATHOGENIC
	c.772G>A	p.Glu258Lys	2	No	Path.	Path.	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.787G>A	p.Gly263Arg	2	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.3592dupG	p.Ala1198fs	2	Yes	Not reported	Not reported	Path.	Path.	PATHOGENIC
	c.994G>T	p.Glu332*	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC

Gene	Nucleic acid change	Amino acid change	BRRD Freq.	LOF	OMGL	LMM	CardioClassifier	Manual Classification	Consensus Classification
MYH7	c.2359C>T	p.Arg787Cys	2	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.2606G>A	p.Arg869His	3	No	Likely Path.	VUS	VUS	Likely Path.	VUS
	c.4066G>A	p.Glu1356Lys	1	No	Likely Path.	Likely Path.	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.5326A>G	p.Ser1776Gly	1	No	Likely Path.	VUS	VUS	VUS	VUS
	c.976G>C	p.Ala326Pro	1	No	Likely Path.	VUS	VUS	VUS	VUS
	c.2081G>A	p.Arg694His	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.1142C>A	p.Ala381Asp	1	No	Likely Path.	Not reported	VUS	VUS	VUS
MYL3	c.170C>G	p.Ala57Gly	2	No	Not reported	Likely Path.	VUS	Likely Path.	LIKELY PATHOGENIC
	c.281G>A	p.Arg94His	1	No	Not reported	Likely Path.	VUS	VUS	VUS
PKP2	c.1237C>T	p.Arg413*	1	Yes	Path.	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.1799delA	p.Asp600fs	3	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2146-1G>C		6	Yes	Path.	Not reported	Path.	Path.	PATHOGENIC
	c.2489+1G>A		3	Yes	Not reported	Not reported	Path.	Path.	PATHOGENIC
	c.2478delT	p.Ser826fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2378_2379dupCC	p.Ser794fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.2194C>T	p.Gln732*	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
	c.1035-1G>C		1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
SCN5A	c.1237G>A	p.Ala413Thr	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.3695G>A	p.Arg1232Gln	2	No	Likely Path.	Not reported	Likely Path.	VUS	VUS
	c.994G>A	p.Ala332Thr	1	No	Likely Path.	Not reported	VUS	VUS	VUS
	c.6017dupC	p.Ser2007fs	1	Yes	Not reported	Not reported	Likely Path.	Likely Path.	LIKELY PATHOGENIC
TNNI3	c.433C>T	p.Arg145Trp	2	No	Path.	Path.	Path.	Path.	PATHOGENIC
	c.484C>T	p.Arg162Trp	2	No	Path.	VUS	Likely Path.	Likely Path.	LIKELY PATHOGENIC

7.4 Future work

Building on the above analysis, a larger study—Secondary Cardiac Findings Evaluation (SCARFE)—will be undertaken to collect data on the clinical utility of these variants when returned as SF, the need for which was highlighted throughout the previous chapters. This study will include phenotypic assessment to explore the predictive value of such variants, as well as the impact—both behavioural and psychological—on recipients. The plans provided here are not finalised, but represent the planning in which I was involved. This section is intended to illustrate the work that would ideally follow from the data collected above, but may not accurately reflect the final design of the SCARFE study.

7.4.1 Study participants

BRRD participants eligible for inclusion in this study have consented to be approached for further research studies, and do not have a known ICC. Eligible participants will have a ‘pathogenic’ or ‘likely pathogenic’ variant in an ICC-associated gene as determined in the previous section, or are a matched control for such individuals. Males and females,

between the ages of 18 and 70, are considered eligible. Participants will be excluded if they are known to have phenotypes that could confound interpretation of cardiac imaging. Participants deemed by their clinical care team to be inappropriate for inclusion in such a research study will also be excluded. Finally, participants indicating after pre-invitation opt out letter (detailed below) that they do not wish to be approached will be excluded.

7.4.2 Recruitment and invitations

The study will employ a genotype-driven recruitment (GDR) strategy, wherein participants are recruited on the basis of previously collected genetic information [301]. Such a recruitment strategy is growing in popularity due to its elimination of the expensive and time-consuming step of screening large numbers of individuals to find those who have the variant(s) of interest [302]. As a result, proponents of GDR have affirmed the great potential of such studies to increase the utility of genomic data and accelerate the translational process towards impacting healthcare [301, 303].

Guided by ethical GDR recommendations [295] SCARFE will employ a two-step recruitment process. First, the investigator team will provide pseudonyms of selected participants based on genotype to the BRRD team, who will check exclusion criteria and request confirmation from the BRRD recruiting clinician that they may be approached. BRRD participants whose sequence data is harbouring one of the above variants will be matched by age, gender and BRRD disease cohort with controls by a central coordination team at the Cambridge BioResource. BRRD participants (both with variants and matched controls) who meet all of the eligibility requirements will then be sent a letter asking if they wish to opt out of research unrelated to the disease that led them to enrol in the BRRD (Appendix H). The letter states: 'It is possible that some of these studies might give you information about your current or future health, or genetic information which can be passed from parent to child. This information may not be related to your [primary condition]' and makes no mention of the SCARFE study or ICCs. Participants are asked to return the enclosed reply slip within four weeks if they wish to opt out of such studies.

Eligible BRRD participants who do not opt out after receiving the above letter will be sent an invitation to participate in the SCARFE study as well as a participant information

sheet (Appendix H). The letter invites them to attend the Clinical Cardiac Research Facility at the University of Oxford for counselling and clinical assessment (Appendix H). Eligible participants will be asked to return a reply slip indicating whether they wish to be sent an appointment, decline participation or request further discussion. Letters will be dispatched early in the week and, where necessary, contact will be escalated to clinically qualified members of the investigator team. Potential participants who do not respond within four weeks will be sent a reminder letter or contacted by telephone.

The participant materials outlined above were the result of discussion with researchers at the university with experience using GDR (albeit usually in the context of common variants), as well as discussion with a Genomic Medicine Patient and Public Involvement (PPI) group. In general, members of the PPI group were positive about the study and articulated that, while initially surprising, that they would be grateful to learn this information. One member of the group, however, did articulate concerns about learning such information. This member acknowledged the importance of an added opt-out step, as well as having an informative website to access on receipt of the invitation. This member also felt that it was important to have prompt access to a healthcare professional. These discussions greatly influenced the design of the final recruitment pipeline: for example, a website has been developed and contact information for a designated counsellor has been provided on all patient materials—specialist genetic counselling and clinical support will be available to participants before, during and after participation in the study.

7.4.3 Informed consent

Informed consent will be obtained at the study visit during an extensive counselling session with the investigators (Appendix H). These investigators, which includes a genetic counsellor and cardiologists, have significant experience seeing patients in the weekly clinic at the ICC Service. This counselling session will cover information about the specific ICC implicated by the genetic variant detected, clinical and psychosocial implications of diagnosis, inheritance and implications for relatives.

During this session it will be made clear that participants are free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. A copy of the signed consent form will be given to the participant. The original signed form will be retained at the study site.

7.4.4 Phenotypic investigation

Following the counselling session, after the provision of informed consent and the collection of demographic information and a family history, cardiac investigations will be performed targeted to the specific disease associated with the detected variant in that individual, or their match if they are a control (Figure 7.1). Clinical assessment will be blind: whether an individual has an ICC variant or is a matched control will be provided in writing by the BRRD team to the clinical study team, in a sealed envelope, to be opened after clinical assessment at the study visit. Regardless of condition, participants will undergo an ECG. For individuals with variants related to HCM or DCM imaging will be by echocardiogram. For individuals with ARVC-associated variants imaging will be by MRI. In the case of individuals with suspected LQTS, all participants will undergo 24-hour ECG and an exercise tolerance test (ETT). Matched controls will undergo the same testing pipeline as their variant-positive counterpart.

The genotype of the participants will be unmasked (with consent) following the above cardiac investigations during the study visit, by opening sealed envelopes containing a research results report. Where results cannot be offered on the same day (following 24-hour tape), participants will be informed of initial findings at the study visit, and of later results in a follow up phone call. If clinical assessment results in the detection of clinical cardiac abnormalities, further investigation may be indicated, including clinical confirmation of the test result in an accredited clinical lab (OMGL). Study visit letters will be copied to participants' general practitioners and follow-up will be conducted through the usual NHS clinical channels, following referral.

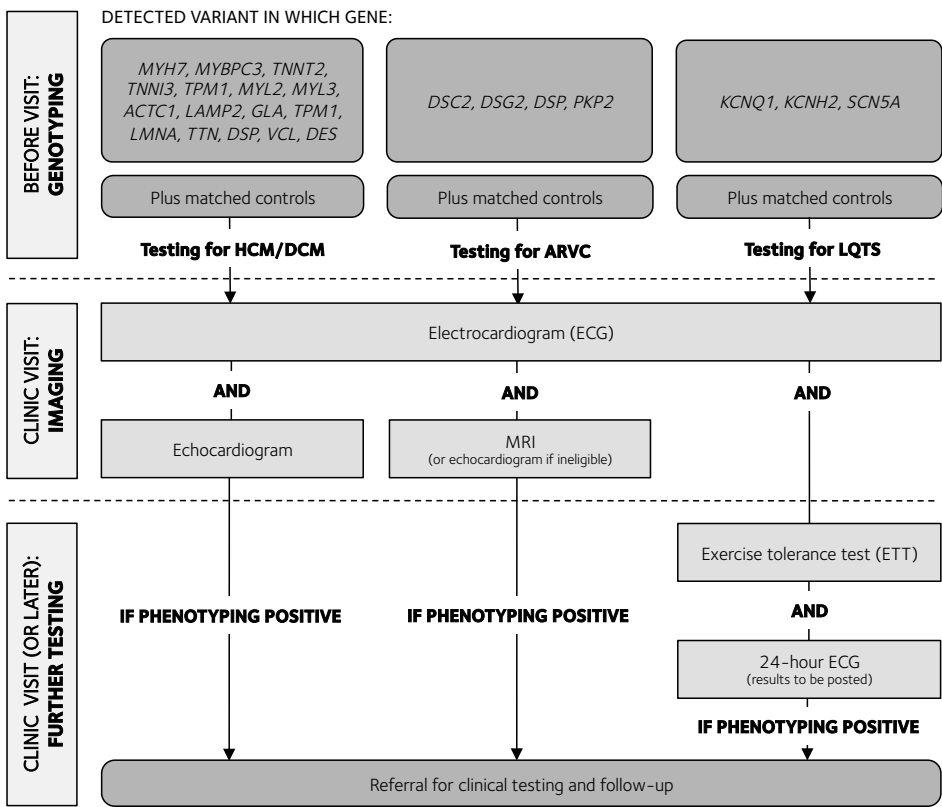


Figure 7.1: Pipeline for clinical investigations in SCARFE based on the variant identified

7.4.5 Psychosocial investigation

In addition to providing valuable clinical information, returning these SF affords an invaluable opportunity to explore the impact their disclosure has on recipients. Thus a variety of quantitative tools will be employed to obtain information at different time points during the period of the study. These will include standard measures for anxiety [304], as well as questionnaires designed to collect demographic data, explore risk perception, assess motivation for participation, satisfaction, and impact of participation—both behavioural and psychological.

To complement the quantitative data, qualitative data will also be collected—as demonstrated in the systematic review in *Chapter 2*, qualitative methodologies can elicit nuanced responses that are not captured by quantitative methods. Participants will be invited to take part in semi-structured interviews exploring acceptability of the GDR strategy, their experiences of receiving the SF, details and motivations for behaviours

that resulted from disclosure. Interviews methods will closely follow those outlined in *Section 4.2.5*.

7.5 Discussion

If secondary findings are to be returned in clinical practice—as appears to be the trend illustrated across the earlier chapters in this thesis—it is imperative that studies such as this one are conducted. In a recent paper, Evans, Powell and Berg [305] caution against genome-scale sequencing of healthy individuals. Consistent with concerns expressed by GM-MDT members in *Chapter 4*, the authors argue that the interpretation of genomic findings ‘fundamentally differs’ between individuals with disease and those in the wider population, with estimates skewed by studying only individuals who present clinically with the associated condition. Although applied to the more faraway possibility of population-wide genome sequencing, this argument equally applies to that of secondary findings—despite enrolling in WGS for a diagnostic purpose, all recipients are effectively ‘healthy’ with respect to secondary conditions, to the best of our knowledge. The authors argue that, ‘a proper evidence base must be established before clinical implementation occurs, determining the true penetrance of genomic variants in diverse, unselected populations and ultimately demonstrating improved outcomes to those screened’. The need for such evidence was made clear in the previous chapter. This evidence base, they propose, should be generated by first investigating well-understood genes known to be associated with preventable disease. The study outlined in this chapter does exactly this. By using a GDR strategy, the issue of small numbers can be overcome to yield useful data to inform interpretation of variants in the wider population. I have demonstrated that it is possible, using a recontactable database with sequenced participants, to detect individuals with pathogenic variants in ICC-associated genes worthy of investigation. It will be vital for these individuals, and others in similar studies, to be assessed to inform penetrance estimates and demonstrate clinical utility, as stressed above.

Variant Interpretation

After detailing concerns from healthcare providers about the challenge of interpreting SF from WGS, the preliminary work in this chapter affords some insight into that process. In order to recruit participants for the clinical study outlined, BRRD participants with ICC-associated variants warranting follow-up were identified. Very stringent filters were employed, only extracting variants with low MAF in population database that had been reported either by a reputable diagnostic laboratory (OGML or LMM), or are LOF variants in genes where haploinsufficiency was a known mechanism of disease. Despite these strict measures, classification of the variants was not straightforward. First, previous classifications were sometimes out of date, published before access to large datasets like ExAC were available. Even where up-to-date, previous classifications were often inconsistent. This is a known issue, with studies highlighting the high variability of classification across diagnostic laboratories [89, 306].

It is for this very reason that the ACMG and the AMP issued guidelines, hoping to standardise the interpretation of sequence variants [217]. The CardioClassifier classifications and my own manual classifications, which both employed the ACMG-AMP framework, were more consistent for this reason. However, although improved since the introduction of these guidelines, interpretation across laboratories is still somewhat inconsistent [112]. During the process of my own manual classification of the extracted variants it became clear that there remains a degree of subjectivity. This contributed to some of the differences between my classifications and those by CardioClassifier. As a result, some of the evidence pieces were interpreted differently, resulting in systematic differences across entire genes—for example, CardioClassifier applied the PP2 criteria¹ to all missense variants in *MYBPC3*, where I did not. It is possible that some form of automation could improve this process, by minimising subjectivity. In a way, this is what CardioClassifier attempts to accomplish. However, automation has its own problems. CardioClassifier was valuable in its provision of pieces of cardiac and gene-specific evidence, such as mutational hotspots and variant locations within important functional domains. The tool,

¹The code PP2 is 'Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease'. Based on consultations with KT and published evidence, we did not believe this to be the case for *MYBPC3*.

however, was unable to verify all of the pieces of evidence, as some required manual curation. Furthermore, automation does not allow classification to draw on disease expertise and experience. In several instances, my manual classification of variants were higher ('pathogenic' as opposed to 'likely pathogenic') on the basis of adding previous reports, or drawing on local experience of a variant in a patient or the expertise afforded by the OMGL cardiac team (KT). Thus, the flexibility afforded by manual classification is also important. As molecular laboratories move to adopt these guidelines, as is currently underway in the UK, it will be important for discussions across laboratories to occur and training to be offered to maximise the consistency with which the guidelines are applied. The authors of the guidelines have issued clarifications to support this process [112].

In the case of the variants analysed in this chapter, the issue of interpretation is further complicated by their secondary nature. In fact, in the ACMG-AMP guidelines, the authors directly caution against their use in this context.² When applying the guidelines to the extracted variants there were pieces of evidence that could never be used due to their being SF. For example, as the findings related to conditions different from those for which the participants have been phenotyped, criterion PP4³ could never be applied. Similarly, criteria relating to the inheritance of the variants could never be used. In this way, the application of the guidelines was particularly challenging. With fewer criteria applicable to SF, this also meant that the threshold for pathogenicity was significantly higher—classifications were more conservative ('likely pathogenic' instead of 'pathogenic') than if phenotypic or inheritance evidence was available. This was particularly noticeable for missense variants, which ordinarily comprise a significant proportion of ICC-causing variants. Many such variants did not reach the threshold for disclosure, skewing the results towards LOF variants (in light of the weight such evidence carries in the ACMG-AMP guidelines). In the absence of accurate estimates of the penetrance of these variants in the wider population and data on their clinical

²In Richards et al. [217] the authors state: 'Although these approaches can be used for evaluating variants found in healthy individuals or secondary to the indication for testing, further caution must be used, as noted in several parts of the guideline, given the low prior likelihood that most variants unrelated to the indication are pathogenic'.

³The code PP4 is 'Patient's phenotype or family history highly specific for a disease with a single genetic etiology'.

utility, perhaps this higher threshold is for the best. Considering the potential harm to participants of over-interpretation, and in light of limited resources, starting with the variants that we think are most likely to cause disease seems a sensible strategy.

Ethical considerations of genotype-driven recruitment

Although still to be completed, the design of the overall clinical study raises important ethical issues relevant to the overall thesis and warrants discussions. Where evidence is desperately needed to support the management of SF, genotype-driven recruitment (GDR) affords a much-needed creative solution to overcome the issue of small numbers preventing the possibility of a randomised control trial with respect to SF. While advantageous, however, this strategy presents a set of ethical challenges that need to be carefully addressed [295, 307]. Of particular relevance to this study are the potential harms of returning such information, especially if false-positive [305, 308], and the right ‘not to know’ [309, 310].

First and foremost, consistent with recommendations from Beskow et al. [295], eligible participants have been informed about the potential for recontact for future studies, and have consented to such recontact. Additionally, initial contact will be made via the BRRD, as per their protocol for initial contact, but also consistent with recommendations that the contacting entity be familiar to the participants. In all cases, as described above, the classification was stringent and conservative: we do currently believe these variants, based on limited knowledge in an *affected population*, have a very high probability of being causative for the associated disease. Thus, returning such variants is in line with current practice. Despite this, Beskow et al. also argue that the same thresholds employed in the usual return of genetic results should not even need to apply in GDR: by their very nature GDR studies aim to determine the clinical utility of genetic results, and thus this cannot be regularly met as a standard [295, 301]. To minimise the potential harms of a false-positive result, phenotyping will be carried out by a team highly experienced in ICCs. To minimise the potential anxiety of receiving such results care has been taken in the design of the participant information materials, and a genetic counsellor experienced in ICCs will be available for immediate

contact upon receipt of invitation and throughout the study period. In order to respect participants' 'right not to know' a two-step process will be employed—participants have the opportunity to opt out of receiving additional genetic information without knowing anything about the subsequent study before being invited to participate. This is in line with authors who argue that the 'right not to know' must be activated by an explicit choice on the part of the participant [309, 310]. An initial opt-out approach, rather than opt-in, is preferred (and is consistent with common GDR practice) in order to maximise the number of variant carriers that can be contacted and, thus, produce higher levels of enrolment. If they have not opted out, participants will then learn about the study, at which point they will have to opt in. Thus, the design maximises the potential that participants can benefit from pre-symptomatic detection of a potentially life-threatening condition, while promoting the 'right not to know'.

7.5.1 Strengths and limitations

The study described is valuable in its provision of prospective targeted phenotyping of individuals with SF from WGS, conducted in the manner analogous to what would follow the disclosure of an SF to a patient in clinical practice. Unlike published data from EHRs, this will allow for careful expert phenotyping targeted to the secondary condition, with the potential to reveal milder subclinical phenotypes to inform the phenotypic spectrum of these variants. This will also better mirror disclosure of SF in clinical practice, and ultimately help to inform how this disclosure will take place. Additionally, this will afford the study of the psychological and behavioural impact of returning SF from WGS, a subject about which much is hypothesised [184], but not yet substantiated. The study takes advantage of institutional experience and expertise in genomic medicine but also ICCs—rather than attempting to explore a wide range of SF, such as those on the ACMG59, the study focuses on genes for which there is unique local expertise and an expectation of an informative baseline phenotype.

I acknowledge that, despite a GDR strategy affording a higher number of participants compared to other strategies, 57 individuals with ICC-variants is still not a very large number. However, this will act as a feasibility study—depending on the clinical outcomes,

future directions will be determined. At present, no such evidence exists, so even a small amount will be valuable for guiding future research and policy development. If many of the recruited participants have the relevant clinical features, this will warrant statistically robust exploration in a larger dataset. Such work may be afforded by data from the 100,000 Genomes Project. Additionally, individuals from the BRRD with VUS in these genes may be studied. If no patients have the relevant clinical phenotype, this warrants a re-evaluation of our policies around such findings. In terms of the planned psychosocial research, 57 is a reasonable number (particularly for interviews).

While small, 57 individuals are not at all inconsequential. At 0.8% of those eligible, this still has serious implications for larger studies. With the 100,000 Genomes Project recruiting 75,000 individuals, over 600 of them could be expected to have such variants. It is worth briefly noting the difference between this figure and those discussed in *Chapter 2*: in the meta-analysis, 3.66% of individuals across the studies had pathogenic variants in ACMG56 genes that were considered reportable. The smaller number in this chapter is likely due to the stringency applied in the filtering and the conservative classification, as well as the focus on ICC-associated variants, which make up only a subset of the ACMG56 minimum gene list. Thus, even at our most conservative, disclosing SF has the potential to impact hundreds of participants, and thereafter their families.

Finally, the content of this chapter is limited to the study design and the interpretation of the filtered variants. It will be critical for the study to be completed, in this form or another, to gather the data on penetrance, phenotypic spectrum, and the psychosocial impact of SF that is so desperately needed.

7.5.2 Implications of findings

This study has implications for research and genetics practice:

- Even when classifying variants very conservatively, participants with ICC-associated variants can be detected in unselected populations.
- Using genotype-driven recruitment, databases where participants have already received WGS and have consented to be re-contacted for future research can be

used to collect the data needed to inform the management and interpretation of SF in WGS.

- Interpretation of these variants, however, is challenging—training and further discussion is needed to ensure variants are interpreted accurately and guidelines are applied consistently.
- The ACMG-AMP guidelines for sequence variant interpretation are not intended for SF. Thus, guidelines covering the unique challenges of interpreting SF should be considered if they are to be returned systematically.

7.6 Conclusions and chapter summary

In this chapter I outlined a study designed to explore the clinical utility of ICC-associated secondary findings in WGS. To our knowledge, no such study—which involves prospective targeted phenotyping—exists, despite many authors calling for the collection of such data. When applying stringent filters and conservative classification, 57 individuals (in a cohort of nearly 8000) were determined to have variants in genes associated with inherited cardiac conditions that warrant clinical review. Using a genotype-driven recruitment strategy, clinical assessment of these individuals will contribute to a much-needed evidence base on the penetrance and phenotypic variation of pathogenic variants in unselected populations. This will also allow for the exploration of the psychosocial impact of disclosure. Importantly, this chapter highlighted the challenge of variant interpretation. Echoing the concerns of HCPs in *Chapter 4*, and the clinical scientist in the case study in *Chapter 6*, interpreting variants in the absence of a phenotype and family history proved challenging. The development of an evidence base will help to overcome these challenges, but so too will guidelines specific to the interpretation of variants unrelated to the indication for sequencing. If genomic sequencing of healthy individuals were to ever become a reality, where all variants are akin to SF in their lack of a prior phenotype or family history, such evidence and guidance would be critical. In the more likely scenario where sequencing resources remain largely focused on individuals with a diagnostic need, these data will still be valuable if maximum benefit is to be derived from WGS moving

forward. Building on this, the movement towards mainstreamed clinical genomics, and the specific challenges posed by SF, will be the focus of the next and final chapter.

DISCUSSION AND CONCLUSIONS

*'For the things we have to learn before we can do them, we
learn by doing them.'*

— Aristotle [311]

8

Moving to mainstream: Secondary findings in the era of clinical whole-genome sequencing

During my time in Oxford, I have witnessed a dramatic shift in the field of genomics: from targeted gene panel testing, we are transitioning to an era of mainstream clinical whole-genome sequencing for the diagnosis of rare disease. This period of transformation has been made most clear through my experience with the 100,000 Genomes Project, which is aiming to move WGS into clinical practice across the National Health Service, and into the hands of specialties beyond clinical genetics. This period of transformation, however, has been accompanied by senses of disorientation and uncertainty. In my regular attendance to the Oxford Genomic Medicine multidisciplinary team meetings, I have seen genetic diagnoses found for previously unsolvable cases, but I have also listened to healthcare professionals endeavour to make decisions in the absence of a sufficient evidence base. Through attending meetings of the Genethics Forum¹ I have heard about how WGS is transforming daily genetics practice, but also challenging traditional models for information sharing and re-contact. I have watched as the 100,000 Genomes Project recruited hundreds of patients and family members in Oxford, and—through observing

¹The Genethics Forum is meeting for healthcare professionals from around the UK to explore difficult ethical issues encountered in genetic medicine [312].

consent sessions for enrolment in the programme—have watched as genetic counsellors grapple with explaining the diversity and uncertainty of possible results. Finally, this transformational but uncertain period is clearly illustrated in the case study that recurred throughout this thesis: David, after enrolling in WGS to find a diagnosis for his son's condition, had a secondary finding in *KCNQ1* and was subsequently found to be at risk for an inherited cardiac condition. During the process of managing David's SF, I listened to how clinical scientists struggled to interpret the variant in the absence of precedent and relevant phenotypic information or family history, and watched his care team contend with disclosing and interpreting the result clinically. Despite these difficulties, David did receive a piece of potentially life-saving information that he would not have received without enrolling in WGS. In all of these examples, although transformational, the promise of genomics is closely followed by a shadow of uncertainty.

Derived from the Latin word, *limen*, for 'a threshold', the concept of 'liminality' denotes a period of *in-between-ness*, and accurately captures the current transformational-yet-uncertain state of genomic practice. Ethnographer and folklorist Arnold van Gennep, in *Rites de Passage*, wrote of ritualistic societies and was the first to describe the 'liminal phase' in rituals [313]. This stage is detached from the laws and customs of the pre-ritual state, and is predominated by ambiguity and uncertainty before reaching a post-transition state. Cultural anthropologist Victor Turner, in *The Ritual Process*, followed van Gennep, famously describing liminal entities as, 'neither here nor there; they are betwixt and between the positions assigned and arrayed by law, custom, convention, and ceremony' [314]. Such threshold phases, which can be found outside the traditional rituals in which they were first described [315], are characterised by uncertainty, but also possibility and transformation [316]. As clearly depicted above, the field of genomics is presently characterised by these same qualities—we are currently in a liminal phase as genomic medicine is translated into mainstream clinical practice.

In this liminal period of genomic transformation, I have illustrated throughout this thesis that secondary findings—such as the one returned to David—are an important consideration. These variants afford great possibility: a shift from a 'clinical diagnosis-to-variant' paradigm to one that is 'variant-to-clinical diagnosis'. It is conceivable that

population-level *preventative genomic medicine* could be a (distant) reality [317, 318]. Together with the possibility and transformation afforded by SF, as with the wider field, liminality manifests as a state of disorientation with respect to SF—one devoid of clear guidance, and in need of resolution. This proves to be problematic and recurs throughout the chapters in this thesis: HCPs struggled to make decisions in the absence of guidance, WGS recipients expressed unrealistic expectations about SF despite the lack of infrastructure, and variants were shown to be difficult to interpret with currently available evidence and guidelines. Importantly, however, such periods of liminality also serve as ‘a stage of *reflection*’ [314]. In resolving this uncertainty and disorientation, there is opportunity to establish new norms and practices—informed by the past, but novel and innovative.

This thesis facilitates such reflection. Using a mixed methods approach, to reflect broad aims, I sought to explore: (i) whether or not SF should be sought and returned in diagnostic WGS, and, if so, which ones; (ii) the extent to which there is sufficient evidence on which to base decision-making around SF; and, (iii) what barriers SF pose to the translation of WGS into clinical practice. Reviewing methodologies were employed to reflect on the past and current state of the field, as well as guide empirical work. This empirical work took qualitative and quantitative forms, to explore the views of stakeholders as well as the utility and impact of SF in practice. Finally, this chapter brings together the work of the previous chapters in light of these questions, and points towards how this period of disorientation might be resolved. Following a brief summary of the specific findings of this thesis, which additionally illustrate this liminal period of transformation and uncertainty, I will discuss the mainstreaming of genomic medicine, with a focus on the barriers to its implementation posed by SF, as well as briefly explore ways in which these challenges might be overcome.

8.1 Summary of findings

Part I: literature reviews

In *Part I* of the thesis I sought to illustrate the state of the field around SF in WGS to situate the work that followed and assess the existing evidence base. Despite agreement on

the importance of participant autonomy, the literature reviews showed that policies and views regarding SF still differ greatly. Some programmes were offering a wide range of SF, while others minimised their generation. Stakeholder views towards SF were similarly varied: views were shown to sit along a spectrum, variably informed by the stakeholder's sense of rights and responsibility, and appreciation of the complexity of offering WGS. In general, stakeholders agreed that SF that point to life-threatening diseases for which treatment or surveillance is available were considered actionable, and thus were the most amenable to return—although some supported expanded definitions of actionability (reproductive decision-making, lifestyle planning). Nonetheless, it seemed that optional screening for SF in WGS that point to treatable and preventable conditions was, for the most part, considered acceptable.

Importantly, *Part I* of this thesis highlighted significant gaps in the literature: chiefly that of its lack of diversity, and its being hypothetical in its discussion of SF. Many stakeholders had not made decisions about SF themselves, and none had actually received SF. Policies and writings on SF were largely anticipatory, and there was little data on the return of actual SF, both in terms of clinical utility and impact on participants. Thus, evidence on which to base decisions around the management of SF—both in their interpretation and their effective disclosure—is essentially non-existent. In this way, *Part I* highlighted a significant need, particularly if such findings are to be sought and returned systematically, as would seem to be the trend.

Part II: interview studies

In *Part II*, taking advantage of local experience in clinical WGS, I analysed interviews with healthcare professionals and WGS participants—contributing views from a unique context to the wider evidence base, as well as less hypothetical views from stakeholders embedded in large sequencing programmes who have made actual decisions around SF.

For the most part, WGS providers and WGS recipients in Oxford articulated complementary views towards SF. Where SF were to be sought and returned, providers and recipients largely felt they should be limited to findings about which there is the greatest confidence in their potential to cause disease, and should be 'actionable'. For both

providers and recipients, and inconsistent with current guidelines (but offered by the 100,000 Genomes Project), actionability invariably included carrier status information, with many interviewees challenging the policies of the current programme.

Although views were diverse, many WGS recipients in *Chapter 5*—seemingly informed by their experience with rare disease and exposure to the healthcare system—expressed comfort not knowing SF. In a search for control, many WGS recipients often preferred to focus limited resources on finding the cause of their primary condition. Some WGS recipients were comfortable allowing providers to make decisions on their behalf. Consistent with a growing body of evidence in other healthcare contexts [150, 158, 172, 174], this highlights an important policy consideration: views of individuals enrolled in WGS to find the cause of a primary condition towards SF are different from views articulated by the wider population. The sense of trust expressed by these recipients seemed to be well-founded, as the healthcare professionals interviewed in *Chapter 4* demonstrated tortured deliberation around SF policies and decisions to return individual results, arguing for a *cautious* approach, so as to minimise harm to potential recipients, that is responsive to accumulating evidence. Providers were particularly concerned about interpreting individual variants in the absence of a phenotype or family history. Echoing the findings of *Part I*, providers highlighted the need for an evidence base to inform the interpretation of SF in WGS: interpreting SF is incongruous with current data, which is ascertained via a proband with the associated disease.

Part III: clinical studies

In *Part III* I took steps towards building this much-needed evidence base. First, I described the process of returning a single secondary finding; second, I described a study that aims to replicate this on a more systematic level. In both pieces of work, the challenges of disclosing SF in practice were made apparent. In the analysis of David's secondary *KCNQ1* variant, in *Chapter 6*, the clinical scientist described a 'steep learning curve' and the difficulty of interpreting the variant in the absence of a phenotype or family history. During the clinical process that followed, there was uncertainty in the absence of precedent and exemplars, and the clinical interpretation proved challenging. When

done on a systematic level, as illustrated in the preliminary analysis of variants in *Chapter 7*, these problems remain; current guidelines and evidence are for primary findings, not secondary ones.

Second, if clinical utility depends on positively changing behaviour to improve health outcomes, the case study highlights an unexpected potential issue around the utility of disclosing SF in the first place. David only reached a selective acceptance of his diagnosis, and thus his risk of sudden cardiac death. This resulted in a similarly selective compliance to clinical recommendations, accompanied by high levels of distress and fear. As outlined at the outset of this thesis, and reiterated by stakeholders in the chapters that followed, support for screening for and returning SF to WGS participants hinges on the *benefits* (ability to provide potentially life-altering information) outweighing the *harms* (potential to cause anxiety, discrimination). Thus, before SF are returned to thousands of individuals, as could be the case if WGS becomes commonplace in clinical practice, policy-makers must ensure there is any benefit to be derived at all. Together with improved understanding of penetrance and expressivity, data from the systematic return of SF are needed to explore the impact of disclosure on participants. As demonstrated in the previous chapter, genotype-driven recruitment from re-contactable sequenced databases appears to be a feasible strategy to collect this data.

8.2 Synthesis

In light of the aims outlined at the outset of this thesis (*Section 1.1*), here I aim to synthesise the findings of the diverse included studies. This leads into a wider discussion of the direction of the field with respect to secondary findings, highlighting some the challenges that will need to be overcome and pointing to ways forward.

8.2.1 Screening for SF in the era of clinical WGS

With respect to the first aim of this thesis, it appears that optional and cautious screening and return of actionable SF is considered beneficial by many stakeholders and will therefore be an integral part of this genomic future. This shift can be clearly seen in our local WGS programme: although the generation of non-primary results was initially

avoided, the policy was changed to allow for the active screening of a list of ‘actionable’ genes, mirroring changing views in the field at large. First, it is important that this screening is *optional*—while largely supportive of screening for SF, some stakeholders (across groups and contexts) expressed less desire for SF. This was particularly true of many providers and recipients with experience with genetic diagnoses—the same individuals who will be the earliest adopters of WGS and those most immediately affected by policies around SF. Providing the ability to opt-out of SF maximises autonomy, allowing for these diverse views to be respected. Screening, however, should also be optional on the part of WGS providers. In light of limited evidence and limited resources, programmes should still have the ability to limit analysis until such a case is made that these variants improve outcomes. Recently published results from the MedSeq project, a randomised control trial assessing the impact of WGS in primary care, showed unclear value [319].

In line with the second aim of this thesis, it has been made clear throughout this project that there is currently *insufficient empirical evidence* on which to base decisions around the management of secondary findings in WGS. While the literature on broad stakeholder views towards SF is large, evidence is otherwise lacking. This includes variant-specific evidence, as well as evidence on the impact of disclosure on clinical outcomes and on recipients themselves. This was made especially clear through the lack of evidence found in the literature, the problems described by WGS providers in *Chapter 4*, as well as my challenges in analysing secondary variants in the absence of such evidence. For this reason it is essential that the screening and return of SF in WGS is also *cautious*, ensuring that variants are returned with care and the utmost confidence, until such an evidence base is amassed.

8.2.2 Moving to mainstream

As described previously, this project sits at a dynamic and liminal time in genetics practice: as transformational projects like the 100,000 Genomes Project expand the reach of genomic sequencing far beyond clinical genetics, genomic medicine is moving towards mainstream. In order to move past the uncertainty of this liminal period into the post-liminal mainstream genomic state, it is essential that challenges be identified so that

solutions can be devised. Efforts, such as by Manolio et al. [318], have been made to anticipate such challenges and to offer potential solutions. However, if SF are to be a part of this genomic future, they present additional and specific challenges. Relevant challenges have previously been described in array testing and karyotyping, such as additional costs and the need to cascade to family members to confirm clinical significance [320]. In line with the final aim of my project, I outline here four significant challenges raised or exacerbated by secondary findings in the mainstreaming of genomic medicine (Figure 8.1). These are not intended to be exhaustive, but are based on the findings presented in this thesis. I also suggest ways to overcome these barriers, such that WGS recipients can derive the maximum benefit from the receipt of SF, and genomic medicine as a whole.

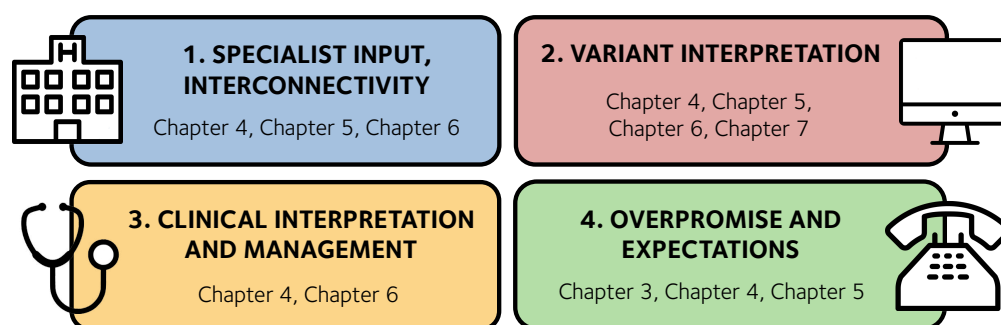


Figure 8.1: Challenges to overcome if secondary findings are to be a component of mainstream genomic medicine, including chapters in this thesis contributing to their identification

Challenge 1: Specialist input and interconnectivity

By their very nature, SF point to a disease outside of the area of expertise of the clinician who ordered the testing. Wanting to ensure the correct decisions were made about SF, healthcare professional interviewees stressed the importance of having specialist input and valued the diversity of specialties represented in the GM-MDT. WGS recipient interviewees stressed that they would want to speak to a relevant specialist immediately after disclosure, highlighting the importance of disease-specific counselling. At present, this appears to be initiated by the referring clinician, and takes on a very ad hoc form. This was clearly demonstrated in the cases where SF were returned to participants. In *Chapter 4*, where a *BRCA2* variant was disclosed, specialist follow-up was afforded by the referring

clinician contacting an oncologist with whom they were acquainted personally. In David's case, the importance of specialist cardiac expertise was clear, but only afforded by the GM-MDT—a structure that is not commonplace. In a future where genomic sequencing is mainstream, a formal system for referral between specialties will be essential to overcome current fragmentation—as indicated by recipient interviewees, timely referral to a relevant specialist is imperative to minimise anxiety. While the 100,000 Genomes Project is making efforts to improve connectivity across hospital systems in order to improve interpretation within specialties (through its Clinical Interpretation Partnerships) greater efforts will need to be taken to improve connectedness *within* hospitals and *across* specialties moving forward. In the absence of sufficient connectivity or a systematic referral scheme for SF, it will be particularly important for programmes offering screening of SF to have timely access to expertise in specialties represented on their SF gene screening lists—namely oncology and cardiology—and systems or designated specialists in place before SF are ever disclosed.

Challenge 2: Variant interpretation

The challenge that became most clear throughout this thesis was that of variant interpretation. As discussed previously, the interpretation of SF is fundamentally different from that of primary findings—where interpretation of genetic findings is usually carried out in light of a disease or family history present, no such information informs the interpretation of SF. Murray [321] explores this fundamental distinction, explaining that the difference in the pre-test probability of disease between primary and secondary findings (high vs. near zero) impacts the predictive value of the test. Obtained in the absence of condition or family history, Murray argues that 'secondary genomic findings should be viewed as biomarkers', and calls for research into the positive predictive ability of SF in unselected populations. This data requires returned SF together with clinical assessment. The lack of such evidence was clearly demonstrated in *Chapter 2*—refined penetrance estimates that reflect the penetrance in unselected populations rather than families with probands are needed. Healthcare professionals in *Chapter 4*, who struggled to make decisions in the absence of this data, made the impact of this evidence gap clear.

Finally, in *Part III* the difficulty of interpreting variants without this evidence base was demonstrated in practice: without precedent, the clinical team faced a ‘steep learning curve’ returning the *KCNQ1* variant to David, and I was challenged to apply guidelines for primary findings to secondary variants. Until a relevant evidence base is amassed, challenges of interpretation will persist.

Challenge 3: Clinical interpretation and management

A closely related challenge is that of clinical interpretation and management. As depicted in the case study in *Chapter 6*, David’s clinical care team faced difficulties interpreting the results of his clinical tests—the line between non-penetrance and a mild phenotype is indistinct, and may grow more blurred as unselected individuals are recruited based on SF. This is further complicated in the case of cancer SF, where no phenotype may be present on clinical assessment, yet disease predisposition may still exist. Long-term follow-up of these participants will be required to inform management of future SF recipients. Furthermore, the impact of disclosure on the participant and the management required is presently unclear—evidence that genetic risk estimates motivate behavioural changes is mixed [182, 183]. One would anticipate motivation to be greater when the genetic result points to a life-threatening condition. However, in *Chapter 5*, some WGS recipient interviewees anticipate difficulties having invasive interventions in the absence of symptoms or a family history. In *Chapter 6*, David, despite receiving a diagnosis of LQTS, struggled to comply with clinical recommendations for a relatively simple intervention for the same reason. It is yet to be seen how these variants will be clinically interpreted when they are returned on a systematic scale, what impact disclosure will have on patient management, and if disclosure will even positively impact clinical outcomes. In the absence of improved outcomes, the utility of disclosing SF will be called into question: careful assessment of the impact of disclosure will be essential to determine whether SF are even worth any resource investment moving forward.

Challenge 4: Overpromise and participant expectations

Nearly two decades following the sequencing of the first human genome, it is becoming even clearer that we still have much to learn. Eric Lander, one of the pioneers of the

Human Genome Project, discussed this in a recent opinion piece, saying that following the project ‘expectations rose that cures for most diseases might be around the corner—which, of course, they weren’t’ [322]. This overpromise of genomics prevails in the public sphere, often contributing to unrealistic expectations among participants (and potential participants) in WGS that need to be mitigated [323, 324]. In the case of diagnostic sequencing by WGS, this overpromise may even be perpetuated by programme materials—the All of Us Research Program in the United States promises ‘precision medicine’ [66], and the 100,000 Genomes Project (although more reserved) promises new treatments and the transformation of the healthcare service [64]. The overpromise of genomics is particularly salient in the case of secondary findings: where it might have once been thought that an individual’s genome sequence could be widely used to predict predisposition to a variety of diseases, this is not the case [325]. Even for prediction of rare Mendelian disease, where evidence for the disease-causing ability of variants is high, there is no evidence to support the sequencing of healthy individuals [305]. Where screening for SF does occur, only a small fraction of participants will actually receive SF. Despite this, the systematic review in *Chapter 3* found healthcare professionals having to manage often-unrealistic expectations. GM-MDT members in *Chapter 4* expressed similar concerns about the overpromise of WGS, highlighting that, in the absence of a sufficient evidence base, any potential benefit of SF could not be realised systematically. Education and greater understanding of the limitations of SF are, therefore, essential to support informed decision-making among participants, and narrow the gap between expectations and the current situation—where providers consider which SF are useful to generate, based on the currently available (limited) evidence and resources.

In some ways, WGS recipient interviewees in *Chapter 5* demonstrated more realistic expectations with respect to SF than feared by the HCP interviewees: after a long diagnostic odyssey, many acknowledged that they might not find a genetic cause or treatment for their condition. However, they did highlight an important unrealistic expectation: re-contact about SF in light of information. Thanks to recent work from Carrieri et al. [198, 221] and Dheensa et al. [222], the challenge of re-contacting in genomic medicine has begun to be delineated. As discussed in *Chapter 5*, while ethically

desirable, re-contact in genetics has been shown to be practically unfeasible [15, 198]. The main barriers to recontact in light of new information in genomics include: limited resources; technological infrastructure; and a lack of clarity on the responsibilities of those involved [198, 222]. As a consequence, there is no duty to re-contact, for SF or even primary findings. Despite this, WGS recipient interviewees in *Chapter 5* demonstrated an expectation that they could be re-contacted with respect to secondary findings. Some who consented to SF felt that non-actionable results should be kept on file should they be actionable in light of new information. Others felt that declining SF meant such results would be put on their files and could be accessed later or relayed when relevant. These misconceptions demonstrate the desirability of re-contact to WGS recipients, but highlight the importance of delineating responsibilities around re-contact, as advocated by the authors above [198, 221, 222]. In the case study in *Chapter 6*, the disclosure pathway and distribution of responsibility proved challenging even without the time lapse that would be present when a result was being disclosed in light of new information, long after sequencing. As an evidence base is gathered around variants that will be detected secondarily, the potential for reassessment and reclassification is real. Thus, as genomic medicine is mainstreamed, it would be ideal (if unrealistic) to have a technological system for re-contact, likely involving a 'joint venture' model where responsibility is shared between HCPs and participants [222]. Regardless of the final form re-contact takes, it is vital that guidelines are produced that outline the responsibilities of the various parties involved, and that these responsibilities are made clear during the consent process. In order to make informed decisions around SF, individuals must understand the long-term impact of their choices.

Ways forward: innovative approaches and evidence-based guidelines

It is clear that what is needed to overcome the challenges posed by screening for SF in WGS comes back, in a way, to the second aim of my thesis: guidelines informed by an SF-specific evidence base. This need is not just specific to SF, but the implementation of genomic medicine broadly [326]. Recent systematic reviews have shown limited evidence on the analytic validity, clinical validity and clinical utility of genomic tests, as well as a

limited knowledge base around implementation science for genomic medicine [327, 328]. The lack of evidence, however, is particularly problematic in the case of SF, where even the most basic evidence—on a variant’s ability to predict disease—is lacking [305]. Thus, useful evidence in the management of SF must be variant-specific, demonstrating the phenotypic spectrum and true penetrance of relevant variants in unselected populations. With pressure mounting to offer raw sequence data to research participants (the 100,000 Genomes Project is offering to do so) [40], where the interpretation of all variants will face the problems discussed here with respect to SF, the timely collection of variant-specific evidence in unselected populations is only heightened. It is also important that the studied populations are more diverse than those in existing genomic literature [328], as the problems caused by lack of ethnic diversity—such as misdiagnosis—have been demonstrated [329]. These data also need to show the impact of these findings when returned, on both recipients and clinical outcomes [305]. The study outlined in *Chapter 7* will contribute to this end. Other similar research studies, collecting high quality and long-term data—data not typical of routine clinical care, including fine phenotypic, psychosocial, economic data—will be essential. Importantly, for participants to benefit from this data, infrastructure will be required to link genomic information to these other types of data in a meaningful way. This will require novel thinking about the use, storage and protection of participant data, and increased integration of clinical practice and research. It will be essential for genomics practice to embrace this evidence and learn as it accumulates.

In the actual collection of this data, it will be important for such a fast changing and innovative field to adopt equally innovative and responsive technologies and infrastructure. A recent publication by Teare et al. [330] demonstrated how digital technology can be used to enable active and ongoing engagement by participants throughout a research project. Such continued participation would be particularly useful in genomics where interpretations change, and opportunities to revisit data arise regularly. Furthermore, an online interface can afford the implementation of a dynamic consent model [192] that seems appropriate in light of WGS recipients’ changing and context-dependent views towards SF (and other results). Such a platform can also allow patients to be

recontacted and reconsented quickly about further studies. It would seem, then, that such a platform could afford recontact about new or updated results over time. However, where counselling—which would ordinarily take place with a genetic counsellor in a clinic—is critical for the consent to such results be informed, tailored approaches (such as requiring a phone conversation with a genetic counsellor to proceed) may need to be implemented if such an interface is employed in genomics. The platform utilised by Teare et al. [330] also incorporated psychosocial metrics. Similar to those outlined in the proposed study in *Chapter 7*, the data collected by such metrics is essential, and an online platform could initiate the collection of these data at scheduled timepoints dictated by the investigators. Finally, through regularly engaging the participant, such a platform would foster the shared responsibility paradigm that seems essential in moving this research forward [126, 222]. Whatever ultimate form such a platform takes, it is critical that creative solutions are devised in order to collect the required evidence in a systematic manner, engage participants in a ‘joint venture’, and maximise the benefit to those involved.

Based on the evidence that is collected from this research, expert panels—such as the Secondary Findings Working Group at the ACMG—need to be convened to produce guidelines based on this SF-specific evidence. Additionally, healthcare system-specific guidelines must be developed alongside broader variant guidelines, to provide institutional guidance on issues such as specialist referral and re-contact with respect to SF. This evidence will also need to inform educational materials and pre-test discussions to ensure participants have realistic expectations with respect to SF. As highlighted in *Chapter 4*, it will also be important to ensure terminology reflects this new evidence base—it might be necessary for new terms to reflect population-level and family-level penetrance, and for previously used terms, such as pathogenicity, to be clarified. By extension, training and education—adaptive to new standards and responsive to accumulating evidence—will also be required for healthcare professionals, particularly as more become involved in the fast-changing field. Until the necessary evidence is amassed, and the true burden and impact of these variants is known, it remains unclear what form this guidance will take. However, if we are to resolve the uncertainties of the current transitional period and derive benefit from the ‘broad view of the landscape of

heritability' afforded by the human genome [4], a guiding framework for the management of SF is necessary—particularly as genomic sequencing spreads across specialties and into routine clinical practice.

8.3 Methodological strengths and limitations

The work outlined in this thesis is particularly valuable due to the context and setting in which it is situated. The work depicted takes advantage of local experience with clinical WGS, and can thus portray the experiences of healthcare professionals as well as WGS recipients who have been intensely engaged in the subject. These are individuals who have made actual decisions around SF, and in some cases—as with David and his clinical team—have experienced SF disclosure first hand. In addition to being embedded in WGS, the work is situated in a context that is different from the majority of literature on the subject; views and experiences of Britons are different from Americans, potentially influenced by culture surrounding the publicly funded NHS, as was apparent in *Chapter 5*.

In order to take advantage of the diverse activities and experiences available for study in Oxford, this thesis employed a mixed methods approach. By combining quantitative methods, qualitative methods, reviewing methods, and clinical study I was able to capture a wider range of facets to the issue than if only one approach were employed alone. While some depth may have been lost in any one area, the mixed methods strategy better reflected the broad aims of the thesis [331]—helping to depict this important moment in time and illustrate the challenges that will need to be overcome in order to move the field forward. The qualitative chapters in this thesis were particularly valuable in their going beyond previous qualitative work on the subject, providing nuanced views and novel insights following the literature reviews. These studies, however, were complemented by the clinical work that followed, in their illustration of the challenges articulated by interviewees in previous chapters.

The sample, however, is limited. The interviewees, both providers and recipients, as well as the case study, were drawn from the same context. All of these individuals participated in the same sequencing programme and had similar discussions, which likely influenced their views. In this way, I would encourage caution in generalising the

qualitative results—they may be specific to the (largely white British, highly educated) individuals who participated in WGS in Oxford. Future work would benefit from capturing more diverse views (non-white British, less education), and the literature would benefit from the experiences of other genomic medicine centres. Future work will also benefit from capturing a wider range of experiences with management and disclosure of SF, something that was not widely available at the time of this study.

That is not to say these results are not important—the views of these individuals, as any, are critical to inform policy development that will benefit all participants. Furthermore, while not necessarily generalisable, these results are *transferable* [332]. As the context has been made explicit, others can determine which aspects of the findings apply elsewhere. For example, aspects of the recipient interviews could apply to other WGS participants with rare disease, and aspects of the provider interviews could apply in other publicly funded healthcare settings. The overall findings, however, which take into account the literature reviews as well as the clinical work, are broader and less context-specific, and should be more straightforward to apply to other settings and contexts.

8.4 Implications for policy and practice

Although the implications of the individual chapters have been outlined, the findings across the thesis as a whole have implications for practice, policy and future research:

1. Secondary findings from WGS can be optionally sought and returned, if consented to by the participant, but should be done so cautiously so as to amass an evidence base to inform their interpretation and management.
2. Genotype-driven recruitment appears to be a feasible strategy to identify individuals with these variants and collect this evidence.
3. Screening for SF should be limited to ‘actionable’ variants, about which we are confident in their pathogenicity. This includes variants thought to be causative of life-threatening but treatable conditions, as well as information that can inform reproductive decision-making—recessive and X-linked carrier status information.

4. In addition to variant-specific evidence, data on the impact of disclosure on participants (behavioural and psychological), as well as clinical outcomes, should be collected. It will be particularly important to assess clinical utility as, due to a lack of symptoms and family history, perceived susceptibility may be systematically lower among SF recipients compared to those who receive genetic risk information in usual genetics practice.
5. The evidence base amassed through the return of these SF should be used to inform SF-specific guidelines to help guide future interpretation and management (including re-contact), and new terminologies should be developed to reflect this evidence.
6. In the meantime, care must be taken during the consent process to ensure participants understand the fundamental difference between primary findings and secondary findings, as well as understand the longterm impact of decisions made around SF (e.g. in terms of re-contact, or lack thereof).
7. Further research into the changing views of individuals towards results over time is needed, particularly exploring the impact of receiving primary results on desire for secondary findings. Dynamic forms of consent should be considered to accommodate diverse and changing views of participants towards genetic results.
8. To facilitate the collection of this data over time, potentially enable recontact, engage participants, share responsibility, and afford dynamic forms of consent, innovative approaches in the design of research studies—such as interactive technological interfaces—should be considered.

8.5 Final conclusions

As we enter the era of clinical whole-exome and whole-genome sequencing, the field has progressed to the point where there appears to be a consensus that optional limited screening of secondary findings is favourable. If done cautiously, WGS recipients may serve to benefit from the additional information SF can provide. While the views of those

interviewed in this thesis were diverse, many felt that screening for SF should include treatable preventable conditions as well as information that can inform reproductive decision-making. However, evidence on which to base management decisions is lacking (both variant-specific evidence and impact on recipients and clinical outcomes), and several barriers exist preventing the return SF to WGS recipients in a meaningful way: specialist input and connectivity between specialties; variant interpretation; clinical interpretation and management; and, overpromise and managing expectations, including recontact in light of new information. In order to overcome these challenges, it is essential that we actively return SF to participants in a controlled manner—we must ‘learn by doing.’ We must prospectively phenotype individuals in diverse unselected populations to derive more accurate estimates of population-level penetrance, better understand the phenotypic spectrum, and explore the impact SF disclosure has on clinical outcomes and the recipients themselves. This evidence must then be used to inform guidelines and future policies. As genome sequencing is mainstreamed—through transformative projects such as the 100,000 Genomes Project—clear evidence-based guidelines will be essential if harms are to be minimised and benefits are to be maximised, both to patients and the healthcare system at large.

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Appendices

A

Critical appraisal

A.1 Quality checklists

The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist tool, published by Tong et al. [134]—adapted using the Critical Appraisal Skills Programme (CASP) checklist [135, 136] to include a set of initial screening questions to test against inclusion criteria—was employed to assess the quality of qualitative studies (Figure A.2). In the case of the quantitative studies, a checklist tool adapted from Boynton and Greenhalgh [137] and Greenhalgh et al. [138] was employed (Figure A.2).

Figure A.1: Quality checklist for quantitative studies

I.	Are the aims of the research clear?*
II.	Is the research relevant to the synthesis topic?*
III.	Was a questionnaire survey an appropriate research design to answer this question?*
*If "No" to any of I-III, paper is to be omitted from synthesis	
Sampling	
1.	<i>Sampling frame:</i> Is the sampling frame clear, and was it sufficiently large and representative?
2.	<i>Understanding and suitability:</i> Does it appear that all participants understood what was required of them, and did they attribute the same meaning to the terms in the questionnaire? Does the instrument appear to take into account the likely range of abilities of potential participants?
Data Collection	
3.	<i>Existing measures:</i> Did the researchers use an existing questionnaire or survey? If not, did they justify their development of a new one?
4.	<i>Consumer views:</i> Were the views of consumers sought about the questionnaire?
5.	<i>Validity:</i> Have the authors claimed that the instrument is valid? Is this claim justified? (i.e. Do the authors make it clear that the instrument measures what it sets out to measure?)
6.	<i>Reliability:</i> Have the authors claimed that the instrument is reliable? Is this claim justified? (i.e. Do the authors make it clear that the instrument provides stable results over time and between researchers?)
7.	<i>Pilot:</i> Was a pilot used on a representative sample? Was the instrument modified accordingly?
Instrument	
8.	<i>Instrument provided:</i> Has the questionnaire or survey been provided?
9.	<i>Title:</i> Is the title of the questionnaire provided? If so, is it appropriate?
10.	<i>Sensitivity:</i> Do the questions cover all relevant aspects of the problem in a non-threatening and non-directive way? (i.e. Are non-threatening questions placed at the beginning, and sensitive ones at the end?)
11.	<i>Types of questions:</i> Are open-ended and closed-ended questions used appropriately?
12.	<i>Briefness:</i> Is it clear that the questionnaire was kept as brief as the study allowed?
13.	<i>Clarity:</i> Do the questions appear clear? (i.e. not ambiguous or overly complicated).
14.	<i>Instructions:</i> Is it clear that adequate instructions were provided in the instrument? (i.e. examples answers, instructions on how to return).
Distribution, Administration and Response	
15.	<i>Method of distribution:</i> Is it clear how the questionnaire or survey was distributed?
16.	<i>Method of administration:</i> Is it clear how the questionnaire or survey was administered?
17.	<i>Response rate:</i> Is the response rate clear and reasonable?
18.	<i>Non-participation:</i> Have non-responders been accounted for?
Data Analysis	
19.	<i>Description of analysis process:</i> Is the analysis process clearly described?
20.	<i>Appropriateness of analysis:</i> Is it clear that quantitative data were subjected to statistical analysis and qualitative data to qualitative analysis (if relevant)?
21.	<i>Accuracy measures:</i> Is it clear that measures were in place to maintain the accuracy of the data?
22.	<i>Free from data dredging:</i> Does the study appear to be free from 'data dredging'? (i.e. No evidence that statistical analyses that were not 'hypothesis driven').
Reporting	
23.	<i>Clarity of findings:</i> Are the findings explicit? Have all relevant results been reported (significant and non-significant)?
24.	<i>Data and findings consistent:</i> Were the findings consistent with the data provided?
25.	<i>Appropriateness of reporting:</i> Are quantitative results presented as definitive (significant, non-significant)? If relevant, have qualitative results been presented with representative quotations?
26.	<i>Relation to current practice and literature:</i> Have the findings been discussed in relation to current practice or research-based literature?

Figure A.2: Quality checklist for qualitative studies

I. Are the aims of the research clear?* II. Is the research relevant to the synthesis topic?* III. Is this qualitative research (i.e. does this article report on findings from qualitative research, and did that work involve qualitative methods of data collection and analysis)? Is a qualitative method appropriate?*	*If "No" to any of I-III, paper is to be omitted from synthesis

Personal Characteristics

1. *Interviewer*: Has the interviewer/facilitator been identified?
2. *Credentials*: Have the researchers' credentials been provided?
3. *Occupation*: Have the researchers' occupations been provided?
4. *Gender*: Have the researchers' genders been provided?
5. *Experience and training*: Have the researchers stated their experience and training?

Relationship with participants

6. *Relationship established*: Is it clear whether or not a relationship was established prior to study commencement?
7. *Participant knowledge of the interviewer*: Did the participant know something about the researcher (i.e. goals, reason for research, etc.)?
8. *Interviewer characteristics*: Have characteristics of the interviewer been reported?

Theoretical framework

9. *Methodological orientation and theory*: Is it clear which methodological orientation underpinned the study (i.e. grounded theory, phenomenology, etc.)?

Participant Selection

10. *Sampling*: Is it clear how participants were selected (i.e. purposive, convenience, consecutive)?
11. *Method of approach*: Is it clear how participants were approached?
12. *Sample size*: Is the sample size given?
13. *Non-participation*: Is it clear how many and/or why some participants chose not to take part?

Setting

14. *Setting of data collection*: Is it clear where the data was collected?
15. *Presence of non-participants*: Was anyone else present besides the participant and researchers?
16. *Description of sample*: Are important characteristics of the sample discussed?

Data Collection

17. *Interview guide*: Has a topic or interview guide been provided?
18. *Repeat interviews*: Have any repeat interviews been conducted?
19. *Audio/visual recording*: Are the data recording methods clear?
20. *Field notes*: Were field notes taken?
21. *Duration*: Is the duration of the interview or focus groups clear?
22. *Data saturation*: Has the researcher discussed data saturation?
23. *Transcripts returned*: Have transcripts been returned to participants for comments/corrections?

Data Analysis

24. *Number of data coders*: Is it clear how many individuals coded the data?
25. *Description of coding tree*: Has a description of the coding tree been provided?
26. *Derivation of themes*: Is it clear how the themes were derived?
27. *Software*: Has software been used to manage the data?
28. *Participant checking*: Were results presented to participants?

Reporting

29. *Quotations presented*: Have respondent quotations been provided?
30. *Data and findings consistent*: Were the findings consistent with the data provided?
31. *Clarity of major themes*: Are the major themes presented clearly?
32. *Clarity of minor themes*: Are diverse cases, or minor themes, discussed?

A.2 Inter-assessor reliability

Inter-assessor reliability was measured by calculating κ coefficients. This statistic measures agreement between assessors for categorical items, accounting for agreeing and disagreeing by chance—making it more robust than a simple percentage agreement [333]. In the case of complete agreement, the value of κ would be 1. As such, arbitrary cut-offs were used to assess agreement: 0-0.20 = slight agreement, 0.21-0.40 = fair agreement, 0.41-0.60 = moderate agreement, 0.61-0.80 = substantial agreement, 0.81-1 = near perfect agreement. Statistics were calculated independently for qualitative and quantitative studies using Stata 14 [139].

A.3 Quality assessment results

Across the studies, quality and comprehensiveness of reporting was highly variable (Table A.1 and Table A.2): scores for quantitative papers ranged from 8-23 (out of 26), while scores for qualitative papers ranged from 11-19 (out of 32). Although reporting of data collection was weak across the studies, with few qualitative studies reporting the theory underpinning analysis, results were generally well reported. Between the reviewers, there was substantial agreement on the scores for both quantitative papers ($\kappa = 0.614$, 95% CI [0.538, 0.690]), and qualitative papers ($\kappa = 0.749$, 95% CI [0.697, 0.781]).

Table A.1: Quality assessment of quantitative and mixed methods papers

Quality Assessment Criteria		Reference																		
		[140]	[141]	[142]	[143]	[144]	[145]	[147]	[146]	[148]	[149]	[180]	[151]	[48]	[152]	[153]	[154]	[155]	[156]	
Sampling	1. Sampling frame		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	2. Understanding	■																		
Data Collection	3. Existing measures								■				■				■			
	4. Consumer views	■							■	■	■	■	■	■				■	■	
	5. Validity			■	■	■			■	■	■	■	■							
	6. Reliability						■	■				■	■	■						
	7. Pilot						■		■	■	■	■	■	■	■			■	■	
Instrument	8. Instrument provided		■	■		■	■	■	■	■		■	■				■	■	■	
	9. Title		■	■		■	■	■	■	■		■	■				■	■	■	
	10. Sensitivity							■				■	■		n/a				■	
	11. Types of questions	■			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	12. Brevity					■	■	■	■	■	■	■	■	■	n/a			■	■	
	13. Clarity					■	■	■	■	■	■	■	■	■	n/a			■	■	
	14. Instructions					■	■	■	■	■	■	■	■	■	n/a			■	■	
	15. Distribution	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Administration	16. Administration	■				■	■	■	■	■	■	■	■	■	n/a			■	■	
	17. Response rate							■				■			n/a			■	■	
	18. Non-participation			■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	
Data analysis	19. Analysis process	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	20. Appropriate analysis	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	21. Accuracy measures																			
	22. No data dredging	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Reporting	23. Clarity of findings	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	24. Findings consistent	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	25. Appropriate reporting	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
	26. Practice and literature	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Total		12	19	19	11	20	22	17	23	15	18	19	21	16	8	12	19	17	20	

n/a Not applicable based on the research methodology employed

Table A.2: Quality assessment of qualitative papers

Quality Assessment Criteria										Reference																													
										[157]	[158]	[159]	[160]	[161]	[115]	[162]	[163]	[164]	[143]	[165]	[166]	[146]	[167]	[168]	[169]	[170]	[148]	[87]	[150]	[180]	[171]	[172]	[173]	[174]	[175]	[176]	[177]	[178]	[179]
Personal characteristics	1. Interviewer																																						
	2. Credentials																																						
	3. Occupation																																						
	4. Gender																																						
	5. Experience																																						
Relationship	6. Relationship established																																						
	7. Participant knowledge																																						
	8. Characteristics																																						
Theory	9. Methodological orientation																																						
Participant selection	10. Sampling																																						
	11. Method of approach																																						
	12. Sample size																																						
	13. Non-participation																																						
Setting	14. Setting																																						
	15. Others present																																						
Data Collection	16. Sample description																																						
	17. Interview guide																																						
	18. Repeat interviews																																						
	19. Recording																																						
	20. Field notes																																						
	21. Duration																																						
	22. Data saturation																																						
Data Analysis	23. Transcripts returned																																						
	24. Number of coders																																						
	25. Coding tree																																						
	26. Derivation of themes																																						
	27. Software																																						
	28. Participant checking																																						
	29. Quotations																																						
	30. Findings consistent																																						
Reporting	31. Major themes																																						
	32. Minor themes																																						
Total		16	14	17	14	15	13	17	15	13	13	12	15	16	16	15	15	15	14	17	14	11	12	19	14	17	15	15	19	16	12	12	12	12	12				

n/a Not applicable based on the research methodology employed

B

Studies included in systematic review

B.1 Quantitative and mixed methods studies

Table B.1: Characteristics of included studies that employed quantitative methodologies and mixed methodologies. *Indicates study population reported in multiple articles.

Author/year	Country	Principal views or experiences investigated	Study Population	Participant direct experience with WGS	Domain	Design	Primary Topic
Arora et al. [140]	USA	Experiences providing WGS	49 genetics healthcare professionals	Yes	Clinical	Online survey	WGS, WGS consent
Barajas and Ross [141]	USA	Attitudes towards opportunistic screening in paediatric genome sequencing	179 physicians (bioethicists and paediatricians)	Mixed	Clinical	Email postal survey	Management of SF
Bui et al. [142]	USA	Attitudes towards participating in and receiving results from genome sequencing	58 patients with psychiatric disorders, or unaffected family members	No	Research	Telephone survey	Return of results
Facio et al. [143]	USA	Attitudes towards learning results from genome sequencing	311 research participants	Yes	Research	In-person survey	Return of results
Fernandez et al. [144]	Canada	Attitudes towards disclosure of clinically significant research findings in context of regulatory guidance	74 genomics researchers	Yes	Research	Postal questionnaire	Return of results, Management of SF
Fernandez et al. [145]	Canada	Attitudes towards return of targeted and incidental genomic research results in setting of paediatric cancer, inherited childhood diseases.	362 parents of research participants	Yes	Research	Postal questionnaire	Return of results, Management of SF
Gray et al. [146]	USA	Views on WGS and SF	167 patients, 27 oncologists	Yes	Clinical	Semi-structured interviews and surveys	Management of SF, WGS
Jelsig et al. [147]	Denmark	Attitudes towards disclosure of SF, and types of SF	127 research participants	Yes	Research	Unclear design	Management of SF
Klitzman et al. [148]	USA	Practices attitudes towards return of secondary findings	241 genetics researchers*, 28 genomics researchers*	Mixed	Research	Internet survey, Semi-structured interviews	Management of SF
Lemke et al. [149]	USA	Attitudes towards genome sequencing and secondary findings	279 genetics healthcare professionals	Mixed	Clinical	Internet survey	Management of SF
Lohn et al. [150]	Canada	Views on the management of SF in clinical context	210 genetics healthcare professionals	Mixed	Clinical	Online questionnaire	Management of SF

Author/year	Country	Principal views or experiences investigated	Study Population	Participant direct experience with WGS	Domain	Design	Primary Topic
Middleton et al. [151]	International	Attitudes towards returning SF from genome research	4961 members public, 533 genetics healthcare professionals, 843 non-genetic healthcare professionals, 607 genomics researchers	Mixed	Research	Internet survey	Management of SF
Scheuner et al. [48]	USA	Attitudes towards secondary findings in clinical genome sequencing	492 members of the ACMG (genetics professionals)	Mixed	Clinical	Internet survey	Management of SF
Shahmirzadi et al. [152]	USA	Preferences for secondary findings from consent forms	200 patients who underwent whole exome sequencing	Yes	Clinical	Review of consent forms	Management of SF
Smith et al. [153]	USA	How ACMG recommendations have influenced practice	46 genetic counsellors	Yes	Clinical	Internet survey	Management of SF
Strong et al. [154]	USA	Views on return of SF from WGS	258 primary care providers	No	Clinical	Internet survey	Management of SF
Wynn et al. [155]	USA	How views towards SF in genomics are influenced by professional background and experience	241 genetics healthcare professionals*	Mixed	Research	Internet survey	Management of SF
Yu et al. [156]	USA	Attitudes toward return of SF from WGS	760 genetics healthcare professionals	Mixed	Clinical	Internet survey	Management of SF

B.2 Qualitative studies

Table B.2: Characteristics of included studies that employed qualitative methodologies. * indicates study population reported in multiple articles.

Author/year	Country	Principal views or experiences investigated	Study Population	Participant direct experience with WGS	Domain	Design	Primary Topic
Appelbaum et al. [157]	USA	Views of informed consent process for SF	28 genomics researchers*, 20 research participants	Mixed	Research	Online survey and semi-structured interviews	WGS consent, Management of SF
Bergner et al. [158]	USA	Experience of the consent process in WGS	15 research participants	Yes	Research	Semi-structured interviews	WGS consent process
Bernhardt et al. [159]	USA	Experiences obtaining informed consent for WGS	21 genetic counsellors*, 8 research coordinators*	Yes	Both	Semi-structured interviews	WGS consent process
Brandt et al. [160]	USA	Perceived importance of recommended criteria when applied to return of SF	50 genetics healthcare professionals (13 medical geneticists, 17 genetic counsellors/RNs, 20 lab professionals)*, 19 genomic researchers 34 IRB chairs*,	Mixed	Clinical	Structured interviews	Management of SF
Christenhusz et al. [161]	Belgium	Views on SF and their communication	25 members of public (19 parents, 6 grandparents), 25 genetics professionals (5 laboratory staff, 7 bioinformaticians, 13 genetics students)	No	Clinical	Focus groups	Management of SF
Christensen et al. [115]	USA	Preparedness around providing WGS	11 primary care providers, 9 cardiologists	No	Both	Semi-structured interviews	WGS
Clift et al. [162]	USE	Preferences towards return of SF in WGS	38 patients and parents of patients	Yes	Clinical	Semi-structured interviews	Management of SF
Daack-Hirsch et al. [163]	USA	Views on SF from genome sequencing in clinical and research situations	63 members of public	No	Both	Focus groups and interviews	Management of SF
Downing et al. [164]	USA	Preferences regarding management of SF	50 genetics healthcare professionals (13 medical geneticists, 17 genetic counsellors/RNs, 20 lab professionals)*	Yes	Clinical	Structured telephone interviews	Management of SF
Gourna et al. [165]	Greece	Attitudes towards clinical sequencing and return of SF	10 genetics healthcare professionals (3 clinicians, 2 bioethicists, 5 geneticists)*	Yes	Clinical	In-depth interviews	Management of SF
Gourna et al. [166]	Multi-national	Attitudes towards return of SF in a clinical setting	30 genetics healthcare professionals (10 clinicians, 6 genetic counsellors, 8 laboratory professionals, 6 legal/ethical specialists)*	Yes	Clinical	In-depth interviews	Management of SF
Grove et al. [167]	USA	Experiences surrounding SF in clinical sequencing, views on current policies/guidelines	35 members of ASHG and/or NSGC (genetics healthcare professionals)	Mixed	Clinical	Focus groups	Management of SF
Hitch et al. [168]	USA	Views on WGS, return of genomic results	19 patients who had undergone WGS for Lynch Syndrome	Yes	Clinical	Semi-structured interviews	Return of results
Kaphingst et al. [169]	USA	Views on return of SF among women diagnosed with breast cancer	60 women diagnosed with breast cancer under 40 years old	No	Clinical	Semi-structured interviews	Management of SF
Kleiderman et al. [170]	Canada	Parental perceptions and experiences regarding the return of SF in paediatric research	15 parents of children with rare disease	No	Research	Focus groups and interviews	Management of SF
Klitzman et al. [87]	USA	Experiences and views concerning return of SF	28 genomics researchers*	Mixed	Research	Semi-structured interviews	Management of SF
Levenseller et al. [150]	USA	Views of for the future implementation of WGS	22 genetics healthcare professionals (clinicians, bioethicists, lab directors, and genetic counsellors), 20 parents, 7 adolescents	Mixed	Clinical	Focus groups	WGS
Miller et al. [171]	Canada	Expectations and experiences of patients and providers who participate in WGS	29 patients, 14 oncologists	Yes	Research	Semi-structured interviews	WGS
Oberg et al. [172]	USA	Challenges to informed consent in paediatric oncology research	25 parents (15 parents of children with cancer, 10 parents of children without cancer)	No	Research	Focus groups and semi-structured interviews	WGS consent

Author/year	Country	Principal views or experiences investigated	Study Population	Participant direct experience with WGS	Domain	Design	Primary Topic
Rigter et al. [173]	Netherlands	First experiences with WGS consent process	11 genetics healthcare professionals (3 clinical geneticists, 3 molecular geneticists, 2 ethicists, 1 legal expert, 1 quality manager, 2 reps from Dutch Genetic Alliance)	Yes	Clinical	Semi-structured interviews	WGS consent process
Sapp et al. [174]	USA	Preferences on receiving four different types of results from WGS	25 parents of children with rare genetic disease	Yes	Research	Semi-structured interviews	Return of results
Simon et al. [175]	USA	How genomic SF should be addressed in informed consent processes	34 IRB Chairs*	Mixed	Research	Semi-structured interviews	WGS consent process
Tomlinson et al. [176]	USA	Challenging experiences in obtaining informed consent for WGS	21 genetic counsellors*, 8 research coordinators*	Yes	Both	Semi-structured interviews	WGS consent process
Townsend et al. [177]	Canada	Attitudes towards disclosure of SF in clinical settings	10 genetics healthcare professionals (3 physician geneticists, 3 genetic counsellors, 4 laboratory geneticists), 8 parents, 10 members of the public	Mixed	Clinical	Focus groups	Management of SF
Yu et al. [178]	USA	Attitudes towards participation in WGS and return of results	41 African American members of the public	No	Research	Focus groups	Return of results
Yu et al. [179]	USA	Attitudes towards participation in WGS and return of results	35 Non-African American members of the public	No	Research	Focus groups	Return of results

C

GM-MDT materials

Included in this appendix are the following, in order:

1. Pro forma for secondary findings in the GM-MDT.
2. Schematic showing the case approval process for the GM-MDT.

Oxford Biomedical Research Centre

Enabling translational research through partnership



Oxford BRC Genomic Medicine Theme: Incidental Finding Pro Forma

Please use a separate form for each individual.

Your Information

Analyst's Name:		Clinician's Name:	
Email:		Email:	
Telephone:		Telephone:	

Application Information

If the patient was enrolled into the BRC whole exome or genome sequencing project, please provide the application reference number in the box below:

If the patient was enrolled into an alternative research project please detail the nature of this research.

Please provide details of the relevant research ethics approval (including REC reference number).

e.g. MGAC (Ref:13/WM/0466)

Clinical Information

Do other individuals in this family have the same variant? If yes, please provide a pedigree diagram distinguishing carriers from non carriers.

Please provide any clinical / phenotypic details (including family history) that may provide evidence in support of (or against) pathogenicity for this variant.

What clinical actions would be appropriate if the pathogenicity of the variant was upheld? Only actionable incidental findings will be investigated.

Is there any evidence in the literature to support further molecular analysis and investigations into the pathogenicity of this variant?

Sample Information

Is a DNA sample stored in the regional genetics laboratory (RGL)? Please circle or delete as appropriate:

Yes / No / Not known

If no DNA sample is stored in the RGL, the variant will **not** be confirmed (e.g. by Sanger sequencing) but the pathogenicity of the variant will still be assessed.

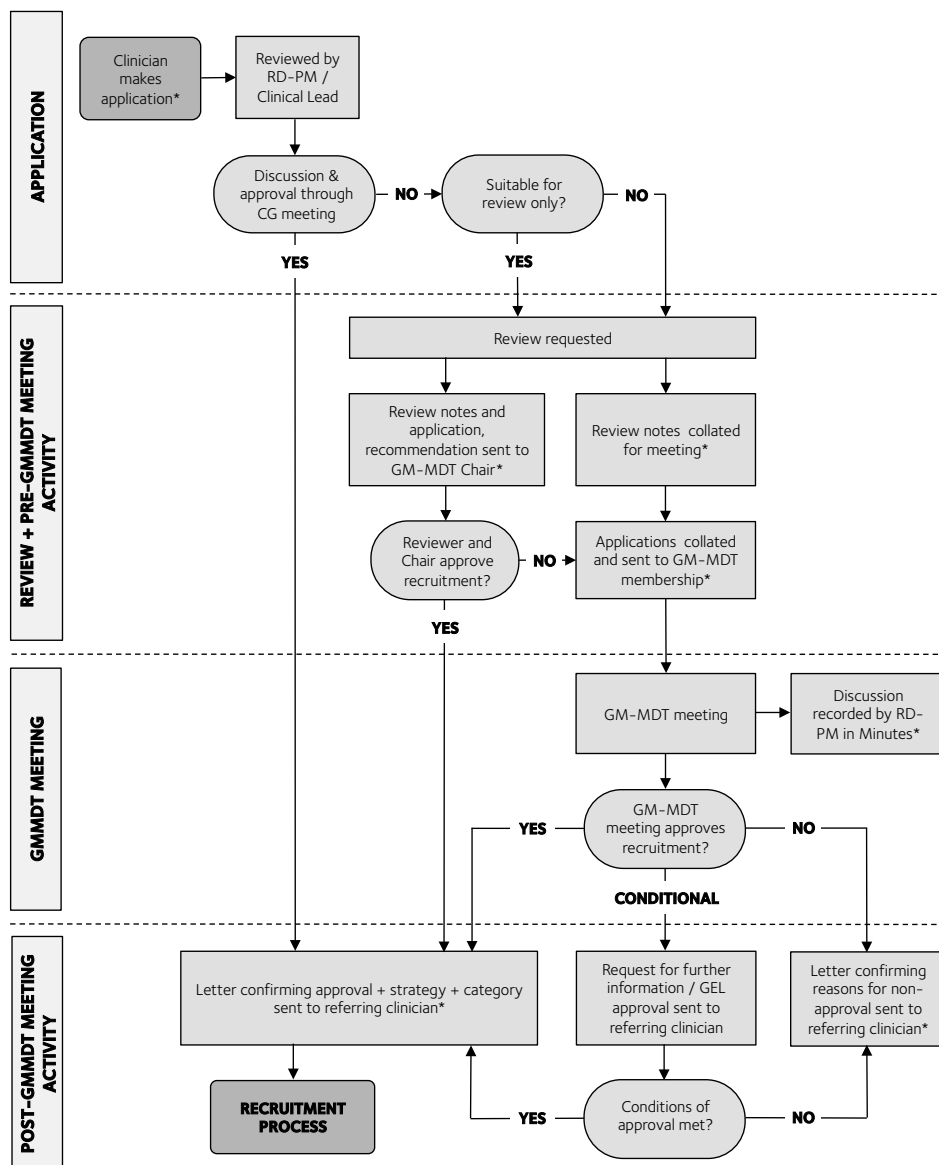
Variant Information (use HGVS nomenclature <http://www.hgvs.org/mutnomen/>)

Please fill in the appropriate information. If more than one variant requires assessment please list the variants in the appropriate row.

DNA sample analysed	
BRC patient ref:	ABC_DEF_O1234567
Single nucleotide variation	
Gene Name (approved HGNC symbol):	BRCA2
Chromosome (including the Genome Reference Consortium Human genome build [GRCh] number) and genomic location:	Chr17(GRCh37): g.32913691C>T
Coding DNA reference sequence (Transcript and coding sequence):	NM_000059.3:c.5199C>T (het / hom)
Deduced protein change:	p.= (p.Ser1733Ser)
Copy number variation	
Intragenic or contiguous gene deletion / duplication:	Intragenic deletion
Gene / transcript / exon(s) involved:	BRCA2 / NM_000059.3 / exon 11

Additional comments

Figure C.1: Case approval process for the GM-MDT. * indicates stage at which document is generated.



D

MGAC materials

Included in this appendix are the following MGAC documents, in order:

1. Consent form for MGAC (2 pages)
2. Letter sent by post to invite participants who consented to participate in substudy (1 page)
3. Questionnaire sent to MGAC participants who agreed to participate in substudy (3 pages)
4. Consent form for MGAC substudy interview with WGS recipients (1 page)
5. Patient information sheet for MGAC substudy interviewees (2 pages)



Oxford University Hospitals **NHS**
NHS Foundation Trust

CONSENT FORM

For Patient or relative age 16 and over

Molecular Genetic Analysis and Clinical Studies of Individuals and Families at Risk of Genetic Disease (MGAC)

Contact details of Doctor/Genetic Counsellor/Research Nurse:

Clinic in which recruited:

Patient sticker

Genetic condition affecting family:

Family ID:
box

If you agree, please initial

1. I confirm that I have read and understand the Information Sheet (Version 3.1, 25.02.16) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time. This will not affect in any way my present or future medical care and legal rights. ☐
3. I agree that study researchers can collect, store and analyse genetic and clinical information, as relevant to the health condition in my family, from my health records. I understand that researchers will keep my information confidential and in a form that protects my identity. ☐
4. I understand that data collected during the study may be looked at by authorised individuals from The University of Oxford, OUH NHS Trust, funding agencies and study monitors where it is relevant to my taking part in this research. I permit these individuals to access my research records. ☐
5. I agree to provide a sample of blood or saliva, and/or allow samples already collected as part of my medical care to be used for this research. ☐
6. I understand and agree that DNA extracted from my sample will be considered a gift to the University of Oxford. If a commercial product were developed as a result of this study, I would not profit financially. ☐

Depending on the investigations required to pursue a diagnosis for your family's health condition, you may also be asked to choose responses to these statements: *Please circle decision **and** initial*

7. I understand that genetic analysis will be performed on DNA extracted from my sample and that **GENES KNOWN TO BE INVOLVED** in the genetic condition affecting my family – if there are any such genes – will be looked at (Phase 1 and 2 analysis). ☐ Yes / No
8. I understand and agree that, in the event that no disease causing variant is found in initial analysis, or when no such genes are known, **GENES NOT CURRENTLY KNOWN TO BE INVOLVED** in the genetic condition affecting my family will be looked at (Phase 3 analysis). ☐ Yes / No
9. I understand and agree that I will be informed of any results of genetic analysis of my sample, where they ARE relevant to the genetic condition (Pertinent Findings) affecting my family. ☐ Yes / No

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Subject:	Consent Form	Ethics Ref:	13/WM/0466
Principal Investigator:	Prof H Watkins	Version/Date:	2.1/25.02.16
Short Title:	Molecular Genetic Analysis and Clinical Studies (MGAC)	Page:	1 of 2

10. I understand and agree that I may be informed of any results of genetic analysis of my sample, found **by chance (Incidental Findings)**, where they are not relevant to the genetic condition affecting my family but are judged to be important for my/my family's health care, and can be acted upon medically.

Yes / No

11. I agree that researchers may **look in my sample** for variants which are not relevant to the genetic condition affecting my family but are judged to be important for my/my family's health care, and can be acted upon medically (Additional Findings).

Yes / No

12. I agree that confirmed results of any genetic analysis performed and reported via my clinician to me may be shared with other health professionals for the benefit of other members of the family if those family members request it.

Yes / No

Additional - Not part of main study:

1. I agree that my de-identified research data may be deposited in managed databases where it can be accessed on request by other investigators undertaking approved research, in both the public and private sectors, in the UK and internationally.
I am free at any time to withdraw my permission for this, but understand that it will not be possible to remove data from research that may already have taken place.

Yes / No

2. I agree to be approached to take part in a sub-study exploring my opinions about this research. I understand that agreeing to be contacted does not oblige me to participate in this sub-study.

Yes / No

3. I agree to be contacted about future ethically approved studies. I understand that agreeing to be contacted does not oblige me to participate in any further studies.

Yes / No

Name of participant (please print)	Signature	Date

In the event of results of analysis becoming available after my death, I would like these individuals to be informed of the results:

Name	Address	Relationship to me

For completion by person taking consent:

I confirm that the purpose of the research, its voluntary nature and its procedures have been explained in terms understandable to this participant.

Name	Signature	Date

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Subject:	Consent Form	Ethics Ref:	13/WM/0466
Principal Investigator:	Prof H Watkins	Version/Date:	2.1/25.02.16
Short Title:	Molecular Genetic Analysis and Clinical Studies (MGAC)	Page:	2 of 2



Oxford University Hospitals 
NHS Foundation Trust

Name
Address
Postcode

Date:

Dear Mr/s

Re: Research Study: Molecular Genetic Analysis and Clinical Studies of Individuals and Families at Risk of Genetic Disease (MGAC). Ethics Ref: 13/WM/0466.

You consented to be part of the above study, and agreed to be approached to take part in a sub-study exploring your opinions about this research.

It is important for the research team to understand your views of the research - I enclose a questionnaire and would be grateful if you could answer as much as possible, and return the questionnaire in the enclosed envelope.

You are under no obligation to take part. Your responses will be kept confidential, and will not affect your medical care or your participation in the main study.

Please do contact me if you wish to discuss this.

Yours sincerely

Liz Ormondroyd
Registered genetic counselor and researcher

01865 234676
Liz.ormondroyd@cardiov.ox.ac.uk



Oxford University Hospitals **NHS**
NHS Foundation Trust

QUESTIONNAIRE

Study name: Molecular Genetic Studies of Individuals and Families at Risk of Inherited Disease (MGAC)

You recently agreed to take part in the above study.

This questionnaire asks about your understanding of and thoughts about that study (MGAC). Your answers will help us to understand what concerns people have, how we should explain the study and to plan further research.

You are under no obligation to fill in the questionnaire but if you are willing, please return it in the enclosed envelope (no stamp required).

About you:

1. Age:
2. Gender:
3. Genetic condition affecting your family:.....
4. Family Identification Number in MGAC (if known):.....
5. Clinic in which recruited to MGAC:
6. Highest education level:
 - ☐ To age 16 or younger (GCSE/O level/CSE/equivalent)
 - ☐ To age 18 (A level or equivalent)
 - ☐ Degree or equivalent
 - ☐ Post degree qualification
7. How would you describe your ethnicity?
8. Do you have a religious affiliation?
 - ☐ Yes
 - ☐ No
 - ☐ Not sure
9. Are you personally affected by the health condition being investigated in the main genetics study?
 - ☐ Yes
 - ☐ No
 - ☐ Not known

Subject:	Questionnaire	Version/Date:	1. 07.1.14
Short Title:	MGAC substudy	Ethics Ref:	13/WM/0466
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10. Which other people in your family are known to be affected by the health condition?

☐ Child/Children ☐ Parent ☐ Brother/Sister ☐ No one else
☐ Not known ☐ Other (please specify)

11. Do you have biological children?

☐ Yes, and would like more
☐ Yes, and not planning more
☐ Don't have children but would like to
☐ Unlikely to have children
☐ One or more of my children is now deceased

Your views:

12. I understand what the main study (MGAC) is about.

strongly agree *agree* *neither agree nor disagree* *disagree* *strongly disagree*
☐ ☐ ☐ ☐ ☐

13. What in your view is the main purpose of this research?

.....

14. I think that the health professional who talked to me about the study (MGAC) gave me the right amount of information about the study.

strongly agree *agree* *neither agree nor disagree* *disagree* *strongly disagree*
☐ ☐ ☐ ☐ ☐

15. It is important to me that the underlying cause for the health condition is discovered.

strongly agree *agree* *neither agree nor disagree* *disagree* *strongly disagree*
☐ ☐ ☐ ☐ ☐

16. If you ticked 'agree or strongly agree' for Question 15, it is important to me that the underlying cause for the health condition is discovered, is that because: (*tick as many as apply*)

☐ a. I want an explanation for why the condition happened.
☐ b. It might help me and my doctors to understand the health condition better, and how it might affect me in the future.
☐ c. I hope that finding the genetic cause may lead to treatment.

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- ☐ d. I would like to know whether my relatives might develop the condition.
- ☐ e. I would like to know to help me make decisions about having children.
- ☐ f. I hope this research will help other people.
- ☐ g. Other reason/s (please specify)

17. I am worried or concerned about some aspect of the study.

strongly agree *agree* *neither agree nor disagree* *disagree* *strongly disagree*

☐ ☐ ☐ ☐ ☐

18. If you ticked 'agree or strongly agree' to Question 17, please state what your concerns are about:

Thank you for taking part in this survey. Please return it in the addressed envelope.

Would you be happy for a researcher to contact you about an interview study exploring your thoughts about genomic research in more detail?

If so, please provide your name and preferred contact details. We aim to interview a wide range of people so you may be contacted by a researcher. You can decide not to have an interview if you change your mind later.

Name:

Telephone/email address.....

Do you have any comments? Please use this space and continue over the page if necessary.

[illegible]

Subject:	Questionnaire	Version/Date:	1. 07.1.14
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Oxford University Hospitals **NHS**
NHS Foundation Trust

CONSENT FORM

Molecular Genetic Analysis and Clinical Studies of Individuals and Families at Risk of Genetic Disease (MGAC) Substudy Interview

Clinic in which recruited:

Genetic condition affecting family:

Participant ID:

*If you agree,
please initial box*

1. I confirm that I have read and understand the Information Sheet (Version X, date) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time. This will not affect in any way my present or future medical care and legal rights. ☐
3. I understand that anonymised data collected during the study may be looked at by authorised individuals from The University of Oxford, NHS organisations, funding agencies and study monitors where it is relevant to my taking part in this research. I permit these individuals to access my research records. ☐
4. I agree to take part in an interview which will be audio-recorded. All recordings will be anonymised, and will be destroyed when the study ends. ☐
5. I consent to the use of anonymised quotations from my interview. ☐
6. I agree to take part in the above study. ☐

Name of participant (please print)	Signature	Date

For completion by person taking consent:

Name	Signature	Date

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Subject:	Consent Form substudy interview	Ethics Ref:	13/WM/0466
Principal Investigator:	Prof Hugh Watkins	Version/Date:	1.07.01.14
Short Title:	Molecular Genetic Analysis and Clinical Studies (MGAC) substudy	Page:	1 of 1



Oxford University Hospitals **NHS**

NHS Foundation Trust

PARTICIPANT INFORMATION SHEET

Contact Details
Tel:

Liz Ormondroyd 01865 234676
liz.ormondroyd@cardiov.ox.ac.uk

Molecular Genetic and Clinical studies (MGAC) Substudy

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and ask us if there is anything that is not clear or if you would like more information.

Part 1 tells you the purpose of this study and what would happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

PART 1

What is the purpose of the study?

The main study, MGAC, is using new technology to perform genetic testing – called Whole Genome or Whole Exome sequencing. This is a more powerful way of looking for genetic causes of disease in patients and families, mainly because it allows doctors and scientists to read all of a person's genetic information, or genetic sequence.

Because this technology is new, healthcare professionals have different ideas and opinions about how to handle the results in the best interests of people who are offered this testing.

For example, it is possible that mistakes may be found in genes which are involved in other genetic conditions, not the one which is being investigated. We think this would be quite rare, but there is no agreement about whether people might want such information.

This study will find out what people who have been offered this testing as part of MGAC think about Whole Genome or Whole Exome sequencing, and how the results should be used.

Why have I been invited?

You have been invited because you have agreed to take part in MGAC and agreed to be contacted about taking part in an interview aimed at finding out what you think about genetic research and what it means to you.

Do I have to take part?

No, it is your decision. We will talk to you about the study and answer any questions you might have before you make a decision. We will ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will be involved if I take part?

We would invite you to talk with a trained researcher for about an hour. The researcher would ask you some questions aimed at finding out what you think and why. The interview would be audio-recorded, with your consent, but an identification number will be used so that your identity would not be known to anyone except the researcher.

Subject:	Information sheet substudy interview	Version/Date:	1/07.01.14
Short Title:	Molecular Genetic Analysis and Clinical Studies (MGAC)	Ethics Ref:	13/WM/0466
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What would I have to do?

The researcher will contact you to discuss the study and, if you then decide to participate, arrange a meeting time and place convenient to you.

Are there any possible risks from taking part?

You might find it upsetting to talk about things that have happened to do with the health condition in your family. If this happens, you can stop the interview if you want.

What are the possible benefits?

It is important that we understand participants' opinions and the possible effects of offering new genetic tests. There will be no personal benefits from taking part.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

PART 2**What will happen to recorded interviews?**

All recordings will be anonymised from the point of recording. Only the researcher conducting the interview will know the identity of the participant. After the study, recordings will be destroyed.

What will happen to the results of the research study?

We anticipate that the results will be published in a scientific/biomedical journal for the benefit of the wider research community. Individual participants will **not** be identifiable in any publication. Quotes from interviews may be reproduced, but they will be fully anonymised. Publications arising from the study will be available on request to participants.

What if there is a problem?

The University has a insurance in place which would operate in the event of any participant suffering harm as a result of their involvement in the research.). If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Professor Hugh Watkins or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office (01865 572224; or the head of CTRG, email ctrng@admin.ox.ac.uk).

Who is organising and funding the research?

The lead investigator is Professor Hugh Watkins. If you wish to know more about any aspect of the study, please contact Prof Watkins on 01865 234676.

The research is funded by the Oxford NIHR Biomedical Research Centre, the Wellcome Trust and the Department of Health.

Who has reviewed the study?

The West Midlands Research Ethics Committee has reviewed and approved the study.

Where can I find independent information about taking part in research?

You can contact local branches of the NHS Patient Advisory Liaison Service (PALS). Their website is: <http://www.pals.nhs.uk/> (Tel for John Radcliffe site: 01865 741166).

Further information and contact details

Liz Ormondroyd 01865 234676 / 07812 391582 / liz.ormondroyd@cardiov.ox.ac.uk

Thank you for reading this information and considering whether you would be willing to participate.

Subject:	Information sheet substudy interview	Version/Date:	1/07.01.14
Short Title:	Molecular Genetic Analysis and Clinical Studies (MGAC)	Ethics Ref:	13/WM/0466
Principal Investigator:	Prof Hugh Watkins	Page:	2 of 2

E

Interview guides

E.1 Interview guide for members of the GM-MDT *(Chapter 4)*

Demographic information

1. What is your role: clinical (genetics), clinical (other, non-genetics) non-clinical researcher, clinician/researcher, clinical scientist
2. How many years of professional experience do you have?

Views and experiences of the GM-MDT

3. What are your impressions of the GM-MDTs in general?
4. What are your opinions on informed consent processes (i.e. written material and consultation) for WGS, specifically MGAC? How far does it facilitate decision making, could it be improved?

Views and experiences of SF and genomic medicine

5. Have you personally consented patients/family members? If so, how did you find this process? Did you feel that the individuals understood/how did you gauge this? Do you think patients will be adequately informed should a secondary finding (SF) need to be reported (as incidental or additional)? Have you changed anything about your approach to informed content based on experience?
6. Do you perceive a tension between clinical duty of care and research agenda in generation of SF?
7. Do you think informed consent choices, such as about secondary findings, should always be respected? Why/why not?

8. What factors do you see as important in reporting decisions around SF?
9. What do you see as the pros and cons of having a list of genes that are analysed for variants? Do you think the ACMG list is reasonable, why/not?
10. We don't currently offer an additional findings screen to individuals under 16—what are your thoughts about disclosing findings in children?
11. Where do you feel responsibility to patients you are involved with lies in the weighing of benefits/harms in secondary findings?
12. Do you perceive any responsibility to patients' relatives re SF? If so, how would you manage this/do you think this should be managed?
13. If you were a participant or parent, how do you think these opinions be any different?
14. How do you think disclosure of secondary findings should be managed? How much should disclosure be contextualised for the patient?
15. How do you think approaches to genomic information generation might change as genomic medicine becomes more routine?
16. Is there anything else you would like to add?

E.2 Interview guide for WGS recipients (Chapter 5)

Introductory questions

1. Please describe the health condition in your family and how it has affected you.
2. What do you understand about the tests that will be done in this study (called whole-genome or whole-exome sequencing); do you see it as being different from what has been done before? If so in what ways?
3. What are the differences between whether testing is done as part of clinical care or as part of a research programme? Do you think these differences are important?
4. What do you hope will come out of this work – for you personally, for your family and more generally?
5. What are the risks or problems with this kind of test (WGS)? If none, please expand.

SF: in feedback category; attitudes, communication

Explain: Secondary findings are results that are related to conditions different from the one for which your testing was conducted. We've said that we will tell people if we find a genetic variant incidentally (i.e. something that we stumble upon) that implies very likely risk of a serious condition, for which there is some action you could take. Note: do not immediately explain actionability, allowing participant to define this.

6. Were you aware that it was possible for things to be found, in the course of this study, which don't relate to the condition in the family?
7. Is that something you've thought about? Did you agree on the consent form that you would like to be informed about SF? Do you feel you know enough, then and now, to be able to decide that?
8. What are the differences between genetic conditions which might affect whether you would want to know about IFs? For example, how serious the condition is, what kind of treatments there are, how likely you would be to develop problems from it, whether other people in the family have had the condition? *(Cite examples of conditions)*
9. In terms of actionability, we have said we will return findings for which there is some form of treatment available, such as medication or increased screening. What do you think about that?

SF: not in feedback category

10. We've said we won't tell you if we find something that is not actionable at present. Eg Alzheimer's. What do you think about this?
11. We've said we won't tell you if we find something that we are not sure will mean you are at risk of the condition. What do you think about this?

12. We've said we won't tell you if we find you are a carrier of a genetic change; that would not be important for your health but would be relevant if the person you have children with is also a carrier. What do you think about this?

Screening for secondary findings

13. Today, some studies actively look for things that we think are clinically actionable (such as cancer, heart conditions). In this study, we've said we won't actively look for things – this is not a 'genome screen'. This means that if there is something in your sample that is serious and actionable, but we don't come across it, we/you would not know. What do you think about that?
14. Who do you think should be involved in the decision about whether to look, and what kind of finding to report back? Why?
15. Do you feel participants should be involved in the process? *(If not raised by participant)*
16. How do you feel about healthcare professionals making these decisions? If positive, do you trust the system to make these decisions? Often a panel of experts is involved in making these decisions? How do you feel about that?
17. Genetics knowledge is changing very quickly. What do you think about the situation where we found something now which we are not sure about and don't tell you, but in 5 years we have new information – should we get back in touch and tell you?

Hypothetical scenario

Explain to the interviewee that it may be difficult to imagine, but you would like them to think about a hypothetical scenario

18. Is it possible to imagine how you might react if you were told about an IF in your sample? *(Cite examples)*
19. What would you do with that information? *(Cite examples, probing different types of action)*
20. In that event, who would you prefer to hear that from?
21. Who would you tell? Relatives? Who, how?

Data sharing

22. An important part of this research is making your de-identified information available to other researchers in the UK and abroad. What are your concerns about this?
23. Is there anything else you would like to add?

E.3 Interview guide for individual who received SF (Chapter 6)

Participation in WGS

1. Please describe events leading up to your participation in the WGS study. What is the health condition that brought you to genetics? How has that condition affected your family?
2. What do you remember about agreeing to take part in the WGS study? What kind of findings did you expect from that?
3. What did you understand about the tests that were done in this study (called whole-genome or whole-exome sequencing); did you see it as being different from what has been done before? If so, in what ways?
4. How much did you think, at the time, about the option to learn things that were unrelated to [affected individual]'s condition?

Disclosure of secondary finding

Remind interviewee that they received a secondary finding, differentiating from the primary condition.

5. Please describe the first contact you had about the secondary finding.
6. Do you remember your first thoughts and reactions on being told about the SF? Can you describe them?
7. After that first conversation whom did you discuss it with? Your partner, wider family?
8. What did you want to happen next?
9. (If relevant) What did your partner think at that time?
10. Did you seek any more information about [the condition mentioned by the doctor who first spoke to you]? If so, what did you find out? Did that affect your thinking?
11. How did your appointment with the specialist (eg cardiologist) go? Please describe your thoughts at that time, eg during/after.
12. Did you learn the information you needed at that appointment?
13. Did you feel that you understood the tests that were undertaken?
14. Did you feel your concerns were being addressed?
15. What was your understanding, after seeing the specialist, about the condition, [eg LQTS] and how it might affect you?

Impact of disclosure

16. Since learning about the SF, have you done anything differently? At work, recreationally, at home? If so, please explain. If so, why do you think you've done these things differently, or made these changes?
17. How much did/do you think about the SF?
18. Do you think about it at specific times of day/night, or when you're doing certain activities?
19. Has this thinking changed over the time since you first learned about the SF? If so, can you think why it's changed?
20. What is your current understanding about your risk of having [the secondary condition]?
21. What is your current thinking about learning about the SF? Would you make the same decision again?
22. Do you feel that there is anything that could/should have been done?

Communication and family members

23. Was your partner was present at some/all of medical consultations?
24. How often do you discuss the SF with her/him?
25. Do you feel her/his thoughts about the SF are similar or different to yours?
26. Have you discussed this finding with anyone else in the family? If so, please describe the decision to talk to them.
27. Who did you tell? Parents, siblings, children
28. What were their reactions?
29. Did you learn anything from any of your relatives that changed your thinking about the SF?
30. Do you know if other family members will be tested as a result of the secondary finding?
31. Is there anything you want to add?

Demographic information (if not provided via questionnaire)

- Gender
- Age
- Ethnicity
- Education

F

Interviewees

F.1 Details of GM-MDT member interviewees (*Chapter 4*)

Table F.1: Details of GM-MDT member interviewees

Code	Gender	Years experience	Consented patients	Role	Specialty
P1	Female	20	No	Researcher	
P2	Female	30	No	Clinical (non-genetics)	Haematology
P3	Female	3	No	Researcher	
P4	Female	10	Yes	Clinical (non-genetics)	Renal medicine
P5	Female	28	Yes	Clinical (genetics)	
P6	Male	8	No	Clinical science	
P7	Male	16	No	Clinical (non-genetics)	Cardiovascular
P8	Male	22	No	Clinical (genetics)	
P9	Male	10	No	Clinical (non-genetics)	Immunology
P10	Male	16	Yes	Clinical (non-genetics)	Gastroenterology
P11	Female	15	No	Clinical science	
P12	Male	16	Yes	Clinical (non-genetics)	Neurology
P13	Female	30	No	Clinical science	
P14	Male	12	Yes	Genetic counsellor	
P15	Male	20	Yes	Clinical (non-genetics)	Rheumatology
P16	Male	20	No	Clinical (non-genetics)	Cardiovascular
P17	Male	15	No	Researcher	
P18	Male	21	Yes	Clinical (genetics)	

F.2 Details of WGS recipient interviewees (*Chapter 5*)

Table F.2: Details of WGS recipient interviewees

Code	Gender	Age	Affected	Relationship to affected	Ethnicity	Education	Specialty	Condition	Primary result
R1	Male	50	Yes	n/a	White British	Degree or equivalent	Neurology	Spastic paraplegia	Positive
R2	Male	33	Yes	n/a	White British	Post degree qualification	Cardiology	Cardiomyopathy	Negative
R3	Female	39	No	Parent	White British	Post degree qualification	Neurology	Epilepsy	Positive
R4	Male	66	Yes	n/a	White British	To age 18 (A level or equivalent)	Cardiology	Hypertrophic cardiomyopathy	None
R5	Female	38	Yes	n/a	White British	Post degree qualification	Cardiology	Hypertrophic cardiomyopathy	Positive
R6	Female	18	Yes	n/a	White British	To age 16 or younger (GCSE or equivalent)	Neurology	Epilepsy	None
R7	Male	49	No	Parent	White British	To age 16 or younger (GCSE or equivalent)	Neurology	Epilepsy	None
R8	Male	63	No	Parent	White British	Post degree qualification	Cardiology	PAIVS	Negative
R9	Female	62	No	Parent	White British	Post degree qualification	Cardiology	PAIVS	Negative
R10	Female	57	No	Parent	White British	Degree or equivalent	Neurology	Epilepsy	None
R11	Male	57	Yes	n/a	White British	Degree or equivalent	Neurology	CIDP	None
R12	Female	85	No	Parent	White British	Degree or equivalent	Neurology	CIDP	None
R13	Female	45	No	Parent	White British	Post degree qualification	Medical	Arthrogryposis	Positive
R14	Female	32	No	Parent	White British	Degree or equivalent	Medical	Osteogenesis imperfecta	None
R15	Female	35	No	Parent	White British	Degree or equivalent	Medical	Unknown developmental disorder	None
R16	Male	39	No	Parent	White British	To age 18 (A level or equivalent)	Medical	Unknown developmental disorder	None

PAIVS: Pulmonary atresia with intact ventricular septum; CIDP: Chronic inflammatory demyelinating



Case study methods

G.1 Sequence analysis methods

Sequence alignment and variant calling was performed within BaseSpace [334] using ISAAC Whole Genome Sequencing v 4 [335]. Sequence reads are aligned to the human reference genome [336]. Single nucleotide variants and short insertions and deletions were annotated and filtered using VariantStudio v2.2 [337]. Structural variant analysis was performed using BreakDancer [338]. Copy number variation analysis was undertaken using BIC-seq software [339]. Sequence variants with a minor allele frequency (MAF) of greater than 1% within all populations of 1000 genomes data [207] and the NHLBI exome sequencing project [206] were not analysed.

G.2 Cardiac phenotyping

- **On examination:** Pulse 40 (regular), JVP not elevated, LV impulse normal, heart sounds normal with no additional sounds.
- **12-lead ECG:** Sinus bradycardia, rate 37 with normal axis and normal conduction. PR interval 176, QRS duration 110. Normal voltages. The pattern of repolarisation is broadly normal, albeit with a prominent U-wave which merges with the terminal T-wave in V2 to V4. QT interval, not including the terminal U-wave, gives an absolute QT value of 498 and a QTc (Bazett formula) for 390.

- **24-hr tape:** None of the absolute QT interval measures were longer than the measurement made on the 12-lead in outpatients and the large majority were below that (in the 410 to 470 ms range). Corrected QT findings are all well within the normal range, although the QT correction algorithm is not completely reliable with the low heart rate. Resting heart rate minimum of 36 beats per minute and maximum of 90 beats per minute.
- **Exercise tolerance test (ETT):** Patient achieved an impressive two minutes of stage VII of the Bruce protocol, with a good haemodynamic response and no arrhythmias. QT interval was somewhat prolonged in recovery. For example QT at 4 minutes into recovery (a time point proposed to have sensitivity and specificity for detecting manifestations of LQTS) was just over 400 ms at heart rate 100, giving a corrected QT in the abnormal range. Peak heart rate response was lower than might typically be expected at 164 beats per minute. Heart rate slowing was also delayed in recovery. This is unlikely to reflect lack of fitness but may be an indicator of some abnormality. The pattern of repolarisation became subjectively abnormal, with some notching of T-waves at peak exercise and early recovery.

H

Clinical study materials

H.1 Further methods

H.1.1 Variant extraction and analysis

Chromosome co-ordinates for each gene and transcript were obtained from Ensembl GRCh37 [297]. A single BED file (tab-delimited text file that lists the chromosome number, start and end co-ordinates for each gene), was created to include all the genes undergoing analysis. The gene name, Ensembl gene reference ID (ENSG) and canonical transcript ID (ENST) were also included in this file. Variant data was then extracted from the relevant genes from BRRD data. A python script was written to combine all the analysis steps detailed in Table H.1 into a single script, taking the relevant details from the BED file. This analysis was guided by KT, a specialist clinical scientist in cardiac genetics.

Table H.1: Variant analysis steps aggregated into a single python script

Analysis steps	Tool used
Extract variant data from regions of interest (genes) from the BRRD merged-VCF files (release 20161012)	Tabix
Generate a list of the sample IDs that are listed in this VCF file	Bcftools
Generate a list of case and control Sample IDs	Grep
Annotate variants in VCF file	SNPEff
Separate the different annotations of each variant for the different transcripts onto a new line	SNPEff perl script
Separate the VCF into case and control VCF	SNPSift
Compress genotypes (remove individual sample genotype data from VCF and create a homozygous/heterozygous/missing count for each variant)	SNPSift
Filter variants (PASS filter, ExAC MAF $< 1 \times 10^{-4}$, ENGS ID, Canonical ENST ID, impact predicted to be HIGH or MODERATE.	SNPSift
Extract fields of interest	SNPSift

H.1.2 Included cohorts

Table H.2: Cohorts included in preliminary analysis of ICC-associated genes

Project	Numbers (n = 7,877)
Bleeding and Platelet Disorders (BPD)	857
Ehler Danlos and ED-like Syndromes (EDS)	15
Genomics England Rare Disease Pilot	1,965
Pulmonary Arterial Hypertension (PAH)	765
Primary Immune Disorders (PID)	1277
Specialist Pathology: Evaluating exomes in Diagnostics (SPEED)	1173
Thrombogenomics (BPD)	55
BPD with Autism Spectrum Disorder	62
Stem Cell and Myeloid Disorders	139
Primary Membranoproliferative Glomerulonephritis	133
BPD Co-segregation	25
Controls for WGS protocol testing	5
Multiple Primary Malignant Tumours	376
Steroid Resistant Nephritic Syndrome	161
Intrahepatic Cholestasis of Pregnancy	140
Neuropathic Pain Disorders	113
Early WGS cohort (PAH, PID, SPEED)	373
Cerebral Small Vessel Disease	184
Leber Hereditary Optic Neuropathy	59

H.2 SCARFE materials

Included in this section are the following SCARFE documents, in order:

1. Opt-out letter (1 page)
2. Invitation letter (1 page)
3. Participant information sheet (3 pages)
4. Consent form (2 pages)



BioResource contact no.:

Participant name

NHS no.

Date

Address

Dear M/s

Thank you for taking part in the BioResource for Rare Diseases (eg Bleeding and Platelet Disorder). The study is continuing and we hope to have results to share with you in the coming year, if you agreed that you wanted this.

You may recall that when you gave consent for the BioResource for Rare Diseases, you were asked to agree to be invited to take part in future medical research studies.

It is possible that some of these studies might give you **information about your current or future health, or genetic information which can be passed from parent to child**. This information may not be related to {...}.

If you **DO NOT** wish to be contacted about this kind of study, please let us know. If you don't feel comfortable with receiving health or genetic information that is not related to {...}, please return the reply slip below, or email.....before {date of letter plus one month}.

With kind regards

Yours sincerely

BioResource Team

Reply slip

Name (pre-printed)

Address (pre-printed)

NHS no.

I do not want to be contacted by the BioResource Team about any study that might provide **information about my current or future health, or genetic information which can be passed from parent to child**, if it is not be related to {...}.

Signature.....



BioResource contact no.:

Participant name

NHS no.

Address

Date

Dear M/s

Thank you for taking part in the BioResource for Rare Diseases { eg Bleeding and Platelet Disorder}. You may recall that when you gave consent for the BioResource for Rare Diseases, you were asked to agree to be invited to take part in future medical research studies.

We would now like to invite you to take part in a study run by a leading clinical research team in Oxford. An information sheet about the study is enclosed.

If you would like to discuss the study by telephone, please ring the number at the top of this letter. Alternatively please visit the study website at: www.scarfeoxford.com

We would be most grateful if you would let us know whether you wish to consider taking part below, then return the reply slip in the envelope below to the Oxford team.

If we do not hear from you within 4 weeks, we will contact you again.

With kind regards

Yours sincerely

BioResource Team

Name (pre-printed)

Address

NHS no.

1. I wish to find out more before deciding to go to Oxford. Please contact me on:
phone/email:

2. I wish to come to Oxford for a discussion. Please send me an appointment and spit collection tube.
3. I do not wish to take part in this study because: (you don't have to give a reason, but it is helpful):

Invitation letter

Version/Date: 1.

Potentially actionable 'secondary genomic findings' in inherited cardiac condition genes: a case-control study evaluating clinical significance and psychosocial impact of disclosure.

Prof Hugh Watkins IRAS Project number: < >

1



PARTICIPANT INFORMATION SHEET

Oxford contact: Liz Ormondroyd 01865 234676 liz.ormondroyd@cardiov.ox.ac.uk
 BioResource contact: 0800 085 3650, rarediseases@bioresource.nihr.ac.uk

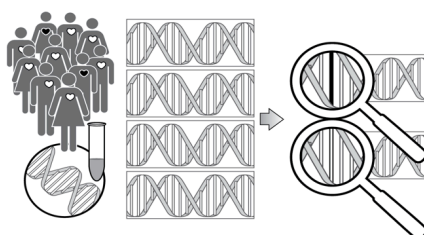
Secondary Cardiac Findings Evaluation (SCARFE)

We would like to invite you to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. *Please contact us if you would like more information.*

What is the purpose of the study?

The study is a follow-on study from the NIHR BioResource - Rare Diseases. As part of that study you gave a blood sample for **Genome Sequencing**, in which the whole of your genetic code was looked at.

Genome Sequencing identifies a very large number of genetic **variants** – differences between one person's genetic code and another's. These variants are not well understood at present.



When the genome sequences of all BioResource participants were analysed, some were found to have variants that MAY be linked to some forms of heart conditions that run in families. These are rare diseases affecting the heart muscle, or the electrical activity of the heart, rather than the more common forms of heart condition caused by blockage of arteries. It is also possible that many people have a gene variant but their heart is not affected.

The heart conditions are often very mild, and many people do not have any symptoms. Occasionally these conditions can be dangerous. These conditions can be picked up by heart tests, such as echocardiogram and ECG (heart tracing). People who are found to have one of the heart conditions can be monitored by specialist doctors, treatment can be provided if needed, and the risk of the heart condition causing problems can therefore be reduced.

The SCARFE study aims to find out:

- whether gene 'variants' actually cause changes in the heart, by doing heart tests, and if so, how often
- what people think about learning about health and genetic information in this way

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- whether people act on any recommendations given by doctors as a result.

As Genome Sequencing is becoming more common, variants with *possible* significance for health will be found more often. The purpose of the study is to collect information that will help doctors and researchers understand whether people should be told about such variants when found in their genome. Results of the research will be useful for developing future policy in the NHS around how different genetic variants are handled.

Why have I been invited?

You have been invited because you are a member of the NIHR BioResource - Rare Diseases. We are inviting adults aged under 70 who are not known to have a heart condition to take part in this study. **Both people with and without a gene variant that might be linked to a form of heart condition are being invited**; this is to ensure that the tests are done without any bias.

Do I have to take part?

No. Taking part is entirely voluntary.

It is up to you to decide whether to take part. If you decide to take part, you are free to change your mind at any time without giving a reason. This would not affect the standard of clinical care you receive now or in the future. If you decide that you no longer wish to continue with the study, we would retain any data already obtained from you unless you request otherwise.

What will happen to me if I decide to take part?

You would be invited to attend one study visit to the John Radcliffe Hospital in Oxford, which could take up to half a day, plus travel to Oxford, and take part in telephone questionnaires two weeks, three months and one year after your visit. All contacts you would have with the research team are shown in the diagram on the next page.

At the study visit, the study team would talk to you about the heart tests and what they might show. The team, which includes experts in this field, would discuss the study fully with you before you decide whether to take part. If you wished to go ahead, we would ask you to sign a consent form. Before and during the heart tests, you and the study team would not know whether or not you have a genetic variant.

1. You would then be offered tests on your heart, to look at the structure of your heart, and at the electrical activity through the heart. You may not need to have all of the tests and the study investigator would inform you at the visit which test would be relevant.

Tests we might want you to have include:

- an echocardiogram (heart scan, ECHO)
- an ECG
- an exercise test (ETT)
- a heart MRI (CMR) including cannulation (further information provided in separate information sheet)
- a 24 hour tape

More information about each test can be found at the end of this information sheet. Please note that not all tests are necessary; we would discuss with you at the study visit which tests we would like to do.

On the same day, the study team would see you after the tests and explain all the results, if you wanted to know them. The BioResource will provide, in a sealed envelope, information

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about whether a genetic variant was found in each participant's sample, which we will open after your heart tests. We would tell you this genetic information, whether there are any changes in your heart and what action, if any, might be recommended for you. We would send a summary letter to you and your GP who would organise for you to be seen in a specialist NHS clinic if necessary.

2. We would ask you to fill in a questionnaire at, and on three occasions (by phone), after your study visit. You would be contacted, at a time convenient to you, 2 weeks, 3 months and one year after your study visit to complete the questionnaires. The questionnaires are short, and can be answered during the telephone call. You will also be able to discuss any concerns, or ask further questions during these phone calls.
3. We might also ask you to take part in an optional interview with a researcher to find out your thoughts about taking part in the study. This would take about one hour and would be arranged at a time and place to suit you – you would not have to travel to Oxford.
4. We would also ask your permission to access data from your hospital notes relating to your participation, if you later see a heart specialist doctor as a result of taking part in this study.



What should I consider?

It is possible that taking part in this study will give you information about your health. There is a chance that we might recommend that you see a specialist doctor, who might suggest taking medication or cutting down on very strenuous activity. Since the group of heart conditions we are studying run in families, we might find genetic information that would also be important for your relatives.

We are happy to discuss this by phone before you come to Oxford, and would discuss it fully at the study visit before you need to decide whether to take part.

Are there any possible disadvantages or risks from taking part?

There is a reasonable chance that, through taking part in this study, you learn that you have signs of a heart condition, or are at risk of developing one. This might be upsetting, and cause worry for you about your own health or the health of your relatives. The study team is made up of specialist heart doctors and genetic counsellors who will go through these risks with you fully, before, during and after the study visit.

Taking part would require you to spend part of a day in a research clinic in Oxford, and having some tests to look at your heart. There are some small risks associated with some of the tests, which are listed at the end of this information sheet.

What are the possible benefits of taking part?

On rare occasions, the heart conditions we are studying can be dangerous, even in people who have no symptoms. The heart conditions run in families, so there could be a chance that your relatives might have a heart condition. We would discuss these issues fully with you: what the results of the tests done in this study might mean for you, and advise whether you should be seen in a specialist NHS clinic.

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The study will NOT tell you about your risk of ALL heart conditions – there are other heart conditions that don't usually run in families, and different tests are needed to detect those conditions.

Your participation may also help us learn whether this approach is useful for developing future policy in the NHS around how different genetic variants are handled; this is likely to be very important as more and more people will be having their genomes sequenced.

Will my General Practitioner/family doctor (GP) be informed of my participation?

If you take part, we will send you a letter summarising your study visit, the results of your tests and whether you should see a specialist in the NHS. A copy of this letter will be sent to your GP.

Will my data and my taking part in the study be kept confidential?

Yes. If you express an interest in the study, the reply slip enclosed with this information will be sent to the study team in Oxford who will then have your name and contact details. They will send you an appointment. Your personal information will be kept confidentially and securely by the study investigators. You will be given a unique study code which will be used wherever possible. The list that links the study specific code with your identifying details and any research data collected during the study will be kept securely on Hospital computers until ethical approval ends, at which point all identifying personal information will be destroyed. Documents that contain your personal information will be stored securely in locked offices in the University. Only authorised members of the research team will have access to this information. Any identifiable information that is stored electronically will be stored on secure password-protected computers. Questionnaire data and interview data will be anonymised, that is, it will be linked to you only via a study code.

The study investigator is responsible for keeping these documents securely.

If you take part in an interview, this will be audio recorded, but will not contain your name or other identifiable information. Anonymised audio-recorded interviews will be stored on secure computers and destroyed at the end of the study.

Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

Will I be reimbursed for taking part?

We will offer a £50 voucher to people who attend a study visit, to compensate for time given up. We will also reimburse reasonable travel costs to Oxford, and reasonable other costs, for example child care or loss of pay, are incurred by a visit to Oxford, if applicable. Compensation and travel costs will be paid even if you decide at the study visit that you do not wish to take part in the study, or later withdraw.

What will happen if I don't want to carry on with the study?

Participation is voluntary and you may change your mind at a later stage. Withdrawal would not affect the clinical care you receive from any relevant service. If you withdraw from the study, unless you state otherwise, information collected whilst you have been in the study will be used for research as detailed in this participant information sheet.

What will happen to the results of this study?

We plan to publish the results in medical journals, which can appear in print and online. We will also present findings at medical conferences. We will take care to ensure that you will not be identifiable from any report, presentation or publication placed in the public domain and your personal and clinical details will remain strictly confidential. We will provide a summary for participants on our website which can also be posted on request. You would have no legal right to a share of any profits that may arise from the research.

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What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Professor Hugh Watkins on 01865 234678 hugh.watkins@rdm.ox.ac.uk, or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrig@admin.ox.ac.uk.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact PALS Office, Level 2, main entrance, John Radcliffe Hospital Headley Way, Headington, Oxford OX3 9DU, Tel: 01865 221473, Email: PALS@ouh.nhs.uk, website <http://www.ouh.nhs.uk/patient-guide/feedback/pals.aspx#jr>.

How have patients and the public been involved in this study?

We have an active Genomics Patient and Public Involvement (PPI) group who have reviewed and contributed to the study design and this information sheet. For more information please email oxford.geneticsPPI@ouh.nhs.uk.

Who is organising and funding the study?

This research has been designed and organised by Hugh Watkins, Professor of Cardiovascular Medicine, University of Oxford. This research is funded by the British Heart Foundation and the Oxford Biomedical Research Centre.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by [insert REC name] Research Ethics Committee.

Further information and contact details:

Please contact BRRD team by telephone on 0800 085 3650, e-mail rarediseases@nhrbioresource.org.uk, or contact Liz Ormondroyd, liz.ormondroyd@cardiov.ox.ac.uk on 01865 234676.

Thank you for reading this information.

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Information about heart tests.

Please note that not all tests may be required. We will discuss with you which tests we will need to do to be able to say whether you have signs of an inherited heart condition.

If we ask you to have an MRI scan of your heart (CMR), we will provide information separately about that.

Tests will take place at the Cardiovascular Clinical Research Facility (CCRF) which is a University research facility located at the John Radcliffe hospital.

Echocardiogram (heart scan/echo; 30 minutes)

This ultrasound scan is a safe and painless procedure. You will be asked to lie on a couch on your left side. A probe is placed on your chest and lubricating jelly is used so the probe makes good contact with the skin. Ultrasound waves then create images of your heart on the scanner monitor.

Risks: Although echocardiography carries no risk of physical harm to the participant, there is a risk of personal discomfort or embarrassment; to minimize this, we will provide gowns to maintain modesty and dignity at all times.

ECG (10 minutes)

Small pads (electrodes) are attached to certain points on your chest and arm in order to monitor the electrical properties of your heart.

Risks: This is a safe and painless procedure. Electrodes attach to the chest with adhesive, which may occasionally cause mild skin irritation.

Exercise tolerance test (ETT; 30 minutes)

The ETT monitors the heart while exercising on a treadmill. The test is carried out by a cardiac physiologist who will stay with you during the test. The physiologist will first monitor your heart while you are sitting down, and then monitor your heart during exercise. 10 electrodes are put on your chest. The electrodes are small, sticky patches, connected to a monitor with leads. The monitor will record your heart's rhythm and electrical activity. S/he will also put a blood pressure cuff around your arm, to measure your blood pressure during the test. After monitoring your heart at rest, the physiologist will ask you to walk on a treadmill. You walk on the treadmill, slowly at first. Every three minutes the treadmill gets slightly steeper and faster, and your heart works harder. After 15 minutes the treadmill slows down gradually. If you feel any pain or discomfort you can ask the physiologist to stop the treadmill.

Risks: ETT is generally considered safe, however, very occasionally some people have significant changes in their heart rate and rhythm that requires medical attention. Medical personnel will be available throughout the testing. Electrodes attach to the chest with adhesive, which may occasionally cause mild skin irritation.

24 hour tape (Holter monitor; 10 minutes to fit)

Three electrodes, connected to a monitor, are attached to the chest. The monitor is small and light (about the size of a mobile phone) and can be kept in a pocket, attached to a belt or worn around your neck. The tape can be returned by post.

Risks: Wearing a monitor has no risks and causes no pain. Holter monitors have small pads (electrodes) which attach to the chest with adhesive, which may occasionally cause mild skin irritation. Participants are unable to bathe, shower or swim while wearing the monitor as it must not get wet.

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Study Full Title	Potentially actionable 'secondary genomic findings' in inherited cardiac condition genes: a mixed methods feasibility study using genotype driven recruitment to evaluate clinical significance and psychosocial impact of disclosure.
Participant ID	
Researchers	Prof Hugh Watkins, Dr Liz Ormondroyd, Kate Thomson

Please initial box

1. I confirm that I have read and understand the information sheet dated <insert date and Version number> for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
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 agree to take part in this study. I understand and agree that participation will involve tests on my heart, as requested by the study team. ☐
4. I understand that, through participation, I might receive information that could be relevant for my health and that of my relatives. ☐
5. I understand that my participation will also involve completing study questionnaires at, and two weeks, three months and one year after, my study visit. ☐
6. I understand that the information collected about me may be used in an anonymous form to support other research in the future. It will not be possible for me to be identified by it. ☐
7. I understand that anonymised information collected during this study may be used in research publications. I give consent for use of information for any publications that may arise from the research. ☐
8. I agree to my General Practitioner being informed of my participation in the study, and the results of any tests I undergo as part of the study. ☐

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9. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities, where it is relevant to my taking part in this research. I permit these individuals access to my records.

☐

OPTIONAL:

10. I understand and agree that I may be asked to take part in a recorded interview about my participation in the study. I will not be identifiable from my interview. I agree to take part in an interview if asked, and to the use of anonymised quotes in research reports and publications.

☐

Name of participant

Signature

Date

Name of person taking
consent

Signature

Date

*For researchers (✓) to document: original kept & copy given to participant (_);
copy inserted into medical notes (_)*

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