UNIVERSITY OF SOUTHAMPTON

Faculty of Medicine

Incidental findings from genomic tests: Exploring the ethical issues and implications for practice

by

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Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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INCIDENTAL FINDINGS FROM GENOMIC TESTS: EXPLORING THE ETHICAL ISSUES AND IMPLICATIONS FOR PRACTICE

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Rapidly declining costs and increasing availability of whole-genome analysis means that clinical genetic testing has shifted from a targeted approach to broad analysis that can provide many more clinical predictions than previously possible. This thesis explores ethical issues in the discovery of clinically relevant findings not suspected from signs, symptoms or family history. In particular the consent and disclosure practices pertaining to such incidental findings (IFs) were explored from both health professional (HCP) and patient perspectives.

Phase 1 reviewed current practices and explored lay and professional experiences of and views about ethical issues surrounding IFs. 27 clinic observations and 48 in-depth interviews (32 HCP and 16 patient) were analysed thematically. Observations demonstrated that the concept of IFs was often not explained at the point of testing, or if it was, this was rarely recalled by patients. In-depth interviews demonstrated that the concept of IFs was variably understood. Some findings, classed as 'incidental' were in fact only potential IFs at the time of reporting. Only a sub-group of these became clear IFs, and then only when other complex investigations, including ones in relatives, had been analysed. Both patients and HCPs thought that seeking explicit consent for IFs was important, often using rights-based language, but both groups also described difficulties in gaining explicit consent for a broad and open ended concept. Some thought that actionable results should be provided regardless of consent but acknowledged that this might result in perceptions of paternalism. Furthermore, there were very different perceptions of what a good definition of actionable would be. Despite these concerns patients who had received an IF without giving specific consent, were pleased to receive them and did not feel their rights had been infringed.

The aim of Phase 2 was to design a questionnaire to examine whether key findings from phase 1 resonate with a larger and representative sample of UK HCPs who manage genetic testing. The questionnaire was developed through a process of cognitive interviewing and pre-testing and is now ready for piloting and administration as post-doctoral work.

Despite the focus on specific or 'informed' consent, this research found support for broad consent for the notion of IFs rather than specific consent to any particular IF or type of IF. This research provides an insight into the gap between the technological advances in genomics and their translation into clinical practice. Infrastructures to support consent and communication of IFs, need to be developed as genetic tests become routine for most medical specialities.

Table of contents

List of tables

List of figures

List of boxes

List of appendices

DECLARATION OF AUTHORSHIP

I, **Gillian Susanne Crawford** declare that this thesis and the work presented in it are my own, and has been generated by me as the result of my original research.

Incidental Findings from genomic tests: Exploring the ethical issues and implications for practice

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:

    a) *Crawford G*, Fenwick A and Lucassen A (2013) A more fitting term in the incidental findings debate: one term does not fit all situations. *Eur J Hum Genet* 22, 957
    b) *Crawford G*, Foulds N, Fenwick A, Hallowell N and Lucassen A (2013) Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. *Genetics in Medicine*, 15, (11), 896-899
    c) Shkedi-Rafid S, Dheensa S, *Crawford G*, Fenwick A, Lucassen, Anneke (2014) Defining and managing incidental findings in genetic and genomic practice. *Journal of Medical Genetics*, 51, (11), 715-23
    d) Dheensa S, Fenwick A, Shkedi-Rafid S, *Crawford G*, Lucassen, A (2015) Health-care professionals' responsibility to patients' relatives in genetic medicine: a systematic review and synthesis of empirical research. *Genetics in Medicine*. Online publication 25th June 2015. doi:10.1038/gim.2015.72
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Signed:

Date: 25TH May 2016

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Finally and most importantly this thesis is dedicated to Fraser Crawford Clark, who we miss every single day. When days were tough, I would think of your smile, laugh and kind heart and this would spur me on.

Abbreviations:

American College of Medical Genetics and Genomics	ACMG
Array comparative genomic hybridization	aCGH
British Society of Human Genetics	BSHG
Clinical Research Network	CRN
Direct to consumer	DTC
European Society of Human Genetics	ESHG
Familial Adenomatous Polyposis	FAP
Food and drug administration	FDA
Fluorescent in situ hybridisation	FISH
Genetic health care professional	gHCP
Genomic medicine centre	GMC
Health care professional	HCP
Human Genetics Commission	HGC
Human genome project	HGP
Incidental findings	IFs
Joint Committee on Medical Genetics	JCMG
Mixed methods research	MMR
National Institute of Health	NIH
National Institute of Health Research	NIHR
Next generation sequencing	NGS
Phenylketonuria	PKU
Public Health Genomics Foundation	PHG Foundation
Shared decision-making	SDM
Thematic Analysis	TA
Wessex clinical genetics service	WCGS
Wessex Regional Genetics Laboratory	WRGL
Whole exome sequencing	WES
Whole genome sequencing	WGS

Development of the research proposal

Whilst finishing a degree in health care studies in 2001 I saw an advert for the post of Genetic Counsellor at the Oxford Regional Genetic Service. Despite not being entirely sure what a genetic counsellor did, my interest was aroused because the post focused on cancer genetics and I had just finished a dissertation on the genetics of breast cancer. I was working as an oncology nurse and had worked in a number of different units, including medical oncology, haematology and bone marrow transplantation.

The role of a cancer genetic counsellor involves the assessment of a family history of cancer; determining whether heritable factors are likely to play a part; discussion about possible genetic testing, surveillance or risk reducing options; and offering opportunities for patients to participate in research studies.

To my delight, I was appointed, and was tasked with seeing families referred to the NHS cancer genetic service as well as offering recruitment to a national chemoprevention trial. Two years later I moved to an equivalent post at the Wessex Clinical Genetics Service (WCGS) in Southampton where I was able to develop this dual clinical/research role, thanks to initial investment from Imperial Cancer Research Fund, later Cancer Research UK. With the advent of the Clinical Research Network (CRN) – and thus help from CRN nurses in recruitment to research – I was able to focus more on issues that arose in clinical practice. For example, I joined a team researching the ethical aspects of genetic testing of children for adult onset disease; another that was examining the boundary between research and clinical care; and a third studying the sharing of genetic information within families.

In 2008 a new genetic technique - array comparative genome hybridisation (aCGH) - was introduced, which increased the resolution by which the genetic code could be examined. This improved the diagnostic rate but at the same time increased the rate of findings that were unexpected, or incidental to the original reason for the genetic investigation. I remember an example where the result in a young girl with developmental delay showed that she also had a high chance of developing breast cancer as an adult. Whilst such

incidental findings (IFs) were by no means new in genetics - or in medicine - these new more sensitive techniques made it likely that the frequency of discovery would increase.

I was interested in exploring the experiences of families in which such IFs were made, from the point at which a test was offered, to the communication of an IF and its subsequent management. I wanted to know what parents thought about the possibility of discovering a predisposition to an adult onset disease when they were primarily interested in finding a diagnosis for their child's current problems. How could the health service best handle such information and how did health professionals think they should adapt their practice?

Over the last 5 years there has been much discussion about these issues and international guidelines have been issued, disputed and amended. Many articles exploring the concept of incidental findings have been published, but very little research had looked at actual patient and health care professional (HCP) experience of managing them. My interest in ethical issues in clinical genetic practice, and my personal experience of managing IFs as a genetic counsellor, led me to develop a research proposal that would enable me to examine these ethical and practical challenges in depth.

I was excited to hear about the National Institute of Health Research (NIHR) programme of doctoral fellowships and the opportunity they presented to further develop my research skills. I applied for, and was awarded, a Clinical Academic Training fellowship to explore issues generated by the identification of IFs, with particular reference to consent and disclosure practices. I planned to employ a mixed methods design, with a qualitative phase one and quantitative phase two giving me a range of research experience and opportunities for training in areas where I had little experience. In phase one I examined patient and HCP views and experience of managing IFs in clinical practice. Phase two was about developing a questionnaire based on the findings from phase one to ascertain whether the views and experiences expressed in phase one were represented in a larger cohort of HCPs who order genetic tests.

When I wrote the research proposal for my fellowship there was no guidance on the management on genetic IFs in clinical practice. By the time I started my research the Joint Committee of Medical Genetics (JCMG) and the Royal College of Pathologists had

produced a report on consent and confidentiality in clinical genetic practice. This included a section on IFs, commenting that:

"Some genetic tests have the potential to reveal incidental or unexpected information. More research is needed as to how this can best be addressed in both consent and disclosure practices, as well as how to address the implications for other family members."[1] (p.10)

My fellowship was therefore very timely and its research findings would contribute to the developing body of knowledge on how best to manage genetic IFs in clinical practice.

Supervision and training

This study has been supervised by Professor Anneke Lucassen and Dr Angela Fenwick, with support from Dr Claire Foster in Health Sciences. I have met with Anneke Lucassen and Angela Fenwick fortnightly with additional email contact, and with my third supervisor, Claire Foster every six to eight months. Clinical supervision was provided by Dr Tara Clancy, Consultant Genetic Counsellor at The Manchester Centre for Genomic Medicine and I have met with her about every six months (more frequently at the beginning of the fellowship) and discussed any issues that arose in between by telephone or e-mail.

Chapter 1: Introduction

Setting the scene

The last few years have seen dramatic changes in the ability of genetic tests to analyse a person's genetic code routinely. The Human Genome Project (HGP) completed the first sequence of an entire human genome at great cost and over several years.[2] The speed at which this sequencing can now be done has increased enormously and the costs similarly decreased, so that the HGP is now being brought into clinical practice.

These recent developments in genomic technologies have changed the nature of genetic testing from a focused, relatively narrow inquiry to broader large scale searches, generating large amounts of data and increasing numbers of genetic diagnoses.[3] Instead of targeting particular sections of the genetic code for analysis, based on signs and symptoms, the clinician can now analyse the entire code with a more realistic hope of discovering either an explanation for clinical features or for a family history of a condition. Some tests are now routinely used in clinical practice (for example, aCGH) and others are still being evaluated in research laboratories (for example, Whole Genome Sequencing or WGS).

A fishing analogy illustrates this change in approach. A genetic test targeted at a particular condition is like fishing with a rod and line for a specific fish, such as salmon. The new technologies examine the whole genome for abnormalities, which is like trawling, where a wide net indiscriminately catches all the fish in its path.

However, this increased efficiency brings potential problems. What if an entirely unexpected finding is made? There may be no family history to suggest this could be picked up in the genomic net, but it still needs to be dealt with once found. Or can we throw it back into the ocean if a patient explicitly says at the beginning of the process that they would not want to know? Should we only respond to certain things in the genetic code and ignore anything that is not relevant to the current clinical question?

Interest in these issues was only just beginning as I wrote the application for my NIHR doctoral fellowship. Whilst answers to some of these questions have been proposed over the years, the debate continues, without, as yet, international consensus. My research

focuses on health professionals, patients and their families and their experiences of these paradigm shifts in genetic technologies.

I begin by outlining genetic developments that have shaped current clinical practice. In order to contextualise this, and the issues that arise from it that I have researched in this PhD, I will first sketch a timeline for genetic knowledge from Mendel to the current day.

Genetics- a brief history since Mendel

Gregor Mendel was a nineteenth century monk much credited with being the first to discover heritable traits through pea plant experiments and the transmission of coloured flowers. His description of recessive and dominant traits is reflected in the term Mendelian inheritance, still used today.

The identification of heritable factors and their contribution to multi-factorial disease genetics has given great insights into disease mechanisms but are limited in their clinical utility since their individual predictive or diagnostic value is low and insufficient details are known about how different susceptibility factors interact with each other. For example, genetic susceptibility factors in diabetes cannot yet diagnose or predict the condition with a high degree of confidence because other factors, stochastic and environmental, are likely to be relevant. Genetic test results will often not translate to a meaningful test for relatives or provide definitive information for the patient about the cause and trajectory of their disease.

Table 1 highlights key genetic discoveries since Mendel's work, upon which current practice is built.

A brief overview of genetics

Most cells in the human body contain 23 pairs of chromosomes. 22 pairs are the same in men and women and one pair determines gender; females have two X chromosomes whilst males have one X and one Y chromosome. An individual inherits one of each pair of chromosomes from each of their parents. Chromosomes are chunks or sections of the genome, tightly coiled DNA. Sections of DNA correspond to genes which often produce proteins that ultimately determine particular characteristics, for example hair and eye colour. The code producing regions of a gene, from which messenger RNA (mRNA) that carries the code is transcribed, are known as exons. The intervening portions of DNA,

Table 1: Timeline of key genetic discoveries over the past 150 years

	Event/discovery
1866	Gregor Mendel publishes work on hereditary traits in peas. He noted that certain traits are passed from parent to offspring. Certain traits are dominant whilst others are recessive
1869	Friedrich Miescher isolates DNA from cells and calls it nuclein
1890s	De Vries – a Dutch botanist- rediscovers Mendel's experiments and coins the term 'pangene' later to be abbreviated to gene, as well as the term 'mutation' when an error is introduced into one of these factors
1904	Bateson, Saunders and Purnett discover genetic linkage through their experiments on sweet peas
1911	Thomas Hunt Morgan's fruit fly experiments demonstrate that genes are located linearly along chromosomes
1944	Oswald Avery, Colin Macleod and Maclyn McCarty show that DNA (not proteins) is the molecule that transforms the properties of cells
1950	Erwin Chargaff discovers base pairs are matched, there is an adenine (a) for every thymine (t) and a cytosine (c) for every guanine (g)
1953	James Watson and Francis Crick described the double helix structure of DNA based on Rosalind Franklin's X-ray diffraction work
1955	Joe Hin Tjio reports 46 as the exact number of chromosomes in human cells Newton Morton developed the LOD score, a statistical test used in linkage analysis
1959	Jerome Lejeune discovers that Down syndrome is caused by trisomy 21 (3 copies of chromosome 21) and this extra chromosomal material interferes with normal development
1961	Robert Guthrie develops a method to test newborns for the inherited metabolic defect phenylketonuria (PKU) which was to be rolled out across the world as a newborn screening programme for a genetic condition
1971	Marina Seabright developed G-banding, a technique to identify chromosome banding patterns. This became the technique most commonly used to look at the number and appearance of chromosomes 'the karyotype'
1977	Fred Sanger developed DNA sequencing technology, the process of determining the precise order of nucleotides within the DNA molecule. This was the most widely used method for sequencing for the next 25 years and is termed first generation sequencing
1981	Prooijen van-Knegt developed the FISH technique (fluorescent in situ hybridisation) to detect specific DNA sequences on chromosomes
1983	A genetic marker for Huntington's disease is found on chromosome 4 allowing for

	predictive testing in families through linkage analysis
1983	Kary Mullis developed the polymerase chain reaction (PCR) that allowed rapid copying of DNA segments, facilitating faster sequencing of DNA
1990	Launch of the Human Genome Project by The US National Institute of Health (NIH) with international collaborations (including the UK) to sequence the entire 3 billion base pairs of one human genome
1990s	Pat Brown developed DNA microarrays a technique that measures the expression levels of large numbers of genes simultaneously. When this technique is used in conjunction with comparative genomic hybridisation (a method to analyse copy number variants) it allows a locus by locus measure of copy number variants, identifying deletions and duplications not previously seen under the microscope
2001	The International Human Genome Sequencing Consortium published the first draft of the human genome in the journal *Nature* with the sequence of the entire genome's three billion base pairs some 90 percent complete
2002	Schouten developed the MLPA test (multiplex ligation-dependent probe amplification) a technique to detect variations in copy numbers of several genes at the same time
2003	Tony Blair and Bill Clinton announce the publication of the full sequence of the human genome
The past decade to today	Next generation sequencing (NGS) is based on massively parallel sequencing, during which millions of fragments of DNA from a single sample are sequenced in unison. Parallel sequencing facilitates high-throughput sequencing, meaning an entire genome can be sequenced in a matter of days, reducing costs and increasing the speed and numbers of samples that can undergo analysis at the same time

often described as 'junk DNA' in older literature but now known to play important regulatory functions, are known as introns. The exact number of genes contained within a genome is not yet known, but is thought to be about 20,000. Some heritable characteristics might be explained by a single gene, others by multiple ones and yet others by a combination of heritable, environmental and random factors.

Diseases, or strong predisposition to diseases, can be attributable to alterations (mutations) in single genes - so called Mendelian inheritance - or the inheritance can be more complex, or as yet unknown. Mutations can range in size from a single DNA base change to deletions, insertions or reorganisations of larger sections of the genome involving millions of base pairs.

One result from the increasing resolution by which we can now routinely study a genome is the discovery that a number of relatively large changes such as deletions, or particularly duplications, can actually represent normal variation rather than pathology. Early results of apparently diagnostic abnormalities have, with the passage of time and reporting in other people, turned out to be no such thing but an example of greater diversity in our genetic codes than we had imagined.

Types of inheritance

Mendel first described patterns of inheritance as dominant or recessive. What this refers to is that a mutation in one of the two copies of a gene may be dominant to the normal copy or recessive to it. For example, a mutation in the cystic fibrosis gene will have no effect on that person if they also have a normal copy of the gene. The mutation is recessive, and cystic fibrosis will only arise if a mutation is inherited from both parents. By contrast, a mutation in the BRCA1 gene is dominant to the normal copy; even if a person has only one mutated copy their chances of developing breast and ovarian cancer are dramatically increased. Subcategories include X-linked recessive inheritance, where the effect depends on whether the mutation is present in females (who have 2 copies of an X-chromosome) or in males (who only have one). For example, haemophilia, the blood clotting disorder of Queen Victoria's family, is due to a mutation on the X-chromosome. Females may carry it but since they have a functioning copy on their second X-chromosome they are unaffected. Males usually have a single copy of the X chromosome and will therefore be affected if it carries the mutation. Knowing how a condition is

inherited in families allows the recurrence risks for relatives to be predicted. It means that family members can be counselled as to whether they, their children or possible future children, are at risk of disease.

Gametes (eggs and sperm) randomly contain one or the other of each of an individual's 23 pairs of chromosomes, so that when they come together the resulting fetus has 23 pairs as usual. So for each conception, offspring have a 1 in 2 chance of inheriting a particular gene from a parent. The mode of inheritance will determine the effect of that gene in an individual. Table 2 summarises the types of inheritance.[4]

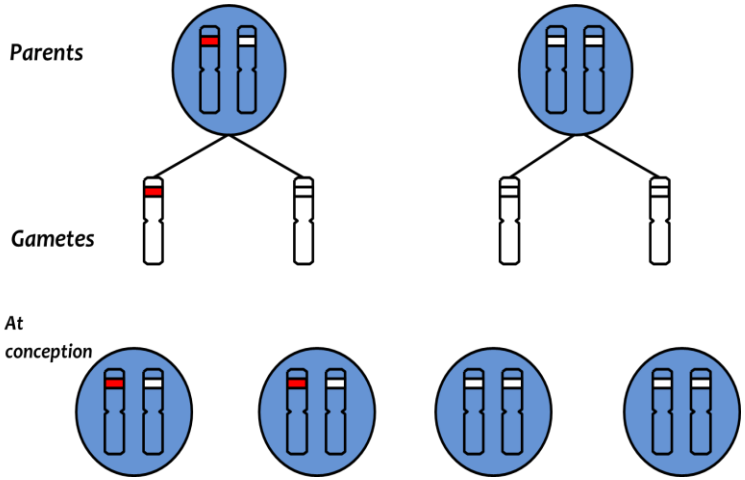
The development of genetic testing since the 1950s

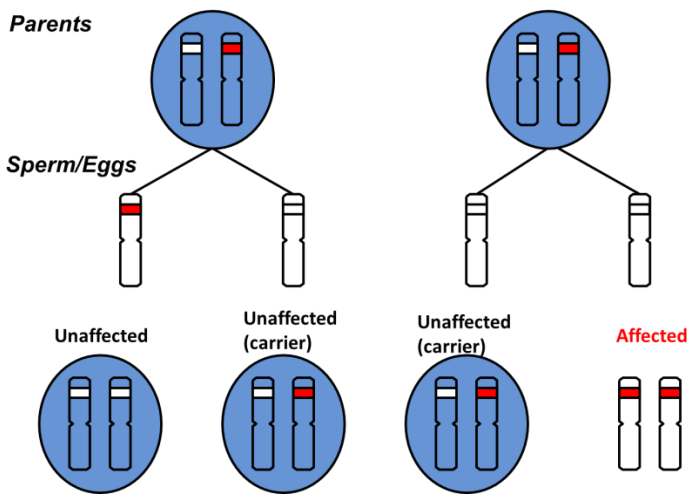
The earliest genetic testing to be introduced in clinical practice was the study of the morphology of chromosomes. Cytogenetics, the study of chromosomes, was the backbone of genetic practice from the late 1950s to the turn of the century. Cytogenetic analysis was offered for children with developmental delay and dysmorphic features.

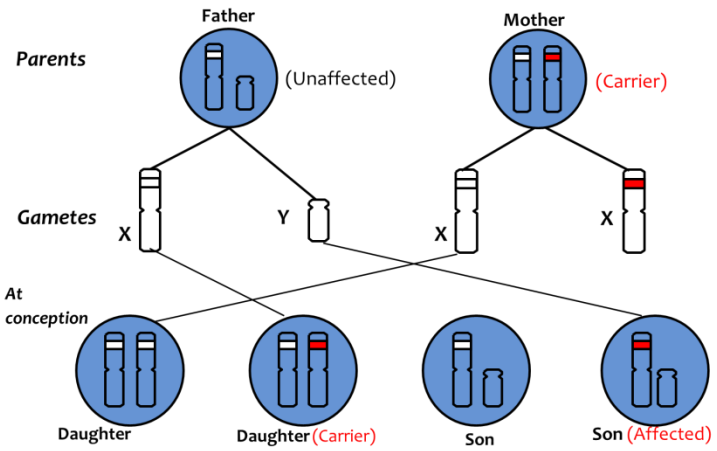
An early example of the detection of chromosomal abnormalities in clinical practice was the ability to diagnose aneuploidy (an abnormality in the number of chromosomes) such as Down syndrome, which is due to an extra copy of chromosome 21. Abnormalities could be visualised under the microscope when cells were grown in culture, chemically treated and stained. Techniques further developed in the 1970s and cytogenetic analysis of banding patterns (so called karyotype testing) remained the primary tool for the clinical assessment of patients with possible chromosomal abnormalities for many years. More recent developments such as fluorescent in situ hybridisation (FISH) enabled greater resolution than with the naked eye and improved the ability to determine a karyotype and report on any abnormalities in chromosome structure. However, this technique was still dependent on the resolution of the microscope and small abnormalities could be missed.

Array Comparative Genome Hybridization (aCGH) was developed in the late 1990s and represented a significant shift in the resolution by which genomes could be examined. Instead of visualising chromosomes, this technique compares a patient's genome with a reference genome and looks for imbalances, detected by colour change. It has the

Table 2: Types of inheritance

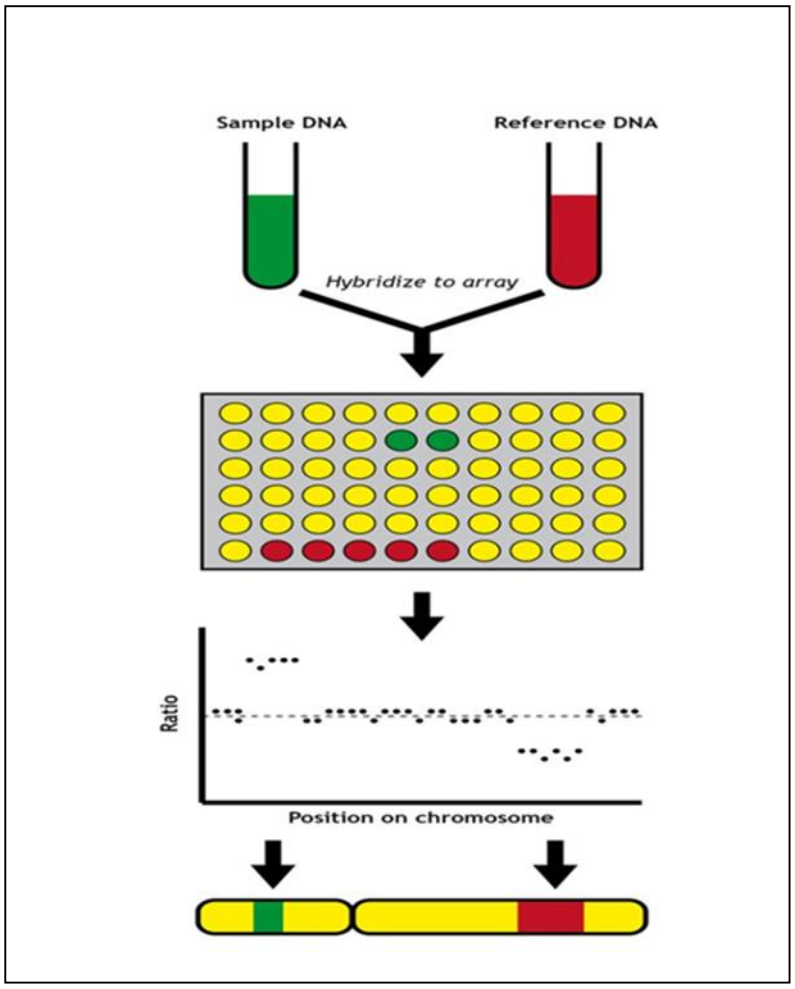
Autosomal Dominant	
	• Only one copy of a pair of genes is mutated for an individual to be susceptible to expressing the condition. • With each pregnancy there is a one in two (or 50%) chance that the offspring will inherit the disease allele from an affected parent. • Sometimes a dominant disease is not apparent in a parent, for various reasons. Firstly, some dominant conditions are the result of 'new mutations', so that neither parent of an affected person may have the condition. For example the new mutation rate in the cancer predisposition syndrome Familial Adenomatous Polyposis (FAP) is 30%. • Secondly, a dominant allele may be present but not evident in a parent. This is called variable penetrance, meaning that the effect of the altered gene may be modified by an individual's other genes and environmental and lifestyle factors. Breast/Ovarian cancer predisposition (BRCA1 and BRCA2) is an example of this. • Thirdly an altered gene may have variable expressivity, meaning that it affects individuals differently with a range of features, some of which may be minor enough to be unrecognised as part of a syndrome or simply accepted as a family trait. Neurofibromatosis type 1 is an example of this, the effects of which can range from minor brown patches on the skin to major physical, intellectual and neurological pathology. • Finally, some individuals may carry an expansion (an increased number of copies of part of the code) in a dominant gene which is not enough to disrupt it but is susceptible to further enlargement into the disease range when passed on. This is called a premutation and Huntington disease is an example of where this could happen.

Autosomal Recessive	
	• Both copies of a pair of genes must be mutated to be susceptible to expressing the phenotype. • The parents of an affected individual are not affected themselves but each has one normal and one altered copy of the gene, so-called gene carriers. • With each pregnancy between carrier parents there is a one in four (25%) chance they will simultaneously pass on their altered genes so that the offspring has no normal copy and will be affected. There is a similar one in four (25%) chance that they will both pass on their unaltered copies of the gene, so that the offspring will neither be affected nor a carrier and a one in two (50%) chance that one will pass on the altered gene and the other the healthy copy, making the offspring an unaffected carrier like themselves. • Examples of diseases with autosomal recessive inheritance include Cystic Fibrosis and Sickle Cell disease

X Linked Recessive	
	• The altered gene lies on the X-chromosome and whether or not the condition develops depends on whether a person is male, typically with one X chromosome and therefore affected, or female, typically with two X chromosomes where the second healthy copy of the gene compensates for the altered copy. • A female carrier will pass on either the altered or unaltered X in this pair of sex chromosomes at each conception. The father will pass on either his X or his Y chromosome from this pair. So there is a one in four (25%) chance that an altered X from the mother will meet a Y from the father and produce an affected male. There is the same one in four (25%) chance that the unaltered X will meet a Y and produce a healthy male, and a one in two (50%) chance that an X from the father will either meet the altered X from the mother, producing a carrier female, or the unaltered X, producing a healthy non carrier female. Affected males cannot pass on the condition to their sons since their sons only inherit the Y chromosome from their fathers, but since they can only pass on the affected X chromosome to produce a girl, all their daughters will be carriers. • Female carriers may be susceptible to manifestations in many X-linked conditions. For example, in Duchenne muscular dystrophy they are at risk of cardiomyopathy and other muscle problems, though these are generally much milder than in males. • Other examples of diseases with X linked recessive inheritance are haemophilia and Fragile X

ability to identify small duplications and deletions throughout the genome that were not detectable with karyotyping. The introduction of aCGH has increased resolution and improved diagnostic yield but is still unable to identify all abnormalities.

Figure 1 illustrates the aCGH technique.[5]



Diagnostic rates have, not surprisingly, improved and more genetic explanations for a patient's signs and symptoms are being found. One study demonstrated a 12.2% increased yield in detecting a genetic cause in patients with cognitive impairment with aCGH testing compared to that identified by karyotyping,[6] such that the latter has now all but been superseded by aCGH and is the first line NHS genetic investigation for children with developmental delay.[7,8] Chromosomal rearrangements such as balanced translocations, where part of one chromosome changes places with part of another

without apparent gain or loss of material, cannot be detected by this technique and so karyotyping is sometimes still used for this.

Meanwhile, a significant shift has also taken place in molecular genetics and the ability to sequence DNA. Sanger sequencing - the gold standard for 25 years - was replaced by massively parallel sequencing which enabled much faster sequencing at dramatically reduced costs. Rather than targeting sections of the genome to sequence, this 'next generation' sequencing (NGS) could as easily be done of the whole genome as Sanger sequencing could of just a few genes. Initially, whole exome sequencing (WES) was developed to sequence the entire coding regions of the genome (approximately 1.5- 2% of an entire genome). Coding regions were a good first target for suspected inherited, or heritable, conditions because many Mendelian conditions arise from mutations in genes. A testament to the speed in which techniques are evolving is the fact that whole genome sequencing (WGS) followed rapidly behind WES even though significantly more data capture and analysis is involved. The regulatory regions and structural rearrangements can be analysed by WGS in a way that WES or Sanger sequencing cannot. Early publications indicate further improvements in diagnostic yields with WES and WGS.[9-11] At the start of my PhD studies both these techniques were still on the horizon, rapidly followed by their introduction to the research laboratory. As I write my thesis, the NHS is about to launch a programme offering WGS to patients as part of their diagnostic work-up.[12 13] This programme will be discussed in more detail later in this chapter.

What do new technologies tell us about heritability of disease?

Whole genome approaches have facilitated assessment of heritable contributions to common diseases, such as diabetes, heart disease and depression, where the aetiology is often multifactorial. Unlike rare single gene disorders where a single mutation might predict a high chance of disease, in common conditions with a multifactorial aetiology, each gene mutation may predict only a small degree of risk. The more we have learnt about genetics the more it has become clear that there are many shades of grey between disease causing mutations (for example, Huntingdon's disease) and population variation (for example, the colour of Mendel's pea flowers). Genetic testing can define what is going on at the DNA code level, but translation into what this means about predisposition

to a particular disease is more complex. The likelihood of developing features of the condition, the time of onset, its progression and severity is often dependent on a variety of other factors, often referred to in terms of penetrance and expressivity. Penetrance is *the extent* to which specific gene mutations are manifested within a population and expressivity is *the way* in which the gene mutation is manifested within an individual. A BRCA2 mutation has a roughly 60-80% penetrance - meaning that 60-80 out of every 100 women will develop some of its effects. The expressivity of BRCA2 mutations could be said to lie in the types of cancer they cause. Of those with the altered gene, some women develop ovarian cancer, others breast or both, yet others develop pancreatic cancer and some men develop prostate cancer.

Expectations of newer and faster genetic technologies

Public understanding about what genetic tests can deliver is sometimes at odds with the current position. This is in part because media tends to portray genetics findings as exciting new discoveries, paving the way to new treatments.[14] The clear-cut mechanisms of Mendelian inheritance are easier for headline writers than genetic findings whose significance is not yet understood or where the clinical utility is limited. Patients may therefore consult a genetic health care professional (gHCP) with unrealistic expectations of what genetic testing might deliver for them and important discussions about what a test result might and might not tell a patient are required. Uncertainty is an important outcome to be included; for whilst the sequence of the letters of the code might be very certain, what this means for disease significantly lags behind.

The provision of genetic testing in the United Kingdom

Regional Clinical Genetic Services

There are 23 NHS funded Regional Clinical Genetic Services throughout the UK, which include laboratory services, for a range of genetic tests including cytogenetic analysis, targeted DNA testing of specific genes, aCGH, gene panels and, increasingly, WES and WGS approaches.

Regional genetic services see patients referred to them from both primary and secondary care. Referrals may be of individuals with particular signs or symptoms suggestive of a genetic cause or of individuals with a particular type of family history, where the referrer wants to know if it might be explained by a heritable factor. The regional genetic service,

in which I have worked over the past decade, covers a population of 2.8 million and receives around 4000 referrals per year. Genetic clinics have evolved over recent years to be disease, gene or organ focussed, for example, a cardiac genetic clinic, cancer genetic clinic or dysmorphology clinic. The health professional in the genetic clinic assimilates personal and family histories, previous or new investigation results and discusses possible diagnoses, mechanisms, diagnostic tests and available interventions.

What is genetic counselling?

In some ways this consultation is like any other clinical interaction, in other ways, the very personal and potentially stigmatising nature of inheritance means that less direction about courses of action should be made. Instead the onus is on the clinician to create a space in which the patient can come to their own considered decision. This process of genetic counselling has been defined as:

"…the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. Genetic counselling integrates the following:

- *Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence*
- *Education about inheritance, testing, management, prevention, resources and research*
- *Counselling to promote informed choices and adaptation to the risk or condition."*[15] (p.79)

Non-directive genetic counselling

Non-directive counselling was an approach adopted in part so that genetics would not be associated with the eugenic movement so prevalent in the first half of the 20th century and originated from Carl Roger's work on client-centred therapy.[16] It involves HCPs helping their patients arrive at decisions that are best for them, rather than guiding them towards any particular decision; to test or not to test, to terminate a pregnancy or to continue it. Following the confirmation of a genetic diagnosis in an individual or family, prevention and/or treatment strategies may or may not be available. If there are no interventions for patients to access, that prevent or mitigate a condition, then it may be argued that non-directive genetic counselling is appropriate, as the patient is best placed to decide if they wish to receive predictive genetic information they cannot act upon.

Although a laudable aim, the achievability and appropriateness of a non-directive approach has been questioned.[17,18] For example, if a patient is unable or unwilling to specify topics for consideration during the consultation or the competing needs of a number of family members means that appointments in reality are not client led but directed by the health professional, then non-directive counselling is unlikely to be feasible.[19]

However, with the advent of evidence based interventions there may also be better reasons to be directive following a genetic test such as where HCPs recommend a particular course of action to patients, for example, having colonoscopy surveillance if identified to be at high risk of developing colorectal cancer and to encourage patients to disseminate relevant genetic information throughout their family. There may also be organisational factors that impact on whether counselling is non-directive or not, such as access to a particular intervention being dependent on first having another test. Furthermore, if patients request something that contravenes professional guidance, HCPs may legitimately want to direct them away from this, for example, when parents request genetic testing of their children for an adult onset condition.

Evidence based medicine has seen a shift towards considering 'nudging' to be appropriate within genetic counselling. The term 'nudging', popularised by Thaler and Sunstein in 2008, has gained momentum in areas such as health policy and promotion, where actions and policies can affect individuals' health behaviour.[20,21] The role of nudging is where A (the policy maker) triggers B's (the patient) automatic cognitive processes so they respond in a particular way, while at the same time preserving B's freedom of choice.[20] Nudging while ostensibly leaving choice up to the individual does not take into account the power relationships present between patient and health professional: critics have argued that preserving freedom of choice requires more than avoiding overt coercion and needs to take into account the control A has over B, which could challenge their freedom of choice.[22]

Now that there are more evidence based interventions in genetic medicine (for example regular colonoscopy in mismatch repair gene mutation carriers has been shown to delay the onset of cancer by detection and removal of precancerous polyps), nudging towards

genetic tests that determine whether interventions are appropriate is seen as good clinical practice. Nudging is one way in which health professionals can influence patient behaviour and, while the professional's actions may be evidence based and for patient benefit, their actions could be considered directive.

With increasing availability of genomic testing more genetic abnormalities are being identified but many have a rather weak or as yet uncertain association with the development of disease. Managing the uncertainty that comes with genomic findings has been argued as an acknowledgement that genetic counselling is a "process of influence".[23] Aribas and Sarangi suggest that non-directiveness is in fact a technique that genetic professionals employ to explore whether patients can be trusted to make autonomous decisions[23] and professionals may then justify a more directive position when they are not confident that patients have considered the uncertainty associated with a result.[23] For example, a couple wanting to terminate a pregnancy, because of misunderstanding the clinical significance of a result may then be nudged or directed into a position where the possibility of having a normal baby is also considered.

Bernhardt and colleagues[24] suggest that where information is unavailable or inconsistent, (for example, an abnormal aCGH result pre-natally that does not explain irregular ultrasound findings), genetic counsellors might be more reluctant to participate in decision-making with patients for fear of being seen as directive. As a result they can dis-engage, deferring all decisions to the patient while minimising their own contribution to the discussion. It has been proposed that health professionals in the antenatal setting have a tendency to step back from involvement in decision-making for fear of being seen as directive, yet this might be perceived as unhelpful by the patient(s).[24] Instead they focus on the level of worry a woman has about a potential fetal abnormality when discussing options, rather than informing and supporting women through their decision-making.[19] This type of non-directive counselling reflects minimal health professional involvement in the decision-making process rather than an approach that helps patients arrive at decisions that are best for them.

Both directive and non-directive approaches have been criticised as resulting in patient withdrawal from decision-making, either because they consider that the course of action has already been decided upon or because they are uncertain about the best decision for

them but have not had the opportunity to explore this in any depth. Presenting genetic counselling as being either directive or non-directive may therefore not be very helpful. Instead, genetic counsellors might draw on certain aspects of many different approaches depending on the patient in front of them.

Why counsel for a blood test?

Discussions around genetic testing may need to be more detailed than for other routine investigations since the output may not only be more complex, but also have long-term implications or risks for others to consider.

Consent for genetic testing involves the same principles as for any medical investigation but because of the complexity may also need to be documented more carefully. Specific genetic testing consent forms have seen increasing use over recent years, though careful documentation of consent in clinical notes is just as appropriate.

One thing apparent from the early days of predictive genetic testing for Huntington's disease is that far fewer patients proceed with genetic testing, after careful discussion of the pros and cons, than are initially referred for testing. The clinician must therefore take care to ensure that it is the patient's considered decision they are acting on, rather than a poorly informed initial opinion.

The difference between predictive and diagnostic genetic testing

Diagnostic genetic testing attempts to confirm a genetic diagnosis for someone who already has signs or symptoms of a particular condition.

Pre-symptomatic or predictive testing is where testing is offered to those who are currently healthy but known to be at an increased risk of having inherited a particular condition, usually because a particular genetic mutation has already been found in a family member.

For strong, single gene diseases the difference between these two is clear. For multifactorial diseases a particular gene mutation may not be strong enough to make either a diagnosis or an accurate prediction, so more care is needed in the use of these terms. Although predictive testing may demonstrate an increased chance of developing a condition at some point in the future, prediction of the age of onset is usually only possible within a wide confidence interval, and incomplete penetrance may also mean

that despite a positive predictive test, the person never develops the condition. These are complex issues to convey to patients.

Types of results from genetic testing

Confirmation of a clinical diagnosis

A genetic test may have been initiated because of specific signs or symptoms which suggest a particular genetic condition. Finding particular mutations in particular genes can therefore lead to confirmation of a clinical diagnosis. For example, an APC gene mutation in a person with profuse gastrointestinal polyposis provides genetic confirmation of a clinical diagnosis of Familial Adenomatous Polyposis (FAP).

Finding a mutation that indicates risk of another condition

With the advent of broader 'trawling' technologies, genetic testing can also reveal new, unexpected diagnoses that are completely incidental to the presenting clinical signs and symptoms. Much like the discovery of a lung tumour on an X-ray done without any clinical indications of this, such new diagnoses can have important health implications for the individual (and possibly other family members). They are therefore incidental to the reason for doing the test, but can be far from incidental in their clinical significance.

Although a challenge for the HCP, the disclosure, that is telling the patient, of clear-cut so called 'incidental findings' is usually thought more appropriate than not doing so, especially if there are proven clinical interventions available that could treat or ameliorate future symptoms.[25,26] The disclosure of such findings may be less contentious than ones where it is not clear what difference the knowledge would make to that person. However, some have expressed concern about revealing such findings (whether a treatment is available or not) if the person providing the sample has not provided consent to IFs up front.[27,28] Since discovery of IFs in the clinical setting has been relatively rare to date, many of the discussions about their disclosure have been in a research or biobank setting and the duties of researchers towards research subjects are often different than those of HCPs towards their patients. The alternative of withholding important predictive information does not seem appropriate either. Later in this chapter I consider some of the ethical issues in consent to and disclosure of IFs.

A negative result or no mutation found

Many genetic tests will reveal variation from 'reference' sequence, because normal variation in the genetic code is common and humans differ in their genetic make-up by about 0.1%. Where variations like this are found between humans, known as polymorphisms, the genetics laboratory will usually not report them if they do not have any known associated health or developmental problems. Such a negative test result is usually explained to individuals (or families) in terms of current testing limitations. That is to say, the best techniques available today have not found any known or suspected abnormality, but it remains possible that future improvements will be able to detect something that we currently cannot.

An uncertain result

For other types of genetic variation the clinical significance may be less clear. That is to say, the characteristics of the result suggest it is not a polymorphism (because it has not been found before, or lies in a gene in which mutations are known to cause disease) but it does not have enough features to call it a mutation either (for example, it does not truncate the protein produced). These types of results are often called variants of uncertain significance (VUS). They have no known effect on health or development but there may simply not be enough data available to be certain. An example might be a 'missense' (a replacement of one letter of the genetic code with another, rather than a deletion or duplication) variant in the BRCA1 gene found in someone with young onset breast cancer. This might be thought to be significant but without evidence from a functional test that shows an abnormal product from the gene, cannot be called pathogenic. The VUS will usually be further investigated where possible, for example, seeing whether it tracks with the disease in question through the family in an attempt to assign or refute pathogenicity. However, often the VUS remains uncertain and patients will be told that future testing or improved knowledge may help to re-categorise the variant, but that for now it is not a result that can be acted upon clinically.

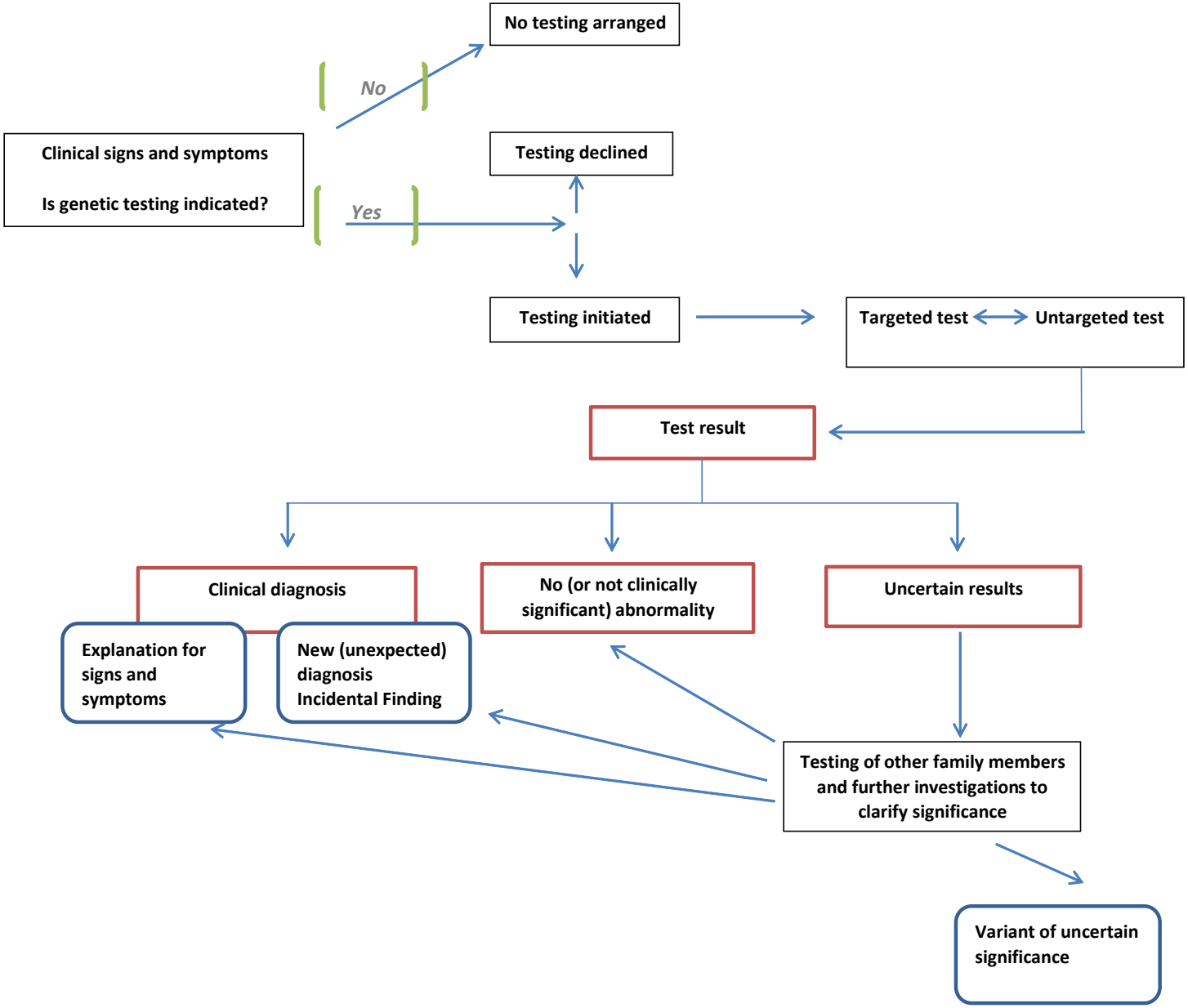
As more evidence is gathered about a particular VUS, it can be reclassified and confirmed as diagnostic (or predictive); continue to be uncertain; or turn out not to be clinically significant. Whether and at what stage to disclose uncertain results is difficult in practice. On the one hand, HCPs might be cautious about doing so in case they raise anxiety or cause misunderstanding, on the other hand family members may need to be engaged in

attempts to try to clarify clinical significance, through familial segregation studies. The latter would be difficult to do without some explanation to the patient and their family that further investigations of a VUS might be helpful and in doing so the uncertain result would be disclosed. Figure 2 outlines the genetic testing pathway.

Mainstreaming of genetic services

In the past genetic tests were mainly requested through specialist genetic services but increasingly all medical specialities and primary care are utilising genetic testing in their day to day practice. The UK Government genetics white paper from 2003; 'Addressing Genetics, Delivering Health' set out a vision for the transfer of genetic testing from specialised clinical genetics into other areas of medicine.[29] A decade later this has happened to some extent, but is still to be fully realised. A report by the Public Health Genomics (PHG) Foundation in 2011 challenged current NHS approaches to genetics in mainstream medicine, and encouraged other services to adopt genomic knowledge and technologies as part of standard care pathways and professional training.[5] Planned restructuring of UK pathology services, as well as developments in technology, mean that laboratory genetic services will see rapid changes over the next decade. It seems likely, for example, that WGS will be centralised and offered by only few centres in the UK. It is the interpretation of the output of WGS that will then be done by the regional genetic services.

Figure 2: A summary of the genetic testing pathway and the different types of results



Genetic test results in a research environment

My project is focused on the communication and disclosure of IFs in clinical practice, but the boundary between clinical and research activities in genetics can be rather blurred.[30-33] This is because in a rapidly evolving field like genetics it has often only been possible to access genetic testing for patients through particular research studies. Throughout my career as a genetic counsellor I have needed to negotiate both clinical and research avenues for patients, sometimes in tandem. Unlike my previous job in oncology - where research often involved trialling a new treatment and comparing it with the old one - in genetics, research is usually utilised because it allows examination of the genetic code in a way not yet possible in the NHS. Recruitment to research studies has been an integral feature of genetic assessment and testing.

Once a genetic abnormality has been identified in a research laboratory, it is usually relatively straightforward for an NHS laboratory to confirm the result using their quality control measures to ensure that the research laboratory has not made an error.

The research- clinic interface

Research into particular conditions or genes can also find significant pathology that is incidental to the reason for doing the research and therefore questions about researchers' obligations to communicate such findings have also been raised, particularly where researchers are also clinicians.[34-37] This is discussed further later on in this chapter.

Recently several research studies have positioned themselves right at the interface with clinical practice. One such project in the UK is the Deciphering Developmental Disorders (DDD) study but recruiting patients from all over Europe. The study cites its aims as *"to advance clinical genetic practice for children with developmental disorders by the systematic application of the latest microarray and sequencing methods while addressing the new ethical challenges raised"* which nicely illustrates how clinical practice and research cannot be clearly demarcated here.[38] In order to address research governance requirements, the study decided at the outset that it would not report any IFs discovered in the course of their analyses. Study participants were told this when they were recruited and it is not known how often a clinically relevant IF that might be actionable has not been disclosed to participants.

Studies with a strong clinical focus, or that include clinicians as members of the research team, may be more likely to include plans in their protocol to disclose research test results while studies that are clear from the outset that their focus is research and running independent of a clinical service are less likely to do so. Research-only studies may not have adequate clinical links to appropriately manage clinical findings, including IFs.

Some research studies might recruit from sources outside the NHS, for example, by public advertisement for participants with particular family histories or features. Research studies may even prefer to do this because the perceived hurdles of obtaining NHS research governance approval are so cumbersome and time consuming. Furthermore, the potential health implications of a research finding for participants may not be clear at the time of the research and it may be deemed more appropriate to withhold such information until the clinical consequences are clarified. By then it may be very difficult to link back to the research participant.

Genetic test results in a commercial setting

Direct to consumer genetic testing (DTC), where genetic tests are marketed directly to consumers, is gathering momentum as genetic technologies improve. DTC tests means that the consumer can access genetic tests without involving a HCP. Although some companies suggest that the consumer have genetic counselling, there is usually no compulsion to do so and they will receive test results directly, often by email. Companies offering such testing claim they can provide a profile of an individual's risk of a wide range of health conditions, such as cancer predisposition, diabetes and neurological disorders, but the tests generally only predict mild risks and are not able to rule out such diseases either.

A number of organisations have expressed concern that this type of testing is unregulated and that clinicians may be asked to interpret clinical information when they were not involved in organising the test in the first place.[39] Professional and policy groups have called for more regulation, ensuring that any tests offered have clinical utility and validity and that the laboratories comply with accepted standards.[40,41] In the United States a company called 23andme offered a test for $99 that could tell the consumer "*hundreds of things about their health*".[42] Several tens of thousands of people

were tested before the Food and Drug Administration (FDA) in North America demanded the company discontinued marketing the health care predictions until it received FDA marketing authorisation.[43] The company continued to offer ancestry checking, whereby genetic markers were used to predict how a person's ancestors had migrated across the world over the last few million years.[44] The combination of interest tests for ancestry with health predictions to steer surveillance is potentially confusing and the health care aspects have not yet been reintroduced in the US. Interestingly, the company has recently marketed the health prediction test in the UK, where the FDA has no jurisdiction, by targeting GPs directly. It remains to be seen what the uptake of this test will be in the UK. [45]

The concern about such DTC testing has been that already stretched NHS services may be asked to pick up the pieces of such testing.[39,41] My concern is that genetic testing for single gene conditions can be highly accurate and predictive but most DTC tests target well people, without a strong family history of a particular condition. The positive and negative predictive values of any test will be much poorer than most of the testing in my clinical experience.

Genomics England and the 100,000 genomes project

When I commenced my PhD, whole genome technologies were still largely an aspiration, but it is a sign of the very rapid developments in this field that by December 2012 the UK government announced plans to offer WGS to certain NHS patients. Genomics England- a company whose only shareholder is the Department of Health- was set up to deliver the sequencing of 100,000 genomes of NHS patients by 2017. Since the official launch in August 2014, pilot work has been undertaken in several centres and 11 Genome Medicine Centres (GMC) have been established to deliver the venture within the NHS. My local GMC – The Wessex GMC, recruited its first patient in June 2015, and plans to recruit a further 5000 or so over the next 2 years. Overall the genomes of 100,000 NHS patients from three groups of disease: cancer, infectious disease and rare diseases, will be sequenced.[13]

There are a number of associated work streams, including an MSc programme in Genomic Medicine and Genomics England Clinical Interpretation Partnerships (GeCIPs).[13] The 100 000 genomes project has had to address issues around the management of the vast

amounts of data it will generate, including IFs. An Ethics Advisory Committee has been established to consider ethical issues raised, chaired by Professor Parker- a member of my advisory group - and my supervisor Professor Lucassen is a member.[46] The group has proposed to use a model of broad consent to WGS, considering that this approach is more appropriate than so-called 'fully informed consent'. The process of broad consent will inform patients about the implications of joining the project, without describing every possible outcome from WGS. Extensive online support for consent has been developed by Health Education England.[47]

Genomics England has decided in the first instance that no IFs will be fed back to patients. However, a specific list of genetic findings, so called 'additional looked for findings' can be searched for and fed back at the patient's request. These additional findings are currently a list of around 10 heritable conditions, mainly cancer predisposition genes such as BRCA1 and 2, but also familial hypercholesterolaemia, for which treatments or interventions are available. Genomics England plans to update the list as more evidence accumulates. The Genomics England project will drive the implementation of WGS into the clinic and it is therefore timely and critical that empirical data -about what HCPs and patients think about incidental or additional findings - are available to guide clinical practice and the management of IFs.

Genetic testing in the prenatal setting

Genetic testing during pregnancy deserves a special mention because of the particular issues raised in testing potential future persons. As whole genome technologies become used more routinely in diagnostics, it is perhaps not surprising that they might also be proposed for the diagnosis of fetal abnormalities or future disease predispositions. During the course of this doctoral research, the situation has changed quite dramatically, from an initial decision not to attempt aCGH testing, following Chorionic Villus Sampling (CVS) or amniocentesis for fetal abnormalities detected on ante-natal ultrasound,[48] to their widespread introduction, as well as the arrival of other new technologies such as non-invasive pre-natal testing (NIPT). DNA from the fetus circulates in maternal blood. This cell-free fetal DNA (cffDNA) results from the breakdown of fetal cells (mostly placental) and can be tested (by NIPT) for quantitative differences in chromosome fragments, for example to identify fetus' with aneuploidies such as Down syndrome. The main

advantages are that this test can be done earlier in the pregnancy (from 10 weeks) and with no risk of causing miscarriage.

The EACH study (Evaluation of Array Comparative genomic Hybridisation in prenatal diagnosis of fetal anomalies) in the UK has offered aCGH to pregnant women in a number of regional services as part of research, but any diagnoses made have been communicated to women via clinical teams.[49] Any IFs identified in the course of the study, that is, findings unrelated to the abnormality or abnormalities detected on ultrasound being investigated and relevant to the current pregnancy, were generally not fed back to parents. The study did however establish a clinical advisory panel to discuss complex genetic results and, on a few occasions, a decision was made to disclose an IF.

Other broad techniques such as WES and WGS are now being introduced.[50,51] Like in the postnatal setting, uncertain and unexpected findings are likely to increase in frequency and pose complex and ethically challenging issues. One of the issues in the pre-natal setting is that termination of pregnancy is one of the possible consequences of finding an abnormality. Where a clear cut abnormality is found, this option might be said to enhance the pregnant woman's reproductive autonomy. However, where the result is uncertain or has variable penetrance or expressivity, choices about termination are not straightforward. Whilst this is also true for abnormalities found on ultrasound, and this has been offered successfully for several decades, generally speaking these findings indicate a current diagnosis for the fetus. Uncertain results and IFs discovered may never result in the phenotype with which they are associated, or in any case not for many years. With a post-natal finding, individuals and or families do not have to make decisions quickly, because they can wait for more evidence to accumulate, or have further tests and investigations to determine significance. They can live in hope that future treatments/interventions may become available. Pre-natally, parents have to make decisions quickly about something that may still be very uncertain. For example, a decision to terminate a pregnancy might be regretted if later evidence suggests a result is not as disease causing as initially thought. Making a decision about termination of pregnancy on the basis of adult onset disease risks is a challenging dilemma to put before a pregnant woman and her partner.

Other countries have introduced pre-natal aCGH as a routine test over recent years. The introduction of testing has often been accompanied by the publication of consensus statements about the new service: the scope of test resolution, interpretation of variants and management strategies for uncertain or unexpected results.[52,53] There have been calls for a similar consensus statement in the UK, but despite several meetings, this has not yet been forthcoming.[54] Although such guidelines might be useful to some extent, many complex cases may have to be managed on a case by case basis. Several studies have demonstrated that, as might be expected because of the increased sensitivity, aCGH increases the yield of abnormalities found, compared to the technique it has replaced - karyotyping.[55-57] Although the uncertainties raised by a much more sensitive test have been acknowledged, their enhancement of reproductive choices and thus, hopefully, of parental autonomy, is used as justification for the application of the test:

"…knowledge of risks, even uncertain ones, can reasonably inform reproductive decisions and help parents prepare for a child's future." (p197)[50]

Genetic testing in the newborn

New born screening in the UK currently looks for distinct rare but serious conditions: http://newbornbloodspot.screening.nhs.uk/.[58] These conditions have been included because they fulfil Wilson and Jungner criteria for screening, including knowledge of the disease, knowledge of the test, the treatment of disease and cost considerations.[59] The advent of genome technologies means that much more could be screened for at birth, but concerns similar to those discussed above remain, including uncertainty and the identification of adult onset diseases. The apparent appeal of broad screening is indicated by politicians' enthusiasm to adopt such new technologies. Jeremy Hunt, the UK health minister in 2013 boasted that "*every child in Britain could have their DNA decoded at birth to predict their risk of disease*" and: "*We could be the first country in the world where everyone's genome is sequenced at birth and we use it to give people the most profoundly detailed diagnosis of what they need to do to stay healthy*"[60] without much apparent concern for the potential disadvantages or complexities of such a venture.

There are several such potential disadvantages to consider: a huge amount of information will be produced but much of it may be currently uninterpretable and is unlikely to meet the Wilson and Junger criteria.[59] In addition, it is not clear if having this information at

birth could be or will be acted upon and will translate into better health outcomes for the individual.

In the US, the National Institute of Health (NIH) has recently launched a programme of pilot projects exploring the use of genomic sequencing in new born healthcare. These projects include genomic sequencing and analysis, research related to patient care and consideration of the ethical, legal and social implications of using genomic information from the new born.[61] One project, the BabySeq Project[62] is planning to randomise several hundred new born babies to receive either conventional new born screening or conventional and genomic screening. The study aims to analyse the benefits and harms of offering genome sequencing in this context but is unclear about plans for the follow up of participants and if this will continue into adulthood. Without long term follow up it will not be possible to establish the views of testees, when they are adults, on having had their personal genome sequenced at birth. The genomic sequence will apparently be available to paediatricians, should the child develop symptoms later in life, but this simple statement covers up many uncertainties such as how it will be accessed and acted upon, when will testing be repeated to confirm findings and whether or not there will be any active re-contact of families should new information come to light.

Other groups have expressed the need for caution in implementing national new born genomic screening: The European Society of Human Genetics (ESHG) in their report on the use of next generation sequencing technologies suggest that there is a general expectation that once next generation sequencing technologies are sufficiently robust and interpretable they will be quickly applied to the new born screening setting.[63] They propose that this view should be challenged and that issues around cost, consent, interpretation of the data and long term storage of the sequence mean that WGS screening at birth is far from ready for national programmes. Instead they suggest that a targeted approach to discover only clear cut findings should be implemented in the first instance. This would also reduce the chance of uninterpretable or incidental findings. There is of course a difficult balance to be held between the best interests of the child and parental interests in receiving as much relevant information as possible about their child's risk of disease. ESHG also drew attention to the fact that international professional guidance recommends against the testing of children for adult onset diseases in the interests of preserving their future autonomy. WGS testing at birth could discover adult

onset conditions, so in order to abide by these guidelines certain results would have to be withheld. This in turn raises questions about whether such results are part of a child's medical record and whether access to them might then in any case reveal them.

Some research has explored parental interest in new born screening. In one US study support from parents for new born screening was high, citing the ability to prevent a child from developing a disease as very important in making the decision to proceed with testing.[64] Of course the difficulty with this is that parents are not able to predict what information will come to light and if this will prove to be treatable or not, either now or in years to come. Another report detailing the finding of a neurodegenerative condition following new born screening, explored the potential advantages and disadvantages of having this information. The availability of genetic counselling in future pregnancies, and the avoidance of a delay in diagnosing the child, were perceived as the main advantages. However, the anxiety of receiving this information in the new born period, as well as sadness and concern for a family, who have an apparently healthy baby, were seen as disadvantages, especially if there is no treatment available for the condition.[65]

Chapter 2: Incidental Findings

This chapter will consider the ethical and practical challenges of incidental findings in medicine, with particular attention to IFs generated through genetic testing. It will draw on ethical principles and existing literature, policy and recommendations that underline the complexity involved in managing this type of result. The need for further research in this area will be explored.

Incidental Findings in medicine

Whilst new techniques are dramatically increasing the sensitivity of genetic testing and providing diagnoses for people where these were previously elusive, the chance of finding other, unexpected, but potentially clinically significant findings (IFs), also increases. In this thesis IFs are defined as abnormalities of potential or certain clinical significance that are unexpectedly discovered during routine genetic testing, unrelated to the original purpose of the investigation. The sensitivity of genetic testing has increased, but with an inevitable attendant reduction in the specificity of the findings it produces. In some ways this is comparable to a full blood count revealing lymphocyte abnormalities when the clinical question was 'does this person have anaemia?' However, the scale of such extra findings and the uncertainty attached to them is different. Far from providing clear-cut diagnoses, many small deletions and duplications detected on aCGH have very unclear clinical consequences. A genetic result therefore may need further work to clarify the significance of a finding. This work may include tracking the finding in the family to see whether it correlates with disease or the phenotypic features in question. This is why the definition of IFs outlined in this thesis covers abnormalities of 'potential' clinical significance as well as those that are certain. Often at the time results are reported their clinical significance is unclear.

Incidental findings are not new in genetics

Incidental findings are not a new phenomenon, either in genetics or in other medical specialities. For example, a karyotype performed at amniocentesis to test for Down syndrome may discover another aneuploidy such as extra sex chromosomes. Other forms of IFs have been around since the days of linkage, where studying segregation of markers in a family might identify mis-attributed paternity. The latter has also been an IF in other

areas of medicine, for example in search for potential organ donors within a family. The consent for, and disclosure of, identifying mis-attributed paternity through genetic testing has been the subject of debate[66-68] and some services have, for example, added in specific reference to mis-attributed paternity in departmental consent forms as a response. Just as clinical services have identified mis-attributed paternity as an area requiring special consideration in the past, they may respond in a similar way to the increasing number of IFs.

The issue of IFs is therefore not so much new as made more likely through the availability of 'trawling' technologies.

Incidental findings in other medical specialities

IFs have been described in most areas of medicine for example, in radiology, biochemistry and haematology where information unrelated to the original purpose of the investigation comes to light. One prospective study that assessed the burden of IFs in clinical practice, found that, of 478 patients consecutively admitted to a Department of Medicine, 28.8% had an IF. Although the majority of these turned out to be clinically insignificant (78.7%), patients had to undergo further investigations in order to determine this, with associated increased anxiety during this process.[69]

Studies in radiology have also identified a significant clinical burden from IFs found as part of routine imaging, leading to additional investigations.[70,71] In such instances clinicians will usually consider that their duty of care to their patient obliges them to assess all abnormalities that are discovered.[72,73] Radiology debates about the management of IFs, discovered during routine imaging, have led to a number of review papers about clinical and research practices.[74,75] These reviews have concluded that most patients with an IF undergo further clinical investigation (even if identified during research) but acknowledge that as the assessment of the medical significance of IFs changes *"…given evolving research and increased experience with indeterminate findings"* (p.330) the numbers of additional investigations are likely to decrease.[74] This could be similar in clinical genetics because, as our understanding of variants identified by genome testing develops the number of potential IFs that lead to further investigation will decrease. Despite this, significant numbers of IFs with clear pathogenicity will continue to require managing and potential IFs will still be discovered as testing techniques evolve.

There can be considerable disagreement on what constitutes incidental pathology and the means by which it is recognised and followed up varies considerably, with European and US guidelines more explicit about this than in the UK.[76] Variations in practice (especially in the UK) may be due to a lack of coherent and easily accessible guidance and one possible reason for this is the absence of a robust evidence base on which guidelines are based. Evidence-based health care is the foundation of care in the NHS and without sufficient evidence for best practice variation will result. Variation may not in itself be a bad thing as decisions will be made case by case, based on clinical expertise, and can avoid unnecessary investigations based on a 'screen all for everything' guideline. Two systematic reviews on IFs in radiology recommended the need to incorporate the possibility of IFs in the consent process, because of the frequent need for further evaluation of uncertain findings[74,75], but suggested that, despite IFs being referred on for further clinical investigation, the possibility of an IF is not regularly discussed prior to the investigation. The current position in radiology may share common themes with genetics as increasing numbers of IFs continue to be identified in each setting as their corresponding technologies improve.

Incidental/unexpected/ unsolicited finding: review of terminology

There has been much debate about the use of the term IF, with many alternative suggestions such as unsolicited, unexpected or secondary findings.[77] [78] On one hand, standardised terminology could be helpful for consistency in the debate, for guidelines or consent forms.[79] [80] On the other hand, it is likely that no single term would do justice to the wide range of settings and circumstances in which additional novel genetic information can be found. Different terms may need to be used by the different parties (clinicians, researchers, patients) involved. For example, a finding that is unexpected to a patient might be quite anticipatable to a clinician or researcher simply because their field of exploration is so broad.[81,82]

Throughout this thesis I use the term IF(s) as an all-encompassing term, as it is the one that has gained the most traction in the debate.[78] Table 3 summarises some of the other terms that have been used to describe additional genomic findings with associated advantages and disadvantages of their use.

Table 3: Summary of the terms used to describe IFs

Term	Advantages	Disadvantages
Incidental finding	Emphasises that in a setting where genetic tests are used to investigate particular signs or symptoms, significant findings that do not explain these are incidental to the aim of the investigation[83]	Finding can provide very significant information so the term 'incidental' may not do justice to the impact it has on testees and may trivialise its significance If examining an entire genome (as with aCGH) it can be said that no finding is incidental since it is actively sought[84]
Unsought/unsolicited finding	Captures the ability of genomic technologies to generate data not necessarily related to the initial diagnostic question[77]	Findings will only be identified if they are looked for or if some follow-up research is conducted to establish the significance of the variant[81]
Unrelated finding	Highlights the fact that the finding does not explain the condition for which testing has been done	Although unrelated to the original investigation, the finding could be related to the current/future health of the tested individual and other family members
Secondary finding/variant	Distinguishes between findings causing the disorder for which testing was performed (primary variants) and other clinically important findings (secondary variants)[85]	Does not capture situations where the so-called secondary variant is the only (clinically significant) variant found. Can inaccurately suggest a temporal relationship where one finding is found first, the other the second The term 'variant' is often used to indicate normal genetic variation or polymorphisms. Using 'variant' to describe a clear predisposition to disease could be confusing[82]

Unexpected result/unanticipatable finding	Dividing findings into expected/anticipatable and unexpected/unanticipatable could remind clinicians that unexpected findings should be discussed with and disclosed to patients in a different way to those associated with the original reason for testing 'Unexpected' is a term patients can easily understand.[86] Maintaining a division between 'expected' and 'unexpected' helps to emphasise that answers to particular clinical questions are the priority. Any other answers do not provide an explanation to the clinical question.[81,84]	Since the entire genome is being examined, findings that are unrelated to the reason for the test should always be expected or anticipated[81,83] Expectations of patients, clinicians and researchers are different, so what is unexpected for one might be expected for the other
Off-target result	Indicates that genomic tests are broader than targeted tests: what is targeted is most clearly seen, but other findings can still be found[87]	Can give the impression that the result is not correct as it has missed a target
Incidentalome	A term that brings together the incidental nature of findings that comes from genome wide testing.	This term is unlikely to hold much meaning for patients and is therefore limited in the contexts in which it can be applied

	A term that will have meaning for clinicians as similar construct to other medical terms, such as haemangioma	
Non-pertinent/coincidental finding	Emphasises that the discovery of some (coincidental) findings is unavoidable (for example, if genes are co-located with those associated with the pertinent finding)	Result may still be pertinent to an individual, just not pertinent to the original question asked
Opportunistic findings	Emphasises that while looking for particular genomic findings, the analyser looks opportunistically for findings associated with unrelated conditions[88]	The opportunity the finding gives patients may be opaque to them

The increased chance of IFs with newer technologies

When I started my doctoral research, aCGH testing had only just been implemented across the UK, and was the first example of broader new generation genetic technologies. In fact in the Wessex region, the service had been offered for 2 years already on a pilot basis. It was the increased number of IFs or potential IFs found during this pilot that stimulated this research. Managing some of these made me realise that consent for genetic testing had not really adapted to this new technology, nor had the communication associated with finding genetic predispositions that were completely unexpected for the patient. The issues are very similar for other new broad technologies such as WES/ WGS but at the time of my research this was still rarely used in clinical practice. The individuals who participated in my research interviews were therefore almost exclusively those who had undergone aCGH.

A number of research studies have examined the incidence and types of IFs identified with health service aCGH testing.[89-92] Most of the IFs found were deletions or duplications in cancer predisposition genes, found incidentally when testing a child for developmental delay. Many of these were in genes where mutations cause adult, rather than childhood, onset cancer conditions, raising immediate questions about timing of their disclosure.

Determining how often IFs happen in clinical aCGH testing will depend on a number of variables such as:

- The population in which it is performed;
- The clinical reasons for which it is done;
- The 'filters' that are applied.

Filters select for a minimum size of genomic imbalance that can be detected and/or the areas of the genome looked at. Some have estimated that up to 1% of the 30,000 aCGH tests performed in 2012, revealed IFs, amounting to some 3000 cases UK wide.[89,91]

Rapid changes over the last few years have meant that WES is increasingly offered and some laboratories are also using WGS. The launch of Genomics England in 2014, with first NHS recruits in 2015, shows how rapidly things have changed.[93] A study published in 2013 assessed the incidence of highly penetrant, 'actionable' pathogenic or likely pathogenic

variants found in the course of exome sequencing. They reported an IF frequency of 3.4% for participants of European descent and 1.2% for participants of African descent.[94] The variant data was identified from participants who were from 18 well-phenotyped populations. The NIH Undiagnosed Diseases Program analysed exome sequence data of 543 individuals and looked for mutations in a pre-determined list of 56 genes. They identified IFs in 8.8% of families.[95] The potential for discovering IFs with WES and WGS therefore seems likely to be even greater than with aCGH testing.

Discovering an IF in clinical practice

The discovery of an IF will often lead to the need for further interactions between clinicians, individuals and their families.[96] The implications of the result and availability of surveillance or treatment need to be discussed and these discussions might be about a condition or predisposition that was entirely unexpected for the patient or their family. Discussion about risks for other family members, and whether they too might need testing, can be all the more difficult when there is no family history of a condition to highlight which and how relatives may need to be alerted. An IF that provides a clear cut additional diagnosis is one thing, but many initial findings are only potential IFs at that stage and need further investigation before their pathogenicity can be determined. Whilst the testing of other family members can be helpful to be clearer about pathogenicity, it can also be confusing: are relatives helping the index patient, or are they potentially receiving a diagnosis themselves?

To illustrate these issues, in box 1 I have outlined a fictionalised typical example of an IF in practice to raise some of the questions I was interested in researching in greater depth.

Box 1: Sophie

Sophie is a 6-year-old girl with developmental delay who has been late in achieving a number of her milestones. She is under the care of a community paediatrician. When she was first referred to paediatric services (aged 2 years) karyotyping was carried out and no abnormalities were detected. At a review appointment, when Sophie was 6 years old, an aCGH test was ordered and this identified a deletion on chromosome 17. The deletion encompassed several developmental delay genes and was highly likely to explain some of her delay. The deletion also encompassed part of the BRCA1 gene (a gene, which when mutated is known to be a breast/ovarian cancer predisposition gene).

As well as being a diagnostic result, it also indicates that she is at an increased risk of developing both breast and ovarian cancer as an adult. She has no known family history of either of these cancers. The BRCA1 deletion is therefore an IF; its future prediction is unrelated to the reason for doing the test in the first place. However, it is a potentially clinically significant result for Sophie and her family. This result raises a number of questions that demonstrate the complexities involved in the management of IFs.

1. Should the BRCA1 result be disclosed to Sophie's parents? If so, should this be done now or only in the future when it becomes clinically relevant for Sophie?
2. How should the BRCA1 result be followed up long term? Who will discuss the result with Sophie when she is an adult and needs to know about risk reducing options?
3. How should the result be recorded in Sophie's notes and whose responsibility is it that this result is not lost?
4. Should Sophie's parents be offered a genetic test to see if either of them have the same deletion?
5. Are there other relatives that may also be at risk of having a BRCA1 deletion and if so should they be offered genetic testing?
6. What impact will Sophie's developmental delay have on her decision-making capacity as an adult, as she manages this BRCA1 result?

During the course of my doctoral research, the clinical challenges of IFs began to be acknowledged with calls for research into the complexities they raised.[26,97-99] Authors were highlighting the complexity and uncertainty associated with generating genomic IFs with one commenting that *"…the probabilistic character of genetic information and the pleiotropic nature of genes makes accurate interpretation and communication particularly challenging."*[97(p.8)] Pleiotropy means one gene is responsible for, or affects more than one phenotypic characteristic in an individual and an example of this is Phenylketonuria (PKU), one of the conditions routinely tested for in the UK new born screening programme, where a mutated copy of the PKU gene can cause developmental delay, seizures, reduced hair and skin pigmentation.

With such a range of possible phenotypic characteristics and associated uncertainty, the counselling of families is not straightforward. Kocarnik and Fullerton suggested that these phenotypic variations in genetics are largely ignored in the IF debate,[100] while in fact they are key issues in talking to families.

Consent and IFs

The process of seeking consent aims to ensure that a person understands the nature and purpose of a procedure or investigation. The practice has its origins in the ethical principle that a person has a right to self-determination. In legal terms, consent is valid only if these questions are satisfied:

- Is the patient competent?
- Was the person giving consent appropriately informed beforehand?
- Was the consent voluntarily given?

Consent is only valid if the implications of a procedure are disclosed and understood, but it is the complexity of these implications that pose a particular challenge in clinical genetic practice and especially now that the possibility of IFs is increased. Can such consent ever be fully informed? What constitutes sufficient information? How much can a patient be expected to weigh up the emotional consequences of a particular result and to what extent can they be said to fully understand its implications for them and their family members? Genetic information can be upsetting to individuals and may have collateral consequences, for example, fear of discrimination or stigmatisation. Some of the issues

that need to be discussed during the consent process for genetic testing can be found in box 2.

Box 2: Issues to be discussed during the consent process for genetic tests

- A family history of a condition or disease, or genetic test results have potential implications for other family members
- Communication of certain aspects of information to family members may therefore be recommended
- A means of contacting those at-risk family members where relevant
- A summary of relevant clinical and genetic information will usually be sent to other appropriate health professionals
- Likely timescales for availability of test results
- The possibility of unexpected findings from genetic testing and how these might be managed
- The uncertain nature of certain genetic test results (for example, the clinical significance of a result may be unclear in the short or long term). The relationship between a finding and disease risks may not be able to be given with any certainty
- The predictive nature of certain genetic tests (for example, indicating risks many years in the future rather than current risks)
- The routine practice of long term storage of samples for possible future analysis and the patient's preferences regarding further testing if it becomes available
- The routine practice of using stored samples from one family member as quality assurance for clinical testing in another family member

Given these complexities, and the fact that competence is decision-specific, what is the bar for determining competence? Is it realistic to expect patients to weigh up all these issues before consenting to genetic testing? If insufficient consideration is given to such implications, then the validity of their consent becomes questionable. This tightrope must be carefully navigated based on the individual.

Broad consent

Broad (or generic) consent is a possible way to manage some of these difficult questions. Generic consent has been used in the research setting, with research participants agreeing to join a study where they can also indicate if they are happy, for example, for tissue samples or DNA to be accessed and used in future research projects. The Human Genetics Commission (HGC) in their document 'Building on our inheritance: Genomic technology in healthcare' in 2012 reported that introducing a national system for routinely requesting generic consent for the confidential use of the genetic and clinical data in patient records, would significantly accelerate the development of new treatments and increase the attractiveness of the NHS as a place to do research. They also proposed that this would put the patient at the heart of the debate as their decision to consent or not would be made easier and simpler to enact.[101] The familial implications of genomic information, generated through genetic testing, provides an argument for a broad consent approach, where the individual's need for information, choice and privacy can be weighed up against a wider family benefit in having this information. With regard to IFs the specific IF that may be subsequently discovered cannot be predicted, so the patient is not able to consent to receive this particular result prior to testing. Even if they decide that they would not want to know, other family members may benefit from having this information and the HCP will struggle not to disclose a result that is clearly of medical significance to both the patient and a number of other relatives.

One proposed model for delivering this approach to consent is presented by Kanellopoulou and colleagues in their dynamic consent model for Biobanks, an interactive IT based system, where patients and researchers access a website and can update the options and decisions during the period of their participation.[102]

Confidentiality and the sharing of genetic information in families

Maintaining patient confidentiality is an important component of trust in the patient/healthcare professional relationship. Genetic information, however, can be relevant to family members of an individual and there can sometimes be a tension between maintaining individual confidentiality and alerting family members to their potential genetic risk.[103] The General Medical Council, in its guidance on confidentiality in 2009, stated that, while confidentiality is an important duty, it is not absolute. There are certain situations where a duty of disclosure outweighs the duty of confidentiality.[104] The

guidance specifically mentions genetic information as a possible reason to breach confidence in rare circumstances, so that family members can make their own autonomous decisions. Facilitation of the autonomy of others (or preventing them from being kept in the dark about their own risks) is therefore a key ethical principle that drives moral obligations to disclose and communicate risks.[105]

Difficulties in managing this individual/ familial tension in genetics have led to proposed alternative approaches. An approach that views genetic information like a joint bank account can be helpful in knowing when it might be appropriate for family members to have access to certain types of genetic information.[106,107] Here, the default position of confidentiality is shifted and HCPs are asked to consider whether disclosure would harm an individual, not whether non-disclosure would harm third parties. This approach has been adopted in the JCMG consent and confidentiality guidance where the model consent form includes a statement indicating that any genetic information generated may be used for the benefit of other family members.[1] By presenting this as an assumption rather than a yes/ no choice it invites patients to acknowledge the familial nature of genetic information. In my clinical experience patients have been happy to sign up to such an approach, in part because one of the most common motivations for attending a genetic clinic is to find out risks for relatives.

As genomic IFs have been few in number to date, it has not been possible to determine whether patients consider these any differently to other genetic test results but it seems likely that their- by definition- unexpected nature might result in the sharing of results with relatives as being seen as less pressing or relevant. When genetic tests are targeted patients may have considered the implication of results for other family members and discussed this with relatives beforehand but with IFs they will not have had the opportunity to do so. While not specifically addressing the dissemination of IFs within the family, some studies have provided insight into the practices of patients disseminating genetic test results to their family members. One study of 12 UK and 2 Australian genetic services found the apparent frequency of non-disclosure of relevant genetic results to relatives to be low, but the study was limited to cases where disclosure was actively withheld[108] and other studies have found higher rates.[105] The definition of disclosure is important in comparing rates, for example, is non-disclosure only the case after a particular period of time has elapsed and to measure disclosure is it to those in the family

for whom it has relevance or to all? Furthermore, what about relatives to whom information is disclosed but which they ignore or do not believe the information, do these examples count as non-disclosure?

In the Clarke et al research, and other studies, reasons given for non-disclosure were complex; more often citing concern and the desire to shield relatives from distress rather than poor family relationships.[108] Issues of guilt and blame along with perceptions about a family member's character were often included as a rationale to justify decisions to defer or delay disclosure. In addition, if relatives were not showing signs of the condition or being told 'right now' was not deemed necessary, disclosure might be delayed.[105] Availability (or not) and timing of surveillance also guided these decisions.[105 109] A recent systematic review of research evidence on the communication of genetic information within the family suggests that instead of focusing on the content of information, professionals should engage with patients to explore the relevance and value of sharing risk information with family members.[110]

Family communication about genetic risk is complex and has been described as a deliberative process, which includes making sense of personal risk and assessing the vulnerability and receptivity of family members. Decisions need to be made about what will be conveyed and the right time to disclose.[111] Disclosure rarely constitutes a single episode and there is no guarantee that information will flow to the next generation.[105] Decisions to disclose genetically relevant information informs existing zones of responsibility within the family. Zones of responsibility relate to who may be responsible or accountable within a social network - in this case the family – for certain actions and knowledge.[112] Genetic information can challenge existing norms and generate new forms of obligations. For example, a 'junior' member of the family may the first to receive genetic information and be tasked with sharing this within the family; thus a new form of obligation emerges within an existing family structure.

Inherent in decisions about disclosure and the processes involved, are conflicting senses of responsibility. For family members there is a tension between providing potentially valuable information and wanting to prevent harm that may arise from sharing this knowledge, such as the breakdown of family relationships.[111] This tension can also be experienced by health professionals as they consider disclosing results to patients, weighing up the benefits and harms.

Capacity/ competence and IFs

The Mental Health Act 2005 makes it clear that capacity is decision specific.[113] It is easier to have capacity for straightforward simple decisions than for highly complex ones. The technical details, the different types of results that can be generated, the implications for family members and the impossibility of knowing what, if any, IFs might be found, means that the threshold for capacity for these sorts of decisions is higher.

Genetic testing of children and capacity

Genetic testing of children may discover IFs that are not clinically relevant, or actionable, for many years to come. Should findings that are relevant in adulthood only be disclosed when the child has the capacity to decide about such testing? International guidelines support genetic testing in children when there is medical benefit in doing so, but if there is not, recommend deferring testing until the child is old enough to make this decision for themselves.[114,115] Testing for adult onset disease in a child removes their future ability to choose whether this is information they wish to access as an adult and thus their right to an open future.[116-118]

The British Society of Human Genetics (BSHG) report on the Genetic Testing of Children acknowledges that new genetic testing technologies can generate substantial amounts of information (the specific details of which may not have been anticipated when consent for testing was obtained) and is different from when IFs are identified in, for example, the radiology setting. It urges careful prior consideration about the information that might be generated, how this can best be covered in the consent process and how it will be interpreted and fed back to the family. [115]

When parents have been asked for their views on receiving IFs in their children, an overwhelming majority wanted to receive all results pertaining to their child. When they were uncertain, this was related to highly penetrant and fatal conditions that did not have any effective treatment options. The primary reasons put forward by parents for wanting to access this information is parental responsibility and having a right to this information. They considered the information empowering even if not clinically relevant for many years in the future.[119,120] This is important as so many patients having trawling types of genetic tests are children, and careful consideration needs to be given as to how these

results are managed long term when their clinical significance may not become relevant for many years.

Best interests and IFs

In general, patients with capacity are best placed to determine their own best interests, with the usual provisos that they have adequate and accurate information to decide, time to consider where possible and can discuss with friends and family. The HCP has a role in ensuring patients' decisions are as informed and considered as possible in accordance with their best interests.

Justice and IFs

Another relevant issue is that genetic test results might reveal that an individual is at risk of, for example, a degenerative condition with no treatment and having this knowledge could potentially lead to discrimination and stigma; impacting on employment and insurance. Concerns of this nature are often raised by patients, as well as explored by HCPs, and the identification of IFs of this nature can be particularly problematic when the patient was unaware that they were at risk of this condition, so did not have the opportunity to consider if they wanted to access this information or not.

Consent as an expression of autonomy

Autonomy today is given a central role in the legal and ethical frameworks governing clinical practice, perhaps in response to questions about the primacy of medical authority over the last few decades.[121] A focus on patient autonomy has resulted in many improvements in patient care including shared decision-making and consideration of consent processes. However, overemphasis on individual autonomy could result in the role of the HCP not being adequately recognised or realised: seeing autonomy as simply an expression of patient preferences is clearly also simplistic, especially where very complex information needs to be understood in order to express autonomy.

Seedhouse discussed autonomy as an intrinsic personal quality, that of 'being able to do'.[122] There may be occasions where some choices are limited but being able to make a decision about anything is better than being excluded from the decision-making process entirely. Autonomy can be viewed as a matter of degree, the better the quality of autonomy the more a person is able to do.

In health care, respecting autonomy is therefore more than saying to patients "the decision is over to you" when there are difficult decisions to be made. While choice might give the impression that a patient is being left to exercise their autonomy, if this is presented without advice, support and education (especially if the patient is distressed or anxious at the time) then they may have little autonomy to exercise. Similarly, too much choice may not enhance someone's autonomy. If an individual goes to a shop to buy a red jumper and they are given the choice of three red jumpers they may find it easier to make a decision on which to buy than if they were presented with fifty red jumpers. The one jumper bought from a choice of three may have been very appropriate and fulfilled all of the shopper's requirements and the individual had no regrets at not looking at all fifty, which would have been unnecessary and possibly confusing. In the same way, asking patients to decide from a list of all possible IFs (which could run into hundreds of conditions) the ones they wish to receive will likely diminish rather than enhance their autonomy. Perhaps a better approach is to discuss with patients the different types of IFs that can occur and begin to find out their views on the types of information they are interested in receiving.

It has been proposed that the debate on disclosing results from genomic tests has focused on how much information should be disclosed and not whether or not it should be.[123] Arguing that the patient has a 'right not to know' appears to help to decide whether or not IFs should be disclosed according to the patient wishes. However, how well a patient can understand an almost infinite range of outcomes is far from clear. To be able to make a valid choice therefore, one would need a priori knowledge of a wide range of genetic conditions, their course and treatment options, or individuals are making decisions based on hypothetical scenarios. The concept of patients being able to know what they don't want to know, when access to specific information is not a reality, is difficult. In addition, any 'right not to know' may well be overridden by HCP responsibilities if results demonstrate a serious, treatable condition. Can a patient apply a right not to know about conditions they are unaware will be discovered and what their implications will be?

In an attempt to make choices for patients more manageable, Berg et al proposed categorising potential IFs into three bins each with a different management approach:[124]

- Bin 1: Clearly pathogenic results with immediate clinical utility. *These IFs should be reported to patients*
- Bin 2: Variants with a known or presumed association with disease but not medically actionable. *Their potential return should be discussed by the patient and HCP at the time of consent*
- Bin 3: Variants of unknown or no clinical significance. *These should not be reported*

However, there are a number of difficulties with such a streamlined approach:

- The pathogenicity of results is not always clear at the time of reporting so engaging other family members in genetic testing may be required in order to establish this. A result will therefore need to be disclosed to the patient and this may eventually turn out to be one that would be managed in bin 3 (and therefore not disclosed) but will already have been revealed.
- Results originally placed in bin 3 may with time, and by collecting data on a number of families, turn out to be clinically significant and these will not have been disclosed. It is unlikely that HCPs will be able to return to these results many years later and re-contact families to tell them about this new information. The infrastructure is not currently in place to do this and it may also be inappropriate to do so after a number of years. It means that individuals may miss out on possible treatments and interventions.
- Bin 1 suggests that to opt out of receiving this category of result is not possible. How can patients then express autonomous choices here?

Shared decision-making

Shared decision-making (SDM) is a central feature of the patient centred care model of health delivery, whereby there is active participation from both patient and professional who ultimately agree on the decision. Both bring facts and preferences into the decisional process and there will be a period of negotiation if an initial agreement is not reached.[125] The focus is on two main aspects: sharing the decision making and consensus where the final decision is mutually agreed upon. According to Charles et al four principles underpinning SDM are:

a.) SDM involves at least two participants, as a minimum the HCP and the patient

b.) Both parties take steps to participate in the process of decision-making

c.) Information sharing is a prerequisite to sharing of the decision-making

d.) A decision is made and both parties agree to it [126]

One criticism of SDM is that HCPs no longer make any judgements but simply provide facts.[127] Savulescu and others question whether HCPs can in fact avoid making value judgements.[17,127] Value judgements in health care are not necessarily a bad thing: the clinical expertise of HCPs means that patients sometimes ask of their HCP what they would suggest or recommend and what they would do if in the same situation. Of course, adopting a model of SDM does not preclude the HCP from bringing more than the facts to the discussion but the line between that and a possible coercive or paternalistic practice is quite thin.

A paternalistic approach

A paternalistic approach to health care, where the HCP 'knows best' could be considered out of date and inappropriate in today's health service but in the sense that HCPs often do know more about genetics and the possibility of IFs, sharing this knowledge might be seen as an appropriate use of paternalism. Libertarian paternalism argues that institutions (and health services could be one such institution) can and should influence behaviour while respecting freedom of choice. This is because an individual's preferences can be ill formed and unclear and steering to avoid random or harmful effects from the decisions made could be better for the patient and avoids what Sunstein and Thaler have termed 'inept neglect', where individuals are left to work their own way through a complex issue.[128]

Savulescu proposed 'rational non interventional paternalism' for the health care setting.[127] He argued that doctors ought to make 'all things considered' value judgements about what is best for their patients. Patients can sometimes make choices that are based on mistaken judgements of value (for example, placing high value on a chemotherapy treatment that has significant side effects with only small gains in life expectancy) and in this way can make choices that fail to express their autonomy. The value of this in genetics might be particularly pertinent where patients expect a result to be more clear cut than the HCP knows it to be, or that HCPs know that considered decisions about a particular form of test are often different from initial intentions.

Levy suggests that people's reasoning is subject to bias and this lowers the quality of their decisions. He considers that HCPs can paradoxically increase patient autonomy by constraining it and this is a particular challenge for a practice that desperately wants to avoid accusations of paternalism.[129]

The use of empirical research methods within ethical philosophical theorising

Within bioethics there has been much deliberation about *what should be*, that is, moral theory, and *what is*, that is empirical evidence, if one can inform the other and how. Can empirical research play a part in moral deliberations? Conversely does moral theory direct the development and value of empirical research? Whilst empirical research can have limitations - defined and narrow sample groups, possible biases, generalisability of results - proponents argue that moral theory requires empirical research for robustness, whilst others suggest it is not useful or necessary to inform ethical theorising. It has been suggested that empirical ethics has often not gone beyond the examination of pre-identified ethical issues[130] and in this way can limit the possibility of investigating new and emerging issues. It has also been critiqued for its focus on how clinicians understand and enact 'ethics' thus confining the value of research to what happens and what are the issues, rather than what should happen and why. However, from another perspective it can be argued that important insights can be achieved from even small empirical research studies because study participants' views can be weighed in the balance, contributing to the quality of ongoing ethical arguments.[131]

Methodological approaches to enhance the value of empirical research in being able to inform and influence moral theory have been proposed. For example, if the research aims to carry out an analysis or critique of behaviour, with the intention to offer an ethical alternative, then philosophical bioethics must engage with empirical social science in more than just a superficial way.[132] Incorporating empirical data into ethical theorising can achieve contextual understanding, sensitivity and meaning and informs the debate. This can take analysis beyond simply reporting on ethical issues and how they impact practice, to a consideration of how these assimilate with ethical theory. This approach can lead to a review of norms governing practice, more than a superficial acknowledgement of "what are the issues?"[132,133].

Others have also argued for new methodological approaches that "broaden the analytical gaze of empirical ethics beyond examining pre-identified ethical issues."[130,134] They advocate "empirically driven, broad-conception empirical ethics"[134] which comprises:

(a) identification of actual ethical issues

(b) making sense of relevant experiences in relation to these issues

(c) using these to inform a course of action, such as guidance or policy.

The research described in this thesis broadly adopted a grounded moral analysis approach where conceptual and normative analysis proceeded contemporaneously alongside data collection and analysis.[134]

Clinical management of IFs

Clinical utility of IF as determinant of disclosure

Much of the debate around whether or not IFs should be disclosed to patients is focused around the clinical utility of the finding which has been defined in a number of different ways.[135-138] Broadly speaking, clinical utility refers to whether the finding could lead to medical intervention, for example, surveillance or treatment that could improve health outcomes. The greater the potential benefit of an intervention the greater the perceived onus to disclose. Potential clinical benefits need to be weighed against the potential harms of disclosing the IF (such as associated distress or uncertainty), especially if no specific consent was given at the time of testing.[139,140] There are a number of important issues associated with determining clinical utility:

Uncertainties about for whom the result has clinical utility and when

In many cases the IF will not have clinical utility for the individual in which it was identified for a number of years, especially if the IF is for an adult onset condition and discovered in a child. However, the IF could have immediate clinical utility for one of the parents of the tested child.[141,142] As already discussed international consensus is that children are generally not tested for adult onset conditions but others consider that potential benefits to adult family members in having this information may outweigh potential harms for the child.[139]

Clinical validity

This refers to the accuracy with which a particular finding predicts the presence of the underlying condition (either now or in the future). This can be unclear if the expressivity of the genetic abnormality is known to be variable and the effects of other factors (for example, other genetic and environmental factors that can play a part) are not yet determined. If these results are not offered as a routine clinical test, should they be reported if discovered as an IF?

Novel findings

Some IFs may appear pathogenic but as yet there is no evidence available to support this. Further studies may clarify this (family and functional studies, for example) but difficult decisions about if and when to disclose such results will need to be made.[96]

Personal utility

Some IFs cannot be said to have clinical utility as there is no availability of a proven intervention to improve health outcomes. Examples of this would include the identification of a neurodegenerative condition with no treatment or the identification of carrier status. Some patients may consider however that these types of results hold personal utility for them. They may wish to receive the information anyway to help with life planning, reproductive choices and behaviour change.[120,143-145] Some argue against disclosure of this group of IFs because of the limited resources to analyse and return all IFs in a way that patients can understand [146] and because there is little evidence that receiving genomic information has any impact on health behaviours.[147,148] As such they conclude that stringent requirements for the return of results based solely on clinical utility should remain.[81,124]

In considering clinical utility to research participants, Fernandez et al explored attitudes of researchers toward the return of incidental genomic findings (and the same may be true for clinical patients):

"It is important to recognize that research participants may find utility in data that do not meet scientists' narrower definition of clinical utility. Therefore, should the disclosure of results be limited to findings with personal health implications or expanded to indications that may encompass reproductive planning and other issues with personal meaning?"[149] p.563

Policy and guidance on IFs in clinical practice

The American College of Medical Genetics and Genomics (ACMG) released a policy statement on Genomic Sequencing (March 2012) recommending that laboratories and clinics that utilise WES/WGS should have clear policies in place related to the disclosure of secondary findings and that patients should be given the option of not receiving them should they choose.[150]

In March 2013 they subsequently issued a report entitled: Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing.[139] The key recommendation in this document is that laboratories performing clinical sequencing should *seek* and report mutations to the requesting clinician in genes from a specified minimum list. They acknowledged that there was insufficient evidence about the benefits, risks and costs of disclosing IFs to make evidence-based recommendations. The ACMG working group prioritised disorders where preventative measures and/or treatments were available and disorders in which individuals with pathogenic mutations might be asymptomatic for long periods of time. Somewhat controversially, the working group did not favour offering the patient a preference as to whether or not the laboratory analysed this minimum list of genes 'opportunistically'. If patients judge the risks of possible discovery of an IF(s) to be unacceptable then their only choice is to decline clinical sequencing and opt for a less detailed test.[139] Once an IF has been identified it will be passed on to the referring clinician and whether it is then disclosed or not will depend on the discussion the clinician had with the patient prior to testing.[151] The first author of the ACMG report suggested that the tradition of genetic testing had served to exceptionalise genetic risk information as potentially dangerous to the wellbeing of patients and in the current era of genomic sequencing this needs to be reconsidered:

"Rather than exceptionalize the return of incidental genomic findings, clinicians and patients should embrace them as adjuvant information of potential utility and as a welcome component of modern medical practice." [152](p.366)

It could be argued that the recommendations proposed by the ACMG have been an accepted approach in clinical medicine for many years.[139]

There have been a number of international responses to the ACMG recommendations and table 4 summarises these.

Table 4: Responses to ACMG recommendations

Source: **Policy Think Tank (PTT)** **Professional Body (PB)** **Academic/Researcher** **(AR)**	**Comments on the recommendations**	**Action(s) proposed**
PHG Foundation (PTT) 2 April 2013[153]	Consider the recommendations to be contrary to international ethical standards regarding consent. Represent a coercive regime, undermining patient autonomy. Denies patients' 'right not to know'	The ACMG proposal is an acceptable and possible option that certain patients may wish to consider; but not to give patients the choice of other options (for example, having access to the test without receiving any IFs) should have no place in the modern practice of medicine
European Society of Human Genetics (PB) 20 May 2013[154]	Opposed to the type of opportunistic screening that throws up large numbers of incidental results Need to find ways of testing that avoid unsolicited findings	Propose using analysis that specifically targets a particular health problem Calls for clear guidance on how to deal with unsolicited findings
Whole genome sequencing in health care: Recommendations of the European Society of Human Genetics (PB) 2013[77]	Targeting is a means of handling the vast amount of data produced by WGS, but if the focus is narrowed too soon potential disease causing alleles might be missed	Protocols should be established as to whether and how WGS information should be documented, shared and stored (11 recommendations in total)
National Society of Genetic Counselors (USA) (PB)	Applaud the efforts of ACMG providing guidance to begin to integrate new genome sequencing technologies into clinical practice	Adequate expertise of physicians will be required throughout the process, especially for pre-test counselling

27 March 2013[155]	Empowering patients does not mean restricting their ability to make choices for themselves	
The Genetics Advisory Committee of the Royal College of Pathologists of Australasia[156] (PB)	The Australian guidelines on the implementation of sequencing in diagnostic genetic testing is broadly in line with European approach Doctors have an obligation to do what the informed patient has requested but also to advise them of other serious health risks revealed by testing	Consider targeted analysis to be a pragmatic approach to minimise the ethical dilemmas of IFs
Association of Genetic Nurses and Counsellors (UK) (PB) 8 January 2014[157]	Recommendations represent a significant change from the current approach. In most clinical settings would not routinely search for additional findings unrelated to the original medical question	Patients should be allowed to consent to or opt out of receiving IFs
JAMA 2013 (A/R) Freidmann-Ross[158] Klitzman et al[159] Science Wolf et al[160]	These three responses to the ACMG guidelines raised concerns about the recommendations. They focussed on the impact of this approach on patient autonomy and the testing of children for adult onset conditions	

The ACMG issued a number of documents in response to their original publication, to address some of the concerns raised about patient choice and autonomy. This included clarifying the role of the clinician and patient; to participate in a shared decision -making process regarding the return of results and that, while IFs will be automatically disclosed to the requesting clinician, depending on earlier discussions, the clinician may opt not to disclose to the patient.[151] [161] The notion of clinicians applying their own professional judgement to the specific clinical circumstances is also picked up by a later ACMG report on points to consider for informed consent with WES/WGS.[162] Following a number of commentaries, criticisms and a survey of the ACMG membership, consensus was reached that patients should have the opportunity to opt out of the analysis of medically actionable genes when their DNA sample is taken, rather than making decisions about disclosure when the results are received by their clinician.[163]

Shortly after the publication of the ACMG recommendations, the US Presidential Commission for the study of Bioethical Issues issued its follow up report to Privacy and Progress in Whole Genome Sequencing (October 2012), to address specifically the question of IFs.[164] The report, Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts, recommended that professionals should anticipate and plan for IFs, make shared decisions with their patient and communicate a clear plan about what to do should an IF arise.[85]

As policy and guidance documents on the management of IFs in clinical practice have begun to emerge and inform the debate it is important to consider the literature and research in this area of practice.

How might management of IFs differ in the research and clinical setting?

In clinical practice, the HCP has a duty of care to patients and is required to consider their interests at all times, based on the best evidence available to them. In research, the aim is usually to obtain generalizable information, relevant to a particular group, which may not bring any personal benefits to research participants. The approach is not personalised, rather a general research protocol is offered to a group instead of tailored to an individual. Consequently the basis of the relationship is more contract based, constrained by what

the participant has consented to, rather than duty of care based, driven by the need to deliver best care.

The National Research Ethics Service (NRES) in its guidance on informed consent says that potential research participants should be told what would happen if other conditions were discovered of which they were previously unaware.[165] Some have questioned if there is an ethical duty to return individual genetic research results, and if so, should this moral imperative be recognised as a legal duty?[166,167] Before considering the details of any perceived legal duty to disclose such research results it is important first to establish if a legal duty exists, which has not yet been tested in the courts.

One systematic review of the literature in 2013, for and against the disclosure of IFs in both clinical and research settings, identified 16 relevant articles.[26] Most articles had been published in the previous 2 years. Only 5 of the studies were directed to the management of IFs exclusively within a clinical setting. There was general consensus, in both research and clinical contexts, that clinically significant IFs should be disclosed. The minority wanting to facilitate a 'right not to know' option suggested procedural requirements to determine potential recipients' wishes. One study considered pre-test discussion between patient and clinician to be vital to clarify and agree what would happen when IFs were identified, but this study did not establish what was actually happening in clinical practice.[146]

One focus group based study of HCPs and two lay groups found that HCPs favoured targeted genetic analysis to limit data handling and the risk of IFs being discovered, while the lay groups emphasised autonomy and patients' right to choose what findings they received.[146] This highlights the possible tension: between HCPs wanting to deal with IFs by avoiding generating them in the first place, and the public wanting IFs to be looked for and the ones they have requested being fed back. This study was limited in that HCPs who routinely order genetic tests, such as paediatricians, were not included and the impact on families of having received IFs was not explored in any detail.

The authors of the systematic review proposed the implementation of a decision-making tree, as a tool to facilitate discussions between researchers or clinicians and patients about whether and how IFs are disclosed, the two main branches of which would be technical and ethical. The authors suggested that technical factors should be dealt with

first followed by ethical reflection.[26] I would argue that implementing such a tool, when results have already been reported to the researcher/clinician, is too late. Decisions around disclosure need to be made (as much as is possible) before testing so that laboratory staff/HCPs and patients know the tests being initiated and what results they can expect.

Further studies that presented hypothetical scenarios about IFs to participants, focusing on consent and disclosure practices, published since 2013 are summarised in table 5.

In summary these studies found that:

- Patients are interested in receiving IFs. There were high levels of support for receiving IFs pertaining to clinically actionable results and although less for other IFs, the majority would still opt to receive them. Participants in the studies were given hypothetical scenarios and their views were not based on 'real life' experiences.

- There is almost unanimous support from parents to receive all IFs in their children, even if not clinically relevant for many years, and parents view themselves as the gatekeepers of health information for their child.

- HCPs had an interest in receiving IFs for themselves when available. They supported patients being given an opt-out facility.

Table 5: Summary of published studies on participant views about IF consent and disclosure practices

Author Date	**Country**	**Study type**	**Study population**	**Aim of study**	**Results**
Christenhusz 2014[86]	Belgium	Clinical Hypothetical	Interviews with 16 parents of children who had undergone aCGH	Exploration of parents' experiences, expectations and opinions, regarding the communication of results (none had an IF discovered)	4 main themes identified when deciding about receiving IFs: - actionability of the result - knowledge of the result - context of the result - characteristics of the result Most parents wished to know all types of results Parents considered themselves as 'gatekeepers' of information for their children
Hitch 2014[144]	US	Clinical Hypothetical	19 Patients diagnosed with Lynch syndrome clinically but with no mutation. Had WES. Interviewed before results were back	Ascertain which results they wanted and how they would like to receive results. Do they want direct access to the data and who will they share it with?	Nearly all participants believed that the benefit of receiving all possible results outweighed any undesirable effects. 63.1% wanted all results, 31.6% wanted all clinically relevant results and 5.3% wanted results related to their cancer only (no IFs) Relative to coping with a cancer diagnosis, the information generated by WES would be manageable.
Rigter 2013[168]	Netherl-ands	Clinical Hypothetical	Interviews with 12 professional experts.	Establish experiences and views of stakeholders	Stakeholders preferred an opt-out for IFs (but identified challenges with this). Context dependent decision-making was observed. An advisory board for IF disclosure was considered helpful

			Observation of 3 counselling sessions where WES was offered	involved in current procedures regarding consent	
Strong 2014[169]	US	Clinical Hypothetical	Survey of 258 HCPs asking about return of genome sequencing IFs for themselves and their children	To establish the attitudes of non-genetics HCPs regarding WES/WGS and the return of IFs	Respondents who were positively disposed to sequencing did not always want to learn about IFs, even if actionable. Most would want clinically actionable IFs (95.9%), not clinically actionable (55.5%), uncertain clinical significance (52.2%). Most would want to know all results for their child
Manchini 2014[99]	US	Clinical Hypothetical	221 genetic counsellors Online survey	An analysis of views and experiences with the clinical integration of WES/WGS	Highlighted challenges including duration and content of consent process, result interpretation and disclosure of IFs/VUS.
Lemke 2013[170]	US	Clinical Hypothetical	Anonymous survey of 279 genetic professionals (laboratory and clinical staff)	To assess views towards genome sequencing and the management of IFs in adults and children	96% were interested in knowing about clinically actionable IFs in themselves and 99% in their child.78% would want to know about adult onset clinically actionable IFs identified in their child.
Shamirdazi	US	Clinical	200 families	Analysis of IF	93.5% chose to receive at least one or more category of

2013[171]		Non hypothetical but not yet had results disclosed	referred for WES. Consent form based project that asked participants about 4 categories of IF and the results they would want to receive	consent among patients undergoing diagnostic WES	results. Only one patient chose to receive no IFs at all.

Rescue obligations in research

Disclosure of IFs in the research setting has seen growing support for researchers having a duty to disclose clinically actionable results[34-37 172] but this is still less often the default position than in clinical practice. Whether the researcher has a duty (or perceived duty) to disclose IFs, and in doing so 'rescue' research participants from possible harm, has been discussed.[173] Garrett suggested that there is a "*purported duty to regularly return incidental findings in genomic and genetic research*"[173(p.3)] but that to apply this principle to the majority of cases could be hasty and problematic. One problem in doing so is that research studies are often not set up with the necessary clinical infrastructure in order to facilitate the confirmation and return of all these results. The CELS research group, of which I am a core member, questioned the prerequisite that the occurrence of random or unpredictable events leads to an obligation to rescue. In the genetic testing context, IFs are both predictable and regular, with the types of tests currently being used and developed.[174] A duty to rescue also brings other issues to consider such as possible wider duties to other family members, in addition to the original research participant, and who is the most appropriate person to act as 'rescuer': the researcher who discovered the IF or a nominated clinician with relevant experience?

If researchers have a duty to rescue participants then the issue of therapeutic misconception may be of relevance. Therapeutic misconception arises when research participants misunderstand the primary aim of research as therapeutic and not about obtaining generalizable data that has no direct benefit to them.[175] If researchers continually disclose research results as a means of rescue from possible harms, research participants could begin to see the research as more therapeutic than it actually is. Decisions to join genomic studies could be made on this basis, as a way of accessing accurate deterministic genomic information that is not yet able to fulfil this remit:

"*Whereas recognition of the personal meaning of genetic information and a conception of clinical utility that exceeds direct medical benefit are appropriate to the goals and norms of clinical genetics, they seem inappropriate as a basis for offering to return research results, given the desirability of reducing therapeutic misconception especially about genetic research*." [27(p.22)]

This is a particular issue with genetic research because the boundary between research and clinical care is often blurred.[32] Of course, accessing interventions, such as particular genetic tests, only available through participation in a research study, can be viewed positively by patients who are keen to take part if it means they get the test. In this circumstance test results (if disclosed) could have direct benefit to them.

Whether researchers have an obligation to disclose individual research results to participants and if so, if there is a limitation on what information is or is not revealed, has been the subject of continuing debate. Reviews of international norms governing genomic research, research consent forms and Institutional Research Boards (IRBs) revealed inconsistencies and IF disclosure was often not specifically addressed.[80,176,177] However, several papers, summarised in table 6, have proposed disclosure policies for IFs discovered in the course of genomic research. The decision to disclose has depended on the seriousness of the identified IF and whether there is any proven clinical intervention to prevent, treat or mitigate the disease. Many researchers propose only to disclose IFs that fulfil this defined set of criteria.

Despite the boundary between research and clinical activities being blurred in genetics it cannot be assumed that models of disclosure written for the research setting can be applied to the clinic. While reporting back serious and actionable findings may be acceptable to both research participants and patients, can the same be said for all IFs? Patients may want additional IFs to these and their experience of having received IFs will inform this ongoing debate.

Table 6: Models of disclosure of IFs discovered in the course of genomic research

Reference	Details of empirical research (if applicable)	Details of disclosure model	Issues with proposed disclosure model
Brandt et al 2013[25]	Telephone study with genetic HCPs, genomic researchers and IRB chairs. Ranked 9 criteria for the disclosure of IFs. Life-threatening IFs were ranked highest	Two tier approach to disclosure: -Disclosure of results for which there is agreement (for example, life threatening conditions) -Disclosure of results that are more problematic	Different stakeholders, for example patients, HCPs or researchers may have different perspectives. The criteria presented were for a hypothetical situation. Responses can only be an indication of what stakeholders may want as they are not context specific not linked to a lived experience
Wolf et al 2008[3]	N/A	Strong net benefit = life threatening or grave conditions and can be avoided: *Disclose result* Possible net benefit = non-fatal condition likely to be serious but cannot be avoided: *May disclose result* Unlikely net benefit = not likely to be serious or of reproductive significance: *Do not disclose result*	Test results may change over time in terms of their clinical significance. If an IF is classified as unlikely net benefit and therefore not disclosed what happens if later it is reclassified as strong net benefit, can it then be disclosed? How would this happen practically?
National Heart, Lung and Blood Institute 2010[178]	N/A	Need to meet criteria as follows in order to disclose IFs: Important health implications, risks are established and substantial Finding is actionable, with therapeutic or preventative interventions available Test is analytically valid Participant has opted to receive results	Is it possible to meet all 4 criteria concurrently? If some categories are met but not all should IF be disclosed or not? If the (one or more) of the criteria change can the decision to disclose change?
Bredenoord	N/A	A standard default package to disclose if life-threatening	Assumes researchers and participants have an

et al 2011[179]		with immediate clinical utility. Obligation to disclose unless individual has specifically opted out. In additions there are three context specific packages (all opt in): -IFs of potential or moderate clinical utility -IFs of reproductive/personal or recreational significance	extensive a priori knowledge of a wide range of genetic conditions, their course and treatment options. At the time of consenting for the test individuals are making decisions based on hypothetical scenarios

Views of the research community

Genomic researchers were asked about their views on disclosing IFs to research participants (one example given was an IF associated with an increased risk of developing bowel cancer) with most indicating they would disclose this result to participants. Reasons given for non-disclosure was either that researchers were not sure how to go about doing it or they felt they needed to adhere to the original study protocol/consent. It appeared that there was little collaboration between researchers and a clinical service within this cohort that would facilitate disclosure and follow up.[180] A questionnaire study sent to researchers involved in cancer research revealed that overall researchers did not feel a responsibility to look for meaningful IFs (only 37% thought they should) but once identified, 68% thought they should be disclosed to participants.[149] Most IFs that had occurred in the course of this research had been returned to either clinician or participant.[149]

While literature is beginning to emerge on the management of genomic IFs in clinical practice (see table 5) most guidance documents and empirical data have come from the research setting.

Why this research?

It is clear that the challenges of managing incidental information in clinical practice require further consideration and debate as genomic technologies advance and integrate into many areas of NHS practice. IFs routinely occur in clinical practice but management strategies remain preliminary and tentative. Genetic testing and subsequent interventions are offered to patients in different areas of medicine, from cancer to cardiovascular disease, making it an essential component of mainstream health services.[181] Current NHS infrastructures and commissioning arrangements will be stretched as they attempt to integrate and manage these new challenges.

When I started my research there was scant empirical research and guidance available to inform clinical practice, and while IFs were mentioned in passing as a possible outcome of genetic testing, how the issue of IFs should be incorporated into the consent process and decision-making about the disclosure of results had not been comprehensively addressed.

Despite recent policy documents and emerging empirical data, many of these have not reviewed current practice and the experiences of patients and HCPs when managing IFs.[118,162] Issues that remain unexplained include whether IFs are being disclosed to patients, if so how and by whom and what has been the patient and HCP experience of having had IFs occur. This is reflected in the following quote indicating the position at the start of my project but was still much the same at the end of my research:

"*Although the literature identifies practical and ethical challenges surrounding IF disclosure in research settings, no current guidelines exist for implementation of whole genome sequencing and the associated challenges of IF in a clinical setting*."[146] (p.2520)

There is a paucity of empirical literature on the views and experiences of families and HCPs on how IFs should best be managed, with a clearly identified need for research to guide future practice and policy. There is a lack of data detailing the experience of patients who have actually had an IF with much of the literature based on reactions to hypothetical situations. A review of current practice, along with in-depth discussions with families and HCPs on their experience and views of genetic testing and having IFs identified, will inform and guide the debate on how best to manage IFs. I aim to get an insight into what happens in 'real life'.

Research aims:

1. Review current practice, including consent and disclosure practices, relating to the identification of IFs in the course of routine genetic testing.

2. Analyse lay and professional views and experiences on the ethical and practical issues surrounding IFs.

3. Design a questionnaire that can examine whether key findings from phase one (qualitative) of the study, resonate with a representative and larger sample of UK HCPs who manage genetic testing.

4. Generate information to advise policy on the management of IFs in clinical practice

Research question:

With the advent of new genomic technologies how are, and how should, clinically relevant (or potentially clinically relevant) IFs be managed in practice, taking into account both practical and ethical considerations?

Chapter 3: Research methodology

This chapter begins with a summary of my thesis including an outline of the design of the research. I then explore the ontological, epistemological and methodological issues of relevance to the study, including the rationale underpinning the adoption of a mixed methods approach and the methods employed.

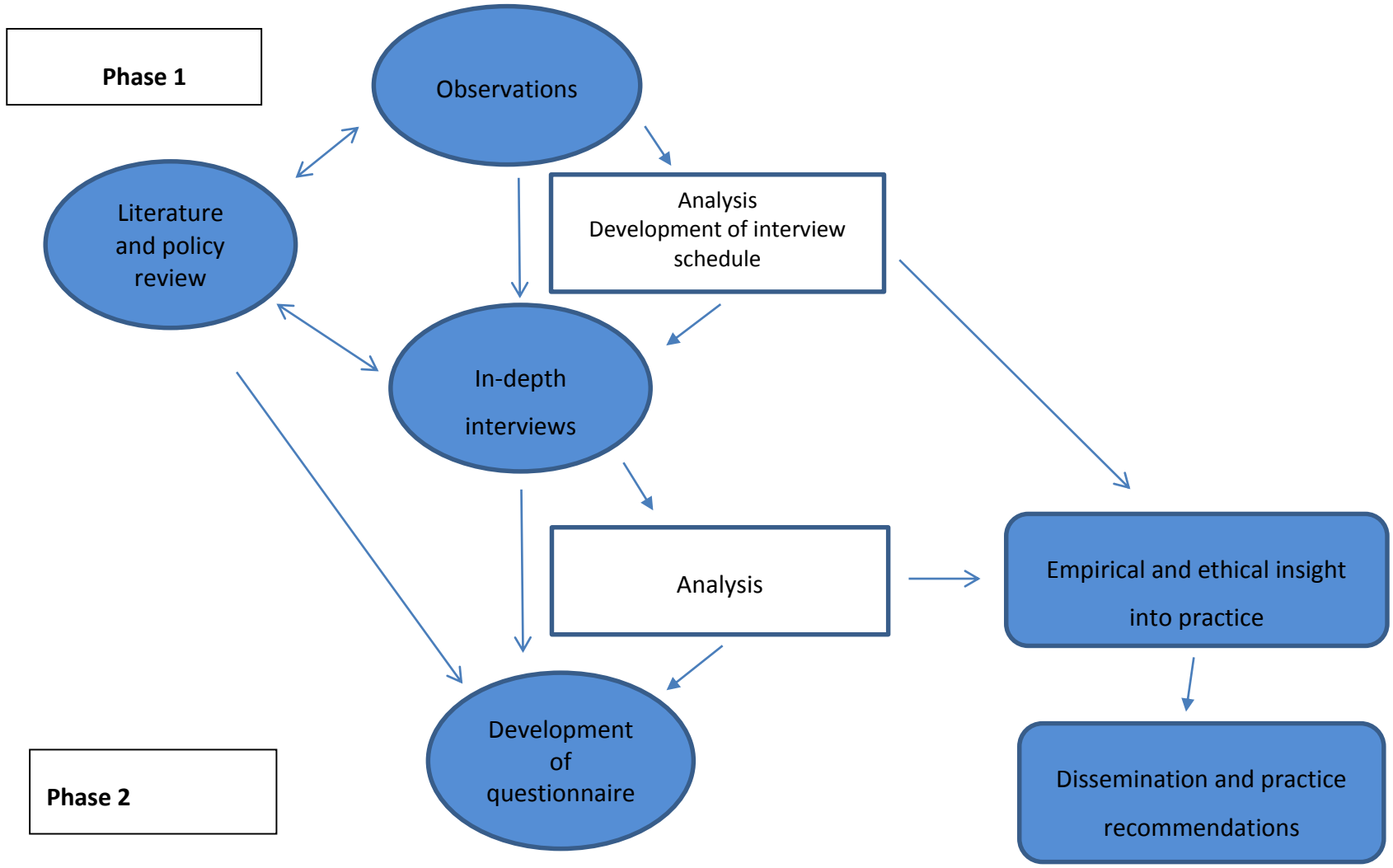
Overview of the research

The aim of this study was to explore the ethical and practical issues generated by the identification of IFs. A mixed methods research design was adopted to address the study aims. Phase one used a qualitative approach to identify current clinical practice, when genetic tests are being organised and results disclosed, and elicit the views and experiences of both HCPs and patients/parents of patients. This was chosen as qualitative methodology allows for an analysis which emphasises richness, depth, nuance, context and complexity.[182] Observations were undertaken to provide contextual data about the setting and to identify the issues to explore in later in-depth interviews (the primary data generation method). Building on the concepts/ issues from this initial phase, phase two employed a quantitative approach to test the findings from phase one in a larger cohort of HCPs. A questionnaire was developed using cognitive interviewing (CI) and then piloted. The wider circulation of the questionnaire was outside the scope of this PhD but will form the basis for my post-doctoral work. Table 7 outlines the main aims for each phase and the relationship between each phase, the overall research aims and the research methods; and figure 3 illustrates the overall plan for the study.

Table 7: Summary of the study aims and the research methods applied to address these

Phase/method	Aim of method	Research aim being addressed
1 Observation	• To ascertain if and how IFs are discussed when genetic tests are being organised. • Inform development of the family and HCP interview schedules and questionnaire	1
1 Interviews	• Explore the views and experiences of HCPs and family members about ethical and practical issues generated when IFs can be (or have been) identified by genetic testing. • Inform the development of the questionnaire	1,2,3, 4
2 Questionnaire development	• Use CI and piloting techniques to develop and refine a survey questionnaire that can be distributed to establish if the findings from the qualitative analysis are also pertinent to a larger cohort of HCPs	1,2,3,4

Figure 3: Summary of the research plan



Ontology, epistemology and methodology

This section considers the components of any research study: ontology, epistemology and methodology, which together characterise the research paradigm or interpretative framework.[182] A paradigm is the set of common beliefs and agreements shared between scientists about how problems should be understood and addressed."[183] A research paradigm encompasses questions about how we view knowledge, how we see ourselves in relation to this knowledge, and the methodological strategies we use to generate knowledge. During this research I have found it challenging to consider such issues in relation to my work and have determined that their usefulness is that they encouraged me to think more deeply about research design. Ontology relates to ideas/ theories about the world; so what is the nature of what I am studying? Epistemology is concerned with different forms of knowledge: what can I know (am able to know) or find out about my area of study? Methodology relates to the variety of ways that will generate knowledge: how can I find out what I set out to study?[182] If I then apply these concepts to my study, I need to consider the following:

Ontology: What are IFs? Do they have a specific meaning? Are they facts/ truths or something else? Does their nature depend on who I ask and/ or when I ask?

Epistemology: What can I understand about IFs in the genetic context? Am I able to know what is happening now in clinical practice and can I derive meaning from individual's accounts of their experiences and views?

Methodology: What are the best ways to answer to my research questions and why?

Different people describe and name a range of research paradigms in different ways and it is not possible to describe them all here. However, they reflect ways of seeing a spectrum of views about the world that spans from the objective to the subjective. An outline of what are generally considered to be the five main research paradigms is presented in table 8.

I think that there is reality 'out there' with truths to be revealed on the subject of IFs but these are not purely objective: research is context driven and subjective to the extent that knowledge is mediated by my interpretation of the data. There are different forms of knowledge that can be understood in relation to IFs: for example, what is happening in

Table 8: Summary of key underpinning beliefs for 5 paradigms of research (adapted from various authors)[184-187]

Research paradigm	Ontology	Epistemology	Methodology
Positivism	There is an objective reality which can be understood using the laws by which it is governed. These just need identifying.	Will employ a scientific discourse derived from the epistemologies of positivism and realism. There is a focus on the need for reliable and valid tools	Experimental and deductive. Usually quantitative methods employed
Post positivism	Critical realism: there is a 'real' reality but it can only be imperfectly and probabilistically known.	A modified objective approach to establish findings that are probably true. Context is needed so a context free experimental design is insufficient	Modified experimental methods. May include quantitative and qualitative methods
Critical theory	Reality exists and has been shaped over time by societal values. Society is full of inequalities and injustice justified by ideology	Strive to understand the views of the opposed to change social conditions. Knowledge aiming to uncover injustice and empower citizens	Critical analysis, historic review, participation in programmes of action. May use qualitative or quantitative methods
Constructivism	World and knowledge constructed and subjective. Each individual constructs his/her own reality so there are multiple interpretations/truths	Understanding a unique person's worldview and discovering the underlying meaning of events and activities	Qualitative methods such as auto/biography, narrative, interviews, observations, case study
Pragmatism	Reality is the practical effect of ideas. Truth can be seen to be what is useful	Ways of thinking/doing that leads to pragmatic solutions to real life problems or answers to questions.	Mixed methods, action research

clinical practice right now can be observed but what I observe, and how I interpret the observation data, inevitably adds a subjective component to the knowledge I convey. I believe that what patients and HCPs can tell me is meaningful knowledge but I understand that it is, to a certain extent, shaped by my interpretation and the context in which is generated. A questionnaire can collect data that can be generalised but such data is still dependant on the decisions I make about what is included and how it is framed. When thinking about what paradigm underpinned my research, I found Seale's stance that these sorts of questions should be seen as "resources for thinking" not "problems to be solved" (p.25) helpful.[188] I essentially worked within a post-positivist paradigm, but I made pragmatic decisions to find out practical truths relating to the management of IFs.

Methodological issues relating to my research

Mixed methods

The research design is the plan and procedures for research which includes both the overview and the details about methods of data collection and analysis.[186] Research designs can be categorised broadly as: qualitative, quantitative and mixed methods. Although mixed methods approaches might relate to the use of a variety of different qualitative (or quantitative) methods in one study (see for example Mason),[189] more commonly the term is used to indicate a mixture of qualitative and quantitative methods.[190] Mixed methods research (MMR) has emerged as a dominant paradigm in health care research.

MMR aims to mix both quantitative and qualitative data within a study in order to address a research question.[191] However, such approaches have been subject to criticism for a number of reasons. For example, can methods with different epistemological and methodological underpinnings really be mixed to achieve this aim? Is there actually a mixing of methods or does MMR really amount to two separate studies addressing the same research question? Howe (2004), suggests that MMR is fundamentally problematic because of the inherent tension between qualitative (exploratory) and quantitative (confirming) approaches.[192] Studies which are dominantly quantitative are seen by some as only consistent within a (post)positivistic paradigm[193], a criticism of those who adopt MMR as a strategy within

other paradigms -such as constructivist - where quantitative methods might be seen as incompatible. Others see MMR as a legitimate alternative to the sole use of a qualitative or quantitative approach and as an approach based on pragmatism.[194]

Leech and Onwuegbuzie refer to different types of MMR:

- Fully mixed methods where qualitative and quantitative approaches run concurrently
- Partially mixed methods where they run sequentially[195]

In either type, one approach may be dominant or both approaches might be equally weighted. Doyle agreed that MMR is acceptable whether the different approaches are equally weighted or not.[194] However, Burke Johnson et al argued that for a study to be truly classed as mixed method, equal weight should be given to both approaches.[196] Bazeley alerts researchers of the need to clarify the purpose of MMR at the outset to make clear the contribution of each method.[197] Undertaking mixed methods research just for the sake of it can produce "disjointed and unfocused" research; however, if the purpose of the research is made clear then potential concerns with mixed methods can be reduced.[189]

I adopted MMR to bring breadth and depth to the study and its use was broadly consistent with the paradigm underpinning the research. My work as a researcher to date had been primarily with qualitative methods but in designing this study I could see a benefit in adding a quantitative element: specific findings from the clinic observations and in-depth interviews could be strengthened and corroborated by using a survey questionnaire to elicit the views of a larger group of HCPs, adding to the body of evidence that had already been generated. Whilst the circulation of the final questionnaire was outside of the scope of my PhD research, the data from this - from my postdoctoral work - will ultimately provide a comprehensive review of current practice with regard to the management of IFs.

In developing my MMR design I considered whether the approach would be primarily qualitative or quantitative – that is, the 'weighting'.[186] My research was primarily qualitative with most of the data generated in phase one and these findings fed into phase two; I used what Cresswell terms a 'sequential exploratory' design. This type of

design has been suggested as appropriate for testing elements of an emergent theory so was ideal for my research.[198] I also asked myself questions about whether the addition of a second research approach, using questionnaires, would enhance my study or could the research question still be answered (or better answered) without this second method. Would mixing methods increase the validity of the study or reduce it? To a certain extent the research question could indeed be answered from phase one of the research; phase two was not an essential requirement, although without it I felt I would lose a valuable opportunity to examine key issues arising from phase one with a larger cohort of HCPs.

Observations

Observations aim to uncover or find out what is actually happening; it is a method commonly used in ethnographic research. Researchers can play different observer roles: some just observe, while others participate in the activities as well as observe what is going on - so called 'participant observation'. The level of participation can differ: Gold developed a typology of observer roles, published in 1958:

- *The complete participant*: the researcher takes an insider role, is fully part of the environment and the observation is often covert
- *The participant as observer*: the researcher gains access by having a non-research reason for being there, the researcher is part of the group being studied
- *The observer as participant*: the researcher has only minimal involvement in the setting being studied. There is some connection to the setting but the researcher is not normally part of it
- *The complete observer*: the researcher does not take part in the setting at all[199]

Covert observation is unusual in the health care setting because of the associated ethical issues of carrying out this type of research; for example how would patients consent to the research if they did not know what the researcher was doing? The observations that I undertook were overt but this type of observation is also problematic; particularly apparent is the effect that the observer has on participants and the action/s being observed.[200] One approach is to attempt to minimise the impact

that the researcher has on the environment so that the research setting remains as 'naturalistic' as possible without the influence of the researcher's presence or bias. Researchers may attempt to achieve this by adopting certain roles and organising themselves in a particular way - out of the way - during the period of observation. Highly structured observations, for example where the researcher uses tick boxes or other types of structure to focus the observer and to ensure pertinent areas are not missed, can also be seen as a method for reducing bias.[201] At the same time, however, they limit the rich data that this method is able to generate. Whilst I agree that taking steps to reduce bias where possible is important, I believe that it is unrealistic to believe that the researcher will have no impact: data gathered are those that the researcher has chosen (before, during or after) and analysis is mediated through the researcher who brings their own assumptions and interests to the process. Another criticism of observations is that, unless you immerse yourself in a setting for long periods (such as living with a group of people), you can never really understand what it is like for the actors in that environment or the context in which actions take place.[202] I would argue that this depends on the purpose of the observation: it is possible to pick up salient points quite quickly especially if these will be explored in more detail at a later date.

Because of my clinical background, I was known to some of the HCP participants and I work in one of the settings I was observing: clinic consultations in genetics. In this sense, using Gold's typology: whilst my role in the consultation was only to observe, to some extent I was also an observer as participant. On a few occasions, my clinical background was referred to by an HCP and I was asked for my views on using consent forms. I write about this in more detail in 'Reflections on my role as the researcher' at the end of my thesis. I chose observations, using a semi-structured schedule to guide my viewing, as a method to both understand the setting/context of genetic testing (from a different perspective than that of the working clinician) and to identify issues that needed exploration during in-depth interviews.

Interviews

Interviews enable the researcher to gather data on people's perspectives and understandings regarding the events and experiences of their lives, providing rich and contextual insights.[203] I wanted to use interviews to explore HCP and patient/parents

views and experiences around the ethical issues and practicalities of managing IFs in clinical practice. My interviews aimed to complement and build on the issues identified during the observation period.

Interviewing is the most common research method used in qualitative research. Mason suggests that qualitative research interviews share the following core features:[182]

- The interactional exchange of dialogue
- A relatively informal style
- A thematic, topic-centred biographical or narrative approach

During my interviews I asked families to give accounts of their experience of undergoing genetic testing and having IFs identified and HCPs were asked to engage in a dialogue about their practice and experiences.

Qualitative interviews aim to generate situated or contextual knowledge.[182] One of their benefits is that they can be responsive to individual participants: pertinent issues can be explored in detail as they arise. However, a potential limitation is that participants may engage in 'face-work',[204] that is telling the interviewer what they think she wants to hear or how they want to be heard. Participants may put up a 'protective front', revealing only surface (public) layers to the researcher.[203] Participants may also choose to withhold information that could be relevant and would affect how the data were interpreted/ analysed. In this respect observation data can act as a check on insights or issues: was this something I had observed? Does this make sense?

It is also important for the researcher to consider the issue of power, especially if vulnerable groups are included in the study. The interviewer is often in a powerful position, leading the interview and asking for personal and private information. The skill of the researcher is crucial to tease out deeper meanings and understandings and to be sensitive to the status and needs of the participants.

Qualitative data analysis

One of the purposes of analysing data is to build or confirm theoretical ideas. Mason outlines three main reasoning approaches to such theory building: deductive (starting

with a hypothesis to prove or disprove), inductive (data drives the theory) and abductive (simultaneous data generation and analysis).[182] In practice these often overlap: scientists who might primarily use deductive reasoning are likely to move to and fro between theory and data; likewise grounded theory includes a requirement for researchers to be 'theoretically sensitive'.

I have used an inductive approach in phase one of my research; phase two is more deductive in approach, although I used a qualitative approach (cognitive interviewing) to the development of the questionnaire, which I will discuss in detail in chapter 7.

An inductive exploratory approach to my data analysis was appropriate for phase one of the research as there was little data on the practical and ethical issues generated by the discovery of IFs, at the start of my research; the aim of phase one was to establish views and experiences of families and HCPs about IFs and in order to achieve this, in-depth, rich, contextual qualitative information was required.

Guest et al outline key characteristics of exploratory research design and analysis which were applicable to this study, see table 9 for summary.[205]

Table 9: Characteristics of exploratory analysis (adapted from Guest et al)[205]

Exploratory analysis
Specific codes/categories are not pre-determined
Codes are derived from the data
Most often uses purposive sampling
An example is: "what do x people think about y?"
Data is usually generated

Exploratory analysis during the observations stage included both content and thematic analysis. These two methods of analysis are often referred to interchangeability but, while there are similarities in the way they both search for patterns and themes, their key difference lies in the opportunity for quantification of data with content analysis.[206] Content analysis uses a systematic coding and categorising approach and

can be applied to determine trends and patterns of words used, along with their frequency (by counting) and the relationships between them. In this study, content analysis was adopted during observations to analyse terms used. It has been criticised both on one hand for not being detailed enough to allow statistical analysis and on the other for not being qualitative enough in nature to achieve in-depth analysis of the data.[207] Text is often obscure and convoluted and as a result content analysis can be a challenge or inappropriately applied, with the potential for poor results.[205] Although content analysis was of limited value in my research, it was a helpful approach during the observation stage, particularly for analysing descriptors of genetic tests and outcomes.

Three common approaches used for in-depth analysis in qualitative research are grounded theory, phenomenological and thematic analysis. While they have common processes they have different features:

Grounded theory: Uses a systematic comparative technique to find themes and create codes. It is interpretive in as much as it does not quantify data and post-positivist in that it is systematic and, to a certain extent, findings should be evidence-based, that is, supported by the data. It is useful when there are small data sets; it can facilitate exhaustive coverage of data and can be used to study a variety of phenomena. However, it is time consuming and logistically impossible for large data sets.

Phenomenology: Focuses on how people make sense of their lived experiences. Interpretative phenomenological analysis is used with small data sets and can help the researcher to interrogate the data in depth. However, it has been criticised for not necessarily being very systematic with findings often appearing to go far beyond what the data seems to say.

Thematic analysis: Systematically identifies key themes in the text and can be used to build theoretical models or find solutions to 'real world' problems. It is similar to grounded theory approaches in that assertions should be evidence-based. It is well suited to larger data sets and team research.[205]

Thematic analysis focuses on identifying and describing both implicit and explicit ideas within the data.[205] The coding process involves recognising an important moment within the data and encoding it, prior to undergoing a process of interpretation.[208] Braun and Clark outline different types of thematic analysis (TA):[209]

- Inductive TA: aims to generate analysis from the bottom up, is not shaped by existing theory but is guided by a researcher's standpoint
- Theoretical TA: analysis guided by an existing theory and theoretical concepts (as well as a researcher's standpoint)

TA can be criticised for being 'something and nothing' particularly if it is the first type above as it lacks the substance of other theoretically driven approaches. There is a concern that without the latter the analysis will lack an interpretative drive and lead to over-descriptive accounts.[209] One of its strengths is that its systematic nature makes it ideal for research undertaken in teams; however, the greater the number of people analysing the data, the greater the possibility of inter-rater variability. This can lead to difficulties in maintaining a sense of continuity within the data as different researchers bring different perspectives to their analysis.[209]

In this study an inductive TA approach was adopted for analysing observation and interview data. It facilitated the analysis of a sizeable data set, generating themes applicable to the identification and management of IFs, in an attempt to understand and identify some solutions of this 'real life' clinical issue.

The process of thematic analysis

Braun and Clark outline different stages of TA: moving from familiarisation with the data and generation of some initial codes, to systematic coding across the entire data set, identifying data relevant to each code.[209] These codes are then collated into potential themes. The themes are continually reviewed and refined in relation to the coded transcripts, presenting the 'analysis story' and final presentation of the findings. These stages are described in table 10.

Although I reviewed other approaches to thematic analysis such as Guest et al,[205] I used Braun and Clarke's approach because their presentation of the process and steps involved in the analysis was the clearest and most logical to follow in practice.[209]

Questionnaires

There is much debate about the use of questionnaires in research and specifically in healthcare.[210] Their advantage is seen to be that they can generate large amounts of quantitative data which are generalizable as they are designed to get answers to set questions. They are a method used extensively by researchers who require numerical data on phenomena, although free-text comment data are sometimes also collected. However, the assumption that questionnaire data are generalizable is questioned especially when there is a concern that different participants understand the questions in different ways.[211]

Table 10: Stages of thematic analysis (adapted from Braun and Clarke 2006)[209]

Phase	**Description of the process**
Familiarisation with the data	Transcribing data, reading and re-reading the data, noting down initial ideas
Generating initial codes	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code
Searching for themes	Collating codes into potential themes, gathering all data relevant to each potential theme
Reviewing themes	Checking the themes work in relation to the coded extracts (level 1) and the entire data set (level 2), generating a thematic 'map' of the analysis
Defining and naming themes	Ongoing analysis to refine the specifics of each theme and the overall story the analysis tells; generating clear definitions and names for each theme
Producing the report	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis

Phase two of my research involved developing a HCP questionnaire for circulation during my post-doctoral period. I chose to target the questionnaire to HCPs rather than patients for two specific reasons: first, because of the urgent need to examine healthcare professionals views on IFs as technology is rapidly introduced both in genetic and mainstream practice, and secondly because I felt that the subject of IFs was too complex a topic for patients to understand in a questionnaire without explanation.

I adopted a cognitive interview method to develop a robust questionnaire based on pertinent findings from phase one.[212] I then piloted the questionnaire. I discuss the process of development in more detail in chapter 7.

Judging the quality of research

In any research study, it is important to consider the issue of the quality of the research and how it should be judged. Within quantitative research, undertaken within essentially a positivist paradigm, research is judged according to defined sets of quality criteria: validity, reliability and generalizability. Reliability refers to the ability to reproduce a finding or a measurement on other occasions using the same method: for example if I filled in a questionnaire today and next week, the data would be reliable if I filled in the questionnaire with the same answers at the different times. Validity is concerned with measuring or collecting the data that is intended: do the questions on my questionnaire relate to my research questions; and could they, for example, prove or disprove the research hypothesis. The criterion of generalizability is used to assess the extent to which research findings can be applied from the sample used to a larger population. For this to be the case, the sample must be statistically representative of that larger population.

Within qualitative research such criteria have been the subject of much debate. Issues such as reliability and validity have been considered irrelevant to qualitative research, particularly in the past: the quality of work being assessed on the reader's acceptance or rejection of the claims that are being made. If the findings 'rang true' then it was considered good quality. However, without a clearly defined set of criteria available for judging qualitative research, all we can conclude is that the research is of *uncertain* quality.[213]

Some people have argued for using alternative criteria, more appropriate to research which focuses on human behaviour, which are more interpretive or which see knowledge

as contingent. In the 1980s Guba and Lincoln proposed that what was important was the 'trustworthiness' of data and proposed a different set of criteria to assess this.[214] However, later Lincoln acknowledged that the very existence of fixed criteria went against underpinning philosophy, for example of constructive approaches that believe in multiple realities.[215]

Those that believe that systematic, rigorous and auditable analytical processes distinguish good from poor research encourage researchers (both qualitative and quantitative) to articulate their research to ensure that: the logical processes by which they were developed are accessible to a critical reader; the relation between the actual data and conclusion about the data is explicit; and the claims made in relation to the data set are credible and believable.[216]

In quantitative research, generalisations are critical to the goals of applying findings to people, situations, and times other than those in a study. Without generalisation, it has been argued, there would be no evidence-based practice: research evidence can be used only if it has some relevance to settings and people outside of the contexts studied.[217] With qualitative research findings may be transferable, that is, they can be transferred to another setting while not necessarily being generalizable in the same way. I support Mason's view that the theoretical and conceptual understanding that is derived from qualitative analysis data can have a wider applicability or 'wider resonance' and it is in this way that generalizability can be understood within qualitative work.[182] This is a view also supported by Popay and colleagues who state that: *"…the aim is to make logical generalizations to a theoretical understanding of a similar class of phenomena rather than probalistic generalizations to a population."*[218](p.348)

Mason sticks with the standard three criteria for assessing the quality of qualitative research but asserts that they should be applied with a qualitative sensibility.[182] Researchers should ask themselves:

- How can I demonstrate that my methods are reliable and accurate? Do findings relate to data?
- How can I demonstrate that my analysis is valid? For example by outlining how I undertook the analysis
- What kinds of generalisations/wider claims can I make?

I find this approach a pragmatic and useful one. I have attempted to show how my findings relate to my data in chapters 5 and 6. In this and my methods chapters I have detailed both the logic behind my choices and the way I went about collecting and analysing data; and in my discussion I have shown how I have moved from my findings to the wider claims I wish to make from this research.

Willis outlines different ways of judging the cognitive interviewing (CI) process that I use in phase two; these include assessing whether CI finds problems and also fixes problems, as well as whether results are reliable and consistent.[212] Chapter 7 details how I went about the CI and piloting process and how I used the different rounds of interviewing and expert panels to assess the validity of the questionnaire. Reliability was more difficult to assess; one way to look at this would have been to give the draft questionnaire twice to the same person at different times but, in the end this was not possible due to lack of time.

A further issue relating to my work is how MMR should be judged. Should each approach be judged separately according to their different criteria or use of the same criteria? While there have been some attempts to develop a conceptual approach for MMR, there are yet to be generally accepted criteria for this.[219]

Cresswell suggests eight possible strategies to assess or ensure validity within a mixed methods design.[186] These are:

- Using triangulation (using different data sources to build a justification for the themes)
- Adopting member checking (participants determine accuracy of findings)
- Using rich description to convey findings which can mean results are more realistic and richer
- Clarifying researcher bias
- Presenting negative or discrepant information that runs counter to the themes
- Spending prolonged time in the field to develop an in-depth understanding
- Peer debriefing to enhance the accuracy of the account
- Using an external auditor to review whole project

I adopted many of these to increase the validity of my work. This included elements of triangulation from the use of different methods; searching for differences as well as similarities during analysis phases; using rich description to convey findings in chapters 5 and 6; reflecting on my role as researcher (at the end of my thesis); using my supervisory sessions for peer debriefing and checking coding through supervision sessions. Whilst I do not ask my interview participants to assess the accuracy of my findings, the questionnaire, once circulated will enable a wider group of HCPs to feedback on my findings.

Teddle and Tashakkori use similar criteria for assessing the qualitative and quantitative components of MMR but add two specifically relating to integration: 'integrative efficacy' (the extent to which each approach is integrated into a theoretical whole); and 'interpretive correspondence' (the extent to which the study itself supports the choice of an MMR design).[220] I will look at these again at the end of my thesis when I return to judging the quality of my work.

Chapter 4: Phase one methods: observations and in-depth interviews

This chapter gives details on the methods I used for phase one, the qualitative phase of my research. I undertook both observations of clinic consultations and interviews with HCPs and patients/parents.

Observations

Observations were my first data generation method and these were carried out over a 9 month period (January 2012 to September 2012). I attended one clinic session for each HCP recruited; in total 27 consultations were observed.

Development of the observation guide

At the beginning of the study I visited a number of clinical and research settings to gather information to facilitate the development of the observation guide. These included attending a paediatric genetic clinic, a paediatric research clinic and a regional child health meeting, giving me an insight into the environment I would be studying and alerting me to potential issues to observe.

I adopted an iterative process to the development of the observation guide, amending this as the observations progressed to incorporate emerging themes; there were three versions in total (see appendix 1).

The first version comprised of five sections and was originally developed from the observation guide for consultations that was submitted for ethics review. It included broad headings as:

- Introduction of genetic test
- Consent
- Disclosure of results
- Disclosure appointment
- Follow up

Each of the sections included tick boxes and space for free text to complete during and immediately after the observation. The content of the observation guide was informed by my prior clinical experience of managing IFs, the visits I undertook and issues raised in the

literature on IFs. The first version was highly structured and I realised quite quickly that its use could result in key data not being noted if it fell outside the observation guide. Having some structure, however, was important to ensure consistency in what I observed and to maintain focus during the observations themselves. The addition of free text sections allowed the recording of other issues that arose during the appointment, especially important for those that were not predicted.

After the first couple of observations I also found the sheets themselves cumbersome to use and distracting for HCPs and families. I condensed and amalgamated the sections, including emerging themes, into three headings: the introduction of the genetic test, disclosure of results and follow up. This version was much easier to co-ordinate and information relating to the appointment could generally be collated on one page. In the end my preference was to write what happened in chronological order during the appointment, enabling me to document the sequence of events and record verbatim what was being said, alongside pertinent non-verbal aspects. The headings and tick boxes were useful prompts, but were often limiting if I adhered to them too rigidly.

Observations: inclusion and exclusion criteria

The inclusion and exclusion criteria for the observation stage are detailed below:

The inclusion criteria:

HCPs	Family Members
HCPs who regularly see families and request genetic testing (including aCGH tests)	Family members who are having an appointment to discuss possible genetic testing and can consent to participate

The exclusion criteria:

HCPs	Family Members
Inadequate grasp of English to give consent	Inadequate grasp of English to give consent

Observations: sampling

Sampling is a key part of the research process and studies have been criticised for not documenting sampling strategies which allow others to review the process followed.[221,222]

Choice of sampling

Higgingbottom recommends a pragmatic solution to sampling which entails inviting a specified number of individuals, who have the appropriate characteristics for the study, to be participants.[222] This is essentially a type of purposive sampling and reflects the sampling choice for phase one of this study. As a result of my previous clinical role as a genetic counsellor it was relatively straightforward to identify a number of individuals to invite to participate in the clinic observations. The characteristics I wanted to ensure I covered were: a range of clinical roles; HCPs who regularly requested genetic tests in clinical practice; and those that held clinics in the designated geographical area. At the time of this study, genetic tests (and specifically aCGH testing), although requested by a range of hospital and community clinicians, were most often ordered by clinical geneticists and paediatricians (community and hospital based) and so it was these two professional groups that were purposively sampled for the clinic observations.

The process of sampling

The sample for the observations involved both HCPs and family members attending the appointment. Study invitations were sent to genetic consultants from the Wessex region; all genetic consultants who ran paediatric genetic clinics were invited to participate. The sample of paediatricians was identified using a snow ball technique;[223] geneticists were asked to identify paediatricians who they knew were regularly organising genetic testing. In addition, the genetics laboratory provided me with a list of Wessex paediatricians who were requesting significant numbers of aCGH tests at that time.

Once an HCP had expressed an interest in participating, and a clinic date for the observation had been arranged, families who were attending that clinic session were sent participant information packs about the study. Patton suggests that the power of purposeful sampling lies in the selection of information-rich cases for study in depth and from which a researcher can learn about issues of central importance to the purpose of the research.[223] While the HCPs selected for invitation fulfilled the criteria for purposeful sampling, (they were regularly involved in organising genetic testing and were therefore

information-rich cases) the sampling of family participants was not able to be done in the same way. I did not have access to clinical information on the families attending clinic beforehand, to know if they had or were likely to be discussing genetic testing. I had to adopt a pragmatic approach and invite all family members attending every clinic appointment that I was observing.

All the observations were undertaken in one region which meant that a comparison of management strategies for dealing with IFs with other regions was not possible; however, this was not the primary aim of the observations.

Sample size

I intended to undertake a total of 5-10 clinic sessions (each clinic session is half a day). Each clinic was likely to include 4-5 family appointments and not all families invited would agree to participate. I had an overall aim – which I achieved - of observing 20 clinic appointments as a sample size of 20 was considered sufficient to ascertain if and how IFs were discussed during the consent process; how results were being disclosed (including IFs); and to identify key issues to be explored in the follow-up in-depth interviews. It was possible that some of the appointments observed would address the study aims more than others. All families were invited to participate but not all observation data collected was analysed. If genetic testing had not been discussed at all then the data from this appointment was not formally analysed.

Recruitment: HCPs

Potential participants were sent a study invitation letter, expression of interest, participant information sheet and a stamped addressed envelope (see appendix 2). When an expression of interest form was returned, the respondents were contacted and a convenient date to observe their clinic was arranged. The recruitment process took place over a series of rounds: I either sent a letter directly to a clinician or gave out letters at meetings. See table 11 for details of the recruitment strategy including the numbers approached and recruited; and table 12 for details of the HCP participants and the settings for the observations.

Table 11: Observations: recruitment strategy for HCPs

Recruitment strategy	Number of genetic consultants approached (in brackets) and recruited	Number of other specialty consultants approached (in brackets) and number recruited
3 rounds of invitation letters to clinician	(5) n=5	(14) n=2 10 non-responders/2 declined
Invitation issued at community child health meeting	(0)	(Unable to confirm number that took study information) n=1
		Total number of HCPs recruited =8

Table 12: Observations: HCPs and settings

Genetic HCPs	Other Specialists	Observation Settings
5 Consultant Geneticists	2 community based Paediatricians 1 hospital based Paediatrician	Hospital based clinics (n=6) in Southampton (n=2), Winchester, Basingstoke, Portsmouth and Isle of Wight (5 genetic clinics and 1 paediatric clinic) Community based paediatric clinics (n=2) in Portsmouth and Southampton, held in Children's Centres

Recruitment: family members

Potential participants - all families attending a clinic session on a date already agreed with the HCP - were sent a participant information sheet (see appendix 3) by the clinic administrator, as I did not have access to the family's contact details. Around 2-3 weeks before their appointment, the administrator informed families that a researcher would be attending (see appendix 4), sending a copy of the participant information sheet, giving them sufficient time to consider if they wished to participate or not. On the day, a number of families did not attend their appointment and others reported that they had

not received the information or declined to participate when approached. In total 27 families agreed for their consultation to be observed.

Prior to the beginning of the clinic observation a seating plan was discussed with each HCP to establish where I would sit during the appointment to minimise any potential disruptions; for example families feeling uncomfortable that a researcher was observing them and their child, especially as I would be making notes. I also wanted the consultation to proceed as normally as possible so I could establish an accurate account of current practice.

Data Analysis: observations

The primary aim of the clinic observations was to review current practice (specifically consent and disclosure practice) surrounding the management of IFs, discovered through routine genetic testing, and for these results to inform the interview schedules (HCP and family) for subsequent in-depth interviews. I undertook both thematic and content analysis of this data.

Content analysis

Content analysis was used to determine trends and patterns of words used during the appointments, establishing their frequency and relationships. This included how genetic technologies and tests were described to patients and how different types of results, and their clinical significance, were explained. Three steps during the content analysis were applied: preparation, organising and reporting. The latter is incorporated in the sections below:

Preparation:

This involved selecting the word or theme for analysis. It became apparent in the early stages of the observations that although the possibility of IFs was sometimes raised during appointments, the issue of VUS being discovered was more often discussed. It seemed that clinicians talked about IFs and VUS inter-changeably or thought they had explored the issue of IFs, when they had only discussed the risk of a VUS so I expanded the analysis to include this. Descriptors used to describe the genetic techniques applied for genetic testing were also included to provide an overview on how these are presented

to patients and whether they gave an indication of the likelihood and implication of an IF being discovered.

Organising:

Data pertaining to terms used to describe and define IFs and VUS were organised into a table that indicated how HCPs and family members described both. This data was spilt into descriptors about a) the features of this type of result and, where possible, b) what the results might mean; the frequency of their use was then determined. These are outlined in table 13.

The analysis showed that the possibility of a VUS resulting from genetic testing was consistently discussed with families: described 17 times during 10 different appointments. Descriptions used either explained what VUS are, what they might mean for the individual being tested or how they might be interpreted. As the issue of VUS is unlikely to be relevant in every appointment (for example, some were general follow up appointments where genetic testing was not discussed) the number of consultations where they were raised represented a significant proportion of the number observed. In contrast, IFs were barely addressed and the notion that IFs would yield unexpected information, unrelated to the original reason for the test but potentially of clinical significance, was not comprehensively addressed. This type of data led me to identify issues to raise during in-depth interviews. It was difficult to assess family perceptions of different clinical findings during the observations as, although raised by the HCP, they were not then discussed by the family who were often very quiet during the appointment and did not ask many questions.

Data on how HCPs described genetic testing techniques were also collated and are summarised in table 14.

Table 13: Terms used by HCPs and family members to describe IFs and VUS

HCP (describing IFs)	**HCP(describing VUS)**	**Family members (describing IFs)**	**Family members (describing VUS)**
Terms that describe the features of the result	*Terms that describe the features of the result*	*Terms that describe the features of the result*	*Terms that describe the features of the result*
Surprising results (FamOb002)	Get results we can't interpret (FamOb002)	Something we've found out along the way (FamOb008)	Is it the same as a carrier? (FamOb003)
Things we are not expecting (FamOb012)	Natural variance (FamOb003)	Find things we are not expecting at all (FamOb017)	Red herring (FamOb016)
	Contributing/predisposition (FamOb010)		
	Could be nothing or a predisposition factor (FamOb011)		
	Can find things that we don't know what it is (FamOb012)		
	Find things that we are not sure of the significance (FamOb015)		
	Unusual/unique finding (FamOb016)		
	Chance/random finding (FamOb016)		
	Could give results that are difficult to interpret (FamOb018)		
	Pick up abnormalities that we don't know the meaning of (FamOb019)		
	Not sure if it is linked to the condition or not (FamOb019)		
	Can get useful/not useful results from array testing (FamOb024)		
	Red herring (ObFam024)		
Terms that describe what the result might mean	*Terms that describe what the result might mean*	*Terms that describe what the result might mean*	*Terms that describe what the result might mean*

	Changed mind about previous result (FamOb003)		Can anything be done? (FamOb03)
	Don’t know enough about it (FamOb010)		Intrigued (FamOb011)
	Overkill (FamOb011)		
	Parents could “hang on to the result” (FamOb018)		
Total number of references			
2	17	2	4

Table 14: Description used by HCPs to describe genetic techniques

Descriptions used to describe the genetic testing technique	**Testing technique applied**
Cleverer tests (FamOb002)	Array CGH
Detailed look at chromosomes (FamOb002)/detailed chromosome test (FamOb007)(ObFam008) Very detailed genetic test (FamOb020) Finely detailed chromosome test (FamOb015) Highly specialised chromosome test (FamOb017)	Array CGH
Check each region of each chromosome by binding (FamOb002)	Array CGH
New test (FamOb002) Fairly new science (FamOb016)	Array CGH
The test allows us to look at all genetic material (FamOb012)	Array CGH
Use markers/probes (FamOb016)	Array CGH
Sub-microscopic way to look at extra/missing genetic material (FamOb024)	Array CGH
Panel of 4-5 genes (might as well do them) (FamOb004)	Targeted gene panel
Good to pin it down (FamOb004)	Targeted gene panel
Spectrum of findings (FamOb004)	Genetic testing in general
Genetic testing getting faster and better (FamOb009)	Genetic testing in general

The observations showed that new genetic testing techniques were usually discussed with families and HCPs informed patients that the test was new. It is unclear why this was the case but new tests were often presented in a positive way – and it is true that they are associated with an improved diagnostic yield – highlighting questions such as: whether family expectations of what the results could tell them were raised; and the possible downstream clinical impact for HCPs as they managed increasing numbers of uncertain results.

Thematic analysis

I initially familiarised myself with data from the transcripts of the observation sheets and the field notes, reading and re-reading them. I made some initial notes on the emerging issues and potential codes. These were then collated and reviewed, eventually generating a thematic map of the data which focussed on factors influencing clinical practice. Appendix 5 contains an example of one observation (FamOb16) to illustrate this process and Appendix 6 shows the initial thematic map. These factors were further refined to produce three key themes which form the basis for developing the interview schedule:

1. <u>Clarity of the testing process</u>

   Multiple tests by multiple clinicians

   Description of new technologies

   Follow up (short term)

   Follow up (long term)

2. <u>Result ambiguity</u>

   The types of result (VUS)

   The types of result (IF)

   The types of result (normal variation)

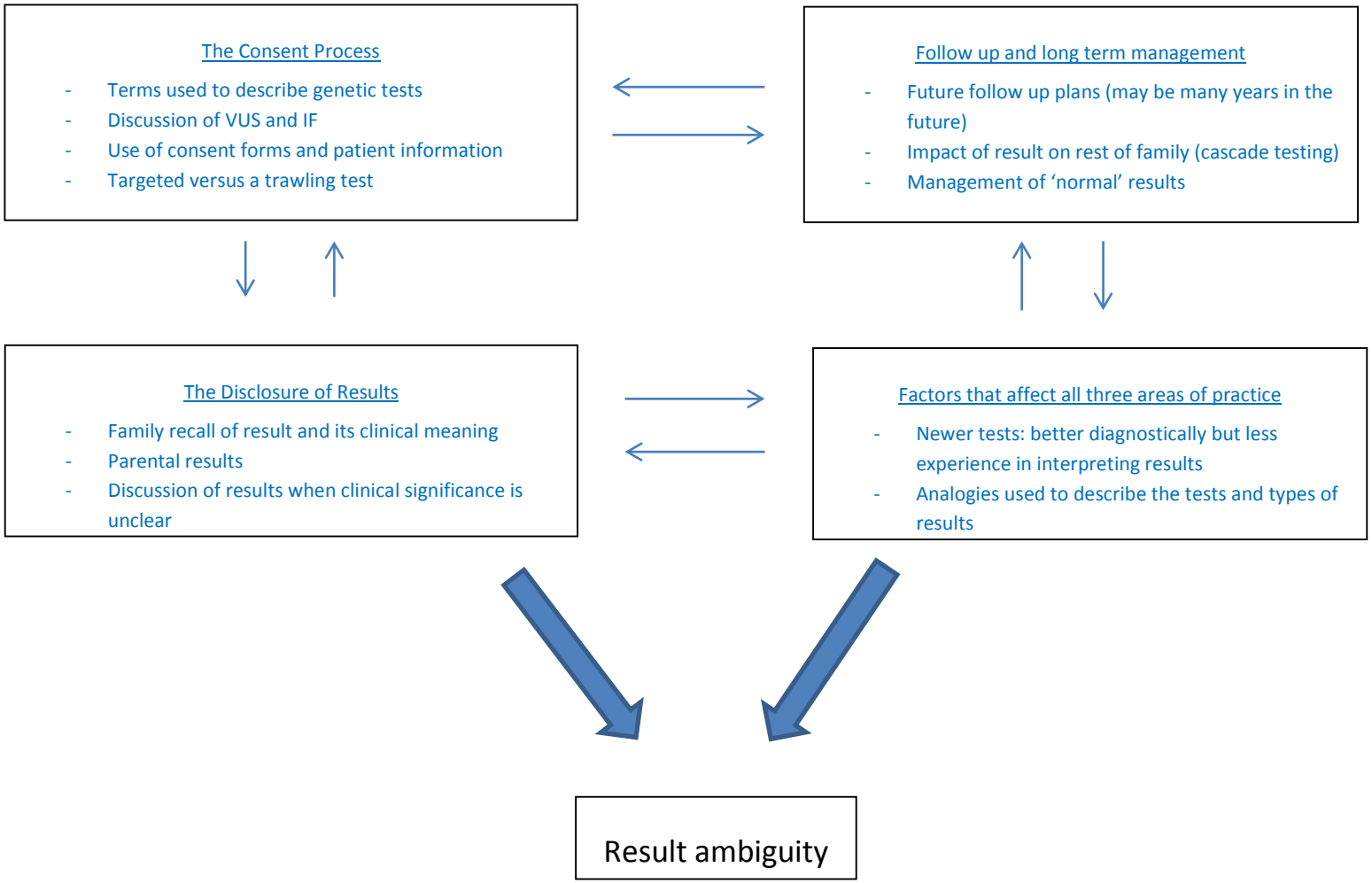
3. <u>Assessing benefit of result</u>

   Benefit of genetic testing for families

   Benefit of genetic testing for clinicians

The second theme and more detail of its component parts are shown in figure 4.

Figure 4: ‘Result ambiguity’: theme from observation



The observation data primarily aimed to provide context and guide the interview stage; however, where relevant, I have also drawn on observation data in my findings chapters.

Interviews

I carried out 32 HCP interviews which were completed between May 2012 and July 2013. The family interviews were completed between April 2013 and March 2014 and I undertook 16 interviews with 13 families (including 3 sets of parents).

Development of the interview schedule

A preliminary interview schedule for HCP and family interviews was developed and submitted for NRES ethics review, before the observation of clinic appointments had begun. Similarly to the observation guide, these were constructed by drawing on issues raised from clinical experience and a review of the literature. These were amended as both the observation and interview data were analysed to incorporate emerging themes from both sets of data. In addition, I added an item around possible disclosure policies for managing IFs, based on clinical significance and actionability, as this was raised in published literature during the interviews.[124,177]

Versions 1-3 of the HCP interview schedule and 1-2 of the family interview schedule can be found in appendix 7.

In the first few family interviews, I gave participants clinical examples and hypothetical scenarios to encourage them to discuss some of the broader ethical and practical issues with IFs which seemed to work well. However, as the interview stage progressed, I used these less, perhaps because I became more experienced at interviewing and because the interviews progressively got more focused as the themes emerged.

Interviews: inclusion and exclusion criteria

The inclusion and exclusion criteria for phase one interviews were as follows:

Inclusion criteria	**HCPs**	**Family Members**
The interviews	HCPs who regularly see families and request genetic	An individual or member of a family where genetic testing has been

	testing (including aCGH tests)	considered that could identify an IF and can consent. This will include: (i) those in whom an IF has been identified and (ii) those in whom it has not

Exclusion criteria	**HCPs**	**Family Members**
The interviews	Inadequate grasp of English to give consent	Inadequate grasp of English to give consent Individuals under the age of 16. For potential participants aged 16-18 they will be recruited if competent to consent

Interviews: sampling

The choice of sampling

As with the observations, purposive sampling was used for the initial interview cohort. HCPs, who regularly ordered genetic tests, where IFs could be discovered in the course of testing, were identified and invited to participate. This approach was adopted to ensure that the HCPs interviewed would provide rich and detailed information about their experience of consenting for, and disclosing results from, genetic testing, as they were regularly managing this in their clinical practice. The observation findings had identified that this source of HCPs provided the information needed to address the research aims. It was important, however, to include practitioners from across the country in the interview data, as all HCPs in the clinic observations were from the one region. As practice may have been different it was necessary to talk to HCPs in other areas to establish this. Family members were also purposively sampled where at least one individual had undergone (or been considered for) genetic testing, some of whom had had an IF identified. Family members were identified by a number of different HCPs so many lived within the same geographical area (Wessex). However sampling though the patient group Unique meant that I interviewed a number of patients (n=7) from other parts of the country.

Theoretical sampling was adopted for some of the later interviews. This sampling approach is chosen to elicit an in-depth understanding of the experience of particular individuals or groups and the researcher should aim to deliberately seek out those who match this.[224] This approach was initially introduced by Glaser and Strauss in the 1960's, and was subsequently modified by Strauss and Corbin.[225-227] Precise techniques and strategies to undertake theoretical sampling are advocated but the general aim is the selection of groups or categories to study on the basis of relevance to the research question(s), the theoretical position and analytical framework, analytical practice and the developing argument. Theoretical sampling is based on the need to collect more data in order to examine the identified categories and their relationships and to assure that representativeness in each category exists; as such, simultaneous data collection and analysis are critical.[228]

An example of how I used this strategy in the interview stage was that I progressively became aware that laboratory scientists should be sampled, as codes emerged about the possibility of limiting the genetic test being ordered to prevent the identification of IFs. As this practice was being proposed by interview participants, it was important to explore this possibility with laboratory staff who would be receiving these requests. It also became apparent during the course of interviews that the inclusion of HCPs who had a dual role as a clinician and researcher should be sampled, as codes about the obligations of researcher versus clinicians began to emerge.

The process of sampling

As with observations the purposeful sample for the interviews began with the identification of clinicians who regularly request genetic tests and families who had been seen by Clinical Genetic services and had genetic testing discussed. This approach was purposive in that it targeted the two main parties involved in managing IFs, for whom it had most relevance. The emerging data then directed how the sampling developed, according to emerging codes and categories.

Sample size

A sample of 15-20 HCP interviews and 20-30 family interviews was initially proposed. This number of interviews for each of the two groups of participants was considered to be both achievable in the time available for interviews and a sufficient number to be able to

generate codes, categories and themes. I aimed for more family participants as I envisaged that in some cases more than one family member would be invited to participate. I planned to conduct individual interviews with family members from the same family where possible, so that each individual could share their own experience, without being influenced by another family member being present. Doing separate family interviews also meant that the process of analysis and coding was more straightforward than if different perspectives were being teased out of the one interview.

How many qualitative interviews are required in order to address a study aim is the subject of debate. A report that collected expert views on how many qualitative interviews is enough generated many responses that concluded 'it depends'.[229] Some did put forward numerical responses. For example, Charmaz considered that while 12 interviews are enough to generate themes, this number would not command respect from the research community. Adler and Adler suggested that a medium sized number such as 30 can be a pragmatic solution: sufficient to penetrate beyond a very small number of people, without resulting in endless data gathering and analysis when time is limited. Becker suggests that when a researcher stops data gathering, the data generated coincides with what you want to say; and that the data supports the conclusions and, at the same time, the conclusions do not go beyond what the data can support.[229] I was confident - and it was the case - that the number of interviews planned for this study would be sufficient to generate themes and confirm findings and at the same time be feasible from a practical and time perspective.

Interviews: recruitment

HCPs

I adopted the same strategy for recruiting HCPs for interviews as with the observations; table 15 details this process and table 16 outlines the roles of the HCP participants. Potential participants were sent a study invitation letter, expression of interest form and participant information sheet (see appendix 8).

Table 15: Interviews: the recruitment strategy for HCPs

Recruitment strategy	No. of Genetic specialists approached (in brackets) and recruited	No. of other specialists approached (in brackets) and recruited
Invitation letters sent to genetic specialists: consultants, registrars, genetic counsellors, laboratory scientists and secondary care specialists	(57) n=21	(17) n=8
Snowballing	(Unknown) n=2	(Unknown) n=0
Community child health meeting	(Unknown) n=0	(Unknown) n=1
Total number of HCPs recruited n=32		

Table 16: HCP interview participant roles

Genetic Professionals	Genetic Laboratory Staff	Paediatric Specialists	Adult Specialists
Consultant Geneticists (n=9) Genetic Specialist Trainees (n=1) Genetic Counsellors (n=12)	Clinical Scientists (n=2)	Community Paediatricians (n=5) Paediatric Cardiologist (n=1) Paediatric Nephrologist (n=1)	Adult Neurologist (n=1)

Family members

Potential participants - identified by HCPs who had seen families to discuss genetic testing - were sent a study invitation letter, expression of interest form and participant information sheet (see appendix 9). After the clinic observations I approached a number of families to ask if they would be happy to receive study information inviting them to participate in interviews. If they agreed they were re-contacted at a later date. I did not

approach all families with this request; I excluded those who were distressed following their clinic appointment or had not had genetic testing organised. Six families agreed to be contacted in the future and two ultimately participated in the interviews.

Once an expression of interest form was returned, I contacted the respondents and discussed the study in some detail, answering any questions. A convenient date and venue to meet for interview was arranged. The UK based rare chromosome disorder support group (Unique) also included a general invitation in their regular mailshot to members. If families were interested in receiving further details they contacted the support group information officer, who forwarded me their e-mail address so they could be sent the study information.

Families were recruited over a period of time so that I could spread out the interviews; the numbers approached and recruited in each round are outlined in table 17.

Table 17: Interviews: the recruitment strategy for family members

Recruitment strategy	**(Number of families approached) and n = recruited**
Round 1	(17 individuals from 12 families including 5 sets of parents) n=3
Round 2	(12 individuals from 7 families including 4 sets of parents) n=2
Round 3	(5 individuals from 3 families including 2 sets of parents) n= 2
Round 4	(7 individuals from 5 families including 2 sets of parents) n=2
Unique patient group	First round: (175 e-mails sent, 13 initial responses) n=5 Second round: (22 e-mails sent, 2 initial responses) n=2 Third round: (45 e-mails sent, 3 initial responses) n=0
Total number: 16 (10 individuals and 3 sets of parents)	

Table 18 gives summary information about the genetic tests that participants had had and table 19 details the IFs and associated interventions discovered in participants.

Practical aspects of data collection

Face-to-face interviews were arranged at the participant's convenience (both timing and location). HCP interviews were done at the participant's workplace and family interviews

Table 18 Clinical summary of genetic testing in family participants

Family details	**Genetic testing completed**	**Details of tests carried out**	**Outcomes of testing**
FamInt001 Patient	Yes	Targeted genetic testing	Nil found
FamInt002 Mother of patient	Yes	aCGH test	Chromosome abnormality diagnosed confirming diagnosis and an IF
FamInt003 Mother of patient	Yes	aCGH test	No result to explain clinical features but discovery of an IF
FamInt004 Patient	No	N/A	N/A
FamInt005 Patient	Yes	aCGH	Chromosome abnormality found to explain clinical features
FamInt006 Father of patient	Yes	aCGH	Chromosome abnormality found to explain clinical features
FamInt007 Mother of patient	Yes	Genetic testing as part of research study	Chromosome deletion found to explain clinical features
FamInt008 a=Mother and b=Father of patient	Yes	aCGH	No explanation for clinical features but discovered an IF
FamInt009 Mother of patient	Yes	aCGH	Chromosome abnormality discovered to explain clinical features
FamInt010 Mother of patient	Yes	aCGH	Chromosome abnormality found to explain clinical features
FamInt011 a=Mother and b=Father of patient	Yes	aCGH	Nil found to explain clinical features but an IF was discovered
FamInt012 a=Mother and b=Father of patient	Yes	Targeted test	Chromosome abnormality found to explain clinical features
FamInt013 Patient	Yes	Targeted testing on a gene panel	Nil found to explain clinical features but an IF was discovered

Table 19: Clinical summary of the IFs discovered

Family ID	**Reason for test** **Type of test organised**	**IF details**	**Intervention for managing IF**
FamInt002 Mother	Developmental delay Array CGH	22qdel including SMARCB1 gene Risk of Schwannomatosis	Referral to two specialist paediatricians for monitoring
FamInt003 Mother	Muscle problems Array CGH	FBN2 mutation Can cause Marfan syndrome phenotype	Referred for cardiac surveillance
FamInt008 Mother and Father	Behavioural and social problems Array CGH	Deletion in Y chromosome leading to infertility	N/A Parents intend to inform of result as an adult
FamInt011 Mother and Father	Developmental delay Array CGH	Deletion including MSH6 gene causing Lynch syndrome	N/A Referral for bowel screening as an adult
FamInt012 Patient	Retinitis Pigmentosa Retinal eye disease gene panel	Mutation in LRP5 gene Can predispose to osteoporosis	Bone density screening

at the participant's home. The University of Southampton lone worker policy was followed to minimise any risks and ensure researcher safety: http://www.southampton.ac.uk/healthandsafety/guidance/loneworking.html

Interviews were digitally recorded and transcribed verbatim. The recording was deleted once I had verified the accuracy of the transcript. Field notes were made both during and after the interview. The interview transcripts and field notes were uploaded to Nvivo to facilitate data management.

Data Analysis: interviews

The aim of the in-depth interviews was to a) explore the views and experiences of patients who had received an IF or had attended a consultation where genetic testing that could identify an IF was discussed; and b) explore the views and experiences of HCPs around managing IFs in practice. Both sets of data were thematically analysed, drawing on constant comparison, and this section details how I applied this technique to the interview data.

The interviews were fully transcribed. Most interviews were transcribed by a professional transcriber but I transcribed the first two in each group of participants to begin the process of data familiarisation; I also typed up my field notes. My aim was to immerse myself in the data, undertaking initial coding until I could see emerging themes which I could then work on and refine into a thematic map. The thematic analysis process, with the different phases, is outlined in table 20.

Table 20: The process of analysis for interview data

Phase	**Description of the process**
Familiarisation with the data	• Transcribing recordings and field notes • Transcripts were read and re-read • Initial ideas were documented. This included emerging issues around the consent and disclosure process and the experience of having received or disclosed an IF
Generating initial codes	• Coding of interesting data across the entire data set and collating data relevant to each code • See appendix 10 for example from interview 017(HCP) and 013(family member) demonstrating preliminary coding of issues such as recall of discussions about IFs pre-test, experience of receiving IFs, whether patients do or do not want to know about IFs that are discovered from genetic testing
Searching for themes	• Collating codes into potential themes, gathering all data relevant to each potential theme • See appendix 11 for an extract from the interview transcripts illustrating emerging themes such as the consent process: preparing for an IF, the experience of receiving an IF, what patients want to know
Reviewing themes	• Checking themes relationship to coded extracts and the entire data set, comparing across data sets, generating a thematic map of the analysis • See figure 5 illustrating themes from the interviews (thematic map): the experience of IFs in clinical practice, issues raised by IFs and implications for practice
Defining and naming themes	• Ongoing analysis to refine the specifics of each theme and the overall story. Generating clear definitions and names for each theme
Producing the report	• Final opportunity for analysis • Writing up findings with key data extracts and conclusions

As the transcripts and field notes from the interviews were read, emerging areas of interest, related to the issue of IFs, began to emerge. Initially these were noted down (see examples in appendix 10) and acted as a conceptual guide as I coded the data.

Coding continued for all interview transcripts and from this process themes began to emerge. As the themes developed, codes were able to be collated under these potential themes enabling me to compare codes and themes across participants and groups of participants.

Two extracts of interviews (one HCP and one family) transcripts which have been coded are in appendix 10, and I have also included one example of how I moved from coding to identifying potential themes (appendix 11). I checked that themes were supported by the coded data and my themes eventually developed into a thematic map, illustrated in figure 5.

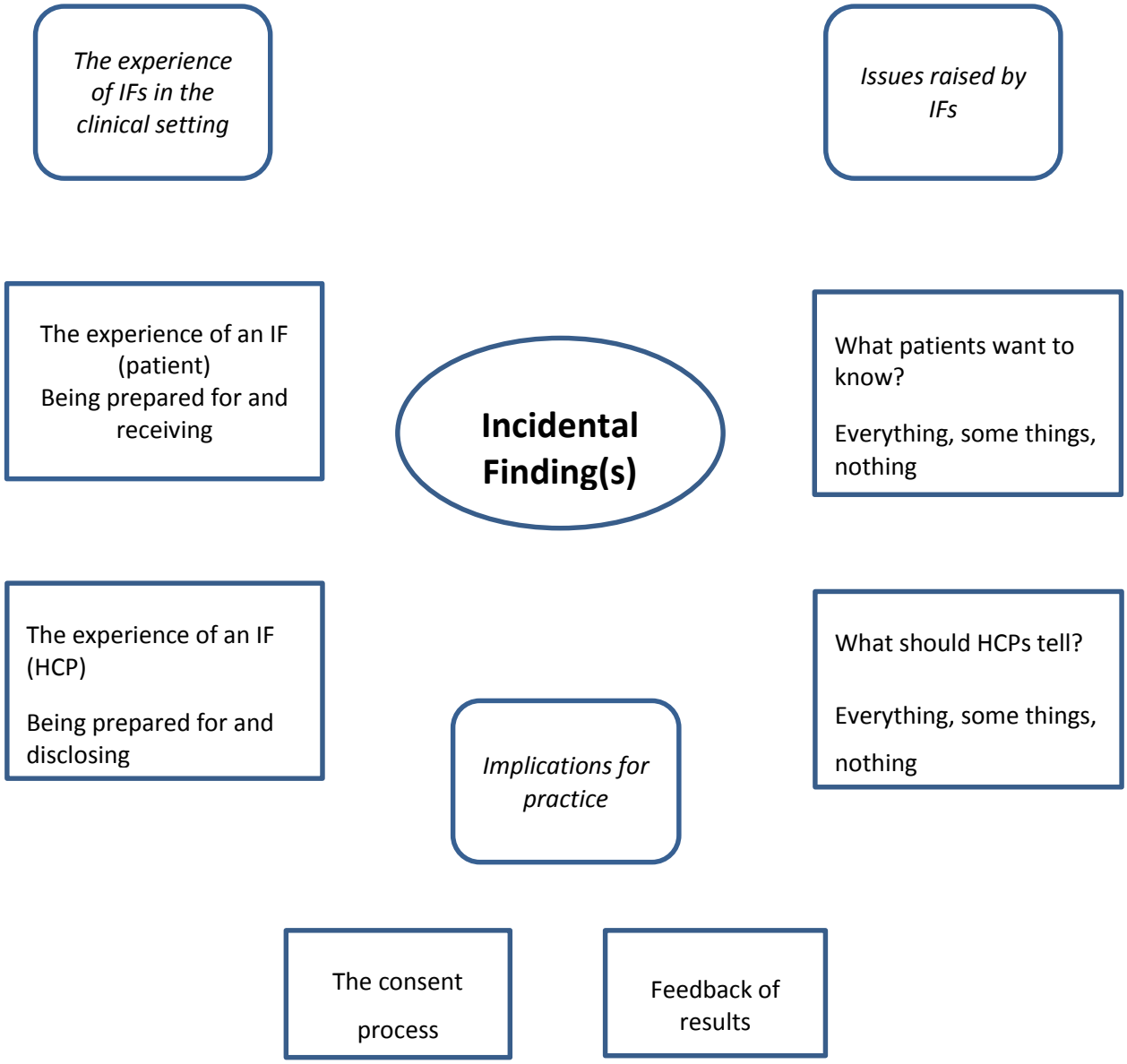
The three main themes continued to be refined and were eventually named:

- The experience of IFs in the clinical setting
- What should we do about IFs in clinical practice?
- The implications of IFs for clinical practice

Each theme included a number of sub-themes; for example 'What should we do about IFs in clinical practice?' included:

- *Raising the possibility of an IF*: information patients want about IFs prior to genetic testing and the information and issues HCPs considered to be important pre-test.
- *Tell me…:* information patients wanted from genetic testing (IFs in particular but also genetic test results in a more general sense) and the perspectives on seeking all information, limited information and no information, outside of the original remit of the test.
- *What should I tell…:* the views of HCPs on the disclosure of IFs and what option patients can and should be given?

Figure 5: Thematic map of data



Ensuring consent, confidentiality and anonymity in phase one

HCPs

On arrival at the clinic/interview venue I met with the HCP and went over the study details. When they had no further questions I asked them to sign the consent form. At this stage HCPs were allocated a unique study identification number (HcpOb001 to HcpOb008 for the observations and HcpInt001 to HcpInt032 for the interviews) and this number was used on all subsequent study documentation. The consent and expression of interest forms, that included identifying information, were stored separately to all other study documentation to ensure that the study data could not be linked to a named participant.

Family members

When potential family participants arrived at the clinic during the observation period, I did not meet with them if they did not indicate they were happy to be approached; I only introduced myself and discussed the project if they had said they were interested when asked by the clinic receptionist. I asked them to complete a consent form prior to their appointment. Families were then allocated a unique study identification number (FamOb001 to FamOb027) which was used on all subsequent study documentation.

For the interviews, on arrival at their home I went over the study and when participants had no further questions, I asked them to sign the study consent form. Participants were again allocated a unique study identification number (FamInt001 to FamInt016).

The family consent data were stored in the same way as HCPs. The different consent forms can be found in appendix 12.

Reflections on issues that were raised during observations and interviews

Use of the term 'incidental finding'

As I developed the participant information documents I realised that including the term 'incidental finding' could potentially influence the study data. The aim of the clinic observations was to establish current practice and see if and how the possibility of IFs arising from genetic testing was discussed with families. I did not want to affect the consultation by raising IFs as an issue in the study information; for example HCPs, having read the details of my study, might discuss IFs during the clinic appointments that were

being observed, when they would not normally do so. To avoid this, I removed any direct reference to IFs in the documentation (invitation letter, expression of interest, participant information sheet and consent form) and re-named the observation part of the study to: *Exploratory study: observation of clinic consultations.* Whilst this might appear to lack openness, I considered this justified to achieve the aims of the observation stage. Reference to IFs was included in the participant documentation for interviews, as this part of the study was a more specific in-depth investigation of the views and experiences of HCPs and family members about IFs.

This issue was also raised by the NHS ethics committee who asked about possible bias to the observation data if participants were aware of the specific area being researched and changed their routine practice as a result and this confirmed my approach was acceptable. One possible impact of changing the study information in this way was that, as a result, documents were less detailed and might have appeared vague to participants. It was not possible to evaluate the impact this had on the recruitment of HCPs as I did not collect this data; however, the main reason families gave for not taking part was that they did not want extra people in their consultation.

Consent from participants without good command of English

Participants who did not have adequate command of oral/written English to consent to join the study were covered in the exclusion criteria. Whilst this was not ideal, this was a practical solution to a lack of funds to translate study information into other languages or have a translator available to talk to potential participants prior to the clinic consultation/interview. However, some families did in fact already have an interpreter arranged to attend their appointment. There were two occasions during the observation period when families needing interpreter services agreed to meet me to discuss the study. Both families seemed not to have read the study information prior to their appointment and, whilst one parent in each family spoke some English, it was difficult to assess their comprehension in one short interaction. I utilised the expertise of the interpreter to explain who I was, give an overview of the study and the process for participation. Both families indicated that they would like to participate.

These interactions were challenging as I was unprepared. I felt that it was unethical to exclude them from participating when they had indicated an interest in the project and

said they had enough information to make this decision and so I went ahead with the observation. When HCPs suggested possible families to contact for interviews, none required interpreter services in order to participate.

Written consent from parents

During observations, in families where a child was the patient, I explored the issue of whether I should obtain written consent from one or both parents (if both attended). My protocol originally outlined that, where multiple family members were present, all should consent to participate, as all were involved in the observation. Where two parents attended both were in fact present for the consent discussion. I took a pragmatic view that, as long as both stated their agreement orally, it was not necessary to ask both to sign the consent form; I documented these discussions in the field notes.

The majority of interviews were one to one but in the one case where two parents were interviewed together, a separate consent discussion took place with each parent - as one joined the interview a few minutes after the other – and so at different times both parents gave written consent.

Assent from adolescents

NRES ethics committees routinely request that adolescents are given information and are asked to 'assent' to their participation and sign an assent form, in addition to a parent consenting on their behalf. The utility and consistency of seeking assent has been questioned, with the suggestion that competent children can and should give consent but that parents should be allowed to consent for incompetent children.[230] Potential problems with assent can occur if the parent and child give different responses and the process can introduce tension into decision-making within a family.[230] A counter argument is that the purpose of assent is not to provide a second consent but to ensure a child has an appropriate level of involvement in decisions that affect them.[231-233] The level of involvement possible is likely to reflect their individual level of cognitive and emotional development.

I had concerns whether this additional form was necessary and I communicated this to the chair of the NRES committee in an accompanying letter to my submission. Whilst I planned to take oral assent from adolescents, alongside parental written consent, I felt the assent form could create an additional bureaucratic burden without adding anything

to the discussion. I did submit an assent form to the committee (appendix 13) as I knew this was a standard requirement. The committee did not respond to my concerns but full ethical permission was given for phase one of the study (see appendix 14).

I subsequently planned to use this form with any young people under sixteen where I was unsure of their capacity to consent to participate. I used it once during the observation period with a fourteen year old boy who attended with his mother. She had read the study information, was keen to participate and happy to provide consent. While at fourteen years a young person will generally be competent to consent this was difficult to assess in this case. It appeared that his mother had not discussed the study with him and overall he was disinterested, passive and reluctant to engage in discussion. It was unclear if this was due to a lack of capacity or that he wanted to defer decision-making to his mother. I asked his mother to sign the consent form and him the assent form. On reflection, if in a similar position again, I would try to engage the young person in more discussion to establish their ability to consent or not, as a lack of engagement may indicate a reluctance to participate. If the latter, I would not have observed his consultation.

Under representation of certain professional groups in the sample

As outlined earlier in the chapter, following initial analysis of the HCP interviews it was clear that the views of laboratory scientists who perform the genetic tests and report back results could usefully be sought. Although not counselling families directly, this professional group are making decisions about the techniques to use when interrogating the genome and then, when IFs are discovered, how they are interpreted and reported back to HCPs. Despite inviting a small number of scientists from the local genetics laboratory in the early stages of recruitment, there had been no response. The scope of genetic tests that are ordered and how this matches with patient views on what incidental information they would or would not want to have disclosed, emerged as salient points in early data analysis. The question of consenting to receive or opting out of IFs has been consistently discussed over the last couple of years.[36,146,234]

I addressed this by contacting a key person in the Wessex Regional Genetics Laboratory (WRGL) working on aCGH testing and also genetic laboratories linked to two large clinical genetic services in the Midlands and North of England and asked them to forward study

details to their colleagues. This resulted in the recruitment of two participants from this group.

For the interview family cohort, it was appropriate and pragmatic to approach families through clinical genetic services. These services keep family notes stored in the department which can be accessed at any time, and they have departmental databases for identifying possible family members and obtaining contact details. Inviting families who had genetic testing organised by other specialists (for example, by a cardiologist) relied on a HCP's recall of these families, sufficient so their contact details could be accessed. I was aware that this approach could have implications for my sample: if early analysis identified emerging codes relating to consent and disclosure practices of non-genetic specialists specifically, then interviews with families who have been seen by this group of professionals and not by genetic HCPs would be needed for a detailed exploration. Initial recruitment included families that had primarily been seen by the WCGS but, as the study progressed, recruitment also included families identified through the Unique charity. A number of these family participants had genetic testing organised by other specialists and had never seen a gHCP. The final interview family cohort did reflect the experience of families both seen by a genetic specialist and those who were not.

Recruitment of family members for interviews

Separate invitation letters were sent to parents by their HCP if they had both been present at a clinic appointment when genetic testing was organised or results given for their child (ren). If only one parent was documented as being present, then only this one parent was contacted. During the recruitment period the expression of interest form was often returned by one parent. I then checked whether both wanted to be involved - separately or together - when telephone contact was made.

In addition, a second parent was often present in my interviews, and might indicate a general interest in the study, but did not participate in the interview. All but one family interview were either carried out with one parent only or, in the one case of two parents, done on separate occasions. The one joint interview began with the mother only and then the father joined the interview after about 10 minutes. This was rather disruptive as I needed to stop recording to check he was happy to participate and answer his questions

about the study. Once the interview was in progress there were a few occasions where the couple entered a discussion between themselves that was outside of the remit of the interview schedule, at which point I tried to re-focus the interview. When analysing this interview I paid special attention to establish their different/similar views. I discuss this further in 'reflections on my role as the researcher'.

Adverse psychological consequences in family members

It is possible that discussing issues around genetic test results could cause anxiety and distress for the family participants. While it was important to be mindful of this I did not consider that the risk was likely to be very significant for the following reasons. I only interviewed families where pertinent issues arising from genetic testing had already been discussed in the clinical setting and where no current test results were outstanding. Furthermore, additional in-depth discussion of the family experience of genetic testing may lessen such concerns rather than increase them. Family members were mostly invited to participate following identification by a member of their clinical team and so including them was a considered decision. If a participant appeared concerned or anxious during, or as a result of participating in the study, I planned to liaise with their clinical team to ask them to make contact with the family. In addition, participants were made aware that they could stop the interview at any time and withdraw from the study.

I am an experienced clinician with a track record in this type of research and I believe am able to identify participants who are upset or distressed and respond appropriately.

HCP concern that their practice was being judged

I was aware that HCP participants might be concerned that I would criticise their practice. I reassured them that I would keep data confidential and anonymous. Participant information sheets for the interviews emphasised that there are no established guidelines surrounding the management of IFs and that my research aimed to seek their views and draw on their experience, not judge their practice against an existing 'gold standard'.

However, as I am a registered clinical practitioner (registered nurse and genetic counsellor), I am required to report unethical practice to the appropriate professional body. This did not occur but if it had I would have discussed the circumstances with my supervisory team.

Introduction to findings chapters

The next two chapters present findings from the observations and interviews. Direct quotations or excerpts from the observation data sheets or interviews are indicated in italics. Notations are as follows: FamOb001 indicates the first observation of a family consultation in clinic and FamInt001 or HcpInt001 the first family or HCP interviewed and so on. The family interview number is followed by details of the person interviewed, for example, father or mother or patient. The annotation … indicates that some text has been removed in order to make quotes clearer and to remove text that such as, 'you know' or repetitions of words.

Chapter 5: The experience of IFs in the clinical setting

This chapter follows the journey of discussions about incidental findings (IFs) for both patients and health care professionals (HCPs). I start by looking at how (or if) IFs are raised at the point of initial discussion about a genetic or genomic test and follow that through to experiences about giving or receiving results. Where patients had received IFs, in some cases 1-2 years had already passed, so I was able to see how their experiences had shaped their views about, and attitudes towards, genetic testing. In the patient group, I include both patients themselves or the parents of patients where patients were too young to be interviewed. I then move on to discuss HCP perspectives on taking consent from patients for genetic testing and disclosing results and focus particularly on the potential for, and the finding of, IFs in these discussions. A number of the HCP participants had reported IFs back to patients.

Pre-test discussion: Preparing for an IF

For patients: is the possibility of an IF raised?

Recall of discussions from clinic observations

During my clinic observations of genetic test results and follow up, I did not observe any participants who remembered being told about the possibility of an IF at the time of consent for genetic testing. While HCPs did not often ask patients directly if they remembered being told about IFs, when genetic tests were discussed recall about any potential outcome from testing, other than a possible diagnosis, was poor. That is, patients or parents generally did not recall that a genetic test might provide uncertain results or no results at all. In fact, many participants did not recall that a genetic test had even been organised, let alone being told that IFs were a possible outcome. All my observations were cross-sectional so it was not possible to establish whether a discussion about IFs had indeed taken place at an earlier appointment. Since I was observing and not participating in the appointment, I did not have the opportunity to ask patients about their understanding of the investigations that had been previously organised and of the possible implications of such tests. However, they raised questions about whether patients remember details of earlier discussions or did such discussions ever take place?

An example from the observation data illustrating that a family appeared to have poor recall of information given about the genetic tests organised is included in box 3 below.

Box 3: Example of observation data reflecting poor recall of information (FamOb014)

I observed a [genetic clinic] appointment where parents were first told about an IF that had been identified in their young child. This excerpt is from the data collection sheet and illustrates that the family did not recall that their son had undergone genetic testing and were not therefore expecting a genetic result at this appointment. I was unable to confirm that the paediatrician had discussed genetic testing with the family but a clinic letter indicated that he had.

Purpose of appointment

An aCGH test [the test that identified the IF] had been requested on a child by a paediatrician. This was the family's first appointment with genetics.

Discussion of testing/results

The parents did not remember the test being discussed and did not know the name of the paediatrician who had organised it. They said that they had not had an outpatient appointment with the paediatrician or one arranged for the future. A deletion was found giving a diagnosis, but also including a gene that has been reported as linked to a risk of schizophrenia (an IF). The parents were not aware of this result when they came to the genetic appointment.

Recall of discussion from family interviews

All participants in interviews, except one, had either undergone genetic testing themselves or testing had been carried out in their child. Most patients (ten out of sixteen) also did not recall being informed that IFs were a possible outcome of genetic testing: *"…I don't think it was specifically mentioned that, that other unrelated things might come up."* (FamInt001Patient). The other six were unsure whether IFs had been discussed during their appointment and of these some thought they might have simply forgotten the discussion:

"To be honest I don't remember her saying a lot about it. I think it was just that there are lots of different rare genetic conditions that we can pick up with this array…. I don't think

she was particularly confident it was anything like that but she just said yeah we'll give it a try." (FamInt008 Mother)

"…I don't remember the conversations in detail but I know she would have explained that." (FamInt009 Mother)

Another participant summarised her recollection about the discussion at the time when her son had his genetic test. She remembered the HCP telling her that the test might not uncover a genetic cause for her son's developmental delay, but not that an unexpected finding could be discovered:

"I know that they did talk to us in quite a lot of detail but I can't really remember everything that they said at the time. Just what the process would be, that it wouldn't be a quick process… that it's quite new, it was quite a new thing they were doing… And they did say they might not actually find anything at all." (FamInt002 Mother)

Some participants remembered being given some information about possible test outcomes other than diagnostic ones, but this was usually about uncertain or clinically insignificant results rather than incidental ones:

"But she did say that it's not a test for something, it's a general test and things might be thrown up that aren't relevant and, aren't of interest." (FamInt008 Father)

Overall none of the participants remembered a specific discussion about IFs having taken place prior to testing. Interestingly, there was no difference in recollection between participants who had an IF discovered and those who did not, suggesting that the subsequent disclosure of an IF did not result in participants being more likely to remember earlier discussions about the possibility.

All of the families where an IF was given were surprised and shocked to receive them, and did not believe that they had been prepared for this in any way:

"…But it was a bit of a shock, because no we didn't know that they could have found anything else out. Nobody said that….No, nobody ever mentioned…I didn't really realise and I thought they were looking for one thing; didn't know that you could find all these other things out…" (FamInt013 Patient)

Since it would be impossible to prepare for every conceivable IF prior to testing, a degree of surprise or shock is likely to remain even if a standard line about the possibility of IFs becomes routine.

Factors that may influence IF recall

Time between test and result

The data suggested that where a long time had passed between consent and results, participants were more likely to have forgotten the details of pre-test discussion:

"Oh, it was a long time ago…I know that they did talk to us in quite a lot of detail, but I can't really remember everything that they said at the time." (FamInt002 Mother)

Although I did not interview matched HCPs and patients, it is interesting to note that whilst no patients remembered discussions about IFs, several HCPs reported that they routinely did discuss IFs with patients. One possibility is that as practice was changing rapidly during the course of my research, HCPs who said they mentioned it routinely may not have done so in the past, when some of the patient participants were tested.

Patients come to clinic for a primary diagnosis

A genetic test may likely be just one of a number of investigations carried out in an individual to make a diagnosis. This was often the case for children who had a number of different congenital anomalies and where multiple tests would be organised in tandem to look for clues to an underlying diagnosis. Any discussion about genetic IFs may therefore simply have been 'lost' in the sheer volume of information shared between the HCP, or several HCPs, and the patient, as suggested by the clinic observations. For most families a number of investigations were being carried out at the same time, (see box 4 for an example) so it is perhaps not surprising that recall about specific genetic tests and their possible outcomes was poor.

Box 4: Example of many investigations being organised at the same time (FamOb020)

Routine follow up appointment with a community paediatrician. The appointment included discussion of several tests results, only one of which was a genetic test result. The family did not appear to remember that genetic tests had been organised or ask about the results. *Purpose of appointment*

A number of investigations had been ordered at the last appointment about four months before. This appointment was to discuss results from these tests.

<u>Discussion of testing/results</u>

No results were available in the patient notes so the consultant kept leaving the room to ask administrative staff to chase up reports. It was unclear from the discussion parent's recall of consent for individual tests but they remembered blood samples being taken from their child. They did not mention any tests by name, for example, fragile X testing, suggesting that they did not recall what each blood test was for (these were both biochemistry and genetic tests) or the types of different tests being ordered.

One of the interview participants whose son had undergone an aCGH test suggested that a lack of recall might be because families were distracted by pressing health or developmental concerns:

"…I don't remember him [paediatrician] saying about anything else, but we were just so caught up in our son's problem, but he might have done and we just didn't hear it." FamInt011 (Mother)

IFs are described in a variety of different ways

The possible outcomes from genetic testing were explained to patients and parents in a number of ways. In both my observations and interviews, I noted that HCPs used different terminology and described complex information by different means, for example, IFs were described in the observations as "*things we are not expecting*" (FamOb012) and a VUS as *"not sure if it is linked to the condition or not."* (FamOb019).This definition of a VUS could also be applied to describe an IF, demonstrating that there can be overlap between the different test outcomes. It is quite possible that the concept of IFs had been explored in consultations but that other terms or descriptors, such as 'unexpected', 'secondary', or others outlined in chapter 2, had been used. It is likely that, because the issue of IFs might have been described using a range of different terms, this might affect recall. However, I generally framed the question in a broad way, such as: *"…do you remember the sorts of things [the HCP] talked about when (s) he was telling you about the test; what things (s) he said about this type of test?"* (FamInt003 Mother) and *"…do you remember when the genetic tests were organised…what the consultant talked about? Did*

*(s) he go through what a genetic test was, what things it could show?" (FamInt009 Mother).*This suggests that their surprise at receiving an IF is not just an issue of terminology, as my questioning was broad enough to capture the issue being explored.

Patients were unsure what the term IFs meant, indicating that even if HCPs used this phrase it may not be clear to patients what type of results they were referring to and this too could affect recall. In addition, patients did not like the term and suggested alternatives. Of the terms commonly used 'unexpected' had the most support and patients thought they this better described this group of results than incidental findings:

"I don't like that, incidental to me doesn't mean, I don't understand it and secondly the other two, unwanted is awful and unexpected as well. Maybe just call it other findings, and then you explain." (FamInt010 Mother)

"Incidental makes it a little bit, sort of blasé about the whole thing, but unexpected is a good word, yes, an unexpected finding, yes that's a good one." (FamInt013 Patient)

An IF may start off as an uncertain finding

It became apparent from what HCPs said in interviews that findings that were eventually termed IFs were often first reported by the laboratory as uncertain findings. For example, many laboratory reports would say something like 'this deletion affects part of the gene responsible for condition X, it is possible that this patient is at risk of condition X but further evidence needs to be gathered for a definitive opinion'. When reports came to HCPs they would often explain to patients that they had received a result that is uncertain, rather than an IF, as they wanted to clarify significance before confirming it to be an IF:

"…I feel as if I need to sit down and work out what having this duplication is; is it just the CMT gene [the PIF] and can we just deal with it as an incidental finding or could there be anything in it at all affecting the boys." (HcpInt006 Consultant Geneticist)

During the course of my research, and prompted by earlier clinical examples, I created a more detailed typology of IFs as detailed in chapter 1. An IF rarely starts as a straightforward IF but is more often a *potential* IF - a PIF.[96] It is only after further investigations – often involving family members or waiting for further research – that a result can be definitively labelled as a diagnostic one, an IF, a variant of uncertain significance (VUS) or normal population variation, not previously described. PIFs, when

first discovered, may be explained to patients as an uncertain finding and even when reclassified, the HCP might not use the term IF. Patients while informed of the result may not be aware that this is an IF.

For HCPs: is the possibility of an IF raised?

Recall of discussions

When asked about the issues they routinely discussed with patients when organising a genetic test such as aCGH, nearly all HCPs reported talking about uncertain results as a possible test outcome, but less often specifically about IFs. Of thirty HCPs interviewed, twelve reported that they discussed the possibility of IFs with families in some detail, eleven that they mentioned IFs briefly and seven that they did not discuss IFs at all. As highlighted above HCPs may use these terms inter-changeably so it was difficult to confirm exactly how often they addressed IFs. This illustrates there was a considerable degree of variability in clinical practice during the research period. One HCP explained that he did not explore the issue of IFs prior to genetic testing:

"…What happens if we find something that we didn't really expect to find? I haven't ever really discussed that with the parents I have to confess." (HcpInt020 Paediatrician)

It is of interest that this HCP used the phrase "*I have to confess*" suggesting that he maybe thought he should have been discussing this. Perhaps he made this comment because he was aware that this project was about IFs and assumed I would think he should mention them. Perhaps he believed that discussing IFs represented good clinical practice, but for whatever reason he had not (yet) integrated this into his own practice.

Despite my finding that more than half of HCPs reported not discussing IFs in detail prior to testing, nearly all thought that it was an important clinical issue that in future they should discuss more. GHCPs reported discussing IFs prior to genetic testing more often than HCPs from other specialties and this was mirrored in the observations. In one of the observations, the geneticist explained that the test being proposed could find *"…things we are not expecting and things we don't know what it is."* This HCP continued by stating to the patient that this explanation was *"… more than I would usually say."* (FamOb012), suggesting that my presence as an observer had affected their usual clinical practice.

Some HCPs acknowledged that whilst they believed it was important to discuss IFs they did not think it necessary to do so in detail. The following HCP quote represents what many said:

"If I'm honest I probably don't go into a great deal of depth, that it may pick up something that we weren't expecting…I mean it's not that I'm unaware of it and it's not that I don't think it's important…but I think perhaps reflecting on it, that practically …I'm less focused on doing that." (HcpInt007 Genetic Counsellor)

This suggests that HCPs focussed their discussion on other matters, such as the possibility of finding a diagnosis, or perhaps identifying uncertain findings, rather than on the possibility of an IF. This may not mean they did not consider IFs important but may indicate they thought they needed to concentrate on outcomes that they considered more likely.

Factors influencing HCPs discussing IFs

Preparation might lessen the shock

Those HCPs who said they discussed IFs in depth did so because they thought they needed to prepare patients for the possibility of receiving an IF. They thought that, even though the preparation for an IF could only be in very broad terms, it would ease the shock for both patient and HCP - if an IF was discovered - if at least the possibility of an IF was raised before testing: *"…but we do have to say it [that an IF could occur], and it would be wrong not to because how on earth do you then follow it up if you haven't warned them it might be there."* (HcpInt031 Community Paediatrician)

Some HCPs who had already encountered an IF in their practice reflected during interviews that this experience had shaped their views about the importance of addressing the issue before testing. One HCP who had found an IF that predisposed to bowel cancer (in a family where they had tested a child because of developmental delay) discussed the difficulties associated with not preparing families to receive this type of information:

"Yes I think the fact that it had come completely out of the blue was the most difficult thing for them to come to terms with. Because the terms of reference for why they were coming to see us had completely changed from what they were expecting. So I imagine… a

better…pre-test counselling would help prepare people for that." (HcpInt009 Genetic Counsellor)

Another HCP who had encountered an IF in the early days of aCGH testing now routinely informed patients that an IF might be discovered. She explained her practice using this early case:

"…what I basically do whenever I'm talking about genetic testing and CGH array I use the same example and tell the parents about, I use this example [finding an IF indicating significant risk of developing a bowel condition]and they always seem to understand it…and the other thing it's important for me to tell you, is that the genetic tests sometimes show up things that are unexpected…this happened to me …and I'm going to tell you what happened so you will understand it." (HcpInt024 Community Paediatrician)

Hypothetical examples were also used, as one HCP explained:

"We also talk about that we might find something completely unrelated to why we're doing the test, that might have implications for your health now or in the future and usually give examples of…we might find something that means you're at increased risk of particular types of cancer or you might be at risk of, cardiac problems and usually give a few examples." (HcpInt017 Genetic Counsellor)

Another HCP acknowledged that experience of IFs would affect future discussions:

"…and it's possibly one of those situations where we've all got it on our radar, this is something we are aware can happen, but until it happens to you it seems like a rather rare event. And then possibly if you've been affected by a case where it's raised particularly difficult issues, you're more likely to talk about it." (HcpInt027 Genetic Counsellor)

IFs are listed as a possibility on consent forms for genetic testing

Some HCPs, or their clinical teams, had tried to formalise discussion of IFs before testing by including a specific reference to IFs on the consent forms they used. One HCP explained that they realised that IFs were now found more often in clinical practice. Previously they had been rare, but now they found themselves regularly discussing incidental findings in their departmental clinical meetings. They had therefore decided to amend their consent form as a prompt to clinicians to discuss the possibility of IFs:

"We do actually have on our consent form now that line saying that [sometimes we get something really unexpected]…And that was one of the things a lot of people said [to include this issue] …we all felt that was quite important…[although] for ninety nine percent I test it's not likely to be relevant." (HcpInt016 Genetic Counsellor)

Many HCPs appeared to assume that I considered the use of consent forms as some sort of gold standard, or best practice. They were often apologetic, or hesitated to share, that they did not routinely use them in their practice. As one put it:

"… but I think it would be hard and probably unhelpful to go through all the possibilities. I don't know. I don't get someone to sign a consent form. I consider the letter to be part of the consent procedure, and whether I'm old-fashioned, I don't know." (HcpInt0013 Consultant Geneticist)

Another HCP, however, assumed consent forms would help with the consent process about IFs:

"We actually have on our consent form now, that line [about unexpected findings] so that we are prompted to remind people as well that we may find something that's either difficult to interpret or unexpected." (HcpInt016 Genetic Counsellor)

Some HCPs thought a consent form was better evidence of consent having taken place than documentation of discussion in the clinical notes. Others thought that since aCGH, for example, was just another investigation along with biochemical tests, ultrasound scans or X-Rays for which a consent form would not be used and which might equally reveal diagnoses, that use of a consent form might encourage a form of genetic determinism. Genetic tests could be viewed as something special and different, requiring a consent form to be filled in when other investigations do not. Whilst this is a subject for future research to shed more light on the advantages and disadvantages of consent forms for genetic testing, it is clear that current practice varies considerably, despite guidance from the Joint Committee of Medical Genetics that recommend their use to help summarise discussions.[1] The use of a consent form was sometimes confused with or conflated with the consent process: some HCPs answered my questions about the consent process with talking about consent forms even though I had not asked about them:

"…there's obviously going to need to be a consent form, because we do it verbally and we write down consent given…I don't think we necessarily get written consent." (HcpInt023 Cardiologist)

A broad discussion may help to prepare

Some HCPs believed that IFs should be discussed in a broad, general way, for example, mentioning the possibility of IFs, but not providing significant detail about what these could be or mean for the patient and their family. They mainly justified this view by saying information about IFs would be too vague at the testing stage, the chance of actually finding one was low, and spending too much time discussing IFs might unnecessarily worry already anxious patients or their parents. HCPs were also concerned about burdening patients with too much information at once, especially information unrelated to the primary reason for the test:

"I explain it, clearly write it in a letter, clearly tell them it might pick up things that we wouldn't expect, I don't go into a long length about what those things might be…Because to a certain extent, they are focused on a cause for the learning disability and the recurrence risk, and that's why they are doing it [the test]." (HcpInt003 Consultant Geneticist)

Many HCPs thought that at the testing stage any information about IFs could not be anything other than vague. The detail could only come when one was discovered and not before. This was illustrated in the following interview: "*How much they really …because they are all theoretical possibilities, how much they really engage with that, I think is hard, is hard to know."* (HcpInt011 Genetic Counsellor)

HCPs acknowledged the downside of this, in that patients might then miss, or not recall, this aspect of the discussion. Some HCPs thus planned to re-visit the issue when they considered it relevant:

"…that could be really scary…this might show a predisposition to dementia or breast cancer or something like that…I would probably think about talking in general, very general terms that it might show up things that were not expected …and take one step at a time." (HcpInt012 Genetic Counsellor)

HCPs tailored information to patients, gauging their family circumstance and potential anxiety, and drip fed information accordingly:

"…is this a family who will be worried or anxious about this or not?…So I would probably say…we may find something that is irrelevant, we may find something that may be significant for his or her health when they're an adult and obviously we'd talk to you about that, if it happened." (HcpInt022 Community Paediatrician)

Time constraints on discussions of IFs

IFs were generally not seen as the most important information to be shared with patients, many other things needed discussing first, for example, family history details, clinical examination and discussion of how testing might make a diagnosis. Uncertain results as a whole are more common than IFs, and with a limited time being available in clinic, these were generally addressed during the consent process, in preference to IFs:

"…much more time preparing people for the fact that there might be uncertain …information that's difficult to interpret…so we make a big deal about that…because that's really common." (HcpInt015 Genetic Counsellor)

Post-test discussion: Giving or receiving an IF

Patients' experience of receiving an IF: surprised but pleased

I have described how patients generally did not recall discussions about the possibility of IFs as an outcome of genetic testing. Next, I went on to explore with patients/families where an IF had in fact been found, what was it like to be told and how they had managed this information?

Of the thirteen families included in interviews, five had an IF discovered and disclosed (see table 19). In three of these families the IF was identified in a child and the result given to both parents. In one family the IF was found in an adult and the IF disclosed to the adult and both his parents. Another adult received information on their own. In six out of seven interviews the views were therefore from the parent(s) of a child in whom the IF had been identified. All the IFs were different from each other.

All participants reported that although they were surprised that an IF had been discovered they were also pleased that this information had been shared with them. In addition, they would want the same information if in a similar position again. A mother of

a 6-year old boy, in whom an adult-onset IF was discovered, and an adult patient commented:

"We were a bit upset, but we were really pleased, because at least we can get him screened …so that he's aware of it as he's an adult, and that something can be done. So we don't want him to have that problem, but we're pleased we know about it…they explained there's no guarantee that he will get it, but at least we can put methods in place to make sure that he is screened, so and if it's [inherited from] either of us, then we've got to be screened. So no, I mean we would rather know, definitely rather than just let him go off and find out maybe when it's too late." (FamInt011 Mother)

"You might want to know about it [an IF] and you might be glad you did…me with this bone density thing, well actually…if I do have it [osteoporosis], I'd be glad you did it and I'd be glad you'd told me, because I can do something about it now." (FamInt013 Patient)

The families also said that the IF caused them anxiety especially because they did not know how or when the condition indicated would manifest. The disclosure process was therefore important to participants. With a number of participants the result was given first by telephone or letter, sometimes at the same time as the primary diagnosis result. The initial contact was usually followed up by a face-to-face appointment but for some this was many months later. The wait made participants anxious as they often had no specific details about the finding, its health implications and possible interventions. Whilst the HCPs may have thought that a general letter or phone call prepared patients for the more detailed information later, patients/parents thought this increased their anxiety.

One participant explained how she waited six months from receipt of the preliminary result from the paediatrician (by letter) to the genetics appointment to discuss the IF in detail, by which time she had sourced information herself via the internet:

"…but by then of course… we'd had six months to come to terms with it [the IF identified in their son] and…so it probably wasn't timed right…I think probably that [possibility of IFs] should be more highlighted…I suppose it just prepares people possibly….Because even though I was prepared, I mean it is still a bit of a shock. And the way we had it wasn't the best I would say." (FamInt008 Mother)

Reasons why patients want IFs disclosed

Perceived to be useful information

Perceived clinical utility was the primary reason given by family participants for wanting to have IFs disclosed. In a number of cases, the identification of an IF had led to an immediate or planned referral of the patient to another specialist for surveillance that might lead to early diagnosis and treatment. Participants described how the IF had made them aware of something they would otherwise not have known about: a new diagnosis with health or social implications for the individual and/or other family members. Participants were hopeful that early intervention would lead to better health outcomes and in some cases prevent serious harm or death. Even if treatment interventions were not currently available, participants were hopeful they would become so in the future. Knowing about the IF now meant that individuals could seek updates and new information. In this way the IF was empowering and had personal utility for participants. One participant said she would want to be informed even of IFs when no prevention or effective treatment was currently available (for example, Alzheimer's disease):

"…perhaps in 20 years [when prevention/treatment may be available]. So if you don't know you've got it then you're not going to bother to go and [ask about the new treatment]…And I have heard about the Alzheimer's thing, there is something they can give you if they find it early enough." (FamInt013 Patient)

Another participant explained how having access to this information now meant that his son would automatically be eligible for bowel screening from 25 years; this risk might otherwise have only come to light when his son presented with a bowel cancer:

"…there was another part of it that was quite a relief, because it's actually a twist of fate if you like, a bit of luck, that had [our son] not had these underlying problems he could have developed this condition later in life and been unaware of it. So actually the fact that he knows about it, it gives him a bit of a lucky break, if that makes sense, because he'd got the opportunity to get screened for it regularly, and if he has got a problem he can manage it." (FamInt011 Father)

Parents believed that being 'forewarned is forearmed'. They could adjust to this information and then make plans for the time when they would discuss the result with their child. They felt they could ensure that their child could access recommended

interventions at the appropriate time. No parents interviewed had yet shared an IF with their child so there was no data available to see if these views were upheld, following parental disclosure. Parents considered themselves – as opposed to HCPs - gatekeepers of this important health information for their child. In the following excerpt a mother explained why having the information now was important to her:

"…we were upset, but they explained there's no guarantee that he will get it, but at least we can put methods in place to make sure that he is screened…So no, I mean we would rather know, definitely would rather know, rather than let him just go off and find out maybe when it's too late…" (FamInt011 Mother)

Participants considered it beneficial to have this information immediately as it prevented unnecessary investigations being carried out later if they or their child was to present with symptoms of the IF. For example, one IF in a young child indicated he would be infertile as an adult. The parents were informed and although it did not indicate a health risk for their child they were pleased to know for two reasons: firstly it was important information to tell their child later when they were considering their reproductive options, and secondly, if they had not been made aware of the IF, their child may have undergone unnecessary investigations as an adult to investigate (in) fertility.

Most parents/patients perceived a clinical benefit to receiving news of the IF, even as above where the benefit is arguably more personal than medical, as in the example of making plans for the future. Would their views have been the same if the IF indicated a predisposition to a serious, degenerative condition with no available treatment, or if the result informed them about future reproductive risks? I could not ascertain this from the families I had interviewed.

To benefit relatives

Whilst the primary purpose of genetic testing for the participants I interviewed was to find a diagnosis, all had considered the potential implications for relatives. They had already, or planned to, inform their relatives where relevant. Some patients had an awareness of the familial nature of genetic testing at the outset and as a result had considered this in deciding to proceed with the test, discussing it with relatives beforehand:

"…if it's hereditary…this could open a right can of worms…but we need to know because of reproduction and all of that. So we did go down that avenue [genetic testing] but I did discuss it with my brother before." (FamInt010 Mother)

Others had not discussed the test with relatives beforehand but said this was one of the reasons they had testing themselves:

"If they discovered I had a genetic disorder that other members of my family might have and that they might benefit from knowing, then I'd like to know about it I suppose." (FamInt001 Patient)

Some had decided to broach test results with relatives if and when it became relevant, but nevertheless had already considered the potential wide-reaching effects of a genetic result:

"The implications were that if that chromosome was missing, it could affect his siblings. And potentially one of us [wife] or I would have that same problem…and then by default, my brother and his family and it would escalate." (FamInt011 Father)

"…I think the family should have some idea about it really…it would be a terrible situation if one of these siblings did get a disease that could have been prevented by some information…I would certainly be in support of that information being given to families." (FamInt006 Father)

Interestingly, both groups of participants supported a staged approach to the sharing of information about IFs. Patient views about informing relatives after an IF was found contrasts with their reported desire to be informed about the possibility of an IF when the genetic test is arranged. This suggests that while patients themselves seek this information from HCPs, the reality of discussing hypothetical test outcomes with family members, for whom an IF is actually quite unlikely, is challenging. This echoed the view of some HCPs when giving their rationale for why they did not discuss IFs prior to testing.

The majority of IFs disclosed to patients in this study were *de novo* meaning that existing relatives were not at risk of developing the same condition, although future children might be. The IF may therefore not have been shared with other family members as there was no perceived need to do so. A number of participants had told some relatives but this was for support rather than because the IF held any clinical relevance for them:

"...but we have chosen not to tell the rest of the family until we know, because there's no point telling them if it's not going to affect them anyway and then again you don't want to worry anybody…I've just told my mum." (FamInt011 Mother)

In one family (FamInt013 Patient) the IF found was relevant to other family members, as it was not a *de novo* mutation. The patient discussed her experience of finding out about this and sharing the information with her daughter. She explained that her daughter was now aware that she is at risk of osteoporosis and this means she can access screening in the future – a benefit - but, at the same time, because she was planning to become pregnant, she found this information worrying. Experience from clinical genetics practice suggests that patients perceive a tension about informing relatives about something they believe they should know, but in doing so cause them worry.[109] The decision to inform relatives may then be guided by the seriousness of the IF discovered and whether it is currently relevant, in that effective interventions can be accessed straight away. Despite advising patients to share results with relatives, it is not always possible for HCPs to check if this has happened. Patients could make a decision not to disclose a result or defer to a later date. Participant 013 described the worry she believed sharing this information with her daughter had caused:

"…so I think that possibly sometimes it's not a good thing. I mean like with my daughter, she's worrying herself to death about this having a baby now…then I kept thinking to myself, well she should have the right to know…it should be her choice…so sometimes I think well you've done the right thing but other times I think perhaps if I'd have just left her." (FamInt013 Patient)

HCPs' experience of giving an IF: "…it proved very hard work"

HCPs reported that IFs had been a challenge in their clinical practice, particularly informing patients about the unexpected nature of the result and especially if they had not discussed this possible test outcome with patients at the time of testing. HCPs had to consider if and how they would share this result, for example, what details they would give during the first result appointment and the information they needed to have to inform patients about possible interventions. Some findings were PIFs when reported, so HCPs had to explain this and that testing family members might clarify the clinical significance. The following HCP discussed his experience:

"…it proved very hard work, explaining that, [an IF predisposing to bowel polyps and cancer] and the mother getting very upset and quite angry…the risk was actually uncertain, but almost that was worse because then there was the accusation that you bring something up and yet you still don't really know if it's important or not." (HcpInt013 Consultant Geneticist)

Others described the experience of having an IF in practice as being helpful to future consultations:

"I was either lucky or unlucky in that fairly early…I ran into a problem with one of the very first tests I did. And I will then say to them [parents of child being tested] and this happened to me…and I'm going to tell you what happened so you will understand it. So I tested a little girl, who had some developmental delay to try to find out why, and her blood test came back with an abnormality in an area that codes for colon cancer; we hadn't expected this at all, this wasn't why we tested, it was nothing to do with her developmental delay." (HcpInt024 Community Paediatrician)

"Anyway the consequence of that is [having disclosed an IF] that I do a couple of things. One is in my letter I try always to remember to write…that such testing can occasionally throw up a result which is difficult to interpret or unexpected. Obviously we can discuss this as necessary…and then in terms of follow up I've set the scene." (HcpInt013 Consultant Geneticist)

HCPs thought patients initial reactions of surprise or shock often changed by the follow-up appointment to satisfaction with being told:

"So in fact for her, she was glad, she was quite reassured that she'd got a reason for why she'd had carpal tunnel [a feature of the IF discovered] really and there wasn't any problem with it really [disclosing the IF]." (HCpInt008 Genetic Counsellor)

"…they'd processed it quite well and they were quite practical about it…they understood that this was a condition that would need monitoring …they'd processed the clinical information." (HcpInt016 Genetic Counsellor)

Sometimes it is better not to give the IF

Most HCPs had made the decision to disclose an IF but a few described situations, mainly concerning PIFs, where they had decided not to disclose straightaway, but to possibly do

so if/when the significance became clearer or recommendations about interventions more certain.

For example, one HCP discovered an IF for an increased risk of cardiomyopathy following an aCGH test on a child with congenital abnormalities and developmental delay. The HCP was uncertain about what, if any, management should be implemented following this result and was unsure whether to disclose now or wait until management recommendations were clearer; the HCP made the decision not to disclose the result at this time:

"I've had a chromosome 10 deletion with a cardiomyopathy gene in it, where I haven't been able to establish what level of screening I should have for her…I don't really know quite what to do about this, wouldn't generally screen for it in childhood, would probably end up having five yearly echoes for no necessarily good reason, and a child who's never going to understand why she's going to have echoes particularly…So I think I could create anxiety in that person with learning disability for no good reason." (HcpInt003 Consultant Geneticist)

HCPs can feel torn between a general wish to be open with patients about test results and the desire not to raise anxiety unnecessarily:

"…I think it's putting you in a situation of knowing something that actually potentially is of use, but actually can create a lot of hassle, upset and downside for screening that in a crystal-bally kind of way where they may never have presented." (HcpInt003 Consultant Geneticist)

During the course of my research, international debate began about whether patients should be given a choice about what types of IF to receive.[3,124,179,235] None of the HCPs I interviewed had offered patients such a choice. In the next chapter I discuss this issue in more detail.

This chapter explored the experience of IFs in clinical practice both for patients and their HCPs. It examined the patient perspective of hearing about the possibility of IFs through to their reactions on receiving the results of their genetic test, as well as HCP perspectives on discussion and disclosure.

Summary of findings

1. Patients did not recall being told that IFs were a possible outcome of genetic testing.
2. IFs were not routinely mentioned by HCPs pre-test and when they were, they were described in a variety of different ways, with HCPs themselves getting confused between IFs, potential IFs and VUSs.
3. However, HCPs did always inform patients when a clinically significant IF had been identified. Patients were surprised but happy to receive such results. They also assumed it must have been mentioned to them but this was lost in complex discussions.
4. Where HCPs did not disclose, or deferred disclosure of IFs, this was because clinical significance of the finding or evidence basis for interventions was lacking. HCPs who had encountered IFs found them to involve a lot of extra work and were concerned about how this would translate on a larger scale.
5. In contrast to observed practice, both patients and HCPs considered it important to explore IFs as a possible outcome of genetic testing.

The finding that none of the patients recalled discussions about the possibility of IFs is not entirely surprising, especially in consultations that routinely cover a lot of complex territory. Poor patient recall of discussions that take place during consent processes are well documented,[30,32,236,237] for example, recall of potential complications from surgical procedures[236,237] or whether interventions offered are clinical or research.[30,32] A recent Cochrane review about interventions that promote informed consent for patients undergoing invasive procedures found that procedure specific interventions, such as the provision of enhanced information or patients being given more opportunity to deliberate, improved knowledge of planned procedures.[238] However, the complexities of genomic testing mean that such procedure specific interventions are lacking and novel approaches to the consent process are therefore required.

It was interesting that variants of uncertain significance were explored more frequently and in more detail than the concept of incidental findings and this likely reflects that HCPs had come across VUSs more often and therefore placed greater emphasis on discussing them. Focusing consent discussions on the most likely outcomes of any intervention is common practice within health care, for example, in discussions on the most common risks of surgery.[239-241] Whilst individual IFs may be very rare, and therefore not hit a common threshold for discussion, the combined chance of an IF may not be, and may indeed be what patients consider to be very pertinent.

Some of the patients that were interviewed had been given incidental findings of uncertain significance and, despite explanation of this uncertainty, most understood the findings to have a clinical significance for them.

One interesting apparent discrepancy was that patients did not want HCPs to decide which results would or would not be shared with them without their input – they considered this paternalistic- yet where this had already happened, patients were quite happy with the decisions HCPs had made. The hypothetical paternalism they objected to played out as trust in their clinician in the actual situation. HCPs also felt this dilemma: on the one hand they wanted to protect their patients from uncertain and unclear results, especially if they were incidental to the clinical question posed, but on the other they did not want to be seen to be making paternalistic judgements about what their patients would want without involving them. They wanted to be professional and help filter results appropriately for their patients and felt that a tick box menu approach[179] was neither paying greater respect to consent nor acting professionally. This tension between wanting to avoid paternalism and wanting to filter some of the complexities for their patients deserves further research, especially in the wake of recent rulings such as Montgomery[242] that appear to argue for more detailed disclosure.

The following chapter moves on from patient and HCP experiences to explore the views of stakeholders on how IFs should be managed in clinical practice.

Chapter 6: What should we do about IFs in clinical practice?

This chapter presents some of the reflections that participants made about the issue of IFs and their implications for future clinical practice. For example, what choices (if any) ought to be made about IFs at the time of consent and how could these choices be realistically made? Participants (patient/parent and HCPs) were asked for their views on whether the possibility of IFs should be raised pre-testing and on what IF data should be disclosed.

How to raise the possibility of an IF

All patients believed that the possibility of IFs should be raised by HCPs before a genetic test is organised, whilst HCPs struggled with the difficulty of facilitating any meaningful consent for something that could not be predicted. Patients said they would value being informed that IFs were a possible test outcome and did not think this would worry them unnecessarily:

"…I would want to be told that…we are looking for this, but in the course of this we might find something else." (FamInt012 Father. Incidental finding discovered in his child)

"I suppose you'd have to warn people that's a possibility and there could be a hundred and one thousand different things that you could pick up this way. You could be looking for something completely benign and then find something really nasty. So I suppose it's important that people are educated beforehand that that could happen." (FamInt004 Patient. Did not have genetic testing)

Most patients indicated that they wanted preparation for the possibility of IFs in general, but did not suggest particular types of IFs they would want to receive before being asked in the interviews. Although HCPs varied in how much they discussed IFs in their current practice, all were aware that unless measures were taken to avoid finding them, IFs would become more likely over the next few years:

"I think things are racing ahead. I think the people who are involved in the development of that sort of technology are a little bit removed from the clinic often and not thinking through the practicalities of how we're going to manage consent and …result disclosure, and yet …already we have so many problems dealing with uncertain variants and

unexpected findings in array, and yet we are racing forward...For new technologies where the problems are going to be exponentially bigger really. So… my feeling is that it should be as important to focus on that as you go along with the development of those sorts of technologies and if you haven't got a good solution for how you're going to implement it, then you shouldn't! Then we're not ready. But it just doesn't work like that." (HcpInt026 Genetic Counsellor)

Many HCPs reported that families appeared to accept the possibility of IFs, raised pre-test, without showing evidence of anxiety. Only one HCP reported having a parent who was unsure about proceeding with a genetic test in her child following information that an IF might be discovered. This parent's primary concern was that she considered herself to be a 'worrier' and thought that if she received unexpected health information about her child it would make her worry more. Following further discussion with the genetic counsellor she decided to proceed with genetic testing in the hope of finding a genetic diagnosis for her child's symptoms. She assuaged her anxiety about receiving incidental information on her child by determining she would be able to access early interventions for it, confirming the HCP view that potential benefits of interventions can allay patient anxiety as discussed above.

Use of examples

Although HCPs favoured raising the possibility of an IF in broad and general ways, they were also concerned that abstract descriptions may not be helpful. Some HCPs were also concerned that talking about particular IFs in detail might lead to consideration of just that particular condition, rather than IFs in general, which would be misleading because the probability of any one IF is always low;

"I tend not to [give examples]; because I think that one of the difficulties is that you can easily become focussed on those things…" (HcpInt005 Consultant Geneticist)

"…if you start giving examples, people do latch on to particular things that you've said, and, you may well really frighten people…I think I would shy away from giving too many examples." (HcpInt026 Genetic Counsellor)

Interestingly patient/parents also thought that using specific examples might provoke anxiety:

"I think that's frightening [using examples such as cancer predisposition], because then you've put it in their head that that could turn up." (FamInt003 Mother)

"It [using examples] would definitely make people more worried, I think so." (FamInt013 Patient)

However, participant 013 went on to reflect that raising examples of serious IFs could help to underline the seriousness and potential implications of undergoing genetic testing:

"…maybe make them seriously think before they sign the form. Perhaps that's a good thing really…that they think of and realise what they're letting themselves in for." (FamInt013 Patient)

Some HCPs agreed:

"I think by giving a specific example, it gives the gravity of what might be found." (HcpInt009 Genetic Counsellor)

Despite urging caution, patients did believe that applying examples could be helpful in making the issue of IFs clearer for families:

"…if people read something very dry on a page that just says we may find incidental information, it isn't going to mean anything. If you say well last year we talked to Kevin and he was just having this investigation, but then we found out this horrible thing, I think people can relate to that. So I think that people need examples, concrete things they can relate to." (FamInt008 Father)

HCPs that used examples often chose a predisposition to cancer or cardiac disease. HCPs identified three reasons for deciding on these examples. First, early reports on the frequency of IF detection through aCGH testing, focused on cancer predisposition, perhaps suggesting that these were the more likely IFs to occur.[91 243] Second, HCPs thought most patients would have some awareness about cancer or cardiac disease; they might know someone who had been affected by one of these conditions and thus these examples might signify something to patients. Some HCPs used specific examples that had occurred in their own clinical practice believing that a 'real life' example would be more meaningful to families. Third, patients would realise that interventions (for example,

regular surveillance) might be available for IFs that indicated cardiac or cancer predisposition:

"I think possibly because of the examples I give… I often talk about cancer and cardiac side of things, I guess because that's the things I've come across in the literature…And the vast majority, when I mention those, say, well that's great, you'd want to know, because then you know what you're looking out for or you might be able to do something about it, there might be screening or treatments and things like that." (HcpInt017 Genetic Counsellor)

"I do talk about it could potentially be missing like tumour suppressor gene or a cardiac gene…I've never had a parent that's said no [to testing], I wouldn't want to know, they've all said well yeah, especially if there's screening that could be put in place and if it has implications for the wider family." (HcpInt018 Genetic Counsellor)

HCPs thought that patient/parents' acceptance of the possibility of receiving incidental information may in part be because the examples they used had associated beneficial/therapeutic interventions. They thought that if they had used other equally likely conditions as examples such as, a neuro-degenerative condition with no available treatment or intervention, families might have been less keen to receive such information. They may have been more anxious and possibly this information would have prompted them to indicate there would be certain types of IFs they did not want to receive. HCPs reflected that to facilitate 'true' consent for IFs, they should perhaps include these types of conditions in their examples, supporting participant 013's view that including these underlines the seriousness of the test. HCPs thought their clinical experience of genetic testing for untreatable conditions such as Huntingdon's disease played a part in this reflection. Individuals at risk of HD often come forward for predictive testing but do not pursue it once they have discussed the pros and cons: their considered opinion is very different to their initial one.[244]

"…something for me about this is making me think when I talk about …heart disease or a cancer gene or things like that…I'll have to see what our [patient information sheet] sheet says, if it talks about …some sort of neuro gene or dementia gene…because obviously something like that would have a massive impact." (HcpInt018 Genetic Counsellor)

What do patients want to know?

Although the patients I interviewed all wanted to be informed about IFs in general, this did not necessarily mean that they wanted all IFs to be reported back to them. Indeed participants showed a range of opinions in what types of IFs they would want to know about.

"Tell me everything"

Some participants indicated that any genetic information about themselves or their child would be of interest to them. This included IFs and variants of uncertain significance (VUS) as well as the diagnostic test they had come for.

"Knowledge is power"

Participants who indicated that they would like all IFs fed back, thought that information in its broadest sense was a good thing and could see little merit in withholding certain types of information. They wanted information first and then would decide how to deal with it:

"If I was going to have a broader testing done…then I'd probably want to know what all the results were, just because I'm curious really and would deal with whatever the outcome was." (FamInt001 Patient)

"No, I'd want all of the information, because things change all the time, and if you've got the information, then you can show that to any doctor that you might meet in the future, as opposed to relying on records being passed properly from one person to the next…..And so, no, I would expect to get a detailed report and then what I chose to do with it would be up to me. But, so I'd want all the information." (FamInt007 Mother)

Participants who demonstrated an interest in receiving all possible IFs considered themselves to be information-seekers, valuing information as useful and empowering, and thought any information the HCP had should be passed to them. They believed information could lead to interventions either now or in the future, and that they would have access to these interventions through having their genetic information:

"No…it doesn't bother me and truly, because I just feel of knowing what I could possibly get, have, would be…I think to me that's a positive thing, because you would want to know, well I just want to know…Totally, I would definitely want to be told…I would much

prefer to know [about IFs]. Some people wouldn't, but I'd want to know. I wouldn't care how many tests that I had…I would just want to know." (FamInt005 Patient)

"…personally I would just say, well look just tell me everything, because I'd want to know. I think nowadays…the more information you've got the better it is for you generally isn't it?…we are being able to treat people for things that we couldn't treat people for…medical science has moved on hasn't it, so I suppose nowadays you'd say well yeah I want to know, because we're always being told the earlier you are diagnosed the better it is for you, because we can then treat it rather than get to a stage where it's too late, so personally I would want to know everything." (FamInt006 Father)

Patients held different views on what they considered treatable to mean. For some it meant curable or preventive interventions and for others it included surveillance or lifestyle changes that reduce the likelihood or severity of the condition. Even if not available now, some of these measures could be relevant in the future:

"…yeah I'd feel I would want to know, because in hindsight if that did manifest and turn out to be what you had expected it, from the testing, then I'd feel like I could have reversed something or I could have had some treatment for it." (FamInt012 Mother)

"I'd still…want to know because it's all about getting yourself in order and doing all your housekeeping stuff, so I would probably, I personally would want to know." (FamInt011 Father)

Participants had an unrealistic view of what their genetic test result could say about them and this influenced their request to have all IFs disclosed. This could in part be due to inadequate explanation provided by their HCP, as well as the widespread deterministic view of genetics that is portrayed in the media and generally presents genetic test results as clear-cut. 'Everything' would include findings of uncertain or unknown clinical significance and so the actual usefulness to patients is questionable.

I asked patients about their views on receiving these uncertain results and many of those seeking all genetic test information also wanted uncertain results disclosed. This might be because they did not appreciate that uncertain results tend not to be followed by any clinical intervention, and might end up being re-classified as normal variation, seen in the

population. One participant gave her perspective when I asked about sharing uncertain results:

Interviewer: "And I don't know what your thoughts are, if you think we should wait until the information is very clear or whether you should tell people as you go along; 'well we may have something, we might know in a few years' time' and that sort of thing?"

Participant: "I think people knowing as they go along is so much better. I mean I know people worry, people always worry about something like that, but if they have… they understand that there could be something, and the testing to me is such a positive, it's, I think it's such a good thing." (FamInt005 Patient)

Overly optimistic views about the clinical utility or predictive powers of genetic testing are perhaps the main reason this group wanted to know 'everything'. It is a challenge for the HCP to ensure that patient expectations of what a genetic test can deliver match current reality.

"Tell me some things"

A number of patients expressed a wish to be informed about some, but not all, IFs and participants who had not had an IF were more cautious about receiving 'everything'.

Some patients suggested that they should be able to make decisions about IFs they may not want to be told about. However one participant summarised the challenge of making these decisions if this option became available:

"It is complex, but you can probably frame it in simple terms, so there's a complete spectrum, a complete grey area of all sorts of permutations of things that can happen, but the extremes are probably quite well defined where you don't find anything or you find something absolutely awful that you didn't want to know and a few examples in between and then people can think well I am most like this kind of attitude and that's probably about as good as you're going to get, because people can't possibly be expected to understand all the possible connotations of such an advanced test." (FamInt008 Father)

Some patients distinguished between categories of information they would want, for example treatable conditions and ones they may not wish to know:

"If it's something that something could be done about then yes I think I would want to know about it." (FamInt001 Patient)

Where there were no available treatments, patients were more likely to consider that they may not want to receive such IFs:

"…if it's something life-threatening and something can be done to prevent it, maybe you should, but if it's not, is it right… to worry them with that as well? I mean it's a bit like in life, we never know what's around the corner, and in some ways it's a good job we don't. You just deal with what's thrown at you at the time." (FamInt010 Mother)

This group of patients were concerned that a blanket disclosure policy to report all IFs could cause anxiety, especially if no treatment was available. They queried the benefit of passing on this type of information. :

"I wouldn't want too much information, because then I think I might be looking for something that may not happen or occur." (FamInt012 Mother)

They were also more concerned about the effect of living with a disease risk that they had previously been unaware of:

"…there is another side of me that says well you've just got to get on with life anyway…there is a risk that you end up just spending you whole life worrying about things…if you've got a risk of having all of these, and you just spend your life worrying about [them]…I personally think that …worrying about things can do you more harm than getting those things sometimes." (FamInt001 Patient)

Whilst there were no patients that would not want to know about any IFs at all, many shifted during the course of the interview, from wanting to choose all the IFs they are told about, to a realisation of some of the potential difficulties in achieving this level of decision-making in practice. This is likely to be reflected in clinical practice; again illustrating that considered decisions may be different to initial ones:

"I suppose getting upfront, getting a clear view from people as to whether they want to be told or not, rather than waiting until you've found something out and then deciding if they may want to know… But then people change their minds." (FamInt001 Patient)

"What about family members?"

Another reason patients were uncertain about what they wanted to know is that they realised a test result in one person might have relevance for family members. Although a

patient could decide not to receive an IF, they questioned whether it was fair to potentially decide on behalf of their relatives:

"I think the family should have some idea about it really… it would be a terrible situation if one of these siblings did get a disease that could have been prevented by some information, so I…would certainly be in support of that information being given really to the families." (FamInt006 Father)

Discussions about familial implications of IFs also included risks to future children and what could therefore be disclosed to potential parents to inform them of reproductive risks:

I: "And do you think people should be able to opt out of certain things, for example, well this test might show other things but I don't want to know if it's something related to dementia or related to cancer?"

P: Yeah. Yeah, I think so. That could be, that, on the face of it, it sounds very irresponsible, especially if they've got children it could be passed on to, but actually , I quite like the idea of you being able to keep your own sanctity and your own information and your own, you would make your own decisions, so I think yeah, if you could tick a box to say I don't…Look for this and if you find something else I don't want to know." (FamInt004 Patient)

"And I know it's difficult. And it makes me feel I can't quite get my head around the idea of that, you would choose to remain ignorant about a condition that your child might potentially pass on to your grandchild. So you're choosing that someone else remains. You've got the right to choose whether you personally want to know, but I don't think you've got the right to make that decision about anybody else. It's a bit like an impossible dilemma." (FamInt007 Mother)

"Tell me everything about my child"

"It is my right and responsibility"

Interestingly, parent participants were more unanimous about results they wanted relating to their child than about the results they would want for themselves, and a language of 'rights' was used more often than for personal disclosure:

"I look upon the results as being the property of the patient I think, so ownership of the results being with the patient…until the patient has the capacity to make an independent

decision about what's done with that information…that information goes with the family, but the family shouldn't have the right to opt not to receive it." (FamInt007 Mother)

That said, the issue of rights was often merged with, or attributed to, a sense of responsibility towards their child, and the desire to decide how the information was managed and shared with their child later. This is consistent with other studies that have asked parents for their views on the genetic testing of children.[245-248] Despite multiple international guidelines that recommend that the genetic testing of children should only be done at a time of clinical utility, rather than to facilitate parental preparation, patient and public attitudes suggest that immediate clinical utility plays little part in requests for such testing.[248]

Parents considered children vulnerable and their role as a parent was to protect and look after them. One of these roles was to look out for any health issues and this included possible future health issues. They wanted as much information as possible on about their child as soon as it was known so that they could make decisions on behalf of their child:

"I think that that information then belongs to, it's the patient's information, so the parents are looking after [the child] and, well it's the parents, and it's not for the professionals to decide what's in the best interests of the child. That's for the parents to decide." (FamInt007 Mother)

As such, parents viewed genetic test results much as any other information or decisions they were charged with making for their children. *"…there are lots of other decisions that the parents make for a child. In that respect…whether or not to have a child vaccinated, for example"* (FamInt001 Patient).

They did not tend to think that future utility might mean deferring testing could be better for a child. Parents were concerned that if a child found out later about information pertinent to their future health, and they had not requested or accessed this information at the time of testing, this would be viewed as irresponsible:

"*Because the child, well they're also taking away the choice from the child of being able to do something about it aren't they? If they're saying that no, we don't want our child to have the test, because we're taking away their choice of knowing or not knowing, they've also taken away their choice of being able to do something about it. I mean how could you, how could possibly think that your child, your young girl could possibly have breast cancer at later in life and not tell her about it."* (FamInt013 Patient)

They did not tend to consider the opposite, where a child might be unhappy in the future that their parent had accessed predictive information about them and thus removed their choice as an adult as to whether they wanted this information or not.

Parents were optimistic that treatments or prevention strategies might become available in the future so if they were aware that their child was at risk of developing a particular condition, they could access interventions as they were developed. Without this genetic information parents would be disadvantaged:

"…if I was a parent I'd want to know, I would definitely want to know if that was my child, because if that child has got some chance…it might not be now, if the child's only ten, but when the child is twenty, there might be things in place that would be able to help, so I'd definitely want to know that." (FamInt013 Patient)

Much like patients' views about IFs and their health, parents believed that having genetic information could direct future investigations if their child was unwell, as possible diagnoses are already known and unnecessary investigations might be avoided.

Parents had some doubts about the appropriateness of feeding back all IFs at the same time, with some suggesting that result disclosure should be age specific. All patients believed that results with immediate clinical utility should be disclosed immediately, regardless of age. Otherwise, as a child neared the age when IFs would become clinically relevant they (or their parents) could then be told about them. As IFs were not the primary reason why parents had brought their child to clinic, parents would not be expecting these results, so it would be possible to defer informing them:

"So yes if that's something that then becomes more appropriate as he gets to that age, then that's maybe something they can then think about discussing…I think you don't need

to bombard with every single thing, because there are going to be some things that aren't really particularly relevant at that point in time." (FamInt002 Mother)

This may be another example where a participant's initial decision may not reflect their considered one, where a 'need to know everything' position may shift once a parent has reflected on how it may be to manage knowing about a result in their child that has no medical relevance for some years.

Testing children at birth/in early childhood

Some parents went further and advocated whole-genome sequencing of children as part of a national new born screening programme. These parents believed that information generated by such technologies would prepare them for the potential health problems their child could develop in the future:

"I think it should be the parental choice, not enforced upon them, but if they want the full genome sequence of their child on file, if they want to know everything that could go wrong…I don't see why that should be prevented, but it's the choice of the parent." (FamInt008 Father)

Another parent believed that WGS would indicate everything that could go wrong with their child's health in the future:

"Which is why… when every child is born, I would put them on the DNA register and I would then test them for genetic abnormalities…because we have that technology, it's like you don't buy a car without checking it out do you? You don't, [you] get someone to make sure that it works and it's functioning and that it's all, so you, so you want to know that that car's safe and sound in later life and it's not going to fail on you, and why you wouldn't apply that, if you've got the technology to do that with a human body why you wouldn't want to do that?" (FamInt011 Father)

This is an example of patients being overly optimistic about how genetic/genomic technology will uncover information that will enable them to fix current or future problems.

However, some parents realised potential disadvantages to finding out future risks in early childhood and in how this information would then be managed over a number of

years; for example, a poor parent/child relationship might lead to IFs being revealed, during an argument:

"…now there are some really bad parents out there...I had a difficult childhood, and it wouldn't surprise me if my mum, out of spite, just shouted out, it's alright, when you're twenty-one you're going to die of breast cancer…and if you've got parents like that in society, then to give them knowledge of certain things is bad…" (FamInt009 Mother)

Another went as far as calling for safeguards so that if parents did not act in their child's best interest they would be accountable for either disclosing a result inappropriately or not disclosing it when it became clinically relevant for the child.

Others expressed concern that knowing future health risks of children could make them worry more every time their child was unwell:

"*So you can almost suffocate the child because they're so worried that this…test result that happened when they were like six is going to affect their life when they are in their forties. I don't think that's fair on a parent. I think they should just grow up. And in some ways it's almost down to an argument, is science helping?"* (FamInt009 Mother)

"My HCP can decide to tell me"

Interestingly, whilst patients thought they should be able to choose the types of IFs they were told about, if this information had serious implications for the health of their children or other family members, then they thought it should be shared regardless of the choices the patient had made. They did not indicate who should give this information to other family members, the patient themselves or a HCP.

Despite patients believing that HCPs might (justifiably) decide that they want to inform a patient of a particular serious result, they did not believe that HCPs were able to do so, if the patient had requested otherwise:

"Well I mean if I was a doctor I'd want to tell them. I think I'd really, really want to tell them, but with this, if the patient signs to say they don't want to know, then you can't tell them can you and a doctor can't say if they've said no, and the doctor can't say, but I would, if it was me I'd want to know." (FamInt013 Patient)

This view could imply that benefit to family members trumps an individual's decision not to know about IFs, and so is an interesting observation about a development that is often described as the 'personalisation' of medicine.

HCPs: "What should I disclose?"

What information should be looked for?

The decision on what IFs can and should be disclosed to patients is not straightforward; it will depend first on what is looked for and reported by the laboratory, what filters, if any, will be applied and what analysis, interpretation and reporting the laboratory is planning to do.

Reducing disclosure options

A number of HCPs discussed whether laboratories should report every abnormality found back to clinicians or limit the data analysed, reported and disclosed. Doing so, would thus limit the numbers of IFs generated, and would moderate patient expectations about the types and potential significance of results they receive. One HCP proposed that when using exome sequencing the best approach would be to "*generate an exome sequence and then ask specific questions of it…trying not to generate them [IFs] rather than the trying to deal with them afterwards"* (HcpInt015 Genetic Registrar). This approach would avoid patients and HCPs having to make disclosure decisions.

Some HCPs believed that filtering tests in this way could restrict the generation of potentially useful clinical information about the reason for referral or incidental to it, and that it could be difficult for a laboratory to set up tests in this way. Both clinical and scientist participants did, however, feel more comfortable with applying filters to avoid IFs, rather than potential IFs being seen but not sequenced or reported. Two HCPs expressed their views:

"I think it's hard to put the onus on the lab, I think they are then holding the responsibility for patients who they are quite removed from and I can imagine that they might feel…very uncomfortable with that, they hold that knowledge but they're the keepers of it… Either you only look for certain things or you only analyse certain data and I think I'd feel most comfortable with one of those options." (HcpInt026 Genetic Counsellor)

"…If it's cheaper to do [sequence] the whole thing [genome] you could then target your analysis… [to] what you think is relevant…otherwise the knock-on costs to the NHS of finding things that you don't know the significance of but you feel obliged to follow up and the counselling involved and the extra clinics and it's actually going to just be exponential." (HcpInt032 Clinical Scientist)

While acknowledging the practical and ethical challenges associated with generating IFs, HCPs and patients both believed that avoiding IFs was not the answer. IFs could represent important clinical information that the patient and their family members could benefit from.

Opportunistic searching for IFs

Rather than taking steps not to look for IFs, there has been an alternative view that when doing WES/WGS testing, it would be feasible and possible to actively look for IFs. To date, IFs have been stumbled upon during the course of testing and when discovered usually reported back to the referring HCP. There is now the option to consider whether laboratories should set up testing in such a way that it can specifically look for a defined list of IFs, with the patient informed about the genes that will be analysed. Incidental findings that are unexpectedly discovered may or may not be disclosed, in addition to the conditions on the list.

During the time of patient interviews the publication of the ACMG recommendations fuelled the debate about whether labs should actively look for a defined list of IFs (for example, those amenable to intervention).[139] Overall, patients were broadly supportive of this approach confirming their generally positive attitude towards having information:

" *I think it's such a good thing to do because when you're testing for one thing, why shouldn't you test for something else that could potentially be part of your life when you're…thirty or forty years down the line. I think that's such a great thing to do."* (FamInt005 Patient)

Many HCPs discussed the possibilities and limitations associated with WGS. On the one hand they were positive about the potential of genomic tests to identify clinically relevant information that might otherwise not have been available to the patient, but on the other

hand concerned at how they would manage the significant number of uncertain results that would be generated. One HCP commented that:

"…I think we're completely unprepared for the tide of data coming our way." (HcpInt029 Consultant neurologist)

"What is my threshold for disclosure?"

What does treatable mean?

HCPs were unanimous that IFs indicating a serious treatable condition should be disclosed. They considered it their clinical responsibility to share such results and that it was in the patient's best interests for them to do so:

"… [and if a finding of] Long QT or sudden death genes [was made], well there are things we can do, we can reduce those risks and…there is a strong incentive to one might say to disclose under those circumstances." (HcpInt019 Consultant Geneticist)

"…Assuming that it's a condition that's important to know about and maybe even if something could be done or needed to be done, then I would discuss it with the patient." (HcpInt029 Consultant Neurologist)

Although HCPs inferred that they would override patient choice in some circumstances - in order to disclose these serious treatable conditions - they were less clear about what constituted a serious condition or an effective intervention. For example, BRCA1 gene mutations are serious in that they confer a lifetime risk of breast and/ or ovarian cancer for women of up to 80-90%. They also have effective interventions available; for example risk reducing mastectomy and salpingo-oophorectomy, known to reduce lifetime risks dramatically. However, HCPs did not agree whether a BRCA1 mutation discovered as an IF should always be disclosed because their perceptions of what was serious and treatable differed:

"…maybe in the future we'll have a list of highly, particular genes like BRCA1, BRCA2…that we could come up with which would be interrogated by a side pipeline where we could say…we know that if you have this mutation then your family has [BRCA]and we know what to do with that information, so that would be an incidental finding and it would need to be included in the consent process, but yes there would definitely be an argument

for saying there will be a medical benefit to making use of these particular incidental diagnoses." (HcpInt015 Genetic registrar)

"…but BRCA1, people react to it very differently. Some say I just don't want to know, I'm going to take my chances thank you very much, and other people, no I want to know now, and I'm going to have bilateral mastectomies, tomorrow if I'm positive…." (HcpInt020 Consultant nephrologist)

HCPs also discussed conditions where no treatments were available that would prevent, cure or improve the disease trajectory and did not consider that it was necessarily appropriate to disclose such results. Many used Huntington's disease as an example. Their main rationale was that in their experience, many patients at risk decided not to find out if they had inherited it and it was not likely to be different for this cohort of patients:

"…people when they go for a predictive test for something that there isn't a cure for, like Huntington's for example, they are talked through all the possibilities, the pros and cons, and many of them drop out because they realise they don't actually want that information, but how can you decide that for someone when it's already done and it's there and the result is there?" (HcpInt016 Genetic Counsellor)

One difference with conditions such as these being discovered as an IF, rather than through a predictive genetic test, is that the patient is unlikely to know much about the condition or have any experience of it in their family. This may make it more likely they will request that these conditions are disclosed, as they are uninformed about the potential downsides of finding out. HCPs were more cautious at sharing such results; they would not have had the opportunity to specifically counsel the patient and were aware that not all their patients known to be 'at risk' proceed with testing.

"What are the implications if I don't tell"?

Another reason given by HCPs for disclosing IFs was that they felt uncomfortable with results being reported to them and then not passed on to patients. HCPs were conscious that decisions to withhold IFs, even if they were made out of consideration for the patient, could be construed as paternalistic. They felt, therefore, that decisions could best be made 'up front', so that both parties were clear about the information that would or

would not be shared. HCPs realised that such decisions could often not be considered in any informed way because to some extent they would always be too abstract until an IF was there to know. Because of this difficulty, HCPs talked about restricting laboratory tests so that IFs were not generated at all. Overall HCPs wanted to be able to apply their clinical judgement as to whether to disclose or not, but found this very difficult:

"I think it's dangerous to withhold information and I don't think you'd ever want to be in the situation where you knew that your healthcare professional knew something and you weren't informed about it at the time. I think however difficult it is to address that when it comes, I think it's worse to withhold it." (HcpInt009 Genetic Counsellor)

Others felt that patient trust in their HCP would be eroded by any attempt to withhold information:

"I think there's a trust that we give them information back….I think they'd be quite concerned if we were withholding information from them. I think what's difficult is we know we're always withholding information to some degree because we have the DNA sitting there and in theory we could test them for all sorts of things… and we think there is a risk as we're doing tests that open the doors around that sort of area of trust that we manage that well, within the NHS and with individual patients." (HcpInt011 Genetic Counsellor)

Telling parents results about their children

HCPs were aware that international guidelines do not support the genetic testing of children for adult-onset conditions unless there is a medical benefit in doing so.[115,245,249,250] As genetic testing in children could reveal IFs indicating a predisposition to adult onset disease, HCPs questioned if these results should automatically be disclosed to parents. But if they did not, how would this information be shared at a later date, when it became clinically relevant? The other argument they raised was that, although not (medically) relevant for the child for some years (decades perhaps), such findings in a child could indicate possible risks for adult relatives now and this was an argument for immediate disclosure:

"…I mean you wouldn't test a child normally for that [BRCA], but…to unearth a BRCA mutation in a family would benefit the rest of the family potentially." (HcpInt002 Consultant Geneticist)

"It depends on what patients want"

Patient choice

Both patients and HCPs held a general view that providing a choice about the IFs that are fed back is preferable. Is this view paying lip-service to the notion of patient choice as can considered choices really be made at this stage? My clinic observations suggested views supporting patient choice had not yet had any real impact on practice. Box 5 illustrates that while the possibility of an IF was often raised, no detailed discussion followed:

Box 5: Discussion with both parents of a young baby with deafness (FamOb017)

Introduction of genetic test (including consent)

Testing so far in the child was targeted testing related to deafness (negative results). Consultant said that it was "worth doing" a "highly specialised chromosome test." The consultant explained the test as follows: "This test can see if little bits are missing or extra. Sometimes the test finds things and sometimes it doesn't, it is a new test. Sometimes we find things we are not sure of and will then test the parents to see if either of them has it [to help interpretation of pathogenicity]." The consultant then explained, "...and sometimes we find things we are not expecting at all". No further explanation of IFs was given, no examples were used to illustrate what these could be and no discussion with the parents to establish their views on receiving this type of information and whether there are some IFs they would want to receive and others they would not. No discussion took place about the possibility of generating results indicating a predisposition in their child to adult onset disease and whether they would be interested in receiving this information.

A number of patients believed that HCPs should ask them what IFs they would or would not want to be told about when arranging their genetic test(s). The two main reasons they gave for this were firstly that not all patients may want to receive the same information and secondly that HCPs should not be solely making decisions about findings that are subsequently disclosed:

"I think they [patients] should be asked what they want. So I think they should be asked that question…So rather than leaving it to a professional to just arbitrarily decide what you are told, I think you should be sat down and say we're going to do this and you've got three thousand conditions…and if any of these things are flagged we'll let you know." (FamInt011 Father)

HCPs were supportive of this view but were not currently having a discussion with their patients about the IFs they did or did not want to receive. This does not necessarily indicate an unwillingness to do so, but rather may reflect the changing field. Genomic tests are being rapidly integrated into clinical practice, prompting HCPs to review their practice, identify what may need to change and make modifications in due course. While agreeing in principle with implementing this discussion into practice, HCPs talked about the challenge of being able to elicit patient preferences in any meaningful way in the clinic or on the ward:

"But it would be very hard for somebody to think about what they would like to hear and what they might not want to hear." (HcpInt010 Genetic Counsellor)

How can HCPs find out what patients want?

Participants were asked to talk about options they had considered for seeking patient views about IFs. They were also asked for views on a number of proposals that had been put forward by others as a way of eliciting patient choices.

By ticking boxes for individual conditions

A number of patients were in favour of tick boxes on forms, where a list of possible IFs would be given and patients asked to indicate conditions they would like to be told about by ticking each box:

"Well I think the alternative is to not give people the choice, which is probably worse…let's say there was a hundred different things you can test for, half a dozen of which are life-threatening and the rest are more trivial, and you can tick one to a hundred what you'd want to get back. As long as each individual person has that choice I don't see an ethical problem with that and I don't see a practical problem with it. It's down to each individual whether they want to know. I think I'd probably tick them all, but I could imagine that some people wouldn't tick any of them and would just rather be completely ignorant." (FamInt008 Father)

A few HCPs agreed:

"…what they can do is they can tick all the different genes they want tested, so you can basically; it's like a pick-and-mix almost." (HcpInt016 Genetic Counsellor)

Although this appears a pragmatic solution to providing a mechanism for indicating choices quickly, HCPs also worried that it would not allow for addressing the complex nature of results, including VUS and PIFs. They thought that if uncertain results arose it would be very difficult to know how to deliver the patient's yes/no option.

HCPs were concerned that patients would not be able to make informed decisions about the IFs they wish to receive because they would not have adequate information about or experience of the conditions included in the lists. HCPs did not generally believe that providing patients with a list of all possible IFs was the best approach. The list would be overwhelming and this comprehensive presentation of all possible choices may in fact lead to less choice for the patient:

"But it would be very hard for somebody to think about what they would like to hear and what they might not want to hear." (HcpInt010 Genetic Counsellor)

"And it is difficult, because if people don't know what it is that they're being asked to know, it's difficult to choose not to know something when you don't know what that thing is." (HcpInt028 Consultant Geneticist)

Without accompanying detailed information, discussion and ongoing re-contact to check patient wishes and understanding, it is questionable if this approach facilitates meaningful choices for the patient.

By ticking boxes for categories of conditions

Another approach that had support from some participants was the categorisation of IFs, for example, life-threatening and treatable conditions or carrier status risks, with patients choosing the categories of conditions, rather than individual ones, they would like to receive:

[Categories are] easier for us to imagine, because we can start thinking about the things that might fall into those categories." (HcpInt026 Genetic Counsellor)

However, HCPs are likely to categorise conditions differently; for example one could classify a condition as serious and treatable and another as not serious and treatable. Also, for HCPs to be able to discuss each category in sufficient detail for patients to be able to make a decision requires significant time and resources, which some participants also recognised:

"…so you've got your categories, so you've got the stuff that impacts you, the stuff that impacts your wider family, you could have a treatable and a non-treatable list. So for the stuff that's not treatable, they don't want to know about it, or they're given the option not to know about it. If there's stuff that's completely treatable and manageable, then they might decide that they want to know about it. So you almost have different bandings of information, but you sit with them upfront…but that's really laborious and when you've got lots of routine testing going on, that would take forever." (FamInt011 Father)

By exploring possible scenarios with patients

HCPs discussed alternative ways to the pick-and-mix approach to support and involve patients in decision-making around IFs. They proposed exploring the possible outcomes of genetic testing, including IFs, with patients so they could then elicit their views about the different types of information that could arise and what IFs they would be interested in receiving. If an IF was subsequently found, then the HCP would have some idea if this was the type of information the patient would want. This approach would shift a limited discussion that focuses on individual conditions to one where the possibilities and limitations of genomic testing can be explored. This HCP acknowledged that while asking patients what they would like to know may be considered good practice, it is not feasible, as practically it is not possible and instead careful discussion is required:

"So I believe that very good information given at the beginning, about what you're planning to do and your limitations of what the test will show and say the idea that it might show something up, almost like would you want to know that…I think the difficult thing is that people can't answer that question practically, because they don't know." (HcpInt007 Genetic Counsellor)

HCPs make the decision on what IFs are disclosed

Instead of asking patients about IFs to be fed back, some HCPs called for a consensus amongst the clinical community about what should and should not be disclosed. With this

approach, patients would be informed prior to genetic testing about the possibility of an IF and told what IFs (or categories of IFs) they would be told about:

"I quite like the idea of saying well look we might find, if we find something of medical importance we feel duty-bound to report that back, and if the family say well hang on a minute, like what…if we'd found a gene that might predispose to something like breast cancer or bowel cancer, sudden adult death from a cardiac arrhythmia or whatever that we could do something about…and we set it in context for them as to what we might or might not find…" (HcpInt019 Consultant Geneticist)

Patients were not directly asked for their views about designated IFs being automatically disclosed. As most patients already had an expectation that HCPs would feedback any clinically significant results found with a proven intervention, it may be assumed that they would be likely to support this category of IFs being fed back. What is less clear is what patients would think about the IFs HCPs did not plan to return, but some patients may still want. Patients could continually worry that there is additional information they would like, but are not made aware of: *"…they don't do these tests and not tell you do they?"* (FamInt003 Mother). This discomfort comes from a belief that HCPs are deliberately not sharing pertinent information and while on the face of it this might be true, this is often because they consider the information unhelpful at that time and not because of a wish to conceal it. This links to the patient views described earlier, that all knowledge is of use and therefore welcome. This suggests that HCP and patient cohorts approached the question of disclosure of IFs through a different lens. That is to say, patients seek all information as they believe it to have utility in some form or other while HCPs prefer not to disclose all information, believing that some of it will have limited (or no) utility and sharing it could be unhelpful.

In this chapter I explored patient and HCP views on how IFs should be managed in clinical practice.

Summary of findings

1. There was a wide range of opinions on how IFs should be raised as part of the consent process for genomic testing.
2. Although patient involvement in decision-making about IFs was deemed desirable, there was no consensus on how this should happen in practice, and no evidence of it taking place on a regular basis.
3. Parents thought they should be told about all IFs identified in their children.
4. Many of the views about choice and disclosure appeared to derive from a perception of genetic information as more deterministic and clear cut than the examples discussed and the reality of current understanding.
5. There was consensus that all serious IFs with an effective intervention should be disclosed, but defining what constituted serious, or effective, in particular examples was more problematic.
6. Both groups believed that the patient should be involved in decision-making about receiving other types of IFs but were uncertain how this could best be operationalised that did not result in tick box exercises.
7. Some HCPs thought there should be a nationally agreed list about which IFs should be reported but acknowledged this could not include all possible IFs and would require regular review.
8. Some HCPs proposed limiting the chance of finding an IF by applying filters to the genomic search. However patients thought this would limit the full potential of any genetic test.
9. It was clear that no single approach appeared to solve all the potential issues of finding IFs in genomic analysis.

There was a lot of variation in the type of IFs patients (or patient's parents) wanted to receive both between patient and during the course of interviews. Some limited the types of findings they would want to certain conditions or certain severities, yet others wanted to receive IFs that would not be considered to have clinical utility. In line with other studies, patients believed these findings would be helpful with life planning, reproductive choices and behaviour change.[120,143-145] In part this might be because life planning and using information to make behaviour choices is difficult to include in clinical utility measurements, but it also likely reflects some belief that the information will have a utility at some point.

This is echoed in research about VUS. A number of studies with parents who had received a VUS following aCGH testing in their child found that parents placed more emphasis on using knowledge about the VUS than HCPs did.[251,252] Parents indicated utility in terms of considering future pregnancies, obtaining medical services and personal validation of their child's condition, things that did not have a clear clinical benefit but may indicate a social one. Parents considered themselves gatekeepers of health information about their child and that it was their right to be given this information. This is perhaps a similar view to that of parents who seek a predictive genetic test for an adult onset condition in their child.[245-248] The responsibility of parenthood may mean parents see themselves as needing to receive information about their child *before* it is of clinical utility.

However, in apparent contrast, and more evident during patient interviews than patient parent interviews, is that although patients wanted to be involved in decisions about IFs they also wanted to trust their HCP to communicate the types of findings they would want to know about. How this might play out in responsible practice needs further consideration and has interesting implications for the consent process.

Regarding the disclosure of IFs that patients do not consent to, HCPs said they would find it difficult to be in possession of IFs that could have clinical utility, and not inform the patient. Both groups thought HCPs would have a duty of care to disclose such information.

The potential benefit of IF disclosure to family members also led both groups to consider disclosure even if the patient themselves did not want it or were unlikely to act on it. Patients appeared to hold rather utilitarian based views about genetic information[253],

wanting the benefits of genetic information to the greatest number of people, even if this might come at the expense of not respecting the consent decisions of one person.

When potential clinical harm to an individual and/or family member can be avoided or acted upon, patients appear to accept an approach to disclosure such as Savulescu's" all things considered" value judgement approach.[127] That is, for doctors to "properly respect" patient autonomy and act as moral agents they must make evaluations of what their patient ought to do.

Key findings from this and the previous chapter formed the basis of the development of a questionnaire for HCPs, designed in phase two. The next chapter details this work.

Chapter 7: Phase two methods and developing the questionnaire

Phase two of the study involved developing, pre-testing and refining a survey questionnaire which aims to examine whether key findings from phase one of the research resonates with a representative and larger sample of UK HCPs who manage genetic testing. I adopted a cognitive interviewing technique (CI) to develop the questionnaire which was then pre-tested with a small group to check how the design worked in practice; identifying any outstanding problems, directing further refinements and establishing if it could successfully collect the information required. I paid particular attention to which findings from phase one was amenable to being explored quantitatively. Pre-testing refers to small-scale testing of particular components of the research and piloting is the process of carrying out a preliminary study, going through the entire research procedure with a small sample.[254] In this study pre-testing focused on the questionnaire design.

Following the pre-testing process, I undertook a review of the design to produce the final draft version presented in this thesis. During post-doctoral research, this version will be subjected to a substantive pilot, and further refinement, before circulation to a larger group of HCPs.

The survey has the following objectives:

1. To review whether incidental findings are currently addressed during the consent process when genetic tests are organised and, if they are, to what extent?
2. To ascertain HCP views on incidental findings and patient choice
3. To analyse HCP's experience of the implementation of whole genome technologies in clinical practice

Intended study design for future survey

In order to address its aim, the final survey will be constructed as detailed below.

The pilot study

Before the final circulation of the survey, I will conduct a substantive pilot with a small sample. The pilot will mirror the final study design and should therefore highlight any

changes required before the survey is delivered nationally. The pilot sample will be taken from one Genome Medicine Centre only (Wessex) with an aim to recruit approximately 15-20 participants, and I anticipate that pilot data will be sufficient to direct any final amendments.

Population

The intended population for the survey are HCPs who regularly organise genomic testing in their clinical practice. Many HCPs not working in the specialty of clinical genetics are now organising aCGH tests directly and with the introduction of the 100 000 Genomes project many more are beginning to refer patients for whole genome testing. The survey population will reflect this, including genetic professionals and paediatricians (the primary clinicians requesting aCGH) but also others, such as neurologists, immunologists, dermatologists and respiratory physicians who have been early implementers in the 100 000 Genomes project. A population target of 600 HCPs will be approached, with an aim to recruit 300 HCPs (50% uptake). This recruitment target is feasible in view of the rapid introduction and development of the 100 000 Genomes project over the next two years.

Sampling strategy

I will adopt a purposeful sampling approach [222] with HCPs who regularly organise genetic tests in their clinical practice. Eligible HCPs will be identified, contacted and recruited via the 11 Genomic Medicine Centres throughout England. The project lead for each centre will act as the primary contact for their GMC and disseminate information about the survey to HCPs within the centre. Initial contact with the project lead will be followed up by a visit to each GMC to explain the survey and organise distribution of the questionnaire. Snowballing will result from this approach as HCPs will identify colleagues who are also referring patients for whole genome sequencing.

Distribution method

The survey will be available as a paper copy and online. Contact details for HCPs who request genomic tests and are not present for the researcher visit, will be passed on by the local GMC and potential participants will be sent a copy of the participant information sheet and questionnaire. Consent will be assumed by completion of the questionnaire. A link will be provided in the information sheet if participants prefer to complete the questionnaire online.

Analysis

The questionnaire data will be subject to quantitative analysis and will result in (i) descriptive and (ii) inferential statistics that (i) summarise the responses of the sample and measures and (ii) infer from the data what the sample population think about the issues in question.

The remainder of this chapter will focus on the development and pre-testing of the future questionnaire. It will begin with a general overview of questionnaire design and the methods used for their development and then detail the particular methods used to develop this questionnaire ready for the substantive pilot and circulation to a larger cohort of HCPs.

Questionnaires: an overview

Questionnaires are a method of data collection which allows participants to respond to questions in a written and structured format. They enable the collection of information from a representative sample of a defined population in a standardised way, with an aim to generalise results to a wider population.[255] They are used extensively in the health care setting but designing a questionnaire that captures high quality data and can elicit a good response rate can be difficult.[210] The use of questionnaires in research therefore requires that careful attention is paid to the design stage and to the recruitment strategy.

Advantages and drawbacks of questionnaires

Aside from providing the means to collect generalizable data, questionnaires can provide participants with the opportunity to give their responses anonymously, unlike many qualitative data collection methods, such as interviews and observations used in phase one. Individuals, who might otherwise not want to join a study or express their views openly, might be more responsive to completing questionnaires. Indeed, responses from such participants may elucidate pertinent data (particularly if the study subject is sensitive) that would otherwise not be collected or only collected from a small number of participants. Questionnaires are usually relatively quick for participants to complete and can be appealing to people who might not have time available to participate in, for example, an interview. A questionnaire can be an economical way to collect data from a large number of people and are usually relatively straightforward to analyse, albeit this needs to be done carefully.[256],[257]

Questionnaires do, however, have a number of potential disadvantages. Depending on the way that they are delivered, they may exclude groups of participants, for example, individuals with impaired vision or literacy.[210] The researcher will often not know who has actually completed the questionnaire: was it the intended recipient or someone else? If the researcher is not present during completion they are unable to clarify misunderstandings the participant may have. Assumptions about the meanings of language and wording need to be explored during the design stage and pre-testing of the questionnaire is critical to minimise potential misunderstandings.[255]

Questionnaires can also be less flexible than other research methods, as there is less opportunity for participants to express their views in detail. While there may be free text options provided these do not allow for as much detailed discussion about a particular issue as, say, an interview. The closed question format of a questionnaire may restrict the depth of participant response and the quality of data may therefore be diminished or incomplete.[257] This could also be an appealing feature for some participants who do not wish to give detailed responses or are short of time.

Recruitment bias can be an issue and careful consideration as to how to minimise this is needed as part of any recruitment strategy.

In general, questionnaires tend not to be the research method of choice when little is known about the subject under investigation; qualitative methods which allow salient issues to emerge and to be explored in depth are more suited in these cases.[210] The purpose of questionnaire research is to generate data from a representative sample of the population under study and to make inferences to a wider population.

Use of validated questionnaires

Some quantitative studies employ already 'validated' questionnaires. One argument for their use is that they are already designed and have been through a rigorous testing process; another is that this allows for comparison between data sets within and across research studies.[210] However, their use is reliant on replication of research questions. There are existing examples of questionnaires that have asked HCPs (and patients/the public) about what IFs they would like/think should be disclosed in a hypothetical setting,[99,169,170] but none have asked HCPs about consent and disclosure practices or specifically about their current experience of managing IFs or how they could/should be

managed in the future. As my study uses MMR and the questionnaire aimed to test pertinent findings from the qualitative phase of the study, it was predictable that there would not be an existing questionnaire that could address the research aims.

Formatting and ordering of questions

There is a plethora of guidance on how questions should be formatted. There is general agreement that they should be short and focused; longer questions (over about 12 words) are acceptable if careful thought is given to them and may be required if the subject matter is particularly sensitive.[210] Different types of questions, scales and response styles produce different types of data and will affect analysis.[255] These include open and closed questions; questions that ask for numerical data; lists or category options; and ranking or scales/grids to indicate response. Structured response formats help participants respond more easily and help the researcher to accumulate and summarise responses more efficiently.[258] But, they can also constrain the respondent and limit the researcher's ability to understand what the respondent really means. In general it is usually considered preferable to avoid hypothetical, imprecise, ambiguous, assuming, double, leading or loaded questions as these types of questions can bias responses and the data the researcher wants to collect may not be captured.[258]

The format of questions is key as respondents can have difficulty with interpreting and comprehending questions which can result in them not following an instruction and failing to answer a question.[259] The process of pre-testing the questionnaire is used to establish if the format of questions is adequate and to identify any difficulties that can be amended.

A questionnaire may contain section(s) for free text responses enabling participants to expand on their more structured responses. Such data are often very useful but is less likely to be completed by all the participants and it can be difficult to interpret as it cannot be easily quantified and compared.

Most questionnaires start with easy, non-threatening questions with more sensitive questions included near the end of the questionnaire. This allows participants to have relaxed into completing the questionnaire making it less likely they will withdraw or fail to complete it.[210] The best position of demographic questions has been disputed: some advocate that they are best placed at the beginning of the questionnaire, as they are

often simple and straightforward questions; others suggest the end of the questionnaire is most appropriate so as to engage participants from the beginning with the focus of the questionnaire, and not put them off with questions that might be construed as intrusive (for example, age, gender, educational level).

Including a mixture of both positively and negatively worded items and carefully considering their order may minimise the potential for acquiescent response bias; that is, a tendency to respond positively to all questions.[255]

Maximising response rates

Questionnaires can be paper-based (handed back to researcher or sent by post) or completed online. The latter has become more popular because it is often cheaper and quicker to administer questionnaires in this way. In order to maximise the response rate the method of distribution does need to be considered. One study that analysed response rates from the two modes of delivery found that, from nine studies (on teaching methods) included, the response rate for paper-based surveys was 56% against 33% online.[260]

There are a number of possible reasons for this: online surveys are often more widely distributed - perhaps with less consideration as to the recipients - because it is easy to do so, resulting in a more disengaged sample. Paper-based questionnaires might engage the target audience more, resulting in higher response rates. Online invitations to participate can easily become embedded in a full inbox. Strategies to increase online response rates include: reminder e-mails, extending the period of time to complete the questionnaire and ensuring the researcher reaches the target audience. The final version of the questionnaire in this study will eventually be distributed via professional mailing lists and purposeful sampling. For the pre-test phase, I used a paper-based format, completed face to face as I wanted participants to engage with both completing the questionnaire and assisting with the design.

Methods for developing questionnaires

A key component of the development of a questionnaire is pre-testing. The aim of pre-testing is twofold: first to improve content and structure to ensure validity and reliability; and secondly to increase the response rate.[261] There are a number of different methods that can be used for pre-testing, including peer review, focus groups, CI and piloting. These all share some features and overlap to a certain extent:

Peer review

This involves enlisting experts to comment and review the questionnaire design and administration process. While peers will often provide informal feedback on the design as it evolves, a more formal process of review can also be instigated. This can be undertaken by experts in questionnaire design, in the subject matter, in questionnaire administration and in computer based systems.[212] They can review specific aspects of the questionnaire based on their own experience/area of expertise. Early input into design and administration procedures is recommended before too much time and energy is put in by the researcher, as significant change once peer review has taken place may be required. Peer review can form an early stage of pre-testing and can be useful prior to CI and piloting.[212] In this study my supervisors provided an initial peer review as they had significant experience in the subject matter and some experience in questionnaire design and administration.

Focus groups

Focus groups can be used to facilitate questionnaire design with researchers generally using either focus groups or CI but rarely both. Generally focus groups are used to investigate topics that are to be included in the questionnaire, while CI is used to develop and evaluate specific survey questions.[212] In this study general themes had already been established in phase one and so focus groups were not considered necessary.

Cognitive Interviewing

CI is a qualitative method used in questionnaire development. Its overall aim is to understand how respondents perceive and interpret questions and to identify potential problems that may arise.[262] It is helpful to identify problematic questions that may elicit response error. The CI method, developed by Gordon Willis, involves conducting a iterative process: questionnaire drafting, interviews and expert panels.[262] It aims to help the researcher to understand the questionnaire from participants' rather than just from the researcher's perspective. In this respect, participants chosen to take part in the CI process should usually match the characteristics of the proposed final sample.

CI is a method that can test content validity in health care research.[262] Addressing issues of content validity is important to ensure confidence in research findings and to achieve consistency about what is being measured across respondents.[263] CI helps to identify

ways to reduce sources of measurement error (where the response provided differs from the real value) and primarily response error (where error is introduced into the study due to respondents providing untrue or incorrect information).[212] It is founded on Tourangeau's model of cognitive theory; he outlines four actions that respondents use to answer a question and these are:

- comprehension of the question
- retrieval of the necessary information from long term memory
- making a judgement about the information needed to answer the question
- responding to the question[264]

Unlike other means of pre-testing, CI aims to address all four of these actions to enable the researcher to view the questionnaire from a participant's eye view. For example, piloting can identify issues relating to comprehension of a question but is less likely to demonstrate how participants make a judgement about the information needed to answer the question.

Drennan et al's literature review examined the process of questionnaire design and how CI can be used to reduce sampling error and increase questionnaire response rates. They concluded that CI is a positive addition to the design process and is most valuable in pre-testing questions that are complex, sensitive and intrusive and for specific groups for whom a questionnaire may prove difficult (for example, children and adolescents).[262] The subject of this questionnaire, asking HCPs about their views on the management of IFs in clinical practice, is complex and both ethically and clinically challenging and, because of this, I adopted CI as part of my design process.

I was particularly keen that questions were worded carefully to ensure that additional difficulties that stem from ambiguity, length or choice of words were minimised and could capture the nuances of the issues I was researching. Of course, it is important to remember that decisions about changes made during the design process are ultimately down to the researcher and that the resulting questionnaire can still include questions that a future participant finds confusing or difficult to answer, but the aim of the process is to minimise this possibility.

CI is usually undertaken prior to the questionnaire being administered in the field but can be carried out at different stages in the process. The aim is to ensure, through

standardisation, that respondents understand and respond to the questions in the same way. Collins presents a model of standardisation where:

- All respondents understand the questions in a consistent way
- The questions are asking for information that respondents have and can retrieve
- The wording of questions provides respondents with all the necessary information they require to be able to answer the questions in the way required by the researcher[261]

CI enables the researcher to identify whether problems with a questionnaire are ones of comprehension, processing or communication.[261]

One criticism of CI is that it is overly subjective (both its process of interviewing and analysis) and artificial.[262] The charge is that CI creates a false environment and participants are likely to be impacted by having a researcher present. This would include individuals changing their behaviour in response to the presence of a researcher, working harder or answering a question they might skip when completing a questionnaire.[265] Retrospective interviewing could reduce this effect as the researcher can probe the respondent once they have finished filling in the questionnaire. The issue is that a researcher's presence, observing the participant, means that the setting is not representative of the final situation. Whilst I take this point, the aim of the interview is to develop the questionnaire, not to generate quantitative data to analyse.

A lack of theoretical grounding and the subjective nature of analysis, without the application of a theoretical framework, has also been raised as an issue with the validity of the CI process, as it can generate large volumes of narrative data.[266] However, this can be seen to be linked to criticisms mounted against qualitative methods in general, which I have dealt with elsewhere. Another issue is that the process may discriminate against less articulate respondents who find it difficult to verbalise their thought processes and may be less inclined to participate in the first place.[261] This was less of an issue within my cohort as all participants were from the same professional group.

During an interview, where a participant in the CI will complete a draft questionnaire and discuss the process with the researcher, two specific techniques are employed: think-aloud and probing; their features are summarised in table 21 below:[261]

Table 21: Key techniques used in CI (Adapted from Willis)[212]

Think-aloud	**Probing**
Respondent driven	Interviewer driven
Lower burden on interviewer as respondent does most of the talking	Lower burden on respondent as respond to interviewer asking questions
Can make the interview more difficult for the respondent	Can make the interview easier for the respondent

The overall aim of probing is to elicit a respondent's understanding; it can include both pre-scripted (probes used in pre-determined situations) and unscripted (probes used at the discretion of the researcher and spontaneously throughout the course of the interview).[262] Probing is particularly useful with self-administered questionnaires as the process can identify items that need changing, which the participant would not necessarily have articulated out loud without being asked. Probing can be carried out whilst the questionnaire is being completed or afterwards.

Think-aloud is where the researcher asks the participant to say what they are thinking as they go through the questionnaire. It is usually carried out when the participant is filling out the questionnaire. The researcher can also observe relevant behaviour and when it happens, such as turning pages back and forward to re-read questions, skipping questions or non-verbal gestures that can indicate uncertainty, for example, frowning. One potential issue with think-aloud is that participants may feel uncomfortable about articulating their thought processes and opinions about the questionnaire 'out loud' and the process may not reflect the issues they experienced. Moreover, taking part in a process of thinking aloud can, in itself, affect how participants work through the questionnaire, indicating problems with the questionnaire, when there is none, and potentially missing others.[259]

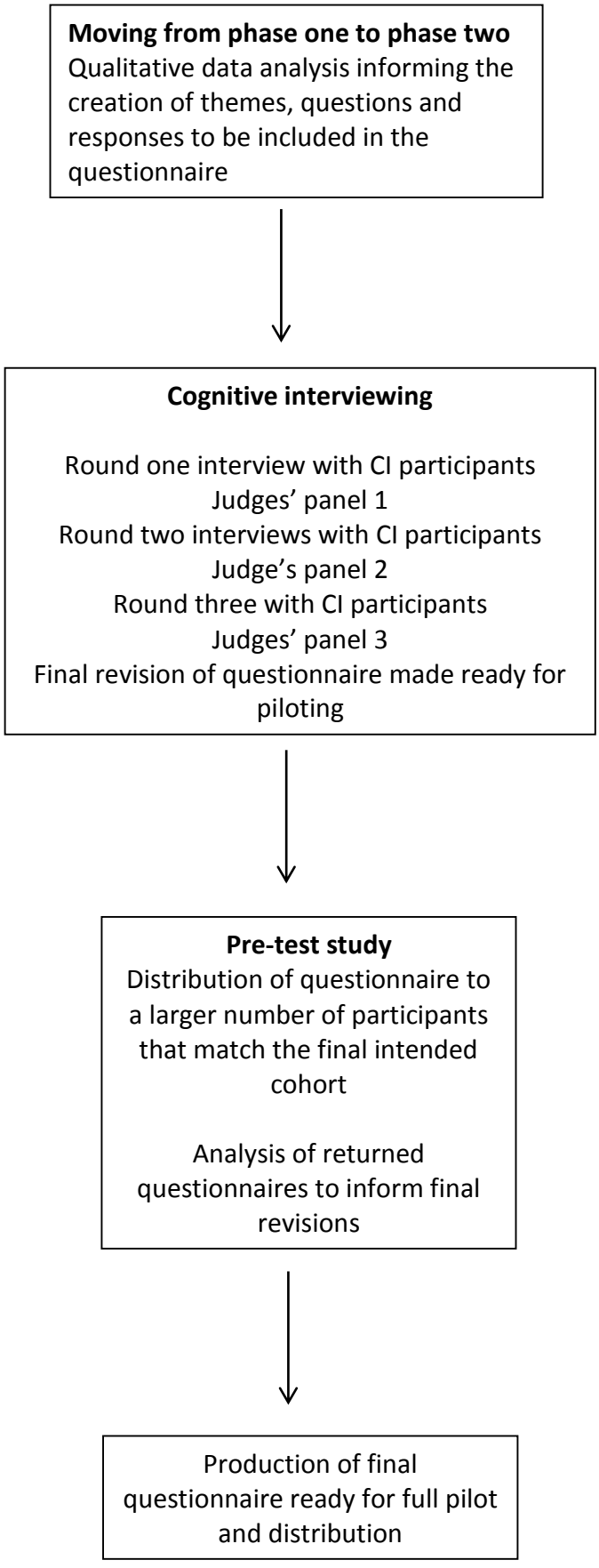
Piloting

The purpose of a pilot is to check that a questionnaire works in practice. The pilot process should include checking the reliability and validity of the questionnaire, removing flaws, establishing how long it takes to complete, assessing if the data are usable and further revision.[210] It is best to pilot a questionnaire with participants who are representative of

the final definitive sample. Piloting should also include planning and testing the recruitment strategy, such as the sampling frame, the response rate and completion rate so that any issues can be addressed.[211] When revising a questionnaire special care needs to be paid to the original research questions to ensure that these are not lost sight of during the process.[255] Piloting may be carried out as an isolated method of pre-testing or subsequent to another method such as peer review or CI. With the latter it provides a final opportunity to review the questionnaire before distribution.

During phase 2 I drafted a questionnaire which underwent brief peer review with the supervisory team, I then undertook a process of CI with a small group of HCPs [n=5] and pre-tested the resulting draft with a larger number of HCPs [n=18] to work towards finalising the development of the questionnaire. Figure 6 illustrates the components of the pre-test process.

Figure 6: The process for pre-testing the questionnaire



Using phase one findings to develop the questionnaire

The majority of genomic tests are still ordered by specialist clinical services (for example, tertiary clinical genetic services) although increasingly tests are requested by secondary care clinicians. With the mainstreaming of genetic tests and initiatives such as the 100,000 genomes project, increasing numbers of tests will be requested by HCPs from primary and secondary care in the future.

In phase one I interviewed HCPs from both genetic services and from other areas of medicine who order genetic tests in their clinical practice. I will eventually want to survey this same cohort as I am still interested in the views of all HCPs who currently order genetic tests and these same two groups of HCPs will also be the key requesters of genomic tests in the future. Comparisons between the two groups can be made and issues such as the impact on clinical practices reviewed. My strategy for involving HCPs in the questionnaire design reflected the groups I will want to complete the questionnaire when it is widely circulated.

In phase one, clinic observations reviewed current practice, providing valuable data on which to construct and focus the interview schedules. In-depth interviews then provided rich data detailing experiences of, and views about, IFs as well as enabling the identification of areas of practice that require further consideration and research. The quantitative phase two aimed to build on the findings from phase one and will, ultimately, add quantitative evidence to the qualitative findings.

In designing the questionnaire I identified three specific areas from phase one that I wanted to incorporate:

1. My findings showed that the possibility of IFs is not consistently discussed when genetic tests are ordered despite patients and HCPs thinking it should be. To what extent are they currently addressed during the consent process on a national level and do HCPs think it is important or not to do so?

2. It would appear there is currently no discussion between HCPs and patients about the types of genetic information, results and IFs that patients would want disclosed. Furthermore, both HCPs and patients reported that they believed it is reasonable for

patients to be given choice on the information they receive. Should patients be given a choice? If so, what sort of choice, and in what circumstances?

3. What are the key implications for clinical practice?

These three areas are detailed in table 22, which also outlines the sorts of questions I wanted to include in the questionnaire.

I wanted to maximise the potential of the CI process by leaving questions 'raw' so that participant responses and suggestions generated in the CI process could be integrated. This is reflected in the first questionnaire draft. I aimed to make the questionnaire easy and quick to complete as HCPs often have limited time for such activities, but might be more likely to complete if it does not appear too onerous or time consuming. Because of this, most questions were initially designed with a yes/no response. As the issues being explored were complex and participants might consider that yes/no did not reflect or do justice to this complexity, space for additional information was also provided. Once the initial questionnaire was designed it was subject to the CI process. See appendix 15 for questionnaire version 1.

Cognitive interviewing

Sample and inclusion criteria

HCPs - genetic specialists and paediatricians - that organised genetic testing in their clinical practice and were involved in consenting patients for testing and disclosing results were targeted for my sample as they are the target group for the questionnaire. The inclusion criteria were:

- HCPs who organised genetic testing as part of routine clinical practice (the frequency with which they order genetic tests did not matter)
- Able to commit to a number of interview rounds until the CI process was complete (for example, excluded if moving jobs or location during course of the interviews)
- Able to read, understand and speak English

Recruitment

Invitation letters with participant information (see appendix 16) were sent by post or e-mail to HCPs involved in genetic testing and working in the Wessex region. They were either already known to myself or their names were passed on by colleagues. I invited a

Table 22: The 3 areas from phase one to be incorporated into the questionnaire design

Theme and sub-themes	Areas of interest to be included in the questionnaire	Questions developed by researcher to investigate the theme
1. Review of current practice: The possibility of IFs is not consistently discussed when genetic tests are ordered. Where the possibility of IFs is discussed there is no consistent practice	What genetic tests are being ordered? What is the current process when tests are arranged? What do HCPs include/exclude in their discussions with patients about IFs?	Do you order genetic tests? What tests have you ordered (ever)? What tests do you order routinely? Do you use a consent form? If not, do you document consent in the patient notes? Does the consent form include specific reference to IFs? Do you think it should? Do you discuss the possibility of IFs with patients/parents? If so, do you use examples to illustrate what these could be? Do you discuss the possibility of Variants of Uncertain Significance (VUS) with patients/parents?
2. Views about consent and disclosure practice: HCPs support patients having a choice about the IFs that are disclosed to them Despite being supportive HCPs see the challenge of offering choice	Do HCPs think patients/parents should be able to choose what IFs are disclosed? If so, is this with all results or some? What role does the HCP have in making decisions about IF disclosure?	Do you think patients should be given a choice on what IFs are disclosed? Do you think HCPs should decide what IFs will be disclosed? Do you think patients should decide what IFs will be disclosed to them? Should the HCP be able to override the patient wishes if they consider it in

Some models of disclosure may in fact limit patient choice		their best interest to disclose a particular result? Should the HCP be able to override the patient wishes if they consider it in the best interest of family members to be informed of the result? Do you think it is possible to make decisions about receiving incidental information if the patient has no prior knowledge or family history of the conditions listed?
3. Implications for clinical practice Consent and disclosure practices need review as genomic tests will increase numbers of IFs The clinical interaction between patient and HCP will be key in managing IFs	Are current consent and disclosure processes adequate in the era of whole genome testing? What changes may need to occur to facilitate the management of IFs? What role will HCPs play in this process?	How much time do you think it will take patients to consent for genome testing? What tests should options for disclosure be available for? Who should be taking consent for these tests?

total of nine HCPs in the first (and only) invite and included HCPs with different types and length of clinical experience. Details of the initial sample are found in table 23.

Table 23: Details of sample for cognitive interviewing

Clinical expertise	**Clinical role**	**Agreed to participate**	**Study ID**
Genetics/Paediatrics	Consultant	No	
Genetics/Paediatrics	*Consultant*	*Yes*	*HcpCI003*
Genetics	Specialist Registrar	No	
Genetics	Specialist Registrar	No	
Genetics	*Genetic Counsellor*	*Yes*	*HcpCI002*
Genetics	*Trainee Genetic Counsellor*	*Yes*	*HcpCI001*
Paediatrics	Specialist Registrar	No	
Paediatrics	*Specialist Registrar*	*Yes*	*HcpCI004*
Paediatrics	*Specialist Registrar*	*Yes*	*HcpCI005*

Participants indicated their expression of interest by e-mail and I then contacted them individually to discuss the study in more detail and set up an interview time if they wished to proceed. In total five HCPs agreed to participate. Although the cohort was less than I had planned, the five did represent a good mix of clinical backgrounds and levels of experience and I decided the numbers to be sufficient to achieve the aims of CI. This reflects the view of Willis, that achieving representation by interviewing the greatest cross-section of the population in question, is more important than producing a statistical sample.[212]

Consent and confidentiality

After discussion at first interview, participants completed the consent form (see appendix 17) and were then allocated a unique identifying number. This number was then used on all subsequent study documentation. Participants were informed that they could withdraw from the study at any time but the data they had already provided could not be removed as this may already have been used to amend the questionnaire. Each CI was digitally recorded – with consent - in order to capture think-aloud and key discussion points. These recordings were destroyed once they had been transcribed and verified.

The first round of CI

Each participant was interviewed at their work place in a private office, free from distractions.

I asked participants to work through the questionnaire, filling it in as they would do normally but to do this thinking out loud. Participants were informed that this was to help me to establish if any questions were unclear, ambiguous, poorly phrased and whether the options given for responding were appropriate. I asked them to be honest and articulate their views on the questions themselves and the questionnaire as a whole. I informed them that I would also ask questions during the interview. If questions were unclear they were asked to seek clarification from me.

I took notes during the interview including:

- Participant's non-verbal actions that may indicate problems with the questionnaire, for example, frowning, turning pages back and forwards
- Questions where the participant repeated the question out loud (and how many times this occurred with each question)
- Questions that were skipped or not fully answered
- Questions where the participant found the response options did not allow them to answer as they wished or wanted to make additions
- Questions where the participant articulated that they thought a question was repetitive or difficult to understand
- Questions where participants asked for clarification or further explanation
- Any questions that participants were unable to answer
- Any questions that participants answered but it was clear they had misunderstood the question
- Suggestions made by participants on how questions could be re-worded or re-structured or if any particular questions required an explanation beforehand or needed a linking question
- Suggestions made by participants on the format and structure of the questionnaire and any proposed changes
- General impression of the level of engagement and interest of the participant

The sorts of probing questions I used were: 'Is that question clear?' Can you think of better wording?' or 'Are the response options as you would want or can you think of better ones?'

Collating the findings

The recording of the CI was transcribed, reviewed with the researcher's notes and any annotations or comments made by the participant on the paper copy of the questionnaire, included. These were all collated into one word document. The document was separated into the questionnaire section headings for ease of navigation. The frequency that each individual question was commented on was noted and those by more than one participant reviewed for possible amendment. In many cases participants either spontaneously, or through probing, made suggestions on how questions could be improved. Where a question was commented on by only one participant I considered this carefully and, if the decision was made to alter the question, this was noted so that I could follow it up in round two to see if other participants agreed with the change.

As the interviews progressed the probing questions changed reflecting some of the comments already made by participants. For example, one participant (HcpCI003) suggested changing some response options from 'yes/no' to 'always/usually/sometimes/never'; and in the interviews that followed, when participants hesitated at the same question, I probed with a question such as, 'do you think always/usually/sometimes/never works better here?' An example of the summary and analysis of round one can be found in appendix 18. The collated comments and proposed changes were taken to the first judge's panel for discussion before final amendments were made and a new version of the questionnaire drafted.

The first judge's panel

The judge's panel was made up of two judges in addition to me; one was a senior research fellow in the fields of clinical ethics and law and health psychology who had expertise in questionnaire design, and the other a paediatric trainee currently working as a researcher. The panel was due to meet after the data from round one had been gathered and preliminarily analysed but unfortunately on the day it was only possible to meet with one judge. The following two panels included both judges. Items and

suggestions for changes had been collated by myself and were then presented and discussed at the panel.

At the panel we discussed the issues raised, indicating those of concern to the majority of participants and those by only one. Details of these and which section of the questionnaire they related to are in appendix 19. Amendments were agreed. Where a minority of participants had raised an issue with a particular question, for example only one had commented, these were sometimes amended and sometimes left untouched on the understanding that this question would be subject to probing in the next round. The outcome of this would either refute or confirm the original point made by the participant in the previous round. Overall issues raised by all five participants were very likely to be amended in line with participant suggestions and then subject to review in the next round. An example of this was question four in the disclosure section, originally as:

4. If patients/parents choose should they be given:

- A list of all known possible IFs and opt in/out of each one

Yes No Please give reasons

- Given categories of results (for example, serious and treatable, serious with no current treatment, carrier status)

Yes No Please give reasons

- Informed about what types of results the HCP would disclose and opt out as they wish

Yes No Please give reasons

At the first round all five participants commented that being given options for disclosure choices and then asking for a yes/no response would not provide as meaningful information as asking participants to indicate which option they agreed with most. As things stood, a participant could tick yes to all options making the analysis of this question problematic. Following discussion the question was re-formulated as:

4. When making decisions about which IFs are disclosed to patients/parents which of the following options are the best approach? Tick one best answer.

a.) Patients/parents are given a list of all possible IFs that can occur and opt in/out of receiving each one individually?

b.) Patients/parents are given categories of IFs that can occur and choose which category(s) they wish to receive (for example, the category of serious and treatable conditions or the category of carrier status)

c.) HCPs inform patients/parents about the IFs (or categories of IFs) that will be disclosed

d.) HCPs inform patients/parents about the IFs (or categories of IFs) that will be disclosed and the patient/parents opt in/opt out of the IFs (or categories of IFs) they wish to receive.

This question was in fact refined following each round of CI and these amendments and the rationale for them will be explained. The second version of the questionnaire is appendix 20.

The second round of CI

All five of participants were involved in the second round. Probing questions were used to explore issues raised in round one and test out suggested amendments. The main comments that arose from round two were:

- Some sentence structure and grammatical refinements were required. Small word changes, for example cheap to inexpensive, in the introduction.
- The introductory sentences added to each section were well received with only some minor changes needed.
- Ongoing issues with formatting of questions
- Free text space title change to 'additional comments' from 'please specify' as this was seen as a more open statement which would encourage a response
- Broaden questions to encompass more clinical settings.
- Disclosure section options: unclear, confusing, too long; key words would benefit from being emboldened.
- Clinic implications section: options given for the time taken for the consent process should include 'under 5 minutes'

These comments were summarised and reviewed ready for discussion at the second judge's panel.

Judge's panel two

Both judges were present at the second panel. Amendments were agreed and the third version of the questionnaire is in appendix 21.

Question four was amended for the third round of the questionnaire:

4. If the patient is involved in the choice of IFs disclosed which of the following options is the best approach? Tick one best answer. *- Patients are given a **list** of all possible IFs that can occur and opt in or out of receiving each one* *- Patients are given **categories** of IFs that can occur and they choose which category(s) they would want to receive. Categories may be, for example, all conditions that are serious and treatable or conditions that are serious with no treatment* *- HCPs inform patients about the IFs that will **automatically** be disclosed and then give the patient the IF **options** they can choose*

The third round of CI

Round three also involved all five participants. The same process was used and the main points that arose were:

- Overall the layout and format of the questionnaire was much clearer and the only remaining issue was with the format of response boxes
- Minor word or sentence structure amendments suggested in the introduction and introductory paragraphs
- The ranking question was well evaluated and participants supported the suggestion of changing question 4 in the disclosure section to a ranking question
- It was thought that question 1 in the disclosure section had lost its theoretical focus, despite a number of attempts to maintain this during re-wording of the question. The question remained unclear and was considered to overlap with question 2 and 3

- Question 4 should be changed to include a ranking response to provide different data indicating which options were acceptable to HCPs and in what order of preference
- Clinic implications section: two participants thought it was important to clarify what was meant by the consent process

Judge's panel three

The aim of the third judge's panel was the final refinement of the questionnaire. Agreement was quickly made to change Q4 to a ranking question. There was more discussion about defining the consent process in clinic implications. Two options were discussed: to change the question to include 'How much time do you think it will take to explain the test or procedures and outcomes of testing' or to change the question to ask participants 'If they think WGS will take more/less or the same time as aCGH [to consent]?' It was agreed that the former question would be included; I felt the second was more of a leading question.

The judge's panel disagreed about including a ranking response for Q1 in the disclosure section as it would be difficult to establish their views on which option they supported the most/least. The wording was, however, changed to make it clear that it was asking participants to rank each option against the other options and not ranking them individually.

Minor amendments relating to the formatting, sentence structure, grammar and replacement of words was also agreed. The fourth and provisionally final version of the questionnaire was agreed and can be found in appendix 22.

Deciding when to stop CI

The decision to stop CI was made after three rounds and three judge's panels as no further substantial issues were being raised by participants. In the third round there were some comments about sentence structure, wording and formatting but these were minor and easily dealt with. In addition, most comments were only made by one individual and not the majority.

In addition, I thought it was important to stop because of participant fatigue. During the third round it was apparent that participants were beginning to find the process repetitive and somewhat arduous. They could see that most of their comments had been

integrated into subsequent versions of the questionnaire and reported that they did not consider they had anything additional to add. The last round of CI took less time than the previous two as participants did not have many significant comments to make that warranted further probing.

The purpose of the pre-test was to evaluate the final changes made (Version 4).

The pre-test process

Pre-testing helps to increase the reliability and validity of the questionnaire, remove flaws and check that the data are usable.[210] It is useful for the researcher to be present during this process as they can respond to questions, note any difficulties participants experience and how long it takes them to complete the questionnaire.

Sample

The questionnaire was pre-tested at the Queen Alexandra hospital in Portsmouth with a group of 18 HCPs who attended a weekly teaching session. The aim of the questionnaire is to explore whether the views about management of IFs, identified in phase are reflected in a larger group of HCPs who organise genetic testing. I wanted a representative group of HCPs who would match the final intended cohort and who had not participated in phase one. It was important to try and get a group together and so I chose a postgraduate teaching session as the setting for circulating the questionnaire. The sample is outlined in table 24.

Table 24: Pre-test sample characteristics

Professional role	**Number of participants**
Medical students	3 (year of training not specified)
GP trainees	2 (both year 1 of training)
Paediatricians (consultant)	8 (all hospital based)
Paediatricians (trainees)	5 (2 were in year 4 of training, 2 in year 1 of training and 1 not specified) **Total number of participants: 18**

Recruitment and response rate

The potential group of participants were informed that I would be attending their weekly meeting to pre-test a questionnaire. They were told that, following the pre-test, I would present my findings from phase one and facilitate a discussion about IFs, as part of the teaching session.

On arrival potential participants were given a copy of the participant information sheet and questionnaire and I outlined the purpose of the pre-test and questionnaire (see appendix 23). They were asked to fill it in if they were happy to participate and add any comments they had about the structure, flow, wording and comprehension of the questions and answer options. I answered any questions they had and, once sufficient time had been given to read the participant information, they filled in the questionnaire. There were 20 in the group in total and 18 started and finished the questionnaire. The main reason for not participating was either that they arrived late to the meeting or were called away.

The pre-test experience

One issue that arose during the pre-test was that participants were arriving at the meeting at different times, so I had to keep explaining about the pre-test as new people arrived. For some participants filling in the questionnaire was quite rushed as the whole session was scheduled for one hour only. A number of people were also eating lunch at the same time so overall the session was rather disrupted. However, this may in fact reflect the circumstances in which HCPs will be filling in the questionnaire in the future as they are likely to do so in the context of a busy working day, with the possibility of interruptions. It was encouraging to note that despite these circumstances all 18 participants were able to fill in the questionnaire in its entirety and on average it took ten minutes to finish. Those that wrote free text comments took a bit longer; however, ten minutes to finish the minimal set of questions seems reasonable and achieves an objective of the final survey, in that the questionnaire will not be too onerous or time consuming to complete.

I had not realised that medical students and GP trainees would be present as well as consultant and trainee paediatricians. Their experience of organising genetic tests would be very limited (if any at all), but I made the decision to include them in the pre-test as I

believed that it would be helpful to evaluate if HCPs with different levels of experience and roles could complete the questionnaire and provide additional data of interest.

Analysis of the pre-test

This pre-test stage was analysed in two ways:

1. Participants were asked to indicate on the questionnaire any questions that were unclear, difficult to answer and any issues with the format, structure or wording of the questionnaire.
2. The second aim was to establish if the questionnaire was able to capture the information required. The data were collated and underwent some preliminary analysis to see if they were able to provide responses that were appropriate for future detailed quantitative analysis and could begin to address the research question of phase two. This was achieved by collating individual question responses and any free text comments and these results were then reviewed to see if any tentative findings could be established that would indicate the future potential of the questionnaire and any immediate amendments that were required. See table 25 for collated responses from the pre-test.

Outcome of the pre-test

Overall all sections of the questionnaire were filled in by most participants. During the pre-test itself participants did not ask any specific questions about the form although I was asked by one participant if they should report what was currently happening in practice or what they thought should be happening. I confirmed the former. On return some questions had been left blank or participants had written “don’t know” or “N/A”. Two participants wrote that the questionnaire was difficult to answer/had difficult questions but it was not clear if this was because they felt the issues were complex and ethically challenging or because the questions themselves are difficult. If the latter I believe that more questionnaires would have been incomplete or I would have been asked more questions during the pre-test. Rather, the comments suggest the complexity of IFs reflecting findings from the qualitative work.

Two of the questions required some further adjustment; both of these were with ranked responses. During the CI one participant suggested that these two questions were unclear: whether they were asking respondents to rank all options against one another or rank

Table 25: Collated responses of the pre-test

Question	Responses	Free text comments
B. Genetic testing		
Q1 Do you order genetic tests in your clinical practice? If yes, please specify frequency over a 6 month period	Yes: 14 No: 4 (2 added never, 1N/A and 1 left blank) Often: 0 Seldom: 5 Infrequent: 9 Never: 2	
Q2 What genetic tests have you (ever) organised in your clinical practice?	aCGH: 14 Karyotype: 14 WES/WGS: 0 Targeted: 13	
Q3 What tests do you routinely organise?	aCGH: 3 Karyotype: 3 WES/WGS: 0 Targeted: 0 10 did not fill in this section: Either left blank or wrote "none routinely"	
C. Consent for genetic tests		
Q1 Do you (or your team) ask patients to fill in a consent form when organising a genetic test?	Always: 0 Usually: 0 Sometimes: 3 Never: 11 N/A: 4	2 participants who said *never* commented that: "Document discussion in notes" and "Usually done by consultant, consent documented but form rarely used" 1 participant who said *sometimes* indicated that used form only for chromosome fragility testing
Q2 Do you detail the consent discussion in the patient notes?	Always: 6 Usually: 1 Sometimes: 4 Never: 1 N/A: 6	1 participant who said always wrote "Should write need for genetic tests discussed with parents and consent gained." This suggests that perhaps they thought HCPs should do this but perhaps were not doing so.
Q3 Does the consent form include specific information about IFs?	Yes: 1 No: 11 Other 5 questionnaires were either left blank or had N/A and 1 wrote "no consent form"	

Q4 Do you discuss the possibility of IFs with patients when organising a genetic test?	Always: 1 Usually: 3 Sometimes: 6 Never: 4 N/A: 4	
Q5 Do you think the consent process should include information about IFs	Yes: 18 No: 0	
Q6 If you discuss the possibility of IFs do you use examples to illustrate the types of results these could be?	Always: 0 Usually: 0 Sometimes: 5 Never: 4 N/A: 7	2 left this question blank (both paediatric trainees). 1 wrote: "I would! But I've not been involved in the consent process (if it happens)." 1 who answered *N/A* wrote "not sure. Probably never that specific." 1 who wrote *sometimes* said "if sending for chromosome fragility"
Q7 Do you discuss the possibility of a VUS with patients?	Always: 0 Usually: 1 Sometimes: 3 Never: 10 N/A: 4	1 who wrote *sometimes* said "may say we sometimes find things that we don't know what they mean" and 1 who said *never* wrote "I have heard it discussed when training in a genetics setting."
D. Disclosure of test results		
Q1 Do you think patients alone should make the decision on what IFs are disclosed to them?	Always: 2 Usually: 6 Sometimes: 4 Never: 4 2 added 'don't know'	1 who indicated *always* wrote "we deal with parents not children so need to wait until child can give informed consent." 1 who indicated *never* wrote "results may have implications for children who are the patient."
Q2 Do you think HCPs should have sole responsibility for deciding what IFs are disclosed to patients?	Always: 0 Usually: 2 Sometimes: 8 Never: 7 1 added don't know	Of those who wrote *never*: 1 wrote "almost" next to their response 1 wrote "this is an extremely difficult and ethical topic with guidelines needed." 1 wrote "it should be discussed with the carer or patient."
Q3 If IFs are disclosed who should make the decision on what information is shared?	6 participants did not rank the options but ticked one response only. 5 participants ranked the same and overall the second option was the most popular	

Q4 If the patient is involved in the choice of IFs disclosed which of the following options is the best approach?	2 participants did not rank the options but ticked one response only. 4 ranked each option (1-3) but did not rank between the 3 options. 12 ranked between the 3 options and all possible combinations were chosen with one having an overall majority 2,1,3.	
Q5 With which genetic tests should options for IF disclosure be available?	6 participants did not complete this question: 3 wrote "don't know" on the form and 3 left it blank (4 consultants, 2 trainees). 11 marked aCGH, 8 karyotype, 7 WES, 8 WGS and 0 for none	Of those who wrote "don't know" 2 commented: "I don't know enough to reply meaningfully." "I don't know the difference between any of the above."
Q6 Do you think it is possible for patients to make decisions about receiving IFs if they have no personal experience or family history of the conditions listed?	Always: 1 Usually: 2 Sometimes: 14 Never: 1	1 participant who answered *usually* also said that it should be always 1 who answered *sometimes* said "if given the correct type of information"
Q7 Should the HCP be able to override the patient wishes if they consider it is in the individual's best interest to disclose a particular IF?	Always: 2 Usually: 5 Sometimes: 8 Never: 3 (1 wrote "almost" next to this response)	
Q8 Should the HCP be able to override the patient wishes if they consider it in the best interest of their family members to disclose a particular IF?	Always: 3 Usually: 6 Sometimes: 8 Never: 1	
E. Clinic implications		
Q1 How much time do you think it will take to explain the procedures and outcomes of testing for:	1 participant just put a ? for the whole question. *aCGH*: 5-15 minutes = most popular response *WES*: 3 left this section blank, 1 wrote "N/A to me" and 1 wrote "don't know". 5-15 minutes = most popular response *WGS*: Same as WES	
Q2 Do you think a follow up discussion is	Always: 5 Usually: 8 Sometimes: 3 Never: 1	One participant who responded with *usually* said

required before tests such as aCGH, WES, WGS are organised to give patients time to consider the options?	1 questionnaire was blank	"depends on prior knowledge."
Q3 Who should be able to take consent and order the following tests?	3 questionnaires were left blank for all options. *GP* Targeted: 9 Karyotype: 9 aCGH: 2 WES/WGS: 0 *Specialist clinician* Targeted: 15, Karyotype: 15 aCGH: 15 WES/WGS: 9 *Specialist trainee* Targeted: 6 Karyotype: 5 aCGH: 3 WES/WGS: 1 *Genetic HCP* Targeted: 14 Karyotype: 14 aCGH: 14 WES/WGS: 14	

each option individually. Following this comment I tweaked the wording and format of the questions to make them clearer. The intention was for participants to rank each option against one another, and whilst the majority did this, some did not so minor amendments were needed.

A number of participants had written "don't know" on the questionnaires indicating that they would support this response being added. The inclusion of 'don't know' had been discussed both in the CI and judge's panels as participants raised this as a possible response option. I decided not to include 'don't know' as I was concerned that participants, if unsure of an answer, would default to tick the 'don't know' box. I was keen that participants thought about their answers and chose one of the options provided, as this would elicit more meaningful data than receiving a number of 'don't know' responses. The 'additional comments' sections do provide participants with a space to qualify and explain their answers if they are not certain about their response. I made a decision to continue not to include 'don't know' in the final version of the questionnaire.

While the pre-tested questionnaire did not undergo a full quantitative analysis, this pre-testing work already began to indicate emerging areas of interest. For example, there was disagreement amongst participants about whether patients should always make the decision about the IFs they receive. A minority said always, with more saying never and it would be interesting to analyse these responses; both in relation to others within the same questionnaire, to see if views are consistent and also amongst the professionals, do particular responses to this question correlate with experience, for example?

Ethical issues

Participants may have thought that the questions indicated that they should be doing things that they are not currently or that I was assessing and judging their clinical practice. I tried to make it clear what the purpose of the study was; to design a suitable questionnaire and to explore current practice with regard to IFs, as to-date there are no published clinical guidelines in place that comprehensively address this issue.

Participants may have been concerned about their anonymity and confidentiality and this was addressed in the participant information, detailing for example, the allocation of unique identifying numbers for each participant to be used on all study documentation and the storage of consent forms (that do contain identifying features) being kept separate so that the two sources of information cannot be matched. No ID numbers were allocated for the pre-test as the questionnaires were filled in anonymously.

Participants were given adequate time to ask questions and consider their decision before being recruited to the study and so any concerns they had could be addressed. Phase two was submitted to the University of Southampton, Faculty of Medicine Ethics Committee and given a favourable opinion (see appendix 24).

Summary of phase two: developing a questionnaire

From the outset in developing this mixed methods study I was keen to incorporate a quantitative element to the research to build on the qualitative findings. I was inexperienced in questionnaire design and knew that an existing validated questionnaire was unlikely on its own to be sufficient to address the issue of IFs. The process of CI and pre-testing has proven invaluable in facilitating the development of the questionnaire with participants articulating inconsistencies, comprehension and clarity issues and design problems, with each version of the questionnaire. Throughout the CI process participants were also able to comment on the evolution and refinement of the questionnaire and say when sufficient improvement had been made for the questionnaire to be ready for piloting. The pre-testing reassured me that filling in the questionnaire in a reasonable time frame was feasible and further highlighted areas that needed attention.

A fifth and final version of the questionnaire can be found in appendix 25.

Judging the quality of my research

In chapter 3, I discussed different ways that the quality of research can be judged and I outlined the measures I took to maximise the validity and reliability of my work and to provide an audit trail of the processes I followed during the research; these are outlined in detail in chapter 4 and 7. In appendix 5,6,10 and 11, I have included excerpts of raw data to illustrate how I analysed these at various levels, in an attempt to keep the stages of analysis as transparent as possible. My discussion shows how I moved from my findings to articulating the 'wider resonance' of my work.

I also want to return to consider Teddle and Tashakkori's (2009) criteria for assessing the integration of mixed methods approaches.[220] 'Integrative efficacy' refers to the extent to which each part, or approach, is integrated into a theoretical whole and 'interpretive correspondence', the extent to which the study itself supports the choice of an MMR design. Phase one of my research led directly into phase two; and while phase 1 could have stood on its own, phase 2 was reliant on its findings. The questionnaire aimed to strengthen phase 1 findings by testing views on key issues with a wider HCP population. In these ways, therefore, the two phases complemented and enhanced each other. Ultimately, however it is difficult to assess whether the research achieves these integration criteria as I have yet to collect data from the wider group of HCPs, and I will need to return to assess this when I have undertaken the post-doctoral work.

Strengths of the research:

- A clear understanding of the concept of incidental findings and its problematic nature
- A greater understanding of the practical and ethical issues surrounding incidental findings in genetic and genomic medicine, both for patients and HCPs
- A deeper appreciation of the complexities within the consent process for genome wide testing
- The development of a robust HCP questionnaire using cognitive interviewing which is ready to be circulated
- The identification of key implications for future clinical practice

Potential limitations:

- I began my study as an inexperienced researcher. The data from my early observations and interviews were not as rich as the later ones. Undertaking quite a large number of interviews helped to compensate for some of the early interviews which I felt produced quite thin data.

- My observations were just a snap-shot of what was happening in the clinic on that day; rather than observations which followed a family through from testing, to when results were given, and beyond. While this was outside of the original purpose of the observations, I feel in hindsight this would have been useful data to complement the interview data.

- At the time of my study genetic incidental findings were only really relevant to a few specialities. I undertook my observations (and recruited HCPs for my interviews) in these settings. However, as genomics is mainstreamed, IFs are relevant to more specialties. It is possible that had I involved participants from these settings I would have picked up additional issues of relevance. In this respect my questionnaire will be invaluable as I can distribute more widely to a range of HCPs across different specialities. On a similar vein, I was not able to establish the experience of patients who had been given different types of IFs: in my cohort mainly cancer and cardiac IFs were disclosed to patient participants and none were considered 'serious with no intervention available'. If I had been able to recruit more participants who were actually given an IF, these sorts of experiences might have been covered. The likelihood is that, had I started my research more recently, it would have been easier to find more patients who had had an IF from a genetic test, across more specialities.

- The family participants in phase 1, who had received an incidental finding, had done so in the fairly recent past and so it was not possible to explore the impact of these being disclosed in the longer term. This is something I would

like to pick up on in future research. I would have also liked to have explored the experiences and views of patients who had been told about IFs prior to the test being carried out; however none of my patients had any recall of this which I felt was missing data from my study.

- On the whole I felt my cognitive interviewing went well; however, I think it would have benefited from a larger group of participants from a wider group of specialities. The pre-test cohort included medical students/GP trainees who are unlikely to be included in the questionnaire cohort. Their input may, at best, not have added much or, at worst, skewed the results. For example: a 'don't know' option could have been chosen because of an inability to respond due to their training or specialty, rather than not being able to answer the question. However, the pre-test was carried out to complete the testing of the questionnaire itself rather than aiming to collect data.

Reflections on my role as the researcher

Taking up a NIHR clinical fellowship has been a very rewarding experience. It provided me with the opportunity to focus on research full time, to approach this work with continuity and without interruption and be supported by training and supervision. I have learnt about research methodology, data analysis, conceptual development and the process of writing. Below I reflect on some of the things that have shaped my development during the PhD period and which will impact on my research role in the future.

The clinician as researcher

When I took up my fellowship I had many years of clinical experience working as a genetic counsellor. I felt I had an excellent understanding of the issues involved in genetic testing; I regularly engaged patients in the consent process and discussed the possible outcomes of genetic testing with them. This experience placed me in an informed position that was very useful for the planning of my research study, but I was aware that I might make assumptions about the views and practices of my participants. Doing so would affect my questioning during interviews and my interpretations of what participants said.

I hoped that the clinic observations would help me to adjust to my role as a researcher and that this data would directly inform the development of the interview schedule, rather than being based on my own assumptions coming into the study. I tried to stay alert to the possibility of making assumptions throughout my research and indeed looked at my observation notes and interview transcripts for any sign of this. During the early interviews I realised that it was important not to interject too quickly with follow up questions, when participants were speaking of their experiences. I was aware that I could presume that I understood what participants were telling me, and tried to focus on encouraging them to share their story, before I moved on to the next question. Just because I had patients in the past, who had experienced IFs, did not mean that I already 'knew' what it was they wanted to share. Similarly, my experience as a clinician was not likely to be the same as other HCPs, for example, I had never actually disclosed an IF in my own practice.

One decision that I had to make was whether I would provide any clinical information, such as inheritance risks for relatives, during data collection. This could be a clear 'no' as my role at this time was as a researcher and not a clinician. However, it was not as simple as this. HCPs and some patient participants were aware that I also worked as a clinician and perhaps had some expectation that I could therefore answer their questions, for example, the age at which surveillance would start. During patient interviews participants sometimes asked a question about an aspect of genetics. I had to make a decision as to whether I answered this question or not. I decided that brief clarifications were generally acceptable, that I should not have a blanket rule, but anything more detailed was better addressed during a clinic appointment, when their clinician would have more time and their patient notes available. Brief clarifications included things such as confirming full names of conditions or tests. After the interview I contacted the appropriate clinical team of any participants that had questions, and agreed to me doing so, and asked them to be in touch with the patient. During a couple of the clinic observations HCPs, aware that I was a genetic counsellor, asked me to check if a patient had been seen by clinical genetics or to follow up a genetic test result. On both occasions I indicated that I would make contact with the appropriate clinical person and ask them to liaise directly with this HCP.

The 'clinician as researcher' and the possible tensions this brings have been widely debated.[267-269] Brody et al described the tension between a "difference position" that is, one that considers clinical research and therapeutic medicine sufficiently distinct that they require different ethical principles, such as consent, versus a "similarity position", where clinical investigators ought to be bound by the same fundamental principles that govern medicine, that is, a duty to provide optimal therapeutic benefit to each patient or participant. They proposed that the "similarity position" is unsatisfactory because it underplays the tensions within the clinician-researcher role. I personally experienced some of these tensions, as outlined above, but I attempted to overcome these by being aware of this potential at the start of my research, so I could think about and respond as they occurred and either be more prepared or put measures in place to address them. I discussed some of the issues during early supervision meetings. This was helped by my previous experience in research, where

tensions such as these had arisen before. Thinking about Brody's two positions was useful: in my research practice I acknowledged the tensions associated with the clinician-researcher role, demonstrated by directing participants back to their clinician, but at the same time I did address some participant questions there and then.

One seemingly straightforward problem was how to introduce myself to participants and how much I disclosed about my professional background. I had initially been open about this as I thought that participants would know what a genetic counsellor was and that I was informed about the subject I was researching and this would be reassuring. In fact at times I was considered too informed and as a result called upon to be a genetic counsellor. I therefore changed the way that I introduced myself; as a researcher from the University of Southampton. I only identified myself as a genetic counsellor if directly asked. Making this change reduced the number of questions raised by participants and meant that interviews were not interrupted by clinical discussions.

I piloted the questionnaire at a paediatric teaching session during phase two. When arranging this I mentioned my clinical background, as I thought this was likely to facilitate access to the group. In return for piloting the questionnaire, I was asked to provide a 30 minute teaching session on the topic of IFs from genetic testing. All participants were then aware of my clinical background. I decided to manage this by introducing myself initially as a researcher, ask them to pilot the questionnaire and once they had finished, I moved on to my teaching session. At this point, I revealed my clinical role and affiliation with the clinical genetic service.

My clinical experience did, at times, prove useful in other ways: it meant that I understood all the terms, descriptions of tests and names of genetic diagnoses that participants were discussing. This meant that I could prompt as necessary, for example, if a patient said: "we had that test, the new one, like the chromosome test they used to do", I could prompt with "the array test?" I believe that this may have encouraged participants to talk or share more about their experiences as they perceived that I understood what it was they were discussing. I could also probe more with my questions as I had an idea what they were talking about and could ask

relevant questions in order to explore issues more fully. On the other hand participants may have shared less, if they understood that I had a direct link to their clinical service and worry that I would go back and tell their clinician all they had disclosed, particularly if they had been critical of the service.

My genetic counselling skills proved useful during the course of interviews as I was able to confidently manage any participants who became upset. No patient participants became distressed but a few were emotional when discussing their child and their problems. I was also skilled at reading non-verbal signs, so I could assess if someone did not understand a question, was finding it difficult to answer or becoming upset. There was one particular interview (the only one I did with both parents present together) where I was required to use my counselling skills. Both parents talked about the genetic diagnosis in their child and began discussing if they had been able to have a test in pregnancy for this condition, would they have done so. It appeared that one parent was suggesting that they would, and the other not, and the atmosphere quickly became tense with one parent questioning the other. I was able to pick up on this and after waiting for them to speak together for a few minutes, moved the interview on, to discuss testing in pregnancy in a more general way. I was conscious of not interrupting them immediately, but at the same time I sensed that while they might have wished to discuss this issue more fully, they would not feel comfortable doing so, with a researcher present.

This interview highlighted the challenge of carrying out a joint interview with both parents together which I had avoided with the other two sets of parents. Interviewing two participants risks them getting into a discussion between themselves, often off the topic, and sometimes more about their views on their own personal situation, rather than on the topic in question. It requires skills to both be able to acknowledge what participants are saying and also to able to move the interview on, to re-engage with its original purpose. This example also underlined the potential that interviews can bring up difficult and emotionally charged topics and the importance of offering follow up if indicated, for example, referral back to the clinical service or GP.

Incidental findings as a shifting concept

As I began my research it was apparent that IFs was not a straightforward concept and this impacted my data collection and analysis. I had chosen to use the term incidental findings, considering it the best shorthand available, to describe results from genetic tests that are unrelated to the reason for doing the test in the first place. During the observations and early interviews I realised that this term meant different things to different people and I needed to look carefully at my data to tease out what participants were actually referring to and what they meant. This complexity was difficult to articulate and as the study progressed, the question of IFs became more and more prominent, with initiatives such as the 100 000 genomes project and its associated issues about what findings would be fed back raising its profile. This meant that understandings about what an IF was and what it meant in different contexts was continually shifting. While this reflected the very timely nature of my work, at the same time it was a challenge to keep abreast of all this debate, integrating it into my data collection and analysis as the study progressed. This is reflected in my work related to the development of the term PIF, which arose directly from my discussions with participants about IFs often not being clear cut at the time they are first revealed, and how this brought specific management challenges into clinical practice. In response to this, I felt that it was important to distinguish between definite IFs of clinical significance and those that were potentially clinically relevant and how this difference could affect disclosure practices.

My reflections about the research process prompted changes during the actual data collection and beyond this as I look forward to realising my future research goals. As I hope to continue to work in a combined clinical and academic role, it is important to keep on reflecting about how these two roles can complement and challenge one other, endeavouring to find a way that utilises them, to both maximise the potential of research and at the same time not compromise it.

Chapter 8: Discussion

This research explored current attitudes of HCPs, patients and parents towards, and experiences of, incidental findings (IFs) in clinical practice. The research questioned if, or how, consent for IFs was sought and how, or when, they were disclosed. Although the term incidental findings is used variably in discussions and research around genomics, the definition used here was of a finding that was incidental to the clinical question that led to the genomic test using broad technologies. An example might be the discovery of an adult onset cancer predisposition whilst examining genetic reasons for developmental delay in a child.

I found this to be a complex territory, where opinions often seemed to evolve during interviews as I probed the various practical and ethical aspects raised. Furthermore, the rapid developments in technology during the course of my research meant that the concept of what constitutes an incidental finding also evolved, both in the international debate and literature, as well as my own thinking about the issues. Despite the difficulty of researching areas that were sometimes difficult to nail down, this study provided insights into actual experiences in clinical practice, a sharp contrast to the largely hypothetical international debates around the issue of incidental findings that had been held to date. This allowed recommendations for clinical practice to be made to support patients through the decision-making process.

Whilst the concept of incidental findings is not new to medicine, the nature of genetic information does pose new challenges to practice. By this I mean that genetic information can predict future disease – for an individual but also for relatives (including future offspring) – in a way that has not previously been encountered on any large scale in medicine. At the same time, although sometimes these predictions are clear and certain, more often than not, the predictions are actually rather hazy, and so their clinical utility – and therefore potentially the onus on the professional to disclose them - is more questionable. When I wrote my research proposal, I had in mind the notion of clear cut, clinically certain incidental findings. My research highlighted that these are rather rare, and that there is a spectrum of incidental findings that ranges from a finding that carries no, or completely uncertain clinical information, through to the highly predictive ones that I started with. Clinical management of results at either end of the spectrum is relatively straightforward,

but deciding where communication, action and intervention is offered with less certain results will need to be decided by individual circumstances. Acknowledgement of this complexity was one of the first outcomes to emerge from this research, shaping subsequent interviews to tease out participant views on how such results should be managed in practice.

Shifting sands of terminology around incidental findings

Although I started with a clear concept of the types of incidental findings to be researched (see the example of Sophie, chapter 2 box 1) I found that the term itself was problematic because what is incidental is both dependent on the context and on temporal factors. At the same time, no better all-encompassing term has emerged from the debate held over the past 4-5 years. There are limitations to this term, as summarised in Crawford *et al.* This paper argued that no one term could fit all the different circumstances in which the term IF was currently applied, and that what might be an IF to a health professional might feel far from incidental to a patient.[82] In Shkedi- Rafid *et al*, I reviewed, with colleagues, the range of alternative terms to IFs that have been proposed , and outlined the advantages and disadvantages of each.[78] Again, we concluded that IF, although not ideal, had gained the widest traction in international debate and was therefore our term of choice.

This research also outlined that many IFs encountered in clinical practice were not clear IFs when the genetic analysis was first reported. That is to say, the initial laboratory report might provide a clear and certain description of the genetic code difference in that person, but the clinical interpretation often lags behind. A result may therefore be a *potential* incidental finding (PIF) at the time at which disclosure – or feed back – to the patient is considered. We were the first to highlight how the evolution of PIF to IF (or other type of result) may require further tests and surveillance both in the individual tested, but also in their family members and how this posed extra challenges to the management of IFs in clinical practice. For example, debates about disclosure or not of uncertain findings are moot if testing of family members is part of the determination of clinical significance. Findings will often move from one category of results to another, as they are further characterised, reflecting the temporal nature of results and need for ongoing review. This teasing apart of PIFs from IFs and variants of uncertain significance or polymorphisms was described in

Crawford *et al*.[96] Furthermore, empirical research then went on to show that both HCPs and patients discussed this range of VUS, PIF and IFs, often under the single umbrella term of IFs (see chapter 5 and 6). When asked about the clear cut IFs described in the original research proposal, they often answered with examples that lay on a different part of the spectrum.

As a result of this research, I am more convinced that the term IF is problematic to some extent. It is not a term people generally choose to use to describe a risk of systemic disease or other life-changing information [270] and it is important to stress that while the information is incidental to the original reason for the test, it does not mean it is insignificant or less important to the patient. At the same time, I have found no single term that better describes the concept being researched here[78] and have therefore continued to use it in this thesis with relevant critique throughout.

How whole genome approaches affect whether findings can be incidental

The more a genetic test aims to interrogate the entire genetic code, the less any finding can ever be said to be incidental, that is, if there is deemed to have been a degree of searching or purposeful looking involved.[78,81] This fellowship application was written with the technology aCGH in mind, since this was the only new genome wide approach in clinical practice at the time. By the end of my PhD this was no longer the case; whole exome sequencing (WES) and whole genome sequencing (WGS) have now entered clinical practice. WGS, for example, can search the entire 3 billion base pair genetic code and this result will then need to be interrogated to search for specific base pair changes that might explain the clinical question posed. Any findings that do not do so – for example, ones that predict a clinical feature not expected on the basis of signs, symptoms or family history is termed an incidental finding but it is hardly incidental to the search itself. To some extent there will be no WGS findings that have not been 'looked for' (although one has to target the analysis of 3 billion base pairs to some extent) but at the same time the finding may be incidental to the reason for the test.

Shifting from a targeted test designed to answer specific clinical questions, to a broad 'trawling' test from which clinical features might be predicted, has an effect on the interpretation of the term incidental. The 100,000 genome project – offering WGS to

NHS patients started in 2015.[13] Although practicalities around this are still evolving, patients are asked to consent to the search for specific 'additional looked for findings' and at the same time to acknowledge that any 'incidental findings' will not be fed back to them whether they want them or not.[13] Genomics England appear to have tied themselves in knots somewhat as they list specific additional findings that will be looked for, but also ask patients to consent to other additional findings not yet on the list but ones that Genomics England might in the future choose to add. They do not define what they consider to be incidental findings that they will not feedback, other than a finding of misattributed paternity. In my opinion, this only serves to highlight the complexities here and that the terms additional, incidental, looked for, secondary and so on findings are used in differing yet overlapping ways.

The empirical research described in this thesis revealed that overall patient participants did not like the term incidental. They believed that it was confusing and that it minimised the potential serious nature of the condition identified. When asked, their preference was to use the term unexpected. Christenhusz et al, who interviewed parents about their views on the communication of IFs concurred.[86] They used the term "unexpected result" with parents, and found it to be a term that parents could more easily understand than their own preferred term, that they used with professionals, of "secondary variant". My research however, showed that professionals were not using the term unexpected in discussions with their patients, arguing that no results would be unexpected for them if broad technologies were used.

Recommendations for clinical practice

Rather than a focus on finding the one perfect term, this research showed that both patients and HCPs found it more helpful to discuss the different possible test outcomes with patients in a general sense. Informing patients that genomic testing can generate a wide range of different results, some of relevance to the original reason that brought them to clinic, some that indicate other health, developmental or reproductive risks, and still others whose relevance may (initially at least) be rather unclear was considered important. Therefore using terms such as additional and unexpected findings in clinic allows patients to be prepared for the concept of

incidental findings as described in the literature and as HCPs understand them. HCPs need to distinguish between different types of test outcomes; one that can be predicted and specifically consented for, and others that need to be discussed in a more general way pre-testing, as their nature cannot be predicted sufficiently to gain specific consent before testing. Professionals need to consider how best to describe these predictable and unpredictable outcomes to their patients so that the consent involves an appreciation of the range of possible outcomes.

Choices about IFs at the consent stage

Whilst my original concept of an incidental finding was one that I thought could not realistically be consented to (thousands of different possible outcomes cannot be considered in any real sense at the point of testing) many of my participants thought that choice about the types of results was important. This was one area where opinions often evolved within the interview as the issues were discussed in more detail. For example, one patient (FamInt011 Father) started off by saying that choice was extremely important and any other approach would be too paternalistic yet later in the interview appreciated that real choice about unknown unrelated findings would be difficult, especially whilst concentrating on finding an explanation for current signs and symptoms. He considered that the process would be "laborious" and "take forever" if done "properly", with the amount of routine testing being organised. Once their views about completely unrelated findings that would have no clinical impact for many years (for example, the case of Sophie) were probed, both patient and HCP views about consent and disclosure became less clear and moved more towards a concept of broad consent.

During my research, a lively international debate emerged about choices around IFs at the time of consent.[124,139,177] The American College of Medical Genetics (ACMG) recommended a search for specific additional findings to which patients had to consent, although the recommendations also left disclosure of any findings up to the discretion of the HCP. Many disapproved of this approach arguing it was paternalistic and removed patient choice. Others proposed a 'menu' approach where certain categories of findings (for example, serious actionable only) would be offered.[25,34,179] The menu approach to patient choice about IFs begs the question: might there be times when an HCP should decide to override this decision? I did not question HCPs

specifically about such an override - mainly because such choices about IFs were not routinely given to patients during the course of my research - nor was the issue addressed in the debate that followed the ACMG recommendations. The participants in my research viewed any results as 'theirs' and therefore did not want their HCPs to decide about disclosing or withholding information without their input. At the same time they acknowledged the difficulties of such input. HCPs were similarly uncomfortable with such decisions; they did not want to be seen to be withholding information, as they believed this could prompt claims of paternalistic practice. However, both groups were agreed that some clinical interpretation of what genetic variants should be part of the 'result' could not be determined purely by patient choice.

For example, patients expected HCPs to share particular IFs, without explicitly checking with them first that they would want this information. All the participants, who had already received an IF, were pleased that their HCP had made the decision to disclose it and none of them had made explicit choice about IFs at the time of consent. Furthermore none remembered their opinions being sought. They stated they were happy with HCPs drawing on their clinical knowledge and experience to make decisions around disclosure. It seemed that the concept of consent for IFs was therefore considered differently than when it played out in practice. Interestingly, none of the patient participants said they would be happy for HCPs to make a decision to withhold information about an IF. Again, this seemed to tap into worries about paternalistic practice, which appeared to overshadow consideration of whether there might be times, or types of information that they would not want to hear about. On the one hand patients wanted to be involved in decision-making about IFs but on the other hand they were happy to have results disclosed to them without such involvement. This illustrates how guidelines advocating patient choice (as called for in the post ACMG recommendations debate) might have limited utility, or indeed be detrimental to good clinical practice if adhered to too rigidly. Much of the debate following the ACMG recommendations was about preserving the patient's 'right not to know'. Yet, how can patients make meaningful decisions about the IFs they do not want to know, when they do not know upfront what these will be and what could be available (now or in the future) to treat any that are found? In my

view, giving the patient complete responsibility for such decisions at the time of consent is unrealistic and potentially unethical because one cannot provide specific consent to a complete unknown. There has to be some clinical judgement involved in some of these decisions, just as there would be in the disclosure of a lung tumour discovered incidentally on X-ray that had not been specifically consented to.

As discussed in chapter 2, the ACMG did respond to international pressure from critics championing the patient's 'right not to know' and revisited their original recommendations, to include an option to not receive IFs.[163] This appeared to be somewhat of a 'knee-jerk' response, with the ACMG making changes to appease their critics, rather than engaging in the debate and defending their position. Interestingly, the ACMG justified a search for adult onset conditions in children (contrary to international guidance)[115,245] on the basis that such findings could be helpful to the child's adult relatives who might also have the same finding and who could already benefit from surveillance. This is very much a public health argument and does not address the ethical concerns about the implications of identifying a disease risk in children many years before anything can be done about it. The American Society of Human Genetics (ASHG) recently acknowledged that whole genome testing techniques have changed the landscape for genetic testing in children. They recommend targeted testing where possible, to reduce the likelihood of such adult onset IFs but also supported the disclosure of any IFs discovered that have clear clinical utility for the child and/or their family members.[271] Assessing clear clinical utility at the time of discovery and potential disclosure will, as discussed above, be difficult.

In the example of Sophie, the BRCA1 result was stumbled upon by accident. Until now, BRCA1 gene testing was only offered if someone had a strong family or personal history of young onset breast and/ or ovarian cancer. Offering such results to Sophie potentially to inform her mother is unchartered clinical territory. However, the question remains as to whether parents should be able to decide if additional findings in their children indicating adult onset conditions, such as BRCA1 mutations, are disclosed in order for them to refine their own cancer risks. To some extent, doing so lends support to a more familial approach to genetics (for example, joint account model[106,107]), which views genetic information at the familial level, and

clinical information at the individual level. However this does nothing to diminish the ethical concern that the child's future autonomy is affected by such disclosure. Adult onset IFs found accidentally are likely to need different clinical management than specific requests for testing of children for adult onset conditions.[272]

If a clinician's duty of care evolves to actively investigating a genome, specifically searching for other genetic variants in more detail than warranted by the presenting clinical signs and symptoms,[150] then some disclosure decisions would have to rest with the HCP.

Clinical utility of incidental findings

While some incidental findings will have clear clinical utility, with evidence based treatments or interventions, it became clear that there were also many shades of grey. Even apparently obvious interventions such as mammography have limited evidence in younger women and conversely some types of results were perceived by patients to have utility, whilst no intervention or treatments were available. Huntington's disease is often used as an example of a finding that has no clinical utility, as no treatments are yet available that alter the course of the disease, yet some patients considered that such results could have utility for them, in that it allows them to make plans for their lives or future generations. HCPs and patients seemed to have a different understanding of the term 'clinical utility' or 'actionability' of results.

Patients often initially held the view that all information had utility and any and all information was welcome. At the same time their considered decision often ended up being different; one where they would only want certain types of information. This has implications for practice; mainstreaming and the increasingly routine nature of genetic tests might allow less time for consideration, so that a different type of decision is made than the one made if more time and discussion was available. It will be interesting to research the implications such routinisation might have for the decision-making process. Both HCPs and patients believed that there were certain IFs, such as serious conditions with no available intervention that should not be automatically disclosed but instead considered on a case by case basis.

This means that some proposed solutions to the issue of IFs are less clear cut than they first appear. Many have suggested that any IF that is 'actionable' should be disclosed, whilst those that are not, perhaps not.[86,169,170] My data shows that 'actionability' is viewed rather differently by patients (acting on a useful result) and their relatives than by HCPs (evidence based medical interventions).

Choice and autonomy

Given that the move towards patient choice is largely justified on the basis of enhancing their autonomy, one has to question whether dramatically increasing the number of choices might actually limit a patient's autonomy rather than enhance it. This data suggests that with genomic testing there is a real risk of doing so. Levy suggests that HCPs might increase a patient's autonomy by constraining it so that a more nuanced exploration of enhancing autonomy in genomic testing is necessary.[129] It will be important to ensure that so called "patient choice" does not become "patient abandonment".[273] Leaving patients with a list of conditions to look through, and tick off what they would or would not want to know about could indeed lead to meaningless choices rather than real ones.

A pragmatic approach might therefore be that HCPs make 'all things considered' value judgements for their patients.[127]. For example, a patient may opt to receive any and all IFs in the belief that this information will accurately predict whether certain conditions will develop. In reality this is rare, with many results being PIFs[96] at the time of discovery or with wide ranges of penetrance or expressivity so it is important for HCPs to explore this with patients upfront. These discussions will then guide HCPs as they make decisions about IF disclosure.

Recommendations for the discussion of IFs during the consent process

Existing professional guidance

Existing professional guidance on consent from the General Medical Council (GMC) and Nursing and Midwifery Council (NMC)[274,275] refer to defined clinical situations, such as consent to a surgical procedure. Findings in this study challenge such guidance, as the outcomes from genetic testing are so broad that the elements of the

consent process for surgery cannot be applied in the same way. Taking consent from one patient, for one test on one occasion, does not reflect the nature of genomic testing where one test can generate a number of different results, relevant now or in the future and with potential relevance for a number of different family members. Rather, guidance on how HCPs can take patients through decision-making relating to the generation of potentially complex, uncertain and predictive information is required. Existing professional guidance on consent is therefore not 'fit for purpose' for genomic testing. Guidance from the JCMG Consent and Confidentiality in Clinical Genetic Practice [1] – which is more focussed on genetic practice than the above- does mention the issue of IFs and recommends that this possibility is explored with patients prior to testing, but arguably is already out of date since in 2011 genetic testing was much more limited than it is today.

Exploring IFs with patients during the consent process

Given the difficulty of specific consent for IFs in genomics, I recommend recognition of this in the consent process in considering information needs of patients. HCPs need to talk about testing in a broad way to explain the concept of IFs and the types of information that might be revealed. For example, a general description such as the following might be helpful:

In the past, genetic tests have looked at specific sections of the genetic code, according to the clinical reason for doing the test. Newer genetic tests can now look at your entire genetic code and therefore have the ability to provide much more information. The difficulty with the newer tests is finding information that will be useful for you. We may find the explanation for the reason we are doing the test in the first place, we may also find predictions about future disease or illness. Some of these results we will be more definite about than others. We may need to do more tests to try to work out if these results mean anything for you and/or your relatives and we may find after further testing that the results have no, or no known, significance for your health. Such testing may be more informative if we are also able to test other members of your family, or we may need to wait for the results of research studies to know what these results mean for you. We may therefore need to get back in touch with you at a later date if new relevant information comes to light.

Examples could be provided and the patient given an opportunity to explore their concerns, wishes and expectations.

The role of the health care professional in disclosing IFs

The approach to consent described above inevitably means that HCPs will be required to play an active role in decision-making around disclosure, even allowing for detailed discussions with the patient before testing. This can sit uncomfortably with professionals, striving to avoid accusations of paternalism or to practice non-directive counselling. HCPs may be concerned that such decisions could be seen as paternalistic and not in the spirit of shared decision-making (SDM). However, I think that SDM could be upheld but in a broader way than currently. Patients might for example, indicate results they would not wish to receive, such as identifying a significant risk of Alzheimer's disease. Health professionals need to avoid the trap described by Fried where the greater the uncertainty surrounding the benefits and harms of various options, the more HCPs ask patients to make decisions, when in fact these patients are the ones that would benefit most from clinician recommendations.[276] Genomic testing, by its very nature is surrounded by uncertainty and HCPs will need to become involved in decisions surrounding the disclosure of results.

Consent forms

I did not specifically set out to research the use of clinical consent forms, but this came up many times during the course of my research. On the one hand consent forms have seen increasingly widespread use for predictive testing, such as Huntington's disease or BRCA genes, over the past few decades. This is in recognition that results may be serious and significant. On the other hand, many HCPS argued that genomic testing was just like many other clinical investigations they ordered for their patients and for which consent forms would not be used. They worried that using specific consent forms for genomic testing might lead to a form of genetic exceptionalism that they wanted to avoid.

Because of this tension, I helped to design and perform a consent form audit in our regional genetic service, during the course of my research. This showed that only 50% of clinicians used consent forms routinely.[277] Furthermore, a tick on a consent form

does not necessarily mean that an issue has been discussed in any detail; the form may receive scant attention and be signed without real consideration of the issues included. A dramatic illustration of this type of lack of attention is from a study demonstrating that individuals wishing to connect to a Wi-Fi hotspot ticked boxes through which they (apparently unwittingly) agreed to give up their first born child (or pet) as one of the terms and conditions of being connected.[278] Whilst the clinical encounter is obviously different from an online 'Terms and Conditions' tick, it could be that patients are even less likely to read documentation carefully since they will often trust the HCP delivering it would not ask anything unreasonable of them. The use of consent forms for clinical genomic testing will now be audited nationally and it will be interesting to see how this tension is managed clinically as genomic testing possibilities expand and enter mainstream medicine.

HCPs believed that consent forms could facilitate discussion, give structure to the pre-test counselling session and act as an aide-memoire and record of the meeting. As genomic technologies continue to develop, many HCPs believed that consent forms would play an increasing role; a number considered that using forms would be necessary to document agreements about what IFs will or will not be disclosed. Concerns about the length and detail of consent forms were raised by HCPs who thought that these factors will be influenced by the reasons why forms are used. They argued that if forms were to include an extensive choice list of different types of feedback or results then two problems might ensue: firstly, the forms might become cumbersomely long, detracting from their value and secondly the forms might reduce the process to a series of 'tick boxes' that detract from real consent. Many HCPs commented that the consent process in the clinic was the most important thing and that making consent forms compulsory in any way might detract from this. While their inclusion may become an integral part of the consent process, they should not be a replacement for tailored, detailed discussion and documentation.

This work is still ongoing but an interim conclusion for practice is that clinical consent forms can be useful aide memoires both to cover essential aspects of the consent process and to standardise documentation of discussions. Making them compulsory,

as a research consent form is, could detract from the clinical encounter that elicits most of the consent components.

Broad versus specific consent

Informed consent is a prevailing aspiration in health care, but as I argued in chapter 2 this to some extent is a tautology, since consent is not consent unless it is informed. I believe that my research shows that the only workable consent with genomic testing is a type of broad consent- a consent where patients can indicate the types of results they would or would not want to receive - and that because of the almost infinite number of possible results, specific consent is not possible until the results are already available, and by then it is already too late to discuss it.

Rather than taking consent for one test on one patient on one occasion the broad scope of genetic testing should be explored with patients. Discussions can be documented in the clinical notes to add detail to any consent form used and should reflect a dynamic approach to genetic testing, that can be accessed and used to inform future contacts with the patient and amongst HCPs. Some have argued that broad consent cannot be sufficiently informed to be valid, and that this might be overcome by means of a technological solution. Kannepolou et al proposed one such solution which they termed 'dynamic consent'(although of course all consent should be dynamic to some extent in that it can be modified or withdrawn over time) which proposes that as future uses of data emerge, patients should be re-contacted (perhaps through a web-account) and given choices along the way. Whilst this has some appeal in a research setting, such technological solutions will be harder to apply in the clinical setting where patients will need to make decisions in the real world with unavoidable uncertainties attached, and where an ongoing duty of care over a patient's lifetime poses challenges not met in the finite world of a research project. As genomic practice becomes more widespread, there are important questions to be answered about re-contacting patients- perhaps already discharged from a service- in the light of new testing, interpretation, or knowledge. The conceptual change from narrow to broad consent will be a challenge for HCPs experienced in taking targeted consent. Broad consent is likely to feel uncomfortable in its open-endedness but is the only approach to tackle genomic diagnostics in clinical medicine.

My research showed that patients rated discussion and reflection highly and could see the complexities associated with managing IFs. They were also supportive of the dynamic ongoing clinical relationship between HCP and patient and valued the role this relationship played in their consideration of IFs.[279,280]

Genomic technologies in the NHS today

As more genetic tests are mainstreamed, propelled now by the 100 000 genomes project in England, the NHS will be required to find new ways to engage with the vast array of potential results such testing will create, both in terms of consent and in terms of result feedback. This in turn will have an inevitable impact on clinic appointment numbers and length. HCPs will need relevant expertise in order to gain appropriate consent and to know what types of results need to be fed back. For example, they will need to be able to recognise normal population variation, VUS, IFs and PIFs aside from the diagnostic result they are seeking. They may well also have to consider the relatives of the patient in front of them, something that most HCPs will only have had to do on rare, if any, occasions in the past (for example, contact tracing in infectious diseases). Genetic HCPs (gHCPs) will be expected to assist with the interpretation of results by fellow clinicians, but it is yet to be seen what the extent and complexity of results generated by WGS will be. As whole genome techniques enter mainstream medical practice and those obtaining consent may not have come across a genomic IF before, I consider that it would be good practice to utilise the experiences of gHCPs who have. I believe that some mention of the possibility of IFs at the time of testing would be better practice than waiting till an IF arises. That said, I do not think that any detailed consent to IFs is realistic, however it seems only logical that as the technologies become much broader and less targeted, that the inevitable consequence is that findings other than those that led to the genetic test in the first place may arise. Many of these issues will investigated further by the survey designed in phase two.

Although I have focussed on consent to, and disclosure of, IFs the downstream consequences of IF discovery also need consideration. Arrangements for long term follow-up of patients and their family members may need to be made and in some cases arrangements to re-contact a patient or a family many years after the IF discovery, at the point at which it becomes clinically relevant. Patient and HCP

participants did not believe that current NHS infrastructures or processes are adequately prepared for this need. There are a number of areas that I consider need addressing:

Areas that need addressing:

1. Review of genomic results over time:

As more knowledge is accumulated, both from research, biobanks and clinical practice, the apparent clinical significance of findings will change. A PIF may turn into an IF or a diagnosis or remain uncertain. New information about the clinical consequences of a finding, or its management, may arise. Mechanisms will need to be put in place to ensure patients are informed of these developments and appropriate clinical advice is given. These mechanisms need to consider lines of responsibility: should the onus be put on a clinician, a laboratory scientist or patient, or combination of these, to review such results?

Further research is needed on what duties clinical services have to re-contact former patients in the light of new technologies. A number of the HCPs I interviewed questioned if re-contact represented an enduring duty of care towards their patient, and if so, for how long might they have such a duty. Once a referral was closed, did a duty still exist? If not, who, if anyone, reviews results and re-contact patients when new information arises? If re-contact is a duty of care how should this achieved in practice and what are the most appropriate means to do so?[281] These and other research questions about re-contact are being addressed in an ongoing study 'Mainstreaming genomic medicine: Is there a duty to re-contact?' (S.E. Kelly (PI); Dr. Peter Turnpenny and Professors Anneke Lucassen and Angus Clarke (co-Is). I am a collaborator on this study. (http://socialsciences.exeter.ac.uk/sociology/research/projects/details/index.php?id=409)

2. Review of existing processes for reporting results:

The fact that laboratory reports, although analytically certain and definitive will need ongoing clinical interpretation in the light of new evidence is a relatively novel concept for both patients and HCPs. We will need to ensure therefore that

this new evidence is appropriately incorporated and systems will need to be set up to do this.[282] HCPs were concerned that the current NHS infrastructure is unable to adequately facilitate ongoing review meaning that decisions about test results will be made at the time of reporting for fear of being 'lost' or not having appropriate mechanisms in place to go back to review uncertain results. This could mean that as the clinical interpretation of results changes, patients are not adequately updated:

"I think practically it's going to be impossible for us to, you know, each time something new from a whole genome sequence is figured out…to go back to all those families; it's just going to be impossible. But I think you need to be clear about the timescale in which you do have an obligation to get back to people." HcpInt026 (Genetic Counsellor)

Further research is needed to look at means of re-contacting in the genomic age. The problem of re-contacting is not new and there may be useful parallels from other areas of medicine, for example, information coming to light about the PIP (Poly Implant Prothese) implant scandal, and a dentist infected with HIV having had contact with patients. Both these examples involved widespread public information, setting up helplines, and putting the onus on patients to re-contact healthcare professionals, rather than leaving the onus on HCPs to contact individual patients. Are these useful parallels for re-contacting in clinical genetic practice?

3. Timing of disclosure of results:

Both my patients and HCPs wanted a system that would allow results to be delivered at a time they were clinically relevant. HCPs in particular said that in an ideal world they would not disclose information that was not clinically relevant for another few decades, yet they also thought that NHS systems did not exist to provide such a service (and could not imagine their development) so they advocated disclosure now, because of these limitations.

Further research is needed to determine the impact of receiving a genetic result that will only have clinical effects many years in the future, or conversely, delaying the

disclosure of such a result until nearer the age at which interventions will be of benefit (for example, the BRCA1 result in Sophie). More qualitative research is needed to explore the experience of HCPs who disclose results of this nature and of patients/parents of receiving this information.

4. The discovery of IFs in children:

IFs in children that predispose to an adult onset condition will need special attention because if they are disclosed at the time of finding, one consequence will be that the onus is left on parents to communicate findings when the child is old enough to understand. If disclosure is left to the parents, or other family members, it will be important to incorporate mechanisms that check this has happened and that any evidence based interventions are organised appropriately. What might be the role of an alert on GP records to flag the issue at an appropriate time, and how can this best be implemented?

In my study parents had only received information about an IF fairly recently and it will be important to research how this information is dealt with over time; when are children told? How can HCPs best be involved in discussions? How can we ensure that appropriate surveillance and treatment is implemented in years to come? In my post-doctoral research I plan to include a longitudinal follow up study of families who have received an IF in their child that is not clinically relevant for their child until adulthood. Such research will help shape and inform future practice as health services develop care pathways about the management of predictive genomic information in children.

5. Direct-to-consumer testing:

It seems very likely that direct to consumer genetic testing will increase. During my doctorate, a company called “23and me” began marketing a genome wide kit for £99 in the UK.[42] We will need to plan how NHS clinical services respond to questions about the results of these kits. This is likely to stretch existing NHS services further.

Future research will need to monitor the number and nature of enquiries generated by recipients – or their GPs- of direct-to-consumer test results and what impact this has on NHS services. This should include patient- and HCP- experiences of dealing

with susceptibility loci that provide rather weak predictions of disease in the future. It will also be important to review if and how information was disseminated to other family members, were customers able to access proven interventions at the correct time and the impact of results on their psychological wellbeing.

6. Prediction of disease:

Much genetic variation determined through genome wide testing will never have the ability to accurately predict disease because they are dependent on other factors in many different ways. For example, finding A may predict diabetes with a 20% lifetime risk in the presence of factors B,C,D and G but not in the presence of factors E,F,H and I. Yet the public discourse on genomics often perceives it to be like single gene genetics, or, in other words, there is still a tendency to see genetic information as more deterministic than it actually is. There are challenges to practice providing patients with a result that is actually less predictive than a patient expects it to be. If interventions are offered on the basis of results that ultimately turn out to not be significant then they may have done more harm than good, for example, the patient has undergone unnecessary investigations, been exposed to radiation in surveillance programmes or been anxious following a screening recall.

The impact of receiving predictive risk information merits further research. This includes patient's understanding of risk, the integration of risk prediction and any measures implemented to reduce risk into their daily lives and the long term impact of receiving such information, especially if risk predictions change over time. Despite there being a significant body of research about patient's understanding of genetic risk much of this work was done with single gene disorders.

Relevance of this research to other areas of health care

This research has relevance to other areas of medicine outside the specialist field of clinical genetics as more and more genomic tests will be ordered through mainstream specialities. Both the uncertainties from looked- for findings and incidental findings will need to be incorporated into routine practice. The notion of broad consent is not new in many areas of routine medical practice, but the predictions of future disease, and the possible relevance for family members provides a novel slant that HCPs will need to incorporate in their practice. Furthermore, the technical ease of genomic testing will mean it is requested more frequently to make pre-conceptual or antenatal decisions. Finding a weak susceptibility to disease in adults is one thing- and difficult enough to incorporate into responsible health care decisions at times - but making such decisions in the time-pressured environment of pregnancy is even more rife with potential problems.

The ethical issues such as using this information to make decisions about continuing with a pregnancy or not require further research. Decisions around the disclosure of adult onset predisposition to disease in an as yet unborn fetus, where the clinical relevance may be many decades hence, is also a key ethical challenge. In this setting and others there is a continuing tension between realising the potential of new technologies, implementing them into routine NHS services as quickly as possible, while having appropriate infrastructures and staff education in place to support this rapid introduction.

The NHS needs to respond to the challenge of genomic testing including the generation of IFs. Practical aspects need to be embedded with ethical practice addressing patient choice, issues around confidentiality and autonomy and the appropriate and equitable use of resources.

Conclusion

The massive advances in techniques to analyse a whole genome, and the speed and low cost by which this can now be done has caused a major shift in genetic and genomic practice, which has continued to evolve during this doctoral research. HCPs, while adapting their practice during the course of my research, often still approached consent to genomic testing as if they were offering a narrow targeted test. Similarly patients (or their parents) wanted the test to help diagnose a specific condition and were surprised by the breadth of possible information that could arise from such testing. Although many described broader testing in terms of a quantitative change (more, quicker information), I found that once both HCPs and patients saw the shift as a qualitative change (from targeted testing to broad; and shifting the phenotype analysis from before a targeted test, to after a broad test) they began to be able to see the need to adapt the consent process.

Broader testing raises many more potential incidental findings that are difficult to predict in advance and that may require ongoing evaluation over many years. I believe the only feasible way of consenting to such findings is to raise the general possibility at the time of testing, but that tick boxes of conditions, or even categories of conditions will not be helpful additions to the consent process. Despite general support from patients and HCPs to offer patients a choice about the IFs they receive, there was no consensus amongst participants on the best way to achieve this. The range of possible outcomes is so vast and I think it is unethical to expect a patient to make such choices and be bound by them when it might change once they know the information available to know. I propose therefore that consent should be broad to reflect the dynamic and ongoing nature of genomic test results and that HCP judgement will have a role in how and what is disclosed. Furthermore, I think this is possible without HCPs being paternalistic. I argue that such an approach increases the patient's autonomous decision-making rather than diminishes it.

Although the technological advances in genomics are clear, the translation into practice is not straightforward, requiring careful thought and debate. My empirical research helps to inform this debate, and is the first to my knowledge to investigate the issue of incidental findings in NHS genomic practice. It will be important to develop several aspects of this research so that the ethical issues in the application of genomics in health care continue to receive appropriate attention.

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Appendix 1: Observation data collections sheet (version 1)

Space for free text minimised for presentation in thesis

Observation data sheet

Introduction of genetic test

Is the word **genetic** test used? ☐

Use of the following terms:

- Variant of Uncertain Significance (VUS) ☐
- Incidental Findings ☐
- Polymorphism ☐

Clinical ☐ Research test? ☐

Consent

Is a consent form used (copy taken) ☐

Examples of IFs given? ☐

Word used to describe IFs

Disclosure of results

Timeframe for results ☐

How will results be given ☐ Letter ☐ Appt ☐ Telephone

Is this patient choice? ☐

Disclosure appointment

Terminology used for IF

Significance unclear? ☐

Distinction made between other results and IF? ☐

Follow up

Onward referral ☐ To whom?

GP informed of IF result? ☐

Long term follow up plan? ☐

Who is responsible for long term follow up?

Referral to patient group ☐

Appendix 1: Observation data collection sheet (version 2)

Space for free text minimised for presentation in thesis

Observation data sheet

Introduction of genetic test (including consent)

Is the word **genetic** test used? ☐

Use of the following terms:

- Variant of Uncertain Significance (VUS) ☐
- Incidental Findings ☐
- Polymorphism ☐

Clinical ☐ Research test? ☐

Is a consent form used (copy taken)

Examples of IFs given? ☐

Word used to describe IFs

Disclosure of results

Timeframe given for results ☐

How will results be given ☐ ☐ ☐

Letter Appt Telephone

Is this patient choice? ☐

Terminology used for IF

Significance unclear? ☐

Distinction made between other results and IF? ☐

Follow up

Onward referral ☐ To whom?

GP informed of IF result? ☐

Long term follow up plan? ☐

Who is responsible for long term follow up?

Referral to patient group ☐

Appendix 1: Observation data collection sheet (version 3)

Space for free text minimised for presentation in thesis

Observation data sheet

Introduction of genetic test or Discussion of test already done and result

Is the word genetic test used? How is it described? Different words used to describe testing techniques and types of results

Use of the following terms:

-VUS
- IF
- Polymorphism

Distinctions made?

Clinical/research test

Time frame given for results?

How will results be given? (Patient choice?)

Follow up plans

Onward referral? To whom?

GP informed of IF result?

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Date
Recipient address

Dear

Exploratory study: Observation of clinic consultations

I am writing to invite you to participate in a study being carried out by researchers from the University of Southampton. This study is looking at the interaction and communication between clinicians and the families they see in clinic when ordering genetic tests and disclosing results. Full details of the study are enclosed in the participant information sheet. This PhD project is part of a National Institute Health Research funded clinical academic fellowship.

During the initial exploratory phase of this study I am looking to observe routine clinics where genetic tests are likely to be ordered. I would therefore be grateful if you would consider permitting me to attend a selection of your clinic appointments to observe the discussion surrounding genetic tests. I will send families the study details with their appointment letter and obtain their consent prior to the clinic if they are happy for me to attend.

If you are interested in participating I would be grateful if you could complete the attached expression of interest form and return in the stamped addressed envelope enclosed. If you would like to discuss this further please contact me on 02380 794462.

With best wishes

Yours Sincerely

Gillian Crawford RGN, MSc
Clinical Doctoral Fellow

Ethics no:

Observation of consultation (HCPs)
Expression of interest

Research team: Gillian Crawford, Anneke Lucassen, Claire Foster, Angela Fenwick

Please complete as appropriate

I confirm that I have read the accompanying participant information sheet and would be happy for a member of the research team to contact me with more information ☐

Signature .....

Date.....

If interested please complete:

Name .....

Address .....

.....
.....

Contact telephone number .....

Best time to contact .....

Contact e-mail address .....

Please return to:
Gillian Crawford (stamped addressed envelope enclosed)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Observation of consultation
Information Sheet

Health Care Professionals (HCPs)

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

Purpose of the study

This research study aims to research the interaction and communication between clinicians and the families they see in clinic when ordering genetic tests and disclosing results. As genetic testing techniques have advanced over the past few decades it is now possible to examine large portions of a person's genetic code at costs acceptable to routine NHS services. However it is not clear if and how genetic testing and its possibilities are discussed with families in the clinic.
The findings from this study will provide an important and timely evidence base for future policy and practice, enhancing communication between HCPs and families around genetic testing.

Why have I been invited to take part?

You are invited to take part because you are involved in the care of families with a possible or definite genetic diagnosis and have discussed genetic testing with them. It does not matter what the outcome from such genetic testing is. We want to see whether you would be willing to permit a member of the research team to observe clinic appointments with families where these tests are routinely ordered. The observations are the initial exploratory phase of a research project that will establish current practice, views and experiences on consent and disclosure from genetic testing. The researcher will use this data to inform the next phase of the project; in-depth interviews with families and HCPs and an on-line survey for health professionals.

Do I have to take part?

No, you are under no obligation to take part in this study. Whether or not you agree to take part is up to you. If you agree to take part and then later change your mind you are free to withdraw at any time and have your study data destroyed.

What will taking part involve?

The researcher will attend clinic consultations where it is anticipated that genetic testing will be discussed with families. This will include both tests being requested and the discussion of results. The researcher will ask you to complete a consent form and also seek consent from the families involved prior to the consultation starting. During the observation the researcher will be positioned to minimise distraction for both clinician and family and will not actively participate in the clinic appointment in any way. The researcher will take notes throughout the observation.

What are the possible disadvantages and risks of taking part?

It is possible that you will feel an initial unease at having your practice observed. However, the aim of the observation is to establish current practice and the researcher will maintain the confidentiality and anonymity of all participants throughout. The researcher will also ensure that there is minimal disruption to the routine appointment. The aim of the observation is to establish current practice.

What are the possible benefits of taking part?

While there may be no personal benefits to you taking part in the study it is hoped that the data collected will contribute to a greater understanding of differing perspectives on the issues involved and lead to improved communication between HCPs and families. In addition, it is anticipated that this data will influence policy on consent and genetic testing.

Will my taking part in the study be kept confidential?

All data collected will be stored securely to ensure its confidentiality. Each participant will be assigned a code number so that it will not be possible for anyone to identify an individual person from the data. All data will be stored using that code number. The data collected will be confidential to the research team. Some events or things that individuals have said may be reported but every effort will be made to ensure that the individual concerned cannot be identified. We may in some cases use direct quotations but these will always be anonymised. In no cases will individual's names be used. Any data relating to individuals which may identify individuals will be excluded from reports or publications. All data will be collected and stored securely.

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to Gillian Crawford on 02380 794462. If you continue to have concerns you should ask to speak to a senior member of the research team (Professor Anneke Lucassen on 02380 794503) or the University Hospital Southampton NHS Foundation Trust Patient Advice and Liaison Services (PALS) on 02380 798498

What insurance provisions are in place?

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the sponsor, University Hospital Southampton NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you. As the Principal Investigator is a student of the University of Southampton, additional professional indemnity and clinical investigation insurance is in place.

What will happen to the results of the research study?

The findings of the research will be published in academic and professional journals. Participants will be given details of the research project website address where they can access progress reports on the project and the study findings when available.

Who is organising and funding the research?

The research team organising the study is Gillian Crawford, Professor Anneke Lucassen, Dr Claire Foster and Dr Angela Fenwick from the University of Southampton. The study is funded by the National Institute of Health Research (NIHR) and is being completed as part of Gillian Crawford's clinical research fellowship.

Who has reviewed the study?

All research in the NHS is reviewed by a Research Ethics Committee. This study has been reviewed and given a favourable opinion by (name and ethics number).

What do I do now?

If you are willing to take part in this study please complete the expression of interest form and return in the enclosed stamped addressed envelope. Gillian Crawford will then contact you to discuss the study in more detail. If you still wish to participate, Gillian will arrange a convenient time to attend your clinic. You will be asked to complete a consent form.

Further information

If you would like further information about the study please contact Gillian Crawford on 02380 794462 or on gc@soton.ac.uk

Thank you for taking the time to read this.

Ethics no:

Observation of consultation
Information Sheet

Family members

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

Purpose of the study

This research project is looking at the interaction between health care professionals and families during clinic appointments. It is particularly focussed on the communication around tests that your clinician may order to confirm a possible diagnosis in your family. This can include genetic tests which may be something that the doctor will discuss with you today. This research aims to gather an insight into the experiences and attitudes of families and health professionals towards genetic testing and its possible outcomes.

Why have I been invited to take part?

You are invited to take part because you have been sent an appointment where genetic testing may be one of the investigations discussed with you today. It does not matter whether you have the test or what the result is but we want to observe the discussion that takes place between you and the doctors. We will use the findings from this observation to develop the next phase of the project which is interviewing families and health care professionals and later on a survey for health care professionals.

Do I have to take part?

No, you are under no obligation to take part in this study. Whether or not you agree to take part is up to you. If you agree to take part and then later change your mind you are free to withdraw at any time and have your study data destroyed.

What will taking part involve?

The researcher will observe your clinic consultation. The researcher will ask your consent and that of your doctor to observe the consultation before the appointment starts. You can ask the researcher any questions you may have beforehand. During the observation the researcher will be positioned in the clinic room in a way to minimise disruption to you and the clinical team. The

researcher will not actively participate in the clinic appointment but will quietly take notes in the background.

As the next part of this study the research team are also completing interviews with families who have undergone genetic testing. If testing has occurred in your family the researcher may ask if you would be happy to receive further information by post about the interview phase of this project, which will take place at a later date. There is **no** obligation to take part in this part of the project if you have your clinic consultation observed today.

What are the possible disadvantages and risks of taking part?

Participants may feel some unease with an observer being present during their appointment but this usually passes after a few minutes. You can withdraw from the study at any time and in this case the researcher will leave your appointment immediately.

What are the possible benefits of taking part?

While there may be no personal benefits to you taking part in the study it is hoped that the data collected will contribute to a greater understanding of differing perspectives on the issues involved and lead to improved communication between health care professionals and families.

Will my taking part in the study be kept confidential?

All data collected will be stored securely to ensure its confidentiality. Each participant will be assigned a code number so that it will not be possible for anyone to identify an individual person from the data. All data will be stored using that code number. The data collected will be confidential to the research team. In reporting the data it may be that some events or things that individuals have said will be reported. In such cases, every effort will be made to ensure that the individual concerned cannot be identified. We may in some cases use direct quotations but these will always be anonymised. In no cases will individual's own names be used. Any data relating to individuals who the team feels may identify them will be excluded from reports or publications. All data will be collected and stored securely.

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to Gillian Crawford on 02380 794462. If you continue to have concerns you should ask to speak to a senior member of the research team (Professor Anneke Lucassen on 02380 794503) or the University Hospital Southampton NHS Foundation Trust Patient Advice and Liaison Services (PALS) on 02380 798498

What insurance provisions are in place?

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the sponsor, University Hospital

Southampton NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you. As the Principal Investigator is a student of the University of Southampton, additional professional indemnity and clinical investigation insurance is in place.

What will happen to the results of the research study?

The findings of the research will be published in academic and professional journals. Participants will be given details of the research project website address where they can access progress reports on the project and the study findings when available.

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Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This study has been reviewed and given a favourable opinion by (name and ethics number).

What do I do now?

If you are willing to take part in this study please complete the accompanying consent form and hand back to Gillian Crawford. She will be available to discuss the study in more detail and answer any questions you may have before completing this form.

Further information

If you would like further information about the study please contact Gillian Crawford on 02380 794462 or on gc@soton.ac.uk

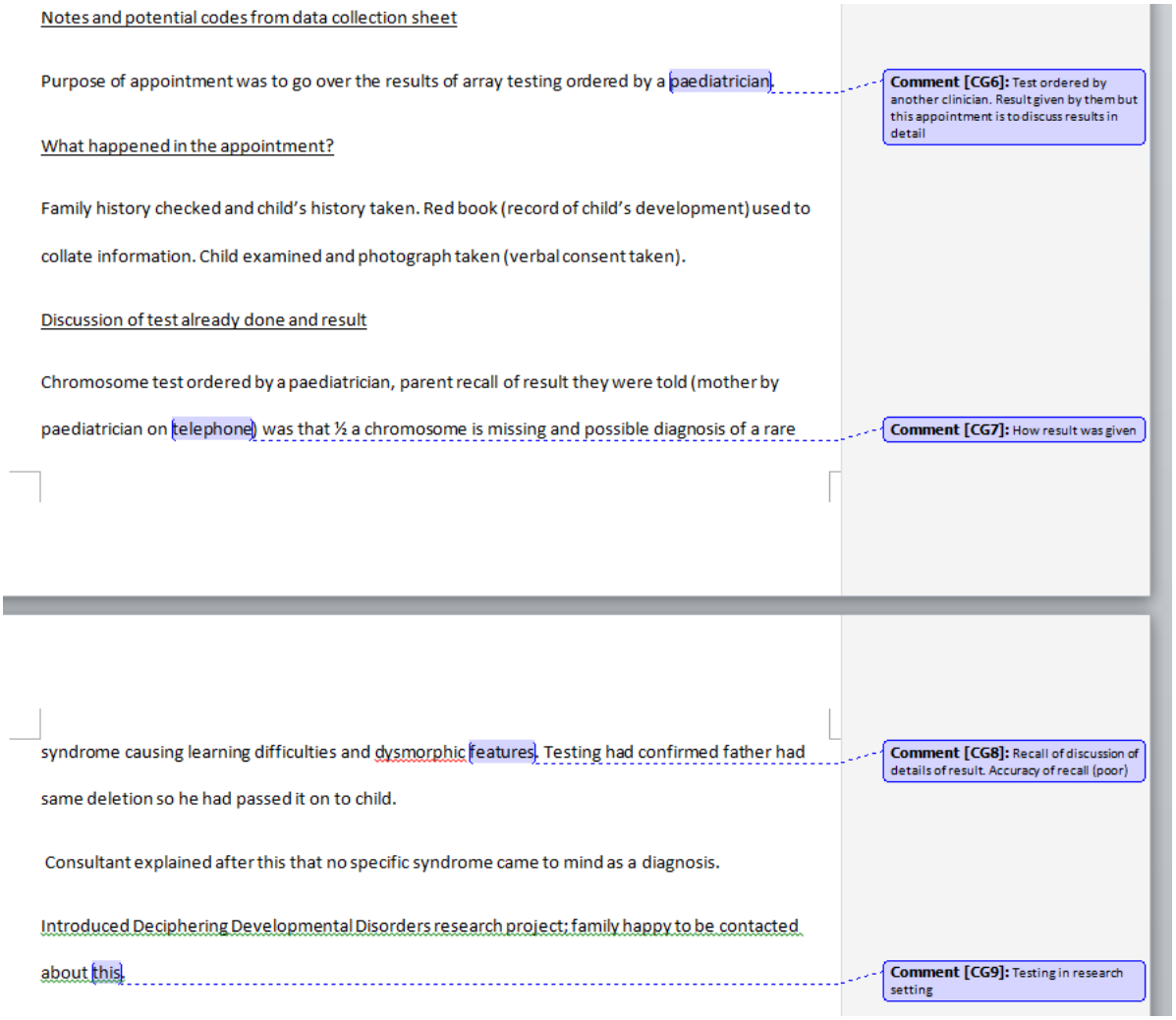
Thank you for taking the time to read this.

Appendix 4: Notification to family members that a researcher was to be present in clinic

On the day of your appointment with Dr … his/her clinic is being observed by a researcher (Gillian Crawford) who is looking at the discussions that take place between patients and their doctors during clinic appointments. Please find enclosed detailed information about this project. We would be grateful if you could read this information before your appointment as when you book in you will be asked by the receptionist if you are happy for you/your child's appointment to be observed. If so, you will meet Gillian Crawford who will answer any questions and complete a consent form with you. If you do not wish to participate then the receptionist will let Gillian Crawford know and she will not attend your appointment. You are under no obligation to take part in this study.

Appendix 5: Example of emerging issues and coding from one observation (FamOb016)

(i) From observation data collection sheet



Notes and potential codes from data collection sheet

Purpose of appointment was to go over the results of array testing ordered by a paediatrician.

Comment [CG6]: Test ordered by another clinician. Result given by them but this appointment is to discuss results in detail

What happened in the appointment?

Family history checked and child's history taken. Red book (record of child's development) used to collate information. Child examined and photograph taken (verbal consent taken).

Discussion of test already done and result

Chromosome test ordered by a paediatrician, parent recall of result they were told (mother by paediatrician on telephone) was that ½ a chromosome is missing and possible diagnosis of a rare

Comment [CG7]: How result was given

syndrome causing learning difficulties and dysmorphic features. Testing had confirmed father had same deletion so he had passed it on to child.

Comment [CG8]: Recall of discussion of details of result. Accuracy of recall (poor)

Consultant explained after this that no specific syndrome came to mind as a diagnosis.

Introduced Deciphering Developmental Disorders research project; family happy to be contacted about this.

Comment [CG9]: Testing in research setting

Discussion of test already done and result

Result passed on to him by mother, came from paediatrician to mother. "Surprised he had the mutation" (patient using genetic language). Consultant explained that the finding could be unusual or unique. Could be a chance/random finding. Discussion of other relatives and how they could now be tested (bother already referred and parents can be offered a test to try to clarify significance (or not) of finding). Patient described finding as "red herring".

Consultant explained that chromosomes were previously looked at with a microscope but can't see individual genes but with the new test it looks in different ways, uses *markers/probes*. Test showed that area of chromosome 18 is missing and therefore 1 or 2 genes are missing, wouldn't be able to see this down the microscope. One of the genes affected by the deletion in some people cause this syndrome. But can also find normal variations and as one parent has the same deletion and is unaffected by any of the features his some has it is probably just a variant.

Consultant: "unusual finding" but not likely to be the cause of the child's problems. Can't say at this stage then why he has the problems he does but may think about testing for one other condition on stored DNA. Consultant describes testing as "Fairly new science". Mentioned VUS in discussion but not called by this name.

Follow up plans Follow up appointment in one year. Not discussed how further results would be given and timeframe.

Comment [CG10]: Impact of result

Comment [CG11]: Types of results we get from testing (could be VUS or natural variance or even an IF)

Comment [CG12]: How results are discussed when significance is unclear

Comment [CG13]: Impact of result on rest of family

Comment [CG14]: Words used to describe findings by patient

Comment [CG15]: Terms used to describe array testing

Comment [CG16]: How new types of tests are described to patients

Comment [CG17]: Clinical significance of result is unclear

Comment [CG18]: Could be a normal result

Comment [CG19]: Can this be classed as an incidental finding in the parent as he has no features of the condition?

Comment [CG20]: Terms used to describe a result

Comment [CG21]: Uncertainty of result

Comment [CG22]: Targeted test versus trawling test

Comment [CG23]: Discussion of array testing as 'newer' How new techniques are described

Comment [CG24]: Types of results we can get from testing

Comment [CG25]: Follow up plans. Clear about next appointment in one year. Not clear on how new results would be given and when

(ii) From field notes

Observation 16

Type of appointment: genetic appointment to discuss recent results

Field notes

Clinic room in children's outpatient dept. in a DGH. Genetic counsellor had asked all family members in waiting area if happy for appointment to be observed prior to coming in to the appointment.

Clinic room, reasonable size, sat away from consultation itself but still in view of family.

Parents are now separated, attended appointment together. Father requested time on own with team after joint appointment. Father's array results had been given to the mother to pass on to him rather than given to him directly by paediatrician. Difficult especially as they are now separated.

He wanted to discuss implications of result for him and future reproduction. Consented both parents for study separately.

Consent taken in the nurses office (not able to sit down as chairs had wheels, health and safety) so I brought in one chair and the other parent had to stand and then swap over to sign form.

Comment [CG1]: Context of family situation

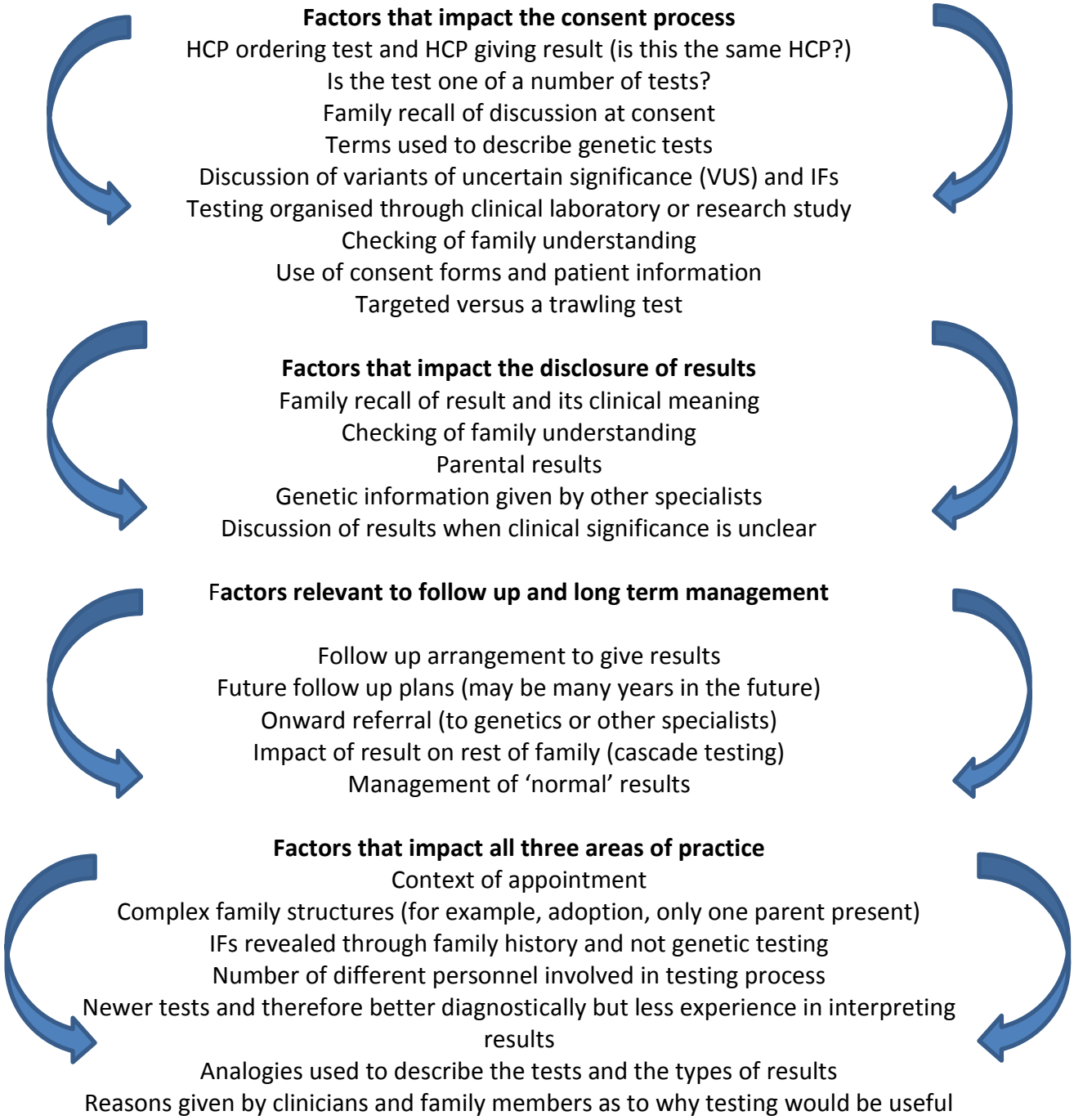
Comment [CG2]: Result given by other specialist but not to patient

Comment [CG3]: Original test requested by another clinician to the one family seeing today

Comment [CG4]: Complex family situation

Comment [CG5]: Reasons why test result may be useful

Appendix 6: Initial thematic map from observations



Appendix 7: HCP interview schedule (version 1)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Interview Framework: Health Care Professionals

Study title: Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

This framework is intended to provide general guidance on areas to cover in the interview. The final interview framework used in the project will be informed by the results from the observation phase so the outline below acts as a guide at this stage. It is expected that the interview will take the format of a conversation/discussion that will begin with an introduction to the project and any outstanding issues around consent.

1. Discussion about the person's professional background and experience/interest in genetic testing. What sort of genetic tests are they organising and what range of results will these give? How often do they order genetic tests?
2. Explore the term 'incidental findings'. What is their understanding of this term? Can they give any examples from their practice where incidental findings have been discovered? What happened in these cases? Any issues to highlight looking back?
3. Discussion of their 'usual' process of obtaining consent for genetic tests. What do they include/exclude in this discussion? Exploration of consent forms used and their content. Who takes consent/involvement of other team members?
4. What is their 'usual' procedure for giving results (at a clinic appointment/by letter etc)? Is there any change to practice if an 'incidental finding' is discovered? Do they discuss these results with anyone prior to giving to the family?
5. How much detail is given about the 'incidental finding'? Is there a follow up plan put in place for families and if so can they given examples of what this may be?
6. Is there a responsibility for long term follow up of these families when adult onset 'incidental findings' are discovered? Whose responsibility is it? What measures are/need to be put in place to achieve this?
7. Are they aware of other cases from colleagues, families or patient support groups?
8. Are they aware of any available guidelines to help direct practice? Explore the role of the HCP and different professions during the request and disclosure of genetic tests?
9. How do they see this issue developing in the future as genetic technologies continue to develop? What measures would they like to see/ find useful to assist in their practice?

Appendix 7: HCP interview schedule (version 2)
Italics indicates the amendments made in this version

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no: 11/SC/0343

Interview Framework: Health Care Professionals

Study title: Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

This framework is intended to provide general guidance on areas to cover in the interview. The final interview framework used in the project will be informed by the results from the observation phase so the outline below acts as a guide at this stage. It is expected that the interview will take the format of a conversation/discussion that will begin with an introduction to the project and any outstanding issues around consent.

1. Discussion about the person's professional background and experience/interest in genetic testing. What sort of genetic tests are they organising and what range of results will these give? How often do they order genetic tests? *Lab protocols for reporting results?**
2. Explore the term 'incidental findings'. What is their understanding of this term? Can they give any examples from their practice where incidental findings have been discovered? What happened in these cases? Any issues to highlight looking back? *How do they describe IFs to families (phrases used?)*
3. Discussion of their 'usual' process of obtaining consent for genetic tests. What do they include/exclude in this discussion? Exploration of consent forms used and their content. Who takes consent/involvement of other team members? *If consent taken by non-geneticists any issues this raises? Issues if consent and disclosure performed by different teams?*
4. What is their 'usual' procedure for giving results (at a clinic appointment/by letter etc)? Is there any change to practice if an 'incidental finding' is discovered? Do they discuss these results with anyone prior to giving to the family*? Family recall of discussions at consent and specifically if IFs were raised as a possibility? How much do families understand the information being given/ask questions?*
5. How much detail is given about the 'incidental finding'? Is there a follow up plan put in place for families and if so can they given examples of what this may be?
6. Is there a responsibility for long term follow up of these families when adult onset 'incidental findings' are discovered? Whose responsibility is it? What measures are/need to be put in place to achieve this? *Ripple effect seen in families?*
7. Are they aware of other cases from colleagues, families or patient support groups?

8. Are they aware of any available guidelines to help direct practice? Explore the role of the HCP and different professions during the request and disclosure of genetic tests?
9. How do they see this issue developing in the future as genetic technologies continue to develop? What measures would they like to see/ find useful to assist in their practice?

Collect consent forms from the centres visited and any other relevant patient information

Appendix 7: HCP interview schedule (version 3)
Italics indicates the amendments made in this version

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no: 11/SC/0343

Interview Framework: Health Care Professionals

Study title: Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

This framework is intended to provide general guidance on areas to cover in the interview. The final interview framework used in the project will be informed by the results from the observation phase so the outline below acts as a guide at this stage. It is expected that the interview will take the format of a conversation/discussion that will begin with an introduction to the project and any outstanding issues around consent.

1. Discussion about the person's professional background and experience/interest in genetic testing. What sort of genetic tests are they organising and what range of results will these give? How often do they order genetic tests? Lab protocols for reporting results?
2. Explore the term 'incidental findings'. What is their understanding of this term? Can they give any examples from their practice where incidental findings have been discovered? What happened in these cases? Any issues to highlight looking back? How do they describe IFs to families (phrases used?)
3. Discussion of their 'usual' process of obtaining consent for genetic tests. What do they include/exclude in this discussion? Exploration of consent forms used and their content. Who takes consent/involvement of other team members? If consent taken by non-geneticists any issues this raises? Issues if consent and disclosure performed by different teams?
4. What is their 'usual' procedure for giving results (at a clinic appointment/by letter etc)? Is there any change to practice if an 'incidental finding' is discovered? Do they discuss these results with anyone prior to giving to the family? Family recall of discussions at consent and specifically if IFs were raised as a possibility? How much do families understand the information being given/ask questions?
5. How much detail is given about the 'incidental finding'? Is there a follow up plan put in place for families and if so can they given examples of what this may be?
6. Is there a responsibility for long term follow up of these families when adult onset 'incidental findings' are discovered? Whose responsibility is it? What measures are/need to be put in place to achieve this? Ripple effect seen in families?
7. Are they aware of other cases from colleagues, families or patient support groups?

8. Are they aware of any available guidelines to help direct practice? Explore the role of the HCP and different professions during the request and disclosure of genetic tests?
9. How do they see this issue developing in the future as genetic technologies continue to develop? What is their experience of gene panels and how do they take consent for these types of tests? What measures would they like to see/ find useful to assist in their practice?
*10. Is there a difference between the obligations of researchers versus clinicians when IFs are discovered? If they are involved in both areas, how does this work in practice?**
11. Is there a spectrum of when IF results should/should not be disclosed, for example, only if a treatment is available?
12. If they have an education component to their role, is the issue of managing incidental information being addressed in training of HCPs?

Collect consent forms from the centres visited and any other relevant patient information

Appendix 7: Family interview schedule (version 1)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Interview framework: Family members

Study title: Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

This framework is intended to provide general guidance on areas to cover in the interview. The final interview framework used in the project will be informed by the results from the observation phase so the outline below acts as a guide at this stage. It is expected that the interview will take the format of a conversation/discussion that will begin with an introduction to the project and any outstanding issues around consent.

1. Open with a discussion about personal and familial experience of the family condition and genetic testing.
2. Explore their experience of genetic testing in their family; what happened, how the family felt, any issues to highlight looking back?
3. Explore their recall of the discussion that took place when the possibility of genetic testing was being discussed and of the consent process that took place. Did they receive written information about this/follow up letter?
4. What is their recall of receiving their results (both the main result and the incidental finding)? How did they receive the result? Did they understand what it meant? Were they able to contact someone to discuss it further?
5. What happened/was discussed at a follow up appointment? Is there a long term follow-up plan? What will/did they tell their children about the results? Whose responsibility is it to discuss the incidental finding result with the children when at a relevant age? Have they a plan of how this will be achieved? What is their expectation from health care professionals in this role?
6. What is their understanding of the term 'incidental finding'? What does this mean? What does it mean within their own family? Would they have welcomed the opportunity to opt to not receive this result? What would be the possible implications from this?
7. What changes (if any) would they like to see in clinical practice around the area of genetic testing and 'incidental findings'? Explore the role of the health care professional and different professions. What information/support did you receive/need?
8. What problems/consequences do they associate with a test/result being undertaken or deferred?
9. How do they see these issues developing in the future as genetic technologies continue to develop? What measures would they like to see in place to help families?

Appendix 7: Family interview schedule (version 2)
Italics indicates the amendments made in this version

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Interview framework: Family members

Study title: Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications fro practice

This framework is intended to provide general guidance on areas to cover in the interview. The final interview framework used in the project will be informed by the results from the observation phase so the outline below acts as a guide at this stage. It is expected that the interview will take the format of a conversation/discussion that will begin with an introduction to the project and any outstanding issues around consent.

1. Open with a discussion about personal and familial experience of the family condition and genetic testing. *How did they come to have a genetic appointment/ process of referral?**
2. Explore their experience of genetic testing in their family; what happened, how the family felt, any issues to highlight looking back?
3. Explore their recall of the discussion that took place when the possibility of genetic testing was being discussed and of the consent process that took place. Did they receive written information about this/follow up letter? *How much information do they think is appropriate/necessary to be able to make decision about testing?*
4. What is their recall of receiving their results (both the main result and the incidental finding)? How did they receive the result? Did they understand what it meant? Were they able to contact someone to discuss it further?
5. What happened/was discussed at a follow up appointment? Is there a long term follow-up plan? What will/did they tell their children about the results? Whose responsibility is it to discuss the incidental finding result with the children when at a relevant age? Have they a plan of how this will be achieved? What is their expectation from health care professionals in this role?
6. What is their understanding of the term 'incidental finding'? What does this mean? What does it mean within their own family? Would they have welcomed the opportunity to opt to not receive this result? What would be the possible implications from this?
7. What changes (if any) would they like to see in clinical practice around the area of genetic testing and 'incidental findings'? Explore the role of the health care professional and different professions. What information/support did you receive/need?
8. What problems/consequences do they associate with a test/result being undertaken or deferred?
9. How do they see these issues developing in the future as genetic technologies continue to develop? What measures would they like to see in place to help families?

10. Do they think there should be a choice of what incidental information they receive/do not receive? Would it make a difference if there was a treatment available?
11. Is there a difference in research or with routine NHS testing on what information is fed back? Should there be?

Appendix 8: HCP recruitment pack (interviews)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Dear

Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

I am writing to invite you to participate in a research study being carried out by researchers from the University of Southampton. This study is looking at the important question of clinically relevant incidental findings discovered through genetic tests and the ethical issues surrounding the consent process and disclosure practices. Full details of the study are enclosed in the participant information sheet.

As part of this study the research team are interviewing health care professionals who are involved in ordering and/or giving genetic test results. I would be grateful if you could consider joining this study, which would involve one interview with a researcher lasting approximately an hour, exploring your experience with incidental findings in your clinical practice. The research team will also interview families where genetic testing has been completed and where incidental findings could have been identified (whether they actually have or not). The findings will enhance communication between health care professionals and families in addressing the possibility of incidental findings and their subsequent management and provide an evidence base for future policy and practice.

If you are interested in participating please complete the attached expression of interest form and return in the enclosed stamped addressed envelope. This research is being funded by a National Institute of Health Research (NIHR) fellowship and is being completed by Gillian Crawford as part of her PhD project. If you would like to discuss this further please contact her on 02380 794462.

With best wishes

Yours Sincerely

Gillian Crawford RGN, MSc
Clinical Doctoral Fellow

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Interviews (HCPs)
Expression of interest

Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

Research team: Gillian Crawford, Anneke Lucassen, Claire Foster, Angela Fenwick

Please complete as appropriate

I confirm that I have read the accompanying participant information sheet and would be happy for a member of the research team to contact me with more information ☐

Signature ..... Date.....

If interested please complete:

Name .....

Address .....

.....

.....

Contact telephone number .....

Best time to contact .....

Contact e-mail address .....

Please return to:
Gillian Crawford (stamped addressed envelope enclosed)

Ethics no:

Interviews
Information sheet

Health Care Professionals (HCPs)

Title of study: **Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice**

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

Purpose of the study

This research study aims to gain an empirical and ethical insight into the experiences and attitudes of healthcare users and professionals towards clinically relevant incidental findings from genetic testing. As genetic testing techniques have advanced enormously over the past few decades, it is now possible to examine large portions of a person's genetic code at costs manageable to routine NHS services. As well as diagnosing the cause of specific clinical signs and symptoms or family histories of disease, such genetic testing will also at times find entirely unexpected, but clinically relevant information about a person, such as future disease likelihood.

The results from this study will provide an important and timely evidence base for future policy and practice, enhancing communication between HCPs and families in addressing the possibility of incidental findings and their subsequent management.

Why have I been invited to take part?

You are invited to take part because you are involved in the care of families with a possible/definite genetic diagnosis and will have discussed genetic testing with them. It does not matter whether incidental findings have been identified through genetic testing or not but we want to see whether you would be willing to talk about your experiences of discussing genetic tests and results with families.

Do I have to take part?

No, you are under no obligation to take part in this study. Whether or not you agree to take part in the study is up to you. If you agree to take part and then later change your mind you are free to withdraw at any time.

What will happen to me if I take part?

The researcher will carry out an interview with you, which will take about one hour. The interview will be conducted at a venue of your choice, usually your work place. The interview will be recorded with your permission. The recording will then be transcribed and the data will enable us to identify key themes/issues and dilemmas. Once the data has been verified the recording will be destroyed. The findings of the research will be published in academic and health professional journals.

What are the possible disadvantages and risks of taking part?

Health care professionals taking part in this study may feel uncomfortable about discussing their experiences of genetic testing in their clinical practice but participants' confidentiality and anonymity will be maintained. You are free to stop the interview at any time and withdraw from the study.

What are the possible benefits of taking part?

While there may be no personal benefits to you in taking part in the study participants may find it helpful to have the opportunity to discuss their experience of identifying incidental findings in clinical practice. The data collected will contribute to a greater understanding of differing perspectives on the issues involved and lead to improved communication between health care professionals and families.

Will my taking part in the study be kept confidential?

All data will be collected and stored securely to ensure its confidentiality. Each participant will be assigned a code number so that it will not be possible for anyone to identify an individual person from the data. All data is stored using that code number. The data collected will be confidential to the research team. However, in reporting the data it may be that some events or things that individuals have said will be reported. In such cases, every effort will be made to ensure that the individual concerned cannot be identified. We may in some cases use direct quotations but these will always be anonymised. In no cases will individual's own names be used. Any data relating to individuals who the team feels may identify them will be excluded from reports or publications. All data will be collected and stored securely.

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to Gillian Crawford on 02380 794462. If you continue to have concerns you should ask to speak to a senior member of the research team (Professor Anneke Lucassen on 02380 794503) or the University Hospital Southampton NHS Foundation Trust Patient Advice and Liaison Services (PALS) on 02380 798498

What insurance provisions are in place?

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the sponsor, University Hospital Southampton NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you. As the Principal Investigator is a student of the University of Southampton, additional professional indemnity and clinical investigation insurance is in place.

What will happen to the results of the research study?

The findings of the research will be published in academic and health professional journals. Participants will be given details of the research project website address where they can access progress reports on the project and the study findings when available.

Who is organising and funding the research?

The research team organising the study is Gillian Crawford, Professor Anneke Lucassen, Dr Claire Foster and Dr Angela Fenwick from the University of Southampton. The study is funded by the National Institute of Health Research (NIHR) and is being completed as part of Gillian Crawford's clinical research fellowship.

Who has reviewed the study?

All research in the NHS is reviewed by a Research Ethics Committee. This study has been reviewed and given a favourable opinion by ...

What do I do now?

If you are willing to take part in this study then please complete the expression of interest form and return in the enclosed stamped addressed envelope. Gillian Crawford will then contact you to discuss the study in more detail. If you still wish to participate Gillian will arrange a mutually convenient time and venue to complete the interview. A consent form will be completed prior to the interview.

Further information

If you would like further information about the study please contact Gillian Crawford on 02380 794462 or on gc@soton.ac.uk.

Thank you for taking the time to read this.

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Date
Recipient address

Dear

Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

I am writing to invite you to participate in a study being carried out by researchers from the University of Southampton. You are being contacted because your family has been seen in a clinic where genetic tests may have been ordered. These tests can diagnose the genetic cause of specific signs and symptoms or family histories of disease. Sometimes when these tests are carried out unexpected genetic information about a person can also be revealed. These unexpected results we call 'incidental findings'.

This study is looking at the experiences and views of families who have undergone genetic testing. **The invitation to take part in the study does not necessarily mean that an incidental finding has been found in your own family.** Full details of the study are in the information sheet enclosed.

Your participation in the study would involve an interview lasting approximately 45 minutes to 1 hour discussing your experience of genetic testing in your family. The research team will also be interviewing health care professionals who order and/or give genetic test results. The findings of the study will enhance communication between health care professionals and families in addressing the possibility of incidental findings before testing is completed and the best way to discuss these results when they occur.

I would therefore be grateful if you would consider being involved in this study and if you are interested in participating please complete the attached expression of interest from and return in the stamped addressed envelope enclosed. If you would like to discuss this further please contact Gillian Crawford on 02380 794462.

With best wishes

Yours sincerely

Gillian Crawford RGN, MSc
Clinical Doctoral Fellow

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics date:

Interviews (Family Members)
Expression of interest

Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice

Research team: Gillian Crawford, Anneke Lucassen, Claire Foster, Angela Fenwick

Please complete as appropriate

I confirm that I have read the accompanying participant information sheet and would be happy for a member of the research team to contact me with more information ☐

Signature ..... Date .....

If interested please complete:

Name .....

Address .....

.....

.....

Contact telephone number .....

Best time to contact .....

Contact e-mail address .....

Please return to:
Gillian Crawford (stamped addressed envelope enclosed)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Interviews
Information sheet
Family Members

Title of study: **Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice**

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Talk to others about the study if you wish.

Purpose of the study

This research study aims to gain an insight into the experiences and attitudes of families and professionals towards genetic testing.

Genetic testing techniques have advanced enormously over the past few decades and it is now possible to examine large portions of a person's genetic material. The tests can diagnose the genetic cause of specific signs and symptoms or family histories of disease. Sometimes when these tests are carried out unexpected genetic information about a person can also be revealed. For example, the testing may indicate that a person has an increased chance of developing a health problem in later life. These unexpected results we call 'incidental findings'.

The invitation to take part in the study does not necessarily mean that an incidental finding has been found in your own family.

The findings from this study will improve communication between health care professionals and families in addressing the possibility of incidental findings occurring and also how families can best be supported if they are found.

Why have I been invited to take part?

You are invited to take part because you have had an appointment with the ( ) genetics service and discussed having a genetic test completed in your family. Your genetic service is collaborating with the University of Southampton in completing this research study. It does not matter whether an incidental finding was identified through genetic testing or not but we want to see whether you would be willing to talk about your experiences of having genetic testing completed within your family.

Do I have to take part?

No, you are under no obligation to take part in this study. Whether or not you agree to take part in the study is up to you. If you agree to take part and then later change your mind you are free to withdraw at any time.

What will happen to me if I take part?

The researcher will carry out an interview with you, which we envisage will take around 1 hour. The interview will be conducted at a venue of your choice, usually your home or local hospital. The interview will be recorded with your permission. The recording will then be transcribed and the data will enable us to identify key themes/issues and dilemmas. Once the data has been verified the recording will be destroyed. The findings of the research will contribute to publications in academic and health professional journals.

What are the possible disadvantages and risks of taking part?

There is the possibility that talking about the genetic diagnosis in your family can be upsetting. If you do become upset the interview can be stopped at any time either temporarily or permanently. You can decide to withdraw from the study. If issues arise during the interview that you feel would benefit from further discussion then the research team can ask your clinical genetics team to get in touch with you.

What are the possible benefits of taking part?

While there may be no personal benefits to you taking part in the study participants may find it helpful to have the opportunity to discuss their experience of having genetic testing completed in the family and the possibility of incidental findings being uncovered. It is hoped that the data collected will contribute to a greater understanding of differing perspectives on the issues involved and lead to improved communication between health care professionals and families.

Will my taking part in the study be kept confidential?

All data will be collected and stored securely to ensure its confidentiality. Each participant will be assigned a code number so that it will not be possible for anyone to identify an individual person from the data. All data is stored using that code number. The data collected will be confidential to the research team. However, in reporting the data it may be that some events or things that individuals have said will be reported. In such cases, every effort will be made to ensure that the individual concerned cannot be identified. We may in some cases use direct quotations but these will always be anonymised. In no cases will individual's own names be used. Any data relating to individuals who the team feels may identify them will be excluded from reports or publications. All data will be collected and stored securely.

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to Gillian Crawford on 02380 795082. If you continue to have concerns you should ask to speak to a senior member of the research team (Professor Anneke Lucassen on 02380 794503) or the University Hospital Southampton NHS Foundation Trust Patient Advice and Liaison Services (PALS) on 02380 798498

What insurance provisions are in place?

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the sponsor, University Hospital Southampton NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanism will still be available to you. As the Principal Investigator is a student of the University of Southampton, additional professional indemnity and clinical investigation insurance is in place.

Involvement of your General Practitioner

We do not plan to inform your GP of your participation in this study but can do so if you would like us to.

What will happen to the results of the research study?

The findings of the research will be published in academic and health professional journals. Participants will be given details of the research project website address where they can access progress reports on the project and the study findings when available.

Who is organising and funding the research?

The research team organising the study is Gillian Crawford, Professor Anneke Lucassen, Dr Claire Foster and Dr Angela Fenwick from the University of Southampton. The study is funded by the National Institute of Health Research (NIHR) and is being completed as part of Gillian Crawford's clinical research fellowship.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This study has been reviewed and given a favourable opinion by (name and ethics number)

What do I do now?

If you are willing to take part in this study then please complete the enclosed expression of interest form and return in the stamped addressed envelope. Gillian Crawford will then contact you to discuss the study in more detail. If you still wish to participate, Gillian will arrange a mutually convenient time and

venue to complete the interview. A consent form will be completed prior to the interview.

Further information

If you would like further information about the study please contact Gillian Crawford on 02380 795082 or on gc@soton.ac.uk.

Thank you for taking the time to read this.

Appendix 10: Examples of coded transcripts

HCPINT017

P: And then also we talk about that we might find something completely unrelated to why we're doing the test, that might have implications for your health now or in the future, and usually give examples of you know we might find something that means you're at increased risk of particular types of cancer or you might be at risk of you know cardiac problems and usually give a few examples. And then we have a consent form, which we run through with them, kind of once we've done that discussion, and as I said, we have a leaflet which we give to them.

I: Yeah, yeah. And I suppose maybe to sort of ask at this stage is sort of what your understanding of the term incidental findings; how would you sort of describe what that means?

P: Like I said, that you've found something that you weren't necessarily looking for, so we're doing the microarray generally speaking the vast majority of these, the people that we do the microarray test on is children with learning difficulties and maybe other features, so it could be congenital abnormalities or you know behavioural issues, things like that, and we might find something that's got absolutely nothing to do with their list of features that we, the reason why they were referred to us.

I: Right, okay.

P: But that is something that has you know implications possibly for their health or well-being now or in the future.

I: Yeah, yeah. And what's been your experience of discussing that with families; have they wanted to explore that or have they sort of just you know?

P: The vast majority just kind of go okay, yeah, that's fine. No, and maybe not the vast majority. Some just say yeah that's fine and just nod. Quite a lot say, oh right, yeah, great, obviously we'd want to know those things. I think possibly because of the examples I give, because as I said, I often sort of talk about cancer and cardiac side of things, I guess because that's the things I've come across in the literature have been those examples. And the vast majority, when I, you know mention those, say, well that's great, you'd want to know, because then you know what you're looking out for or you might be able to do something about it, you know there might be screening or treatments and things like that. So the vast majority of people see it as a positive thing that they would want to know. And I've actually only had one lady, one mum who was really, I don't want to know, I wouldn't want to know that, why would I, you know I'd just worry about it and I worry enough about everything that's going on, and she was really quite, ehrm anxious about that.

Comment [CG1]: Terminology

Comment [CG2]: Consent process Possibility of IFs

Comment [CG3]: Nature of an IF

Comment [CG4]: Possibility of IFs: Use of examples

Comment [CG5]: Consent form

Comment [CG6]: Patient information

Comment [CG7]: Description of an IF

Comment [CG8]: Description of an IF

Comment [CG9]: Nature of an IF: Clinically relevant now or in the future

Comment [CG10]: Experience of discussing IFs with patients

Comment [CG11]: Experience of discussing IFS with patients

Comment [CG12]: Patients want to know about IFs

Comment [CG13]: Examples used

Comment [CG14]: Reason for choice of examples

Comment [CG15]: Reasons for wanting to know about IFs

Comment [CG16]: Availability of screening/treatment

Comment [CG17]: View of patients (from HCP perspective)

Comment [CG18]: Patients may not want to know

Comment [CG19]: Experience of discussing the possibility of IFs in the clinic

Comment [CG20]: Reasons why patients may not want to know

P: But you see I'm, personally I'm the type of person who would want to know. And some people don't do they, they'd rather not know about it and if it happens it happens, but I'm more of a need to know person, that's the thing.

I: Yes.

P: So really what's good for me might not be good for Joe Bloggs you know.

I: Yes, yes. And do you remember when they talked to about doing the testing originally, did they mention at all that they might find other things, was that ever raised as a possibility?

P: No. That was a shock actually, when my brother had his done, his blood test, he just had to go up and get a blood test done, well for the RP thing, and it was out of the blue. He couldn't believe it when he got this letter saying about it, and which was horrible for him, because he's not very, he is blind and he's not very good at being blind, if you know what I mean. Some people are better at it. My mum was brilliant, but my brother has never, ever been very good. My mum would do everything, and she lived on her own and she did everything, but my brother has never been one to do that, so for him to have to go for more tests and scans, it's a big deal you know.

I: Right, okay, yes.

P: But I mean he did it. It was good, he did it, but so it was a bit of a blow for him to have to do that. But then they told him you know, I said to him, and he was doing for me really, because if it had been left to him, he wouldn't have done anything, he wouldn't have had the test in the first place and then he wouldn't have had the blood test and then he wouldn't have gone for the scan, he wouldn't, but he was doing it for me because I'd told him by then about my adopted son, and so he was doing, and for … , so he was doing it for us really. But no, he wouldn't have bothered. But you know it was a bit of a shock, because no we didn't know that they could have found anything else out. Nobody said that.

I: And did he get the results in a letter or in an appointment or; do you remember how he got them?

P: No, he definitely didn't have an appointment. He must have had a letter.

Comment [CG21]: Would want to know

Comment [CG22]: People may not want to know

Comment [CG23]: Attitude to predictive information

Comment [CG24]: Would want to know

Comment [CG25]: People can hold different views

Comment [CG26]: Consent process: Possibility of IFs

Comment [CG27]: Recall of discussions pre-test

Comment [CG28]: Experience of receiving an IF: Shock

Comment [CG29]: Experience of receiving an IF: Shock

Comment [CG30]: Experience of receiving an IF: Shock

Comment [CG31]: Experience of receiving an IF: How it felt

Comment [CG32]: Effect of receiving an IF: Need for further investigations

Comment [CG33]: Effect of receiving an IF: Significant information

Comment [CG34]: Reasons for genetic testing: Benefit of family members

Comment [CG35]: Reasons for genetic testing: Benefit of family members

Comment [CG36]: Reasons for genetic testing: Benefit of family members
Would have made different decisions if not for benefit of family

Comment [CG37]: Experience of receiving an IF: Shock

Comment [CG38]: Recall of discussions pre-test (no recall)
Consent process: Possibility of IFs not discussed

Comment [CG39]: Consent process: Possibility of IFs not discussed

Comment [CG40]: How IFs are disclosed (letter)

Appendix 11: Examples of emerging themes

FAMINT013

P: But you see I'm, personally I'm the type of person who would want to know. And some people don't do they, they'd rather not know about it and if it happens it happens, but I'm more of a need to know person, that's the thing.

I: Yes.

P: So really what's good for me might not be good for Joe Bloggs you know.

I: Yes, yes. And do you remember when they talked to about doing the testing originally, did they mention at all that they might find other things, was that ever raised as a possibility?

P: No. That was a shock actually, when my brother had his done, his blood test, he just had to go up and get a blood test done, well for the RP thing, and it was out of the blue. He couldn't believe it when he got this letter saying about it, and which was horrible for him, because he's not very, he is blind and he's not very good at being blind, if you know what I mean. Some people are better at it. My mum was brilliant, but my brother has never, ever been very good. My mum would do everything, and she lived on her own and she did everything, but my brother has never been one to do that, so for him to have to go for more tests and scans, it's a big deal you know.

I: Right, okay, yes.

P: But I mean he did it. It was good, he did it, but so it was a bit of a blow for him to have to do that. But then they told him you know, I said to him, and he was doing for me really, because if it had been left to him, he wouldn't have done anything, he wouldn't have had the test in the first place and then he wouldn't have had the blood test and then he wouldn't have gone for the scan, he wouldn't, but he was doing it for me because I'd told him by then about my adopted son, and so he was doing, and for ... , so he was doing it for us really. But no, he wouldn't have bothered. But you know it was a bit of a shock, because no we didn't know that they could have found anything else out. Nobody said that.

I: And did he get the results in a letter or in an appointment or; do you remember how he got them?

P: No, he definitely didn't have an appointment. He must have had a letter.

Comment [CG41]: Would want to know What patients want to know

Comment [CG42]: People may not want to know What patients want to know

Comment [CG43]: Attitude to predictive information What patients would want to know (leave to fate/chance)

Comment [CG44]: Would want to know What patients want to know

Comment [CG45]: People can hold different views What patients want to know

Comment [CG46]: Consent process: Possibility of IFs The consent process: Preparing for an IF

Comment [CG47]: Recall of discussions pre-test The experience of IFs: Recall of discussion

Comment [CG48]: Experience of receiving an IF: Shock The experience of IFs: what is it is like getting an IF

Comment [CG49]: Experience of receiving an IF: Shock The experience of IFs: what is it is like getting an IF

Comment [CG50]: Experience of receiving an IF: Shock The experience of IFs: what is it is like getting an IF

Comment [CG51]: Experience of receiving an IF: How it felt The experience of IFs: what is it is like getting an IF

Comment [CG52]: Effect of receiving an IF: Need for further investigations The experience of IFs: what is it is like getting an IF

Comment [CG53]: Effect of receiving an IF: Significant information The experience of IFs: what is it is like getting an IF

Comment [CG54]: Reasons for genetic testing: Benefit of family members Reasons for testing

Comment [CG55]: Reasons for genetic testing: Benefit of family members Reasons for testing

Comment [CG56]: Reasons for genetic testing: Benefit of family members Would have made different decisions if not for benefit of family Reasons for testing

Comment [CG57]: Experience of receiving an IF: Shock The experience of IFs: what is it is like

Comment [CG58]: Recall of discussions pre-test (no recall) The experience of IFs: Recall of discussion ...

Comment [CG59]: Consent process: Possibility of IFs not discussed The ...

Comment [CG60]: How IFs are disclosed (letter) Disclosure of results

Appendix 12: Consent form (Observations/HCPs)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Consent Form: Observation of Consultation: Health Care Professionals

Please initial the boxes below

1. I have read and understood the information sheet provided to me about this study (version ....). 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 without giving any reason ☐

3. I understand that direct quotations may be used in reporting the study but that these will anonymised ☐

4. I agree to take part in the above study ☐

.....	.....	.....
Name of participant	Date	Signature

……	……	……..
Researcher	Date	Signature

(copy for participant, copy for research file)

Appendix12: Consent form (Observations/Family members)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Consent Form: Observation of Consultation: Family Members

Please initial the boxes below

1. I have read and understood the information sheet provided to me about this study (version ....). 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 without giving any reason ☐

3. I understand that direct quotations may be used in reporting the study but that these will be anonymised ☐

4. I agree to take part in the above study ☐

.....	.....	.....
Name of participant	Date	Signature

……	……	……..
Researcher	Date	Signature

(copy for participant, copy for research file)

Appendix 12: Consent form (Interviews/HCPs)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Consent Form: Interviews: Health Care Professionals

Incidental Findings (IFs)

Please initial the boxes below

1. I have read and understood the information sheet provided to me about this study (version ....). 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 without giving any reason ☐

3. I understand that audio recording will be used to assist with the accuracy of participant's responses ☐

4. I understand that direct quotations may be used in reporting the study but that these will be anonymised ☐

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

.....	.....	.....
Name of participant	Date	Signature

.....	.....	.....
Researcher	Date	Signature

(copy for participant, copy for research file)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Consent Form: Interviews: Family Members

Incidental Findings (IFs)

Please initial the boxes below

1. I have read and understood the information sheet provided to me about this study (version 2). 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 without giving any reason ☐

3. I understand that audio recording will be used to assist with the accuracy of participants' responses ☐

4. I understand that direct quotations may be used in reporting the study but that these will be anonymised ☐

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

.....	.....	.....
Name of participant	Date	Signature

……	……	……..
Researcher	Date	Signature

(copy for participant, copy for research file)

Appendix 13: Assent form (adolescents)

Southampton NHS
University Hospitals NHS Trust

UNIVERSITY OF Southampton

Ethics no:

Assent Form

Your parent(s) have agreed that I can sit in on your clinic appointment but I'd also like to know whether you are happy for me to be there. If you are not then I won't sit in the appointment.

Please initial the box below if you are happy for me to be in your appointment

☐

.....	.....	.....
Name of participant	Date	Signature

……	……	……..
Researcher	Date	Signature

(copy for participant, copy for research file)

Appendix 14: NRES approval

NHS
National Research Ethics Service
NRES Committee South Central - Portsmouth
South West Research Ethics Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1382
Facsimile: 0117 342 0445

07 October, 2011

Ms. Gillian Crawford
University of Southampton
Wessex Clinical Genetics Service
Level G, Princess Anne Hospital
Coxford Road, Southampton
SO16 5YA

Dear Ms. Crawford,

Study title: **Incidental Findings (IFs) from genetic tests: exploring the ethical issues and implications for practice**
REC reference: **11/SC/0343**

Thank you for your letter of 02 September, 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Appendix 15: Questionnaire (version 1)

Medicine

UNIVERSITY OF Southampton

Preliminary outline of questionnaire

Demographic information

Clinical role Geneticist

Genetic Counsellor

Paediatrician (hospital based)

Paediatrician (community based)

Specialist registrar (specify specialism)

Genetic testing (general)

Do you order genetic tests?

Often Seldom Never

What tests have you ordered (ever)?

aCGH Karyotype WES WGS Targeted tests (e.g. FRAX, DMD, CF)

What tests do you order routinely (e.g. at least every month)?

aCGH Karytoype WES WGS Targeted tests (e.g. FRAX, DMD, CF)

Consent for genetic tests

Do you use a consent form?

Yes No Sometimes (please specify in what circumstances)

If not, do you document consent in the patient notes?

Yes No Sometimes (please specify in what circumstances)

Does the consent form include specific information about IFs?

Yes No

Do you think it should?

Yes No Not sure

Do you discuss the possibility of IFs with patients/parents?

Yes No Sometimes (please specify)

If so, do you use examples to illustrate what these could be?

Yes No Sometimes (please specify)

Do you discuss the possibility of Variants of Uncertain Significance

(VUS) with patients/parents? Yes No Sometimes (please specify)

Disclosure of test results

Do you think patients/parents should be given a choice on what IFs are disclosed?

Yes No Sometimes (please specify)

Do you think HCPs should decide what IFs will be disclosed (e.g. serious and treatable conditions)

Yes No Sometimes (please specify)

Do you think patients/parents should decide what IFs will be disclosed to them?

Yes No Sometimes (please specify)

If patients/parents choose should they be given:

- A list of all known possible IFs and opt in/out of each one

Yes No Please give reasons

- Given categories of results (e.g. serious and treatable, serious with no current treatment, carrier status)

Yes No Please give reasons

- Informed about what types of results the HCP would disclose and opt out as they wish

Yes No Please give reasons

Should the HCP be able to override the patient/parent wishes if they consider it is in their best interest to disclose a particular result?

Yes No Sometimes (please specify)

Should the HCP be able to override the patient/parent wishes if they consider it is in the best interest of their family members to be informed of the result?

Yes No Sometimes (please specify)

Do you think it is possible to make decisions about receiving incidental information if the patient/parent has no prior knowledge or family history about conditions listed?

Yes No Sometimes (please specify)

How much time do you think it will take patients/parents to consent for genome testing?

What tests should options be available for?

All Some (please specify)

Who should be taking consent for these tests? (please tick all that apply?)

GP

Specialist clinician (e.g. paediatrician)

Trainee

Geneticist

Genetic Counsellor

Appendix 16: HCP recruitment pack (cognitive interviewing)

Medicine

UNIVERSITY OF Southampton

Ethics no: 9913

Date:

Dear

Incidental Findings from Genetic Tests: Exploring the ethical issues and implications for practice. Development of a questionnaire using cognitive interviewing

I am writing to invite you to participate in a study being carried out by researchers from the University of Southampton. This study is looking at the interaction and communication between clinicians and the families they see in clinic when ordering genetic tests and disclosing results. Full details of the study are enclosed in the participant information sheet. This PhD project is part of a National Institute Health Research funded clinical academic fellowship.

Following qualitative work I am now developing a questionnaire that will be sent to HCPs nationally that routinely order genetic tests. The initial questionnaire design has been informed by the outcomes from the qualitative work. Prior to sending the questionnaire out I am looking for a small group of HCPs who will help me to refine the questionnaire using a technique called Cognitive Interviewing (CI). Full details of this technique can be found in the participant information sheet but it will involve meeting up a few times (likely to be 4-5 occasions) to complete and comment on the questionnaire.

If you are interested in participating I would be grateful if you could e-mail me on gc@soton.ac.uk and we can discuss the study in more detail. If you have any questions please contact me on 02381 205082.

With best wishes

Yours Sincerely

Gillian Crawford RGN, MSc
Clinical Doctoral Fellow

Appendix 16: HCP recruitment pack (cognitive interviewing)

UNIVERSITY OF Southampton

Participant Information Sheet (Cognitive Interviewing)

Study Title: Incidental Findings from Genetic Tests: Exploring the ethical issues and implications for practice. Development of a questionnaire using cognitive interviewing

Researcher: Gillian Crawford **Ethics number**:9913

Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

You are being invited to participate in the development of a questionnaire as part of a larger study: Incidental Findings from Genetic Tests: Exploring the ethical issues and implications for practice. The results from this study will provide an important and timely evidence base for future policy and practice, enhancing communication between Health Care Professionals (HCPs) and families in addressing the possibility of incidental findings and their subsequent management. The qualitative phases of this study are now complete and the findings from these now need to be tested through a survey questionnaire which will distributed nationally to HCPs who are involved in discussing and organising genetic testing.

You are being invited to participate in the development and refinement of the questionnaire. I will be employing a technique called Cognitive Interviewing (CI) which will involve looking at how people understand, mentally process and respond to the questionnaire being presented, with special emphasis on any potential problems with it.

This project is funded by NIHR and the research is work towards my PhD.

Why have I been chosen?

You have been invited because you look after families with genetic diagnoses and will often discuss genetic testing in your clinical practice. It does not matter whether incidental findings have been identified in your patients or not. Findings from the qualitative work has identified that HCPs are not routinely discussing the possibility of IFs with families or establishing what incidental information patients would like to have disclosed. Despite this they reported that the issues were important ones to raise with families. The next step is to find out if the findings from the qualitative work are replicated in a much larger cohort of HCPs.

What will happen to me if I take part?

We will need to meet on a number of occasions to complete the full CI process. An initial appointment will be arranged to carry out the first round of CI. This will involve either a face to face meeting or a Skype call and you will be asked to complete the questionnaire as usual but to speak aloud any questions you have about it or when questions are unclear. I will also ask you some questions about the questionnaire as you are filling it in. The meeting will be audio recorded so I do not need to make notes. There will be approximately 6-8 other HCPs doing the same process. I will then look at all the comments that have been made and following discussion with my

supervisors make changes to the questionnaire. I will then arrange another meeting with you and we will go through the same process. This will continue until no new issues emerge. This is likely to be in the order of 4-5 times, either face to face or via Skype (or similar). Each meeting will take about 30 minutes.

Are there any benefits in my taking part?

There are unlikely to be any direct benefits to you by taking part. However, you may find the process interesting. Once the questionnaire has been refined and circulated to a wider audience, the data collected may in due course contribute to the development of clinical guidelines on managing IFs.

Are there any risks involved?

It is not envisaged that there are any significant risks involved in taking part. Participation will take up some of your time on a number of occasions. This process is about refining the questionnaire so it can best answer the research questions and is not assessing any aspects of your clinical practice.

Will my participation be confidential?

Once you have agreed to participate in the study you will be allocated a unique identifying number that will be used on all subsequent study documentation. Study data will be stored on a password protected university computer. Consent forms will be stored separately to other study documentation so that your personal details cannot be matched to your questionnaires. Data will be stored in line with University policy and destroyed after 10 years

What happens if I change my mind?

If you no longer wish to participate in the study you are free to withdraw at any time. Data you have already given will still be used as it would not be possible to remove these as the questionnaire will have already been amended.

What happens if something goes wrong?

In the unlikely case of concern or complaint, you should in the first instance contact the study chief investigator Gillian Crawford on 02381 205082. You can also contact Professor Anneke Lucassen on 02381 206841 who is supervising this project. If you remain unhappy you can also contact the Research Governance office on 02380 595058 or rgoinfo@soton.ac.uk.

Where can I get more information?

If you have any questions or wish to discuss this project further please contact Gillian Crawford on 02381 205082.

Appendix 17: Consent form (cognitive interviewing/HCPs)

UNIVERSITY OF Southampton

CONSENT FORM (version1)

Study title: Incidental Findings from Genetic Tests: Exploring the ethical issues and implications for practice. Development of a questionnaire using cognitive interviewing

Researcher name: Gillian Crawford

Ethics reference number 9913
Please initial the box(es) if you agree with the statement(s):

I have read and understood the information sheet (insert date /version no. of participant information sheet) and have had the	☐
I agree to take part in this research project and agree for my data	☐
I understand my participation is voluntary and I may withdraw at	☐
I understand that the cognitive interview(s) will be audio recorded	☐

Name of participant (print name)……

Signature of participant……..

Date……

Name of researcher (print name)……

Signature of researcher ……..

Date……

Appendix 18: Example of analysis of cognitive interviewing round one

This includes analysis of the recording, notes written on the questionnaire and notes made during the CI process itself.

CIHCP001

Demographic : clinical role to include trainee

Genetic testing (general): Give parameters/a range for often and seldom (i.e. numbers per clinic). Definitions for WES/WGS needed. Add a cancer example to the targeted list of tests.

Consent for genetic tests: Add in a N/A to the second question or re-format order/wording so clearer. Define IFs (as first mention). With question about do you discuss the possibility need to have some option for N/A if only doing testing that has a low chance of an IF. Think about structuring for questions that follow on from one another i.e. if so, …

Disclosure of test results: Add in an introductory paragraph about the issue of disclosure of IFs. Define HCPs. Think of an alternative word for sometimes (not sure/it depends). Re-word question 1 and 3 as reads very similarly. With option questions do you want participant to pick one as their answer or can say yes or no to each one? Doesn't think categories need more explanation (but works in genetics, it would be important to see what a paediatrician thinks). Keep in please give reasons and leave space for free text. How much time… change to consent process. Add in different tests as may want to indicate that different types of tests will take different time. What tests should option… may need to list the type of tests you want participants to comment on or change to what tests the participants think should include a discussion about IFs. For who should be taking consent thinks you should differentiate between the different types of tests as may want to indicate different people for different results. Specify what is meant by trainee. Add other to list of HCPs and then ask to please specify. Short explanation at start to give context for questions. Supports using tick boxes to indicate responses with a box for free text. Make sure layout flows so all options are on one page and don't go onto the next page as may get missed. Good length. Add a free text box at the end for other

comments. Ensure list of HCPs includes all those who will form the sample. Add question numbers.

CHHCP002

Questions need numbering. Genetic testing (general): Define WES/WGS. Add in a 'other' option for lists of tests with place to specify what this is. Often/seldom is subjective so may be helpful to clarify. Use of word 'routinely', what does that mean?

Consent: Re-word if not, do you document in the notes as may do before so perhaps split question into two. In question about using examples could include a space and ask participant to given details of an example they would use. If ask for examples with IFs and VUS questions could this help pick out confusions over what it is they are discussing.

Disclosure of test results: Add in space for comments as may wish to explain answers. Consider if questions 1 or 2 should be amalgamated to give an either/or response. Stumbled at Q 1 and 3 but can see they are different questions so not saying what they should be changed but needs considering as not clear at first reading. List of options assumed this was on one page so need to ensure they responses are not spilt over 2 pages. Would prefer not to have to choose between 3 options as not exclusive and see if respondents are picking contradictory responses. Add free text boxes to the more complex questions so people can add to their response. Add in vignettes to illustrate questions and can also help with seeing if responses are consistent. Add time slots to the time question. Keep in genome testing but maybe explain/define so participants talking about the same test so can be compared. Add in a question about needing more appointments to consent or can they consent at the first appointment or should have more time to consider. Option question comes after the other questions about options so confusing as to what it is actually asking. Use the tests listed on page 1. List should or could or both. Add in other.

Format: Doesn't mind tick boxes or circling but currently not clear and questions need numbering. Order is logical. Demographics: prompted by me and thinks a good piece of information to capture about their experience and/or experience of genetic testing.

CIHCP003

Demographic: nil

Genetic testing: Aware of WES/WGS. Could add in to questions on testing is on a clinical basis only (to differentiate from research). Numerical scale: would be helpful but may not be accurate but likely to be more precise than as it is now.

Consent: Sometimes ok in first question. Add in the word process to the document question. When probed agreed to change document question so all can fill in even if say yes to previous question. Can we replace sometimes with usually or have both. Instead usually often or change to always, usually, sometimes, no. Take out if not.

Disclosure: Needs introductory paragraph to explain what types of results from what types of tests. Add a question about whether decisions are individual clinician or national consensus. Q 1 and 3 not clear immediately but subtly different so need re-wording and possibly put next to each other. Whole section to be more binary and a step by step question sequence and separate patient/parent and HCP questions. Start with should they be given choice and if so some or all and if some which. 3 options, could list all and tick all you agree with or rank them. Option 2 and 3 overlap and not clear. Override, separate parent and patient as the two are different. Replace please specify with expand and include a line to encourage free text. Time question: useful for data collection to put in time slots. But danger of questions being leading so maybe free text is better as get the reality and not just choose for example, the middle one. Agrees with putting in the different tests and asking about time to consent. What option needs to go further up with the questions about this. For constancy include targeted as on page 1 even though not so relevant. Add another question who do you think is qualified to take consent or what training does someone need? Clarify trainee. Last section could have separate heading. Other option of formatting could be current practice, role of the patient, role of the HCP.

Format: Like tick boxes as makes it clear that filled in correctly. Ordering of sections.

CIHCP004

Demographic: Change specialist registrar to specialist trainee.

Genetic testing (general): First question: Could have yes/no first and then frequency. Parameters for seldom, often etc. would be helpful but not specific numbers.

Second question: need to clarify aCGH is an array. Targeted test to include trisomy test. Definitions need for WES/WGS. Does not know targeted conditions except CF.

Consent for genetic tests: ? include a question about availability of procedure/guidance etc. on consent for genetic tests. Take out if not, as always write in the notes, regardless if a consent form is used or not and can refer to consent form.

Third question: need to define what mean by IFs. Need to keep these questions in even if have said don't use a consent form as if documenting in notes (and taking consent) can make a comment about IFs etc. Can write out IFs in full but will still need to explain it upfront. Do you think it should: add in rest of sentence above…include specific…

The later questions in this section are about the process of consent rather than a form per se so may need to broaden question? Helpful to add an example to the question about using examples. Helpful to define VUS as this participant believes that many paediatricians will not be familiar with this term and that genetic testing has changed so much over recent years that they will not be familiar with these terms.

<u>Disclosure of results:</u>

Question 1 may need to clarify that this is before the testing is done and not when you have the results.

Question2: define HCP. Change response as before to always, sometimes etc. Add in free text boxes.

Question 3: should be next to number 1. Current wording does not bring out the different nuances of the two questions.

Question 4: Need space for free text. Better rather than say yes/no to each one instead list all possible and choose best one. Third option could be split into 2 questions, one option where HCPs say what would normally be disclosed and get patient to choose and the other where informed what HCP will/will not disclose and not given a choice.

Question 5: Can ask for illustration of a situation where they would/wouldn't override patient decision. Supported vignette at beginning of this section about an IF.

No prior knowledge question, move to consent section (and can be a yes/no response).

Time question: Consent is not a one off thing it is ongoing. Could give time parameters and if ask is it more a process rather than a one off event then this could be leading and the right answer. Make the time question a free text answer as this will give you more information. Can add a question early in the consent section about how participants view consent in relation to genetic testing.

Can ask a question at the beginning about what are incidental findings/VUS and then come on to other questions. Might put people off though or (me people might go back and change their answers).

What tests should options be available for? Doesn't understand the questions, needs rewording and moving to another part of the questionnaire. Would be better to list the tests included at the beginning.

Who should be taking consent? Make trainee more specific.

General: headings: can take out demographic, can take out general from genetic test heading. Could move the more practical questions about consent at the end to earlier in the consent section. Free text at end unlikely to be filled in so better to have after each question. Prefers tick boxes or circling, doesn't like numbers or scales.

Feels like a questionnaire for people in the know (genetics) but need to make more user friendly for people not doing these tests all the time (e.g. paediatrician).

CIHCP005

Demographic: specialist trainee best term (to include junior and senior trainees). Could add specify year of training.

Genetic testing: Q1 Does not consider that she orders tests as decision to proceed made by consultant (and discusses with parents) but does take blood, do the forms.

How to integrate this into the question? Agreed with adding parameters for frequency of ordering tests. Q2: define tests, change to array.

Q3 Add a N/A option if someone has indicated that they don't order tests

Consent: Q1 Junior may not do the form (if one is done) but consultant, can this be reflected in question.

Q2 Take out if not so can say yes to both and not one or the other. Could ask if aware of a consent form for genetic tests.

Q3 Define IFs, define and short summary.

Q4 Nil

Q5 Would like a N/A option as would want to discuss but as not discussing tests with parents then wants to say N/A rather than no.

Q6 N/A

Q7 VUS, definition and summary and difference between IFs or VUS (or do we want to see if people think they are the same thing).

Disclosure: Q1 not clear, could change what to whether. Make more clear that it is a more philosophical question rather than a practical, how would you do it question. Question more about the right to find out or right to choose or have access to or right not to know.

Q2 Define HCPs, instead of patients. Could make them choose between one or other (patient or HCP).

Q3 Too like number 1, need to make difference clearer. Difficult to make it clear in the questions if asking about patient having choice or how could they exercise their choice and if they can't is asking if they can have a choice worth asking?

Vignette might help with these more difficult questions. Add in something about 'based on your current knowledge' so not seen as judging practice, based on current clinical practice. Q 1 or 2 should be a choice of either one, can't answer both.

Q4 third option split into 2 questions. Re-structure to make a choice for the best answer. Re-phrase question into who decides and then what options as have an HCP option so doesn't make sense for the patient to be deciding. Split last option into two. Need to be able to establish views on where patients sit on a spectrum on patients being given all choices and deciding or no choices and those in between.

Q5 Would want an addition to this question that if patient has been fully consented but I think participant needs to add their own views to the text box and tick the sometimes option.

Q7 prior knowledge, specify if this is no knowledge before the initial appointment rather than when the HCP has gone through some of the conditions as part of consent. Could add another question about whether the HCP can/has time to discuss all the possible IFs? Add prior to consenting process.

Q8 Do you want this question to reflect the different option e.g. time if patients are to be given all options or time if HCP decides. Include timeframes. May need question of number of appointments/cooling off period etc.

Q9 re-word question and move to consent section. Include same list of tests. Choosing two things in this question as who chooses and which test. First question and then which ones should patients be given options or not. Paediatricians may not know difference between the different types of tests e.g. WES and WGS. Information column down the side with definitions or if on computer put a i button with details.

Q10 Clarify speciality consultant with an example and then speciality trainee, not just trainee. Please specify year of training.

General: tick boxes or circling. Consistency important. Logical. Perhaps a question about would you appreciate more training on this?

Appendix 19: Issues taken for discussion at first judge's panel

JUDGE'S PANEL (1)

From the first round of interviews the following issues were raised. The numbers in brackets indicate the number of participants who raised this issue. Italics indicated issued I was unsure about changing.

General

Questions need numbering (5)

Think about question order if one follows on from the other

Explanations at beginning of sections to give context (2)

Page layout, questions completed on one page (2)

Provide free text option (5)

Tick boxes or circling (4)

Demographic

Add trainee genetic counsellor (1)

Change specialist registrar to specialist trainee (2). *Separate junior and senior and add year of training (1)*

Experience (1)

Genetic testing (general)

Give parameters for often/seldom (some numerical range) (3)

Definition for WES/WGS needed (4) Full term for aCGH (2) Define targeted tests (2)

Add a cancer example to list of tests (1)

Add other to list of tests (1)

Could add testing is on clinical basis (not research) (1)

Add in something to indicate consultant orders test but ST organises it (1)

Consent

Define IFs (3) VUS (2)

Do you discuss the possibility, add N/A if low chance (1)

Re- word question about if not, as many will do both and this takes away this option (4)

Space for examples/free text (4)

Add process to question 2 (2)

Change option to always, usually, sometimes, never (1 and then next 2 agreed when probed)

Include a question about availability of guidance/procedures (1)

Change no to N/A or have both (1)

Disclosure

Introductory paragraph (2)

Define HCP (3)

Question 1 and 3 need re-wording as too similar and confusing (5)

Re-order Q 1 and 3 (4)

Options question (pick best one rather than yes/no) (5)

Add in the list of different tests from earlier section (5)

Add vignettes (3)

Add question about whether decisions are individual or national consensus (1)

Separate parent/patient (1)

Q1 clarify this is before testing is done (1)

Q4 spilt into 2 questions the last option (2)

What tests should options be available for (doesn't understand question) (1)

Clarify prior knowledge (1)

Clinic implications

Who should be taking test? Link to different tests (1)

Specify trainee (3)

Add other to list of HCPs (2)

Add time slots (4)

Add question about needing more time/second appointment (2)

Add list of tests to the time question (4)

Use information boxes or i button (1)

Appendix 20: Questionnaire (version 2)

Medicine

UNIVERSITY OF Southampton

Second version of questionnaire

Genetic testing has developed over recent years and a number of different tests are now available that are relatively quick and cheap to carry out. As testing becomes more detailed the number of possible diagnoses identified will increase but also the possibility of finding other unrelated genetic information will rise. An example of this would be carrying out a genetic test in a child with developmental delay and discovering an inherited predisposition to an adult onset cancer syndrome at the same time. These types of findings have been called Incidental Findings (IFs).

This questionnaire is asking HCPS who arrange genetic testing in their clinical practice for their views and experiences of organising these tests particularly with regard to consenting patients and disclosing results. Results from this survey will be collated, analysed and used to inform practice and guideline development.

Thank you for participating in this survey. It should take no more than 10-15 minutes to complete.

A. Demographic information

1. What is your clinical role?

Geneticist ☐

Genetic Counsellor ☐

Trainee genetic counsellor ☐

(please specify year of training)

Paediatrician (hospital based) ☐

Paediatrician (community based) ☐

Specialist trainee (please specify specialism ☐

and year of training)

B. Genetic testing

Section B is asking about the frequency and types of genetic tests that you request in your clinical practice.

1. Do you order genetic tests in your clinical practice?

Yes ☐ No ☐

If yes please specify the frequency over a 6 month period:

Often (in most clinics) ☐ Seldom (1-2 clinics per month) ☐ Never (or very infrequently) ☐

2. What genetic tests have you (ever) ordered?

Array CGH ☐ Karyotype ☐ Whole Exome Sequencing ☐

Whole Genome Sequencing ☐ Targeted tests (e.g. Fragile X, Cystic Fibrosis) ☐

Other (please specify) ☐

……..

3. What tests do you routinely order (e.g. at least in one clinic every month)?

Array CGH ☐ Karyotype ☐ Whole Exome Sequencing ☐

Whole Genome Sequencing ☐ Targeted tests (e.g. Fragile X, Cystic Fibrosis) ☐

Other (please specify) ☐ ……..

C. <u>Consent for genetic tests</u>

Section C is asking about your views and practice when taking consent from a patient/parents of a patient for genetic testing.

1. Do you ask patient's/parents to fill in a consent form when organising a genetic test?

Always Usually ☐ Sometimes ☐ Never ☐

Please specify ……

2. Do you document the consent process in the patient notes?

Always Usually ☐ Sometimes ☐ Never ☐

Please specify ……

3. Does the consent form include specific information about Incidental Findings (IFs)?

Yes ☐ No ☐

IFs are findings of (potential) clinical significance discovered during routine genetic testing, unrelated to the original reason for the test.

4. Do you think it should include specific information about Incidental Findings (IFs)?

Yes ☐ No ☐ Not sure ☐

Please specify……

5. Do you discuss the possibility of IFs with patients/parents when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Please specify……..

6. If you discuss the possibility of IFs do you use examples to illustrate the types of results these could be (for example, identifying adult onset cancer predisposition)

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……

7. Do you discuss the possibility of Variants of Uncertain Significance (VUS) with patients/parents? These are genetic test results where the clinical significance of the result is uncertain at the time of reporting.

This is an alteration in the normal sequence of a gene, the significance of which is unclear at the time of reporting. Further work is needed to confirm clinical significance or not

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……

D. <u>Disclosure of test results</u>

Section D is asking about your views and practice about the disclosure of genetic test results with specific reference to IFs.

1. Do you think patients/parents should have a choice on what IFs are disclosed to them?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……

2. Do you think patients/parents of patients alone should make the decision on what IFs are disclosed to them?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify ……

3. Do you think Health Care Professionals (HCPs) alone should decide what IFs are disclosed to patients/parents (e.g. only serious and treatable conditions)?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……

4. When making decisions about which IFs are disclosed to patients/parents which of the following options are the best approach? Tick one best answer.

a.) Patients/parents are given a list of all possible IFs that can occur and opt in/out of receiving each one individually?

☐

b.) Patients/parents are given categories of IFs that can occur and choose which category(s) they wish to receive (for example, the category of serious and treatable conditions or the category of carrier status)

☐

c.) HCPs inform patients/parents about the IFs (or categories of IFs) that will be disclosed

☐

d.) HCPs inform patients/parents about the IFs (or categories of IFs) that will be disclosed and the patient/parents opt in/opt out of the IFs (or categories of IFs) they wish to receive.

☐

5. With which genetic tests should options for disclosure be available to patients/parents? Tick all that apply

Array CGH ☐ Karyotype ☐ Whole Exome Sequencing ☐

Whole Genome Sequencing ☐ Targeted tests (e.g. Fragile X, Cystic Fibrosis) ☐

None ☐

Please specify……

6. Do you think it is possible for patients/parents to make decisions about receiving IFs if they have no prior knowledge or family history of the conditions listed?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……

7. Should the HCP be able to override the patient/parent wishes if they consider it is in their best interest to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……..

8. Should the HCP be able to override the patient/parent wishes if they consider it is in the best interest of their family members to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please specify……

E. Clinic implications

Section E is asking about practical aspects of organising genetic tests in the clinic.

1. How much time do you think it will take patients/parents to undertake the consent process for:

a.) Array CGH Under 15 minutes ☐ 15-30 minutes ☐ Over 30 minutes ☐

b.) WES Under 15 minutes ☐ 15-30 minutes ☐ Over 30 minutes ☐

c.) WGS Under 15 minutes ☐ 15-30 minutes ☐ Over 30 minutes ☐

2. Do you think a follow up appointment is required before genome testing is initiated to give patients/parents time to consider the options?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Please
specify……

3. Who should be able to take and order consent these tests? (please tick all that apply)

GP ☐

Specialist clinician (e.g. paediatrician) ☐

Specialist trainee (please specify) ☐

Geneticist ☐

Genetic Counsellor ☐

Other (please specify) ☐

Please write any other comments here

Thank you for your time and completing this questionnaire.

Third version of questionnaire

Genetic testing has developed over recent years and a number of different tests are now available that are relatively quick and inexpensive to carry out. As testing becomes more detailed, the number of possible diagnoses identified will increase but also the possibility of finding other unrelated genetic information. An example of this would be carrying out a genetic test in a child with developmental delay and discovering an inherited predisposition to an adult onset cancer syndrome at the same time. These types of findings have been called Incidental Findings (IFs).

This questionnaire is asking Health Care Professionals (HCPs) who arrange genetic testing in their clinical practice for their views and experiences of organising these tests particularly with regard to consenting patients (or parents of patients) and disclosing results. Results from this survey will be collated, analysed and used to inform practice and guideline development.

Thank you for participating in this survey. It should take no more than 10-15 minutes to complete.

A. Demographic information

1. What is your clinical role?

Clinical Geneticist ☐

Genetic Counsellor ☐

Trainee Genetic Counsellor ☐
(please specify year of training) ☐

Paediatrician (hospital based) ☐

Paediatrician (community based) ☐

Specialist trainee ☐
(Please specify year of training) ☐

Specialty …….

☐

Other (Please specify) ……..

B. <u>Genetic testing</u>

The frequency and types of genetic tests you request in clinical practice.

1. Do you order genetic tests in your clinical practice?

Yes ☐ No ☐

If yes, please specify the frequency over a six month period:

Often (weekly) Seldom (once or twice a month) Infrequent (once every few months) Never

☐ ☐ ☐ ☐

2. What genetic tests have you (ever) organised in your clinical practice?

Array CGH (aCGH) Karyotype Whole Exome Sequencing (WES)

☐ ☐ ☐

Whole Genome Sequencing (WGS) Targeted test (e.g. Fragile X)

☐ ☐

Other (please specify)

……

3. What tests do you **routinely** order (a few times each month)?

aCGH Karyotype WES

☐ ☐ ☐

WGS Targeted tests (e.g. Fragile X)

☐ ☐

Other (please specify)

……

C. <u>Consent for genetic tests</u>

Your views and practice when taking consent for genetic testing.

1. Do you (or your team) ask patients to fill in a consent form when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

2. Do you detail what was discussed in the patient notes?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

3. Does the consent form include specific information about Incidental Findings (IFs)?

Yes ☐ No ☐

IFs are findings of (potential) clinical significance discovered during routine genetic testing, unrelated to the original reason for the test.

4. Do you discuss the possibility of IFs with patients when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

5. Do you think the consent process should include information about Incidental Findings (IFs)?

Yes ☐ No ☐

Additional comments:

6. If you discuss the possibility of IFs do you use examples to illustrate the types of results these could be (for example, identifying adult onset cancer predisposition)

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

7. Do you discuss the possibility of Variants of Uncertain Significance (VUS) with patients?

A VUS is an alteration in the normal sequence of a gene, the significance of which is unclear at the time of reporting. Further work is needed to confirm if clinically significant or not

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

D. <u>Disclosure of test results</u>

Your views and practice about the disclosure of genetic test results with specific reference to IFs.

1. To what extent should patients have a choice on what IFs are disclosed to them? Please rank the following four options (1 = statement you agree with most, 4= statement you agree with least)

- Patients should always choose ☐
- Patients and HCPs should choose together ☐
- HCPs should always choose ☐
- Neither will choose as national guidelines have already made these decisions ☐

2. Do you think patients alone (after genetic counselling) should make the decision on what IFs are disclosed to them?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

3. Do you think HCPs should have sole responsibility for deciding what IFs are disclosed to patients?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

4. If the patient is involved in the choice of IFs disclosed which of the following options is the best approach? Tick one best answer.

- Patients are given a **list** of all possible IFs that can occur and opt in or out of receiving each one ☐

- Patients are given **categories** of IFs that can occur and they choose which category(s) they would want to receive. Categories may be, for example, all conditions that are serious and treatable or conditions that are serious with no treatment ☐

- HCPs inform patients about the IFs that will **automatically** be disclosed and then give the patient the IF **options** they can choose ☐

5. With which genetic tests should the option for IF disclosure be available? Tick all that apply

aCGH ☐ Karyotype ☐ WES ☐

WGS ☐ Targeted tests (e.g. Familial Adenomatous Polyposis) ☐

None

☐

Additional comments:

6. Do you think it is possible for patients to make decisions about receiving IFs if they have no personal experience or family history of the conditions listed?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

7. Should the HCP be able to override the patient wishes if they consider it is in the **individual's** best interest to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

8. Should the HCP be able to override the patient wishes if they consider it is in the best interest of their **family members** to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

E. <u>Clinic implications</u>

Practical aspects of organising genetic tests in the clinic.

1. How much time do you think it will take you to undertake the consent process for:

aCGH Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

WES Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

WGS Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

2. Do you think a follow up appointment is required before testing such as aCGH, WES, WGS is initiated to give patients time to consider the options?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

3. Who should be able to take consent and order the following tests? (please tick all that apply)

	Karyotype	aCGH	WGS
GP	☐	☐	☐
Specialist clinician (e.g. paediatrician)	☐	☐	☐
Specialist trainee (please add specialty)……..	☐	☐	☐
Geneticist	☐	☐	☐
	☐	☐	☐

Genetic Counsellor

Other (please specify) ☐ ☐ ☐

Please write any other comments here

Thank you for your time and for completing this questionnaire.

Appendix 22: Questionnaire (version 4)

Medicine

UNIVERSITY OF Southampton

Fourth version of questionnaire

Genetic testing has developed over recent years and a number of different tests are now available that are relatively quick and inexpensive to carry out. As testing becomes more detailed, the number of possible diagnoses identified will increase, as will the possibility of finding other unrelated genetic information. An example of this would be carrying out a genetic test in a child with developmental delay and discovering an inherited predisposition to an adult onset cancer syndrome at the same time. These types of findings have been called Incidental Findings (IFs).

This questionnaire is asking Health Care Professionals (HCPs) who arrange genetic testing in their clinical practice for their views and experience of organising these tests particularly with regard to consenting patients (or parents of patients) and disclosing results. Results from this survey will be collated, analysed and used to inform practice and guideline development.

Thank you for participating in this survey. It should take no more than 10-15 minutes to complete.

A. Demographic information

1. What is your clinical role?

Clinical Geneticist ☐

Genetic Counsellor ☐

Trainee Genetic Counsellor ☐
(please specify year of training) ☐

Paediatrician (hospital based) ☐

Paediatrician (community based) ☐

Specialist trainee ☐
(Please specify year of training) ☐

Specialty …….

Other ☐

(Please specify) ……

B. <u>Genetic testing</u>

The frequency and types of genetic tests you request in clinical practice:

1. Do you order genetic tests in your clinical practice?

Yes ☐ No ☐

If yes, please specify the frequency over a six month period:

Often (weekly) Seldom (once or twice a month) Infrequent every few months) Never

☐ ☐ ☐ ☐

2. What genetic tests have you (**ever**) organised in your clinical practice?

Array CGH (aCGH) Karyotype Whole Exome Sequencing (WES)

☐ ☐ ☐

Whole Genome Sequencing (WGS) Targeted test (e.g. Fragile X)

☐ ☐

Other (please specify)

……

3. What tests do you **routinely** organise (a few times each month)?

aCGH Karyotype WES

☐ ☐ ☐

WGS Targeted tests (e.g. Fragile X)

☐ ☐

Other (please specify)

……

C. Consent for genetic tests

Your views and practice when taking consent for genetic testing:

1. Do you (or your team) ask patients to fill in a consent form when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

2. Do you detail the consent discussion in the patient notes?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

3. Does the consent form include specific information about Incidental Findings (IFs)?

Yes ☐ No ☐

IFs are findings of (potential) clinical significance discovered during routine genetic testing, unrelated to the original reason for the test.

4. Do you discuss the possibility of IFs with patients when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

5. Do you think the consent process should include information about Incidental Findings (IFs)?

Yes ☐ No ☐

Additional comments:

6. If you discuss the possibility of IFs do you use examples to illustrate the types of results these could be (for example, identifying adult onset cancer predisposition)?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

7. Do you discuss the possibility of Variants of Uncertain Significance (VUS) with patients?

A VUS is an alteration in the normal sequence of a gene, the significance of which is unclear at the time of reporting. Further work is needed to confirm if clinically significant or not.

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

D. <u>Disclosure of test results</u>

Your views and practice about the disclosure of genetic test results with specific reference to IFs:

1. Do you think patients alone (after discussion with their HCP) should make the decision on what IFs are disclosed to them?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

2. Do you think HCPs should have sole responsibility for deciding what IFs are disclosed to patients?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

3. If IFs are disclosed who should make the decision on what information is shared?

Please rank the following four options: 1 = statement you agree with most, 4= statement you agree with least

- Patients should choose ☐
- Patients and HCPs should choose together ☐
- HCPs should choose ☐
- Neither will choose as national guidelines will make these decisions ☐

Additional comments:

4. If the patient is involved in the choice of IFs disclosed which of the following options is the best approach?

Please rank the following three options: 1 = statement you agree with most, 3= statement you agree with least

- Patients are given a **list** of all possible IFs that can occur and opt in or out of receiving each one ☐
- Patients are given **categories** of IFs that can occur and they choose which category(s) they would want to receive. Categories may be, for example, all conditions that are serious and treatable or conditions that are serious with no treatment ☐

- HCPs inform patients about the IFs that will **automatically** be disclosed and then give the patient the IF **options** they can choose ☐

Additional comments:

5. With which genetic tests should options for IF disclosure be available? Tick all that apply

aCGH	Karyotype	WES
☐	☐	☐
WGS	None	
☐	☐	

Additional comments:

6. Do you think it is possible for patients to make decisions about receiving IFs if they have no personal experience or family history of the conditions listed?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

7. Should the HCP be able to override the patient wishes if they consider it is in the **individual's** best interest to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

8. Should the HCP be able to override the patient wishes if they consider it is in the best interest of their **family members** to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

E. <u>Clinic implications</u>

Practical aspects of organising genetic tests in the clinic:

1. How much time do you think it will take to explain the procedures and outcomes of testing for:

aCGH Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

WES Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

WGS Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

2. Do you think a follow up discussion is required before tests such as aCGH, WES, WGS are organised to give patients time to consider the options?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

3. Who should be able to take consent and order the following tests? (tick all that apply)

	Targeted	Karyotype	aCGH	WES	WGS
GP	☐	☐	☐	☐	☐

Specialist clinician (e.g. paediatrician)	☐	☐	☐	☐	☐
Specialist trainee (specialty)……	☐	☐	☐	☐	☐
Genetic HCP	☐	☐	☐	☐	☐

Other (please specify

Please write any other comments here

Thank you for your time and for completing this questionnaire.

Appendix 23: HCP recruitment pack (piloting)

Participant Information Sheet (Piloting of questionnaire)

Study Title: Incidental Findings from Genetic Tests: Exploring the ethical issues and implications for practice. Piloting of a questionnaire.

Researcher: Gillian Crawford **Ethics number**: 9913

Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

You are being invited to participate in the piloting of a questionnaire as part of a larger study: Incidental Findings from Genetic Tests: Exploring the ethical issues and implications for practice. The results from this study will provide an important and timely evidence base for future policy and practice, enhancing communication between Health Care Professionals (HCPs) and families in addressing the possibility of incidental findings (IFs) and their subsequent management. The qualitative phases of this study are now complete and the findings from these now need to be tested through a survey questionnaire which will be distributed nationally to HCPs who are involved in discussing and organising genetic testing.

You are being invited to participate in the piloting of the questionnaire. The questionnaire has already been through a process called cognitive interviewing, a technique that studies how people understand, mentally process and respond to the questionnaire being presented, with special emphasis on any potential problems with it. This process is now finished and the questionnaire will now be piloted.

This project is funded by NIHR and the research is work towards my PhD.

Why have I been chosen?

You have been invited because you look after families with genetic diagnoses and will often discuss genetic testing in your clinical practice. It does not matter whether incidental findings have been identified in your patients or not. Findings from the qualitative work has identified that HCPs are not routinely discussing the possibility of IFs with families or establishing what incidental information patients would like to have disclosed. Despite this they reported that the issues were important ones to raise with families. The next step is to find out if the findings from the qualitative work are replicated in a much larger cohort of HCPs.

What will happen to me if I take part?

If you are happy to participate you will be given a copy of the questionnaire to complete. You will be asked to fill this in this straight away and it should take about 15 minutes to do. Once you have finished please put it in the envelope provided. If you are unable to do this now you can take it away with you and return in the stamped addressed envelope within the next week As you will be piloting the questionnaire you are asked to write any comments you have about the questionnaire (such as; marking questions that are unclear and why, wording that is ambiguous, whether it is too long or short) on the questionnaire itself. The data you provide on the questionnaire will be used to finalise the questionnaire before it is distributed. Your completed questionnaire will not form part of the final analysis but used for piloting only.

Are there any benefits in my taking part?

There are unlikely to be any direct benefits to you by taking part. However, you may find taking part interesting. Once the questionnaire has been finalised and circulated

to a wider audience, the data collected may in due course contribute to the development of clinical guidelines on managing IFs.

Are there any risks involved?

It is not envisaged that there are any significant risks involved in taking part. This process is about refining the questionnaire so it can best answer the research questions and is not assessing any aspects of your clinical practice.

Will my participation be confidential?

The questionnaire will not ask you for any identifying features except stating your clinical role. As there will be a number of colleagues participating in the pilot it should not be possible to identify you from this information. Data from the questionnaire will be stored on a password protected university computer and your questionnaire will be allocated a Unique Identifying Number (UIN) for this process. Data will be stored in line with University policy and destroyed after 10 years.

What happens if I change my mind?

If you no longer wish to participate in the study you are free to withdraw. However, if you withdraw after completing the questionnaire the data you have already given will still be used as it would not be possible to identify your questionnaire to remove it. If you withdraw when in the process of filling it in, then your questionnaire will be destroyed and the data will not be used.

What happens if something goes wrong?

In the unlikely case of concern or complaint, you should in the first instance contact the study chief investigator Gillian Crawford on 02381 205082. You can also contact Professor Anneke Lucassen on 02381 206841 who is supervising this project. If you remain unhappy you can also contact the Research Governance office on 02380 595058 or Rgoinfo@soton.ac.uk.

Where can I get more information?

If you have any questions or wish to discuss this project further please contact Gillian Crawford on 02381 205082.

Appendix 24: Faculty of Medicine Ethics Committee approval

Copied from e-mail:

Submission Number: 9913
Submission Name: Developing a survey questionnaire for HCPs on Incidental Findings
This is email is to let you know your submission was approved by the Ethics Committee.

Comments
1.Dear Gillian, Re: 9913 - Developing a survey questionnaire for HCPs on Incidental Findings Thank you for submitting your revised application relating to the above study. I am pleased to inform you that full approval has now been granted by the Faculty of Medicine Ethics Committee. Approval is valid from today until 30.09.14, the end date specified in your application. Please note the following points: â¢ the above ethics approval number must be quoted in all correspondence relating to your research, including emails; â¢ if you wish to make any substantive changes to your project you must inform the Faculty of Medicine Ethics Committee as soon as possible. Please note that this email will now constitute evidence of ethical approval. Should you require a paper signed copy of this approval, please contact the FoMEC Administrative Team via email at: Medethic@soton.ac.uk. We wish you success with your research. Yours sincerely Dr Catherine Hill Chair of the Faculty of Medicine Ethics Committee

Click here to view your submission

ERGO : Ethics and Research Governance Online
http://www.ergo.soton.ac.uk

Appendix 25: Questionnaire (final version)

Medicine

UNIVERSITY OF Southampton

Final version of questionnaire

Genetic testing has developed over recent years and a number of different tests are now available that are relatively quick and inexpensive to carry out. As testing becomes more detailed, the number of possible diagnoses identified will increase, as will the possibility of finding other unrelated genetic information. An example of this would be carrying out a genetic test in a child with developmental delay and discovering an inherited predisposition to an adult onset cancer syndrome at the same time. These types of findings have been called Incidental Findings (IFs).

This questionnaire is asking Health Care Professionals (HCPs) who arrange genetic testing in their clinical practice for their views and experience of organising these tests particularly with regard to consenting patients (or parents of patients) and disclosing results. Results from this survey will be collated, analysed and used to inform practice and guideline development.

Thank you for participating in this survey. It should take no more than 10-15 minutes to complete.

A. Demographic information

1. What is your clinical role?

Clinical Geneticist ☐

Genetic Counsellor ☐

Trainee Genetic Counsellor ☐
(please specify year of training) ☐

Paediatrician (hospital based) ☐

Paediatrician (community based) ☐

Specialist trainee ☐
(Please specify year of training) ☐

Specialty …….

Other (Please specify) …… ☐

B. <u>Genetic testing</u>

The frequency and types of genetic tests you request in clinical practice:

1. Do you order genetic tests in your clinical practice?

Yes ☐ No ☐

If yes, please specify the frequency over a six month period:

Often (weekly) Seldom (once or twice a month) Infrequent (once every few months) Never

☐ ☐ ☐ ☐

2. What genetic tests have you (**ever**) organised in your clinical practice?

Array CGH (aCGH) Karyotype Whole Exome Sequencing (WES)

☐ ☐ ☐

Whole Genome Sequencing (WGS) Targeted test (e.g. Fragile X)

☐ ☐

Other (please specify)

……

3. What tests do you **routinely** organise (a few times each month)?

aCGH Karyotype WES

☐ ☐ ☐

WGS Targeted tests (e.g. Fragile X)

☐ ☐

Other (please specify)

……

C. <u>Consent for genetic tests</u>

Your views and practice when taking consent for genetic testing:

1. Do you (or your team) ask patients to fill in a consent form when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

2. Do you detail the consent discussion in the patient notes?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

3. Does the consent form include specific information about Incidental Findings (IFs)?

Yes ☐ No ☐

IFs are findings of (potential) clinical significance discovered during routine genetic testing, unrelated to the original reason for the test.

4. Do you discuss the possibility of IFs with patients when organising a genetic test?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

5. Do you think the consent process should include information about Incidental Findings (IFs)?

Yes ☐ No ☐

Additional comments:

6. If you discuss the possibility of IFs do you use examples to illustrate the types of results these could be (for example, identifying adult onset cancer predisposition)?

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

7. Do you discuss the possibility of Variants of Uncertain Significance (VUS) with patients?

A VUS is an alteration in the normal sequence of a gene, the significance of which is unclear at the time of reporting. Further work is needed to confirm if clinically significant or not.

Always ☐ Usually ☐ Sometimes ☐ Never ☐ N/A ☐

Additional comments:

D. <u>Disclosure of test results</u>

Your views and practice about the disclosure of genetic test results with specific reference to IFs:

1. Do you think patients alone (after discussion with their HCP) should make the decision on what IFs are disclosed to them?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

2. Do you think HCPs should have sole responsibility for deciding what IFs are disclosed to patients?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

3. If IFs are disclosed who should make the decision on what information is shared?

Please **rank** the following options:

1 being the option you agree with most and 4 being the option you disagree with most

- Patients should choose ☐
- Patients and HCPs should choose together ☐
- HCPs should choose ☐
- Neither will choose as national guidelines will make these decisions ☐

Additional comments:

4. If the patient is involved in the choice of IFs disclosed which of the following options is the best approach?

Please **rank** the following options:

1 being the option you agree with most and 3 being the option you disagree with most

- Patients are given a **list** of all possible IFs that can occur and opt in or out of receiving each one ☐
- Patients are given **categories** of IFs that can occur and they choose which category(s) they would want to receive. Categories may be, for example, all conditions that are serious and treatable or conditions that are serious with no treatment ☐

- HCPs inform patients about the IFs that will **automatically** be disclosed and then give the patient the IF **options** they can choose ☐

Additional comments:

5. With which genetic tests should options for IF disclosure be available? Tick all that apply

aCGH	Karyotype	WES
☐	☐	☐
WGS	None	
☐	☐	

Additional comments:

6. Do you think it is possible for patients to make decisions about receiving IFs if they have no personal experience or family history of the conditions listed?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

7. Should the HCP be able to override the patient wishes if they consider it is in the **individual's** best interest to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

8. Should the HCP be able to override the patient wishes if they consider it is in the best interest of their **family members** to disclose a particular IF?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

E. Clinic implications

Practical aspects of organising genetic tests in the clinic:

1. How much time do you think it will take to explain the procedures and outcomes of testing for:

aCGH Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

WES Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

WGS Under 5 minutes ☐ 5-15 mins ☐ 15-30 mins ☐ Over 30 mins ☐

2. Do you think a follow up discussion is required before tests such as aCGH, WES, WGS are organised to give patients time to consider the options?

Always ☐ Usually ☐ Sometimes ☐ Never ☐

Additional comments:

3. Who should be able to take consent and order the following tests? (tick all that apply)

	Targeted	Karyotype	aCGH	WES	WGS
GP	☐	☐	☐	☐	☐
Specialist clinician (e.g. paediatrician)	☐	☐	☐	☐	☐

Specialist trainee (specialty)……..	☐	☐	☐	☐	☐
Genetic HCP	☐	☐	☐	☐	☐

Other (please specify)

Please write any other comments here

Thank you for your time and for completing this questionnaire.

Appendix 26: Steering Group Membership

Name	Professional title	Area of expertise
Professor Anneke Lucassen	Professor of Clinical Genetics, University of Southampton	Primary supervisor Consultant Geneticist and leads Clinical Ethics and Law at Southampton (CELS) Extensive research experience in clinical ethics
Dr Angela Fenwick	Senior Lecturer in Medical Ethics and Education, University of Southampton	Supervisor Extensive qualitative research experience in clinical ethics
Professor Claire Foster	Professor of Psychosocial Oncology, University of Southampton	Supervisor Extensive research experience (qualitative and quantitative)
Dr Tara Clancy	Consultant Genetic Counsellor Honorary Senior Lecturer, Manchester Centre for Genomic Medicine	Clinical supervisor Programme lead of MSc in genetic counselling course Extensive research experience in clinical ethics
Professor Michael Parker	Professor of Bioethics, University of Oxford	Director of Ethox Extensive research experience in clinical ethics
Dr Anna Middleton	Ethics Researcher, Wellcome Sanger Centre, Cambridge	Genetic Counsellor Extensive research experience, currently researching IFs in the research setting
Dr Nina Hallowell	Associate PHG Foundation, Cambridge	Extensive qualitative research experience in clinical genetics
Dr John Crolla	Head of Cytogenetic Laboratory (retired), Wessex Regional Genetics Laboratory, Salisbury	Set up aCGH testing in Wessex Genetics Laboratory. Member of management team for EACH study
Dr Katherine Hunt	Senior Research Fellow, University of Southampton	Extensive quantitative research experience
Mrs Alison Hall	Senior Policy Advisor, PHG Foundation, Cambridge	Policy development in area of whole genome sequencing
Administrator: Mrs Lisa Scott		

Appendix 27: Awards, publications and key presentations during fellowship

Papers:

1. Dheensa S, Fenwick A, Shkedi-Rafid S, *Crawford, G*, Lucassen A (2015) Health-care professionals responsibility to patients' relatives in genetic medicine: a systematic review and synthesis of empirical research. Genetics in Medicine, advanced online publication: 25 June 2015. doi:10.1038/gim.2015.72

2. Fenwick A, Dheensa S, *Crawford G*, Shkedi-Rafid S, Lucassen A (2015) Rescue obligations and collective approaches: complexities in genomics. *AJOB*. 15 (2) 23-5

3. Shkedi-Rafid S, Dheensa S, *Crawford G*, Fenwick A, Lucassen, A (2014) Defining and managing incidental findings in genetic and genomic practice. *Journal of Medical Genetics*, 51, (11), 715-23

4. Middleton A, Patch C, Wiggins J, Barnes K, *Crawford G*, Benjamin C, Bruce A and on behalf of the Association of Genetic Nurses and Counsellors. (2014) Position statement on opportunistic genomic screening from the Association of Genetic Nurses and Counsellors (UK and Ireland). *Eur J of Hum Genet*. Aug 22 (8) 955-6

5. *Crawford G*, Fenwick A and Lucassen A (2013) A more fitting term in the incidental findings debate: one term does not fit all situations. *Eur J Hum Genet* 22, 957

6. *Crawford G*, Foulds N, Fenwick A, Hallowell N and Lucassen A (2013) Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. *Genetics in Medicine*, 15, (11), 896-899

Awards and Achievements:

1. Visiting research scholarship to Brocher Foundation, Geneva, Switzerland (2 month residency). Invited speaker at Lausanne University during this period.
2. Faculty of Health Sciences post-graduate conference 2014: 1st prize for an oral presentation
3. Organised a public engagement event 'What do my genes say about me?' Seacity museum, Southampton. 2013
4. Recorded a piece for BBC Breakfast on incidental findings. May 2013

Key presentations:

1. Invited speaker: Centre for Biomedical Ethics and Law, University of Leuven, Belgium. Returning incidental findings: a non-issue? 2013
2. Invited speaker: Cancer Genetics Group annual spring meeting. New genomic technologies: health care professionals' experience of managing incidental information 2013
3. Invited participant: PHG Foundation, Cambridge, workshop on 'Realising Genomics in Clinical Practice' 2013
4. Accepted abstract: European Meeting on Psychosocial Aspects of Genetics, Milan. Genomic investigations: HCP and families' experiences of managing incidental information in clinical practice 2014
5. Invited speaker: British Society of Genetic Medicine annual conference, NIHR session. Genomic investigations: Health care professionals and family experiences of managing incidental information in clinical practice. 2014
6. Invited speaker: University of Southampton/UHS clinical research conference. Whole genomes and incidental findings. 2015
7. Study dissemination event: Genethics forum, Wellcome Trust, London. Genomic investigations: managing incidental findings in clinical practice. 2015

Glossary

Comparative Genome Hybridisation Array (aCGH: A technique that allows the detection of chromosome imbalances that are smaller than can be seen through looking down the microscope

Exome sequencing: A technique to selectively sequence the coding regions of the genome

Genomic: Study of genes, their functions and related techniques

Genotype: The genetic makeup of an individual

Karyotype: The characterisation of the chromosome complement of a species

Karyotyping: The technique to characterise the chromosome complement of a species

Mutation: A permanent change in the DNA sequence of a gene

Pathogenicity: The ability to produce disease

Phenotype: The composite of an individual's observable characteristics or traits

Variant of Uncertain Significance: An alteration in the normal sequence of a gene, the significance of which is unclear until further study of the genotype and corresponding phenotype in a sufficiently large population

Whole genome sequencing: A laboratory process that determines the complete DNA sequence of an individual's genome at a single time