

**A CROSS-NATIONAL INVESTIGATION OF PROFESSIONALS' ATTITUDES
REGARDING CLINICAL SEQUENCING AND INCIDENTAL FINDINGS**

Thesis submitted for the degree of
Doctor of Philosophy
at the University of Leicester

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~ June 2016 ~

ABSTRACT

A Cross-National Investigation of Professionals' Attitudes Regarding Clinical Sequencing and Incidental Findings

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Background

Technological developments and discussions around autonomy and paternalism in clinical practice have made the return of Incidental findings (IFs) from clinical sequencing a hotly debated topic. Limited guidance and empirical evidence, combined with the recognition that both patients and professionals should be supported in what can be a life-changing experience, make the investigation of this topic both necessary and timely. To that end, the attitudes of clinical professionals were sought regarding clinical sequencing and the discovery of IFs.

Methods

The attitudes of genetics professionals were investigated through a mixed-method research project conducted in two phases. Phase I consisted of a qualitative cross-national comparison using interviews with genetics experts from three countries, Greece, the UK and the USA; phase II was a quantitative piece of work using an online questionnaire with Greek geneticists.

Results

Professionals showed a reluctance towards widely using clinical sequencing or returning IFs, due to the lack of a comprehensive practice framework, their limited ability to interpret genomic results, consent practices that need updating and the familial nature of genomic information inevitably affecting others than the patient. Moreover, Greek professionals reported a lack of practical support and no recognised medical specialties of clinical genetics and genetic counselling, rendering the management of IFs even more challenging. To better support their patients, Greek professionals urgently asked for guidance and support to help them integrate clinical sequencing into their professional practice and manage IFs.

Conclusion

A points-to-consider document for Greece was created based on the literature and an analysis of empirical data collected. This guidance, prepared using quality criteria, took examples from other countries, but with country-specific characteristics taken into account. It is based on the bioethical principles of respect and fostering trust. It is aimed at supporting Greek genetic services providers in their practice and the patients who use those services.

ACKNOWLEDGEMENTS

This thesis is dedicated to my family

I owe an enormous amount of gratitude to Dr. Susan Wallace for believing in my potential and offering me a place as a research student at the University of Leicester. I am also grateful for her continuous support, academic and personal, provided along the way. I would also like to express my gratitude to my second supervisor, Dr. Natalie Armstrong, for her help and support and wise academic guidance. I would have never reached this point without their help.

I would also like to thank the College of Medical, Biological Sciences & Psychology of the University of Leicester for funding my Ph.D. Studentship allowing me to pursue my research and for their support along the years, and my postgraduate Tutor Prof Nuala Sheehan for being there for me every time I needed her.

I am grateful to all the participants in this study; my Greek, UK and US experts for their time and insight; and for their input all the Greek geneticists that completed the questionnaire. Without their insightful comments, this work would not have been possible. In particular, I would like to thank Dr. Eleni Frysira and Dr. Kouli Yannoukako for giving me access to all registered Greek geneticists.

I owe great thanks to my friends, fellow Ph.D. students and colleagues: Sze-Huey, Maria, Chin, Felix, James, Michael, Ioanna, Vicky and Amadou for sharing this trip with me and making it a great experience I will always cherish; and to my Greek friends, Sonia, Gianno, Grigori and Lidia for their practical support and encouragement.

And last but not least, I would like to express my gratitude to my beloved family, my parents Katerina and Georgio, my sisters Maria-Aliki and Stamatia, my “nona” Aggeliki and my husband Kosta for their unconditional love and support, for all the encouragement and for sharing with me all kinds of feelings that emerged through the process, from total excitement to complete frustration. Though all of my family are away, which has been a challenge on its own; they have always been here for me. This thesis is dedicated to them.

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LIST OF ABBREVIATIONS

AAP	American Academy of Paediatrics
ABI	Association of British Insurers
ACGS	Association for Clinical Genetic Science
ACMG	American College of Medical Genetics and Genomics
AGNC	Association of Genetic Nurses and Counsellors
ASHG	American Society of Human Genetics
BSGM	British Society for Genetic Medicine
CAQDAS	Computer-Assisted Qualitative Data Analysis Software
CEC	Clinical Ethics Committee
CGH	Comparative Genomic Hybridization
CGS	Clinical Genetics Society
CLIA	Clinical Laboratory Improvement Amendments
CMA	Chromosomal Microarray analysis
CMC	Computer Mediated Communication
CMS	Center for Medicare and Medicaid Service
DHHS	Department of Health and Human Services
DNA	DeoxyriboNucleic Acid
DTC	Direct-to-consumer [for genetic tests]
ELSI	Ethical, Legal and Social issues
ES	Exome Sequencing
ESHG	European Society of Human Genetics
FDA	Food and Drug Administration
FTC	Federal Trade Commission
GINA	Genetic Information Nondiscrimination Act
GMC	General Medical Council
GP	General Practitioner
GS	Genome Sequencing
HAMG	Hellenic Association of Medical Genetics
HSMG	Hellenic Society of Medical Genetics
IFs	Incidental Findings
IRB	Institutional Review Board
ISO	International Organization for Standardization
MDT	MultiDisciplinary Team
MRC	Medical Research Council
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NHS	National Health Service
NGS	Next-Generation Sequencing
RGS	Regional Genetics Services
PHG	Public Health Genomics Foundation
RCPA	Royal College of Pathologists of Australasia
RoR	Return of Results
SPSS	Statistical Package for the Social Sciences
UK	United Kingdom
USA	United States of America
VUS	Variants of Unknown Significance

CHAPTER 1: INTRODUCTION

1.1. Introduction

Despite an increasing use of clinical sequencing, there is a paucity of literature concerning the best way to manage the incidental findings arising. It is important that this issue is explored because clinical sequencing is expected to be used widely in the coming years and evidence regarding its uses and incidental findings need to be collected before its full integration into the clinical practice. In this thesis, I begin to address this gap by examining the attitudes of genetics professionals to the use of genomic tests, specifically clinical sequencing, and the management of incidental findings. Given this paucity of formal frameworks or guidance to support professionals, this work represents an important contribution to informing the future development of such guidance.

Incidental Findings (IFs) are findings unrelated to the diagnostic indication for which a test was ordered. IFs are not a new concept within medicine and date back to the 1950s when IFs were revealed in autopsies and surgical procedures [1, 2]. More recently, the issue of IFs has become pertinent in imaging and, subsequently, in genetic testing. These discussions [3-7] have also arisen in clinical settings with the advent of the use of clinical sequencing as a means of diagnosing suspected genetic disorders [8, 9].

The discussion of genomic IFs intensified in March 2013 when the American College of Medical Genetics and Genomics (ACMG) published its recommendations for reporting IFs from clinical sequencing online [10]. These guidelines recommended that a list of 56 variants concerning 24 genetic conditions should be actively looked for and reported every time a clinical exome or clinical genome sequencing test was performed. A number of objections were immediately raised. The first related to the prioritising of variants, and how the specific list had been determined. Second, there was a reaction to the recommendation that the results should be reported back to patients regardless of their preferences or their age. Depriving patients of choice, and importantly the opportunity to opt out of receiving IFs, was seen as problematic and different stakeholders and academics raised concerns about patient autonomy being disregarded. Third, contrary to existing guidance (some of which came from the ACMG itself) and practice, the recommendations were in favour of returning results about late or adult-onset conditions to minors.

These reactions resulted in the recommendations being updated in March 2014 [11]. Preliminary empirical evidence demonstrating stakeholders' objections, and commentaries from experts in different areas (including legal experts, experts in medical ethics and clinicians) were collated to inform the revised guidance. The original recommendations were changed to state that patients should be allowed to opt out of the analysis of additional variants.

These discussions about the use of clinical sequencing and the management of IFs during 2013 and 2014, highlighted ethical, legal and social issues that I believe required investigation. An agreement might be finally reached where IFs would be returned to patients, based on their expressed wishes. However, there is an ongoing lack of empirical evidence to support this decision, and with constant new developments in the field of genetics, further research is required to provide an evidence base to inform future guidance [10].

Using empirical data on professionals' attitudes, my study seeks to provide a base from which future guidance can be drawn. Although this remains an international problem, my contribution has been to benchmark my home country, Greece, against other countries, in order to identify lessons that can be learned. Subsequently, my aim is to provide a framework to support Greek geneticists in the use of clinical sequencing and the return of IFs. To address this issue, I investigated professionals' attitudes using a mixed-method research approach consisting of a qualitative cross-national comparison (phase I) using in-depth interviews with genetics experts from three countries, Greece, the United Kingdom (UK) and the United States of America (USA); and a quantitative phase (phase II) using online questionnaires with Greek geneticists. These two combined phases provide empirical evidence for use in the preparation of points-to-consider for the Greek context.

1.2. Clinical sequencing

Before exploring the different issues arising from clinical sequencing, a common understanding of the terminology involved is required.

The term clinical sequencing refers to exome sequencing (ES) and genome sequencing (GS). Until recently, especially in the clinical setting, genetic tests only included targeted tests, i.e. gene-specific or locus-specific tests. Using these tests a clinician, usually a clinical geneticist (or a non-specialised clinician with or without collaboration with a geneticist), would, based on a patient's symptoms, suspect a genetic condition and then order a test specifically targeting the gene(s) associated with that condition.

As a step forward, following single-gene tests, gene-panel tests were developed for use in some situations, such as when multiple variants were associated with the condition under investigation. This development allowed the investigation of several variants simultaneously, thus, producing a greater range of results in less time. Disease-targeted gene-panels were seen as valuable diagnostic tools with high validity¹ [12]. Additionally, as only known genes were targeted, the interpretation of results was relatively easy and efficient.

Recently, ES and GS were introduced in clinical laboratories. ES is a test in which all coding regions of the genome are sequenced. The exome covers less than 2% of the genome, yet according to estimates, includes over 80% of recognised mutations causing diseases [13]. ES is used not only to test for known variants associated with a genetic disease but also to investigate new gene-disease associations. Although the cost of ES might remain higher than the cost of disease-specific targeted gene panels, the cost of ES is lower compared to the use of multiple gene-panels that could be required to test multiple genes if the usually-suspected genes do not reveal a variation that could point to the disease. After performing the ES test, laboratories initially choose to interpret genes with known associations with the disease, thus limiting the issues with variants of unknown, or not well-documented, significance. If no significant results are produced, original data produced by the test will be re-investigate thus eliminating the need for further tests. The technical characteristics of ES (analytical sensitivity² and specificity³) have received criticism that falls outside the scope of this thesis, nevertheless, it is worth mentioning that regardless of these technical issues, ES could produce results especially in rare and ultra-rare disorders and/or cases with non-typical phenotypic characteristics [8, 9, 14] as illustrated in the following example (box 1 and the following section 1.3.).

¹ Validity is the overall ability of a test to detect a type of variant

² Analytical sensitivity is the “proportion of biological samples that have a positive test result or known mutation and that are correctly classified as positive”.

³ Analytical specificity is “the proportion of biological samples that have a negative test result or no identified mutation (being tested for) and that are correctly classified as negative”.

Box 1: Example of patient getting a diagnosis after the use of exome sequencing

A 3-year old female patient with static encephalopathy, developmental delay, hypotonia, and seizures was referred to the Department of Molecular and Human Genetics at Baylor College of Medicine, one of the clinical genetics laboratories in the United States offering whole-exome sequencing for diagnostic reasons. The patient had had prior laboratory testing including biochemical tests, thyroid function studies, chromosomal microarray and single-gene tests, all of which were inconclusive and unable to produce a diagnosis. When exome sequencing was performed, the results revealed a variation in the SLC2A1 gene responsible for an autosomal dominant genetic condition called “glucose transporter deficiency syndrome”. After the diagnosis, the patient was able to receive appropriate treatment and adjust her diet (to ketogenic diet). The six-month evaluation revealed no seizure, increased activeness, improvement in balance, motor skills and speech [15].

GS is a process in which both coding and non-coding regions are sequenced. Causative mutations (mutations causing or being associated with the condition) are searched for, initially in the coding areas (exome) and if not discovered, test data is re-analysed and non-coding regions are investigated [12]. Although the cost of GS keeps decreasing, as does the time needed to perform the test, GS remains the most costly method. However, as with the ES test, data can be re-interrogated at no further cost if results are not produced from regions with known associations.

Following the generation of the DNA sequence (regardless of the test used), the data produced are analysed. For this process to be completed, high-level computational and data management skills are required, combined with clinical knowledge [16]. Following this, the sequence of the patient is compared to a reference DNA sequence and alterations of genes (or variants) are filtered according to their clinical relevance. The filtering takes place with the help of several types of software; nevertheless, this is the most time-consuming and expensive step of the process, hence the expression “\$100 genome, \$1M interpretation” [17]. The outcome of the analysis is a number of “candidate variants” that will be examined by the clinical team (potentially with help from the laboratory geneticists) and considered for feedback to the patient. The process is summarised in figure 1.

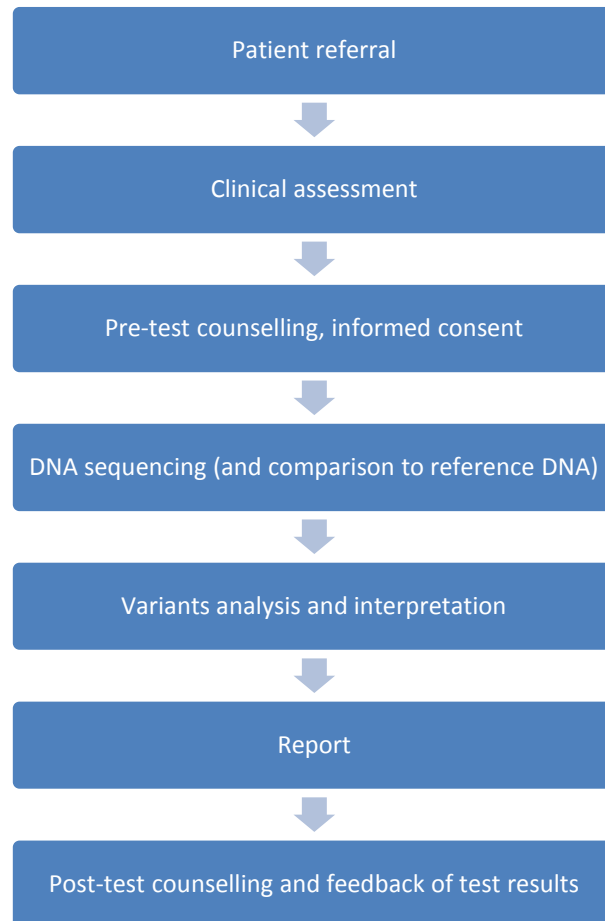


Figure 1: The typical process of DNA sequencing [modified from Amor et al., 2015]

Traditionally, genetic tests were used to confirm or reject a diagnosis made by the ordering clinician based on the patient's symptoms, family history, and other tests. The genetic test would be used to analyse variants associated with the suspected condition. Disease-specific gene panels were, therefore, seen as the "logical extension" of single-gene tests and were used for genetically heterogeneous disorders where more than one gene is associated with the disorder. Contrary to targeted tests, ES and GS provide the data for a "... broader hypothesis-free approach to testing the patient" [12: p.736]. ES and GS sequencing can produce results in cases where targeted tests have revealed no variants explaining the clinical features of the patient or where targeted tests are unavailable (see following section). Despite their potential usefulness, ES and GS produce huge amounts of data. These data include variants associated with the suspected genetic condition, potentially associated variants, variants associated with other non-related genetic conditions and variants of unknown significance. Hence, data interpretation, already of importance in every test, becomes even more important with the use of ES or GS. Variants of genes associated, or potentially associated, with the suspected genetic condition are referred to as primary findings; all other

findings, unrelated to the diagnostic indications for which the test was ordered, are referred to as secondary or incidental findings (see section 2.2.). It is therefore the case that, although IFs could be revealed with any type of test (genetic or otherwise), when ES or GS are performed the amount of data produced increases and subsequently so does the possibility of discovering IFs that might be important to the patient.

1.3. Application of clinical sequencing

Clinical sequencing, and specifically exome and genome sequencing, is gradually being integrated into everyday clinical practice [18]. Existing practice involves the undiagnosed patient (who usually presents uncommon phenotypic characteristics), the ordering clinician (who usually suspects a specific genetic condition but does not have test results to verify these suspicions and to whom results will be returned), the laboratory geneticists (who perform the test and contribute to determining the variants that will be returned to the clinician), and, potentially, a genetic counsellor to support the process. The involvement of lab-geneticists is determined by legal constraints, as in the case of the USA, or available infrastructures, as in the case of Greece [10, 19] and might include the interpretation of results and the return of clinically significant variants to the ordering clinician.

In recent years, evidence derived from a number of medical specialities has shown that clinical sequencing could be a very useful diagnostic tool [20-22], mainly for undiagnosed patients with a broad range of phenotypic presentations, while it has been claimed that GS could be the solution for heterogeneous genetic conditions [17]. Clinical sequencing could be used as a diagnostic tool when a genetic condition is strongly suspected but traditional clinical tests have proven negative [23-25], but at the same time, it could also reveal other helpful information [18]. If there is a suspected genetic condition, studies have shown that ES/GS could provide a diagnosis where other tests have failed, for example, in children with intellectual disabilities [23]. Although originally limited to tumour sequencing, Mendelian disorders [9] or investigation of the genetic aetiology of developmental delay [26], clinical sequencing is expected to become an integral part of medicine in the near future [16]. It has the potential to diagnose conditions with high genetic heterogeneity [27], or in patients without a prior hypothesis about the genetic explanation for their symptoms [28, 29]. More specifically, recent evidence suggests that exome and genome sequencing could be used for the diagnosis of rare and ultra-rare diseases [26, 30]; neurological [31] and neurodevelopmental disorders [20]; unexplained congenital anomalies [32]; autism spectrum disorders [21]; and ataxia disorders [22]. For the conditions mentioned above, it has been reported that exome and genome sequencing could

yield a diagnostic rate in around 15-20% of the cases reaching up to 41% as in the case of diagnosis for neurodevelopmental disorders achieved after ES [20]. In addition, as well as rare and high impact diseases [33], it has been suggested that exome and genome sequencing should also focus on genetic causes of disorders that are treatable (using a specific treatment process) even if not life-threatening. Additionally, clinical sequencing could be used for the detection of variants with potentially clinical importance in patients without family history of the suspected disease [34].

Nevertheless, the use of ES, or even more the use of GS, could lead to unnecessary or unjustified screening. This potentially problematic issue was discussed in the past both by the UK [17, 35] and US experts [25, 36, 37]. These experts added to the literature regarding screening and its preconditions by discouraging the use of genetic and genomic tests as screening tools [38-41].

With lower cost, higher analytic sensitivity and specificity, and easier interpretation of results, targeted tests remain the primary test used in the clinical setting. However, ES and GS could produce results where other tests have failed, ending the diagnostic odyssey for patients with non-typical forms of genetic conditions as illustrated above. With a cost that keeps decreasing and research facilitating data interpretation, ES and GS are expected to be used more frequently in the future and are increasingly becoming a valuable tool that could improve health services [28, 30]. Their increased use has, and will, throw up more challenges but their potential usefulness should not be disregarded. Ongoing research is investigating ways to maximise benefits from their use and minimise risks emerging from these new technologies, always aiming to best serve patients' interests.

With the progressive integration of clinical sequencing into routine clinical practice [30] caution is required when managing clinical sequencing and the issues derived from IFs [25]. Subsequently, guidance is required to protect stakeholders, patients and healthcare providers alike. At present, existing guidance is scarce, or completely absent as in the case of Greece. Thus, the aims of my study are to develop a set of preliminary recommendations, i.e. points-to-consider, that can be used to inform professional bodies in the development of nationally accepted guidelines.

The goal of the first phase of this project was to gain insight into experts' experiences and collect data concerning not only current practices that could be appraised and used as examples for other contexts, but also data regarding future practices that could be used to facilitate the integration of clinical sequencing and the management of IFs. Approaching UK and USA experts provided examples of best practice that could be implemented in Greece, as both countries have a long tradition in health services guidance and offer different perspectives. Although sequencing is becoming more commonplace as a diagnostic tool, Greece currently lacks any such guidance. My goal for the second

phase was to collect additional evidence on Greek professionals' attitudes, concerns, and needs. Online questionnaires were used to increase participation and engage genetics professionals from all over Greece in investigating clinical sequencing and IFs. Evidence from other published studies and theoretical papers identified in the literature (chapters 3 and 4) were used in combination with the evidence gathered throughout this project (chapters 5-7), to formulate points-to-consider for the Greek context (chapter 9).

1.4. Structure of thesis

This thesis is structured in the following way:

Chapter 1

The chapter has offered an introduction to the background of this research, in which I have described chronologically the events that lead the discussion of IFs in the clinical settings. Furthermore, I have introduced the different types of genetic tests included under the general term "clinical sequencing" aiming at offering to the reader what I consider to be the necessary information about genetics.

Chapter 2

In Chapter 2 I review the literature related to clinical sequencing and the return of IFs. I define the term IFs and present different terms suggested. A short discussion about the return of IFs from research settings precedes the main discussion about IFs from clinical settings reflecting the way the discussion has evolved. To complete the literature I provide a critical commentary on the ethical terms used in order to show how they are used in this thesis, to show the basis on which I have worked through my studies. The aim of the chapter is to describe in detail the current knowledge and present available empirical evidence on the related topic to show how I identified the gaps that I felt needed to be addressed and also to lay the groundwork for the discussion that will follow in the last chapters.

Chapter 3

In Chapter 3 I explore the theoretical and methodological framework underpinning the study. Methods used will be analysed together showing the rationale behind each decision I made. A step-by-step description will follow, presenting the specifics of each part of the study. The aim of this chapter is to guide the reader through my process of data collection and data analysis, and how they

led me to create the points-to-consider for this project. The chapter ends with a section where I discuss the quality of the different methodologies used and why a mixed methods strategy was chosen.

Chapter 4

In Chapter 4 I explain why I chose the three countries that were used in the cross-national comparison phase and give their country-specific characteristics. Information about the availability of genetic and genomic tests is presented followed by information about access to such tests and the available legal and other non-binding documents concerning clinical sequencing and the return of IFs. The aim of this chapter is to provide the background of each country thus allowing the reader to better understand professionals' attitudes and the context within which clinical sequencing is offered and to show why I chose them for my analysis.

Chapters 5, 6 and 7

In Chapters 5 to 7 I present the results of the qualitative and quantitative phases of this project. The first two chapters (5 and 6) present the themes emerging from the in-depth interviews with experts from the three countries, while in chapter 7 I present the results from the online questionnaires addressed to Greek registered geneticists. In chapters 5 and 6 the results are presented thematically, reflecting the themes that I found emerging during the interviews. In chapter 7, I give the results from the questionnaires, using descriptive statistics, tables and pie charts. I will also show how I moved from the qualitative to the quantitative phase by showing what results from the interviews helped me to choose what questions would be asked in the quantitative phase. This will show how my research questions changed over the period of my thesis in reaction to the data that I collected.

Chapter 8

In Chapter 8 I discuss the findings from my study reflecting upon the aim and research questions. My findings will be discussed iteratively with the available literature leading to the specific considerations I discovered and used to focus on the Greek context.

Chapter 9

In Chapter 9 I present the points-to-consider prepared especially for Greece. I intend these points to provide an initial base for further discussion and support for the creation of formal guidance in Greece. I also show how I moved from my general findings to these specific points for Greece. In this final sections of this thesis, I discuss the contributions of this project to the future discussions on this topic, followed by a critical appraisal of its strengths and limitations. Areas that could be further investigated will also be proposed.

References and Footnotes

References used throughout the thesis are presented after chapter 9. A numerical format has been used where a number is given in square brackets (e.g. [1]) and references are presented by order of appearance. This format is widely used for health-related documents in various peer-reviewed journals and is the citation system with which I am most familiar, which is why I have chosen it. When direct quotes are used, the page of the book or paper cited will be mentioned. As most studies cited are recent, some papers are only available online (in Epub format) and consequently do not have pages to reference.

Footnotes are used occasionally, usually to provide a brief explanation about a term used in the text. They are numbered using the arithmetic system and they are referred in the text with a superscript number (e.g. ¹). When a superscript number occurs, please see the relevant footnote for an explanation.

CHAPTER 2: LITERATURE REVIEW

2.1. Chapter outline

In this chapter, I present the available theoretical and empirical evidence concerning the current debate on the return of incidental findings from clinical sequencing. It was important for me to conduct this review because it enabled me to gain a general understanding of the implementations of clinical sequencing and the return of incidental findings. It also helped me identify gaps in the literature and formulate my research questions that guided this project.

This chapter is divided into five sections. First, I provide a summary of the current discussion on the terminology employed. Then, before discussing the details of the literature on the return of results in the research and clinical settings, I briefly discuss the ethical concepts that emerge in the discussion. This section aims at laying the groundwork upon which I have built my research.

As mentioned in the introduction, genomic IFs were initially discovered in research projects using exome and genome sequencing. Therefore, a short description of that literature is given, as many of the arguments are related to the discussion about the return of genomic IFs in the clinical setting. This literature is only summarised, as a detailed discussion falls outside the scope of this project and, in any case, has been presented elsewhere [42-44].

The main focus of the chapter is the literature on the return of IFs in clinical sequencing. A variety of studies has been conducted ranging from commentaries to empirical studies. To aid the reader, the studies concerning IFs from clinical sequencing are divided into two groups. The first group includes commentaries, guidelines, opinions, and other theoretical papers while the second group includes studies using empirical methodologies. Finally, I review the evidence presented and identify the gaps I found in the existing literature and discuss the research questions that I feel could address these gaps.

Despite my efforts, the review that follows is not exhaustive as new studies are published on a weekly basis. However, it is extensive as I have included all influential theoretical papers and all the empirical studies identified up to April 2015. The goal of this review is to identify the gaps in the literature, some of which I aim to fill as a result of this work, and demonstrate why there is a need for more research in this area.

2.2. Defining Incidental Findings

Incidental Findings (IFs) have long existed in both research and clinical settings. Issues around their return have been acknowledged and discussed by all stakeholders involved, but it has only been relatively recently that this topic has been approached in a more systematic way.

Even long before the introduction of genetic testing in the diagnostic process, IFs and their disclosure concerned clinicians and academics. IFs were initially discovered in the 1950s during autopsies and surgical procedures [1, 2, 45, 46]. Clinicians in those days noticed unexpected findings but their feedback was not widely discussed. More recently, the debate was revived when IFs were discovered through the use of imaging techniques revealing “abnormal findings” in asymptomatic individuals [47]. This was initially referred to as “incidentalomas”, a term used to describe a finding (most commonly a mass) found when using imaging techniques (computed tomography or magnetic resonance imaging) ordered for symptoms or concerns totally unrelated to the gland in which the mass was found [48, 49].

With the development of genetics, the discussion was widened to include IFs from genetic tests [48]. The most commonly discovered incidental finding emerging from genetic tests in those early days was misattributed paternity, which even today remains a problem [50-52].

One of the most commonly used definitions, originally intended for IFs from research, was suggested in 2008 by Wolf et al, and has since been widely used with minor modifications for all settings.

According to Wolf:

An IF is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. This means that IFs may be on variables not directly under study and may not be anticipated in the research protocol [4: p.3].

Another definition, also frequently used in the past couple of years and intended mainly for clinical sequencing, was suggested by the ACMG. Their definition was based on a comparison between incidental findings and primary findings. According to them:

Primary finding: This term is used to describe pathogenic alterations in a gene or genes that are relevant to the diagnostic indication for which the sequencing was ordered (e.g., a mutation in MECP2 in a girl with loss of developmental milestones).

Incidental finding (IFs): This term has been used in a variety of clinical and research contexts to indicate unexpected positive findings. Other terms have been used to describe these findings, particularly when they are actively sought (rather than being unexpectedly discovered). These terms include “serendipitous and iatrogenic” findings, “non-incidental secondary findings,” “unanticipated findings,” and “off-target results.”[10: p.566]

As noted in the ACMG definition, other terms were suggested to describe findings unrelated to the original diagnostic indication. Alternative terms include, among others, ‘unexpected’, ‘unanticipated’, ‘unsolicited’, ‘coincidental’, ‘pertinent’ or ‘secondary’ findings [53]. Particularly the term ‘secondary’ has been suggested more than once as the most appropriate term to describe this type of finding [34, 54]. Although there is an extensive literature about the most appropriate term, this debate will not be presented here as it falls beyond the scope of this thesis. Furthermore, after a systematic review, Shkedi-Rafid et al concluded that there might not be a single term that captures all the issues concerning these kinds of findings, hence, more than one term might have to be used simultaneously to accurately describe findings from different tests or settings [35].

For the purpose of this project the term “Incidental Findings” (IFs) has been used as it was the term used in the original ACMG guidelines, it was used by participants during the interviews and appears to be one of the most commonly used terms in this context. It should be noted here, however, that in the revised version of the ACMG guidelines the term IF was replaced by the term “secondary finding”[11].

2.3. Background to the literature

Before moving on to the analysis of the literature, I believe it is important to present and critically comment on some of the ethical concepts that underlie the literature and that will be discussed in the latter chapters.

Long before the publication of the ACMG guidelines, there have been discussions around issues surrounding a patient’s autonomy and informed consent. Throughout the history of medical ethics, these concepts have been central, but it was only around 1950s-60s that the term “informed consent” was formally established. Driven by the atrocities perpetrated during the Second World War that came to light during the Nuremberg Medical Tribunal in 1947, cases of research abuse caused an international outcry and led to the establishment of the Nuremberg Code [55, 56]. Other notable cases, such as the ones in Tuskegee [57] and Willowbrook [58-60], demonstrated the need

for changes in the ways in which researchers considered the ethics of the way they conducted their work, discussion on which continue as medicine and technology change.

As a reflection of the increased emphasis on autonomous choice, medical and research practice started moving towards requiring a patient's informed consent to participate in research or clinical investigations. Until then, paternalism, i.e. where the physician (or researcher) made all the choices [61-63], including the one to disclose information to the patient, other practitioners or their families, was the prevailing approach in both medical ethics and clinical practice. Paternalism was justified by the perceived asymmetry in knowledge between the patient and the physician, which allowed the latter to make what was perceived as a decision in the patient's best interest [62]. From paternalism, we have gradually moved to the idea of having the patient (or the research subject) being informed in a comprehensive way, adjusted to his or her capabilities, and giving them the right to authorise or refuse a biomedical intervention, including receiving (or declining) information. This change was supported by the idea that the patient could act as an autonomous agent if informed and supported to become one and by the realisation that the idea of a clinician's view of a patient's "best interest" might be more of a perception than an indisputable truth [62, 64-66].

Providing a simple working definition of consent is a fairly easy task. Consent could be described as the "voluntary and informed expression of the will of a person, or if incompetent, his/her legal representative" [67]. Nevertheless, acquiring consent from a patient is anything but easy.

Demanding full disclosure and complete understanding would make informed consent almost impossible to obtain in most cases because of the complexity of medical practice. It becomes obvious that consent has a dual meaning which is what renders it so hard to obtain. It is both a) the "autonomous authorisation" by an individual, giving permission to a healthcare provider to do something, and b) the document that conforms to available laws and policy documents and depends on social and institutional context [61, 68]. Informed consent in the second sense is easier to obtain and has become the mainstream practice. However, obtaining an informed consent with the first meaning, understood as the gold standard of an autonomous choice, is much harder.

This discussion about consent is important because I believe it becomes even harder to obtain when it comes to genetic and genomic tests. It is impossible, by definition, to have a full disclosure and for an individual to have a complete understanding of all the potential results, and therefore have an informed consent in the sense of a complete autonomous authorisation [69]. It is impossible for a clinician to predict or expect results that are unpredictable [69] and it is also impossible from a practical point to have adequate time to discuss all potential findings with a patient [69]. In addition, genomic test information can have implications for family members. This raises the difficulty of

whether clinicians or researchers should be disclosing information to family members or whether individuals, when making choices to receive information, realise that decision may affect the health of their families as well as their own [69]. These considerations need to be taken into account when discussing the concepts of autonomy and choice in this context. What is possible, however, is to inform the patient in advance about the possibility of unexpected findings, related, or unrelated to the diagnostic indication for which the test is performed, and allow them to make the best choice possible for themselves [69].

Respect for the individual's right to make their own choices regarding his or her health constitutes a position of principle. As constitutionally recognised and suggested by different commentators, every individual should enjoy the right of information, including health-related information, to enable them the freedom to make their own decisions [11, 70-72]. This right is included in the Fundamental Rights to individual and socially defined health (Articles 5(5), 21(3)[70]). In addition, an individual using health services (for any purpose) should have full control over the relevant information that he or she receives from the physician through informed consent (Article 5,[70]). The choice in question should be exerted even in exceptional cases or even when the individual chooses to deny information, and authorises the physician to proceed to the necessary acts at the latter's own discretion. This possibility of refusing information is officially recognised and is described as the "right not to know" or the "right to ignorance" (Article 10(2)[70, 71]).

However, although consent and patients having the choice to make their own decisions might be recognised in our society, there are still numerous cases where patient's autonomy and informed consent is or might be challenged. The most common case is when the right to make own decisions contradicts another of the traditional bioethical principles, for example beneficence and non-maleficence. The most characteristic example of that are the multiple cases made public with Jehovah's witnesses. Jehovah's witnesses reject, for religious reasons, any blood products thus making any major intervention, i.e. surgery, particularly dangerous. Jehovah's witnesses are willing to die rather than accepting a blood transfusion that might be needed to save their life. This is a typical example where patient's right to make own choices conflict physicians' obligation, legal and moral, to act in the patient's best interest [73-77]. Numerous scholars have argued in favour of each side with autonomy defenders claiming that free choice should be the guiding principle even if it contradicts with the moral imperative to provide treatment [76] and beneficence defenders stating that in cases of emergency or immediate danger medical interventions are permitted [78]. This example easily demonstrates how choosing between the positions of autonomy and 'acting in the best interest of the patient' might not be clear choices. A wide variety of stakeholders including IRBs,

ethics committees, individual physicians and healthcare providers, academics, legal experts and patients advocates have taken part in these discussions about these difficult issues.

2.4. Literature about Return of Results from Research Settings

The discussion concerning genetic and genomic IFs began in the research setting [79-82]. To differentiate between the return of findings from research and clinical settings, I use the term return of results, hereafter RoR, for results from research; and the return of IFs for results from clinical sequencing.

Return of results (RoR) to research participants is usually discussed within biobank settings; cancer research; and research being conducted with participants who are diagnosed with a certain condition. RoR from studies using healthy individuals is less frequent but should not be neglected. Interestingly, studies report similar attitudes toward receiving results across research and clinical settings, as is discussed later (see 2.5.2).

Numerous arguments have been presented both in favour and against the return of results from research, nevertheless, supporters of RoR seem to prevail. As Knoppers has suggested “[a]t the international level there may be an emerging ethical ‘imperative’ to return results in genetic research” [83: p.1176]. Thus, a shift might be observed toward RoR to participants [84, 85] that also follow the empirical evidence that suggests that (potential) participants are in favour of receiving results in contrast to professionals’ scepticism.

The main reason why RoR seems to be supported is that researchers feel they have a moral obligation to share findings that might affect participants’ lives. Apart from this, such a gesture would also be beneficial for the research as it would increase trust and might increase research participation. The main arguments supporting RoR are summarised in table 1.

Table 1: Main arguments supporting return of results to research participants

Main arguments supporting return of results to research participants	
▪	Beneficence requires RoR as individuals might have access to possible treatment or prevention [86-89]
▪	Results from research might be the only way to gain access to health information if clinical tests are unavailable or unobtainable (e.g. they are very expensive or at an experimental stage) [90]
▪	Reciprocity requires RoR [44, 86, 89, 91-95]
▪	RoR would increase participation in research [88, 95, 96]
▪	RoR would maximise openness and transparency and would increase people's trust in research [88, 97]
▪	RoR improves public understanding of genetics [98, 99]
▪	Researchers might face lawsuits if they were not to disclose medically actionable results to research participants [100]

In contrast, the main arguments presented against returning results to research participants include RoR making the distinction between research and clinical treatment less clear [44, 101], thus, promoting therapeutic misconception, and that disclosure would impose many difficulties (practical and otherwise) for the researchers. The main arguments against RoR are summarised in table 2.

Table 2: Main arguments against return of results to research participants

Main arguments against return of results to research participants	
▪	RoR might be harmful (e.g. unnecessary follow-up tests) [88]
▪	RoR might cause anxiety [102, 103]
▪	RoR might cause discrimination and stigmatisation [102]
▪	RoR promotes the therapeutic misconception [79, 93, 104-107]
▪	RoR might have implications for family members [93, 108]
▪	Participants would have to be informed in advance, which is not feasible as it is hard for researchers to predict all types of possible results and it would require participants to have a very good understanding of the study in which they participated [109-111]
▪	Researchers are not trained adequately to communicate results [96, 103, 112]
▪	There is still a limited understanding of genetic and genomic data [103]
▪	Unclear clinical utility [103] or pathogenicity [113] of results
▪	RoR would pose an untenable burden on research infrastructure [48, 79, 85, 86, 105, 114-116]
▪	There is no explicit legal duty to disclose IFs from research [117]

Another issue discussed in the literature is the type of results that should be returned.

Commentators have made the distinction between aggregate, i.e. general findings and conclusions of the research project, and individual results [118]. While professionals express a preference toward returning aggregate results [119, 120], participants and lay people prefer individual results

[121-126]. Interestingly, when healthy participants were compared to participants with a diagnosed condition, there was no clear conclusion on whether healthy participants asked for individual results more often than those with a diagnosed condition [127, 128]. This is unusual because one would assume that those with an illness would want more information as it might aid their treatment.

Apart from this distinction, the discussion has also spread to more specific types of results.

Commentators have discussed criteria to facilitate grouping of results, but they have also mentioned specific variants as potentially useful to return. This is important as it might help limit the number results it would be helpful to return, making the discussion easier with the participant. The main criterion mentioned was the treatability of the condition or the medical actionability of the results [108, 115, 119, 129-134], while other criteria suggested include seriousness [121, 135], clinical significance or utility [93, 109, 116, 124] and accuracy [115]. Actionability also has been seen as a useful criterion. As described by Berg et al, clinically or medically actionable is a variant that has “direct clinical utility based on the current medical literature” for which there are “established clinical management recommendations” such as available drug treatment [136]. The term “direct” was added to the definition to distinguish from other variants that have a clinical utility as they provide useful health-related information but for which there are no significant clinical implications; for examples low-risk SPNs variations or variants of high risk, high penetrance but with no available treatment [136]. Finally, the term “clinically or medically” precedes “actionable” to distinguish from results that are actionable in a more general term. They might not provide information that could lead to clinical management but their perceived utility might differ among patients and could potentially inform patient’s decision-making health-related or otherwise [69]. Findings from other studies reported that several specific variants have been examined and proposed as appropriate for disclosure [137, 138] but, for the time being, the main criteria seem to be that variants have to have clear clinical validity and utility [88, 139, 140] .

Empirical studies have suggested that both research participants and lay people (as potential participants) would like to have their health results returned [121-125, 141-144]. Research participants are interested in receiving all health-related results discovered, even if they are about untreatable and non-actionable conditions [99, 143-145]. It has been suggested that participants are less willing to receive results of unknown significance [145], however, some evidence suggests that it would be inaccurate to say that all participants want more results. For example, individuals with Miller syndrome⁴ participating in a study expressed reluctance about receiving results about other genes or conditions unrelated to Miller syndrome [146]. This shows that all people are not the same

⁴ a rare, autosomal recessive disorder characterised by craniofacial and limb anomalies

and more empirical evidence is required before clear conclusions could be drawn upon which guidance will be built.

Regarding results of unknown significance, healthy participants and people diagnosed with a condition appear to have different attitudes. People with a diagnosis are in favour of receiving results of uncertain significance as they believe that even results without clinical utility or validity could help them understand something about their disease or perhaps prove useful in the future [128]. For all participants (healthy and those with a diagnosis), it seems that maintaining control over the return of results was seen as more important than the type of results that they would receive [95, 115, 147, 148].

The conclusions I have reached from reviewing the literature about RoR from research settings is that actual and potential participants are generally in favour of receiving results for RoR, even if they are uncertain as to the implications of such a decision. In contrast, professionals and commentators, although they acknowledge this shift in attitudes towards the return of results and agree, have not yet agreed on the type of results that could be offered to participants. As people will be wanting these results, there is a need for clear guidance for professionals [6]. These discussions continue and have moved into clinical practice.

2.5. Literature about return of IFs from clinical settings

2.5.1. Available guidance

Currently, there is limited guidance and that which is available greatly varies across countries and national organisations. Only the USA and Australia have guidance from a governmental body and this is limited; all other guidance comes from professional bodies.

At a European, or international level, guidance comes from the European Society of Human Genetics (ESHG). Their guidelines encourage the use of targeted tests, when possible, to avoid IFs and call for “prudence” when less targeted tests are used. They underline the need for guidelines regarding the return of IFs to minors and regarding the procedure through which IFs should be returned. They also suggest the possibility of re-contacting patients at a later date if new evidence is discovered about their results [149, 150]. The Royal College of Pathologists of Australasia (RCPA), while acknowledging clinicians’ obligations to inform patients and also stressing the need to consider blood relatives of the patient, have not reached a consensus concerning return of IFs to patients. Once more, targeted tests are preferred to avoid IFs if possible. The RCPA guidance also suggests

that if a patient is unwilling to receive actionable IFs, clinicians should try to offer targeted tests instead of genomic tests that might produce unwanted findings [151].

At a national level, the UK is one of the few countries that has topic-specific guidance available. The Association of Genetic Nurses and Counsellors (AGNC) and the Public Health Genomics Foundation (PHG) provide some preliminary frameworks [152, 153]. They suggest pre-test counselling and underline the need to inform patients about the possibility of discovering IFs. They consider that patients should have the choice to opt out of receiving IFs and they both consider that actively looking for other variants not associated with the diagnostic indication, as suggested by ACMG, should be seen as opportunistic screening. Interestingly, the AGNC suggests patients should be able to choose the results that they want from the opportunistic screening and the laboratory should only look for the ones for which patients have consented [152]. In contrast, the PHG Foundation suggests that clinical criteria should have more influence on the results returned than the patient's choice [153].

In the USA, the available guidance comes from the ACMG, as discussed (see 1.1.), and the Presidential Commission for the Study of Bioethics Issues, which underlines the need to inform patients in advance about the possibility of discovering IFs [154]. Although not officially categorised as guidance, one more publication has greatly influenced the management of IFs in the US and potentially elsewhere, and is, thus, relevant here. Berg et al suggested a “binning” process according to which findings should be categorised into three groups and managed accordingly. Bin 1 includes findings with clinical utility and these should be returned to patients; bin 2 includes findings that are not medically actionable but are associated with a disease; and bin 3 includes variants of unknown significance. While findings belonging to bin 3 should not be returned, the feedback of findings from bin 2 would be a choice made by the patient and his/her clinician during pre-test counselling [136]. This approach has been widely discussed and has been referenced (cited more than 140 times as of April 2015 according to the Web of Science database) as a very useful practice in categorising and managing variants.

However, these examples are specific to their local setting and while there is some agreement, countries continue to seek additional guidance elsewhere. It is this gap I hope to fill with my guidance for Greece.

2.5.2. Commentaries, opinions, and other theoretical papers

The goal of this section is to present an overview of the context within which the current discussion is taking place. The literature has been systematically reviewed, however, this is not an exhaustive review as the literature is developing simultaneously with the writing of this thesis. Therefore, only

a selected number of publications are discussed here, mainly the papers that have significantly informed the debate internationally and influenced my work.

Two broad groups of publications by commentators, i.e. academic and clinical professionals who have published views on these issues, have been identified. The first includes papers discussing arguments in favour and against the return of IFs from clinical sequencing, similar to the ones presented earlier about the return of results from research. The second group of papers reports a consensus that IFs should be reported and discusses the practical issues deriving from such a practice. To facilitate the discussion these two groups of studies are presented separately below.

2.5.2.1. Arguments in favour of and against returning IFs from clinical sequencing

The potential shift observed in the literature about the return of results from research has inevitably influenced the literature about the return of IFs from clinical sequencing. This is because practices cannot completely differ between the two settings, as clinical sequencing is used both for diagnosis and for research. Furthermore, as potential participants and potential patients overlap, and clinicians work in both settings, some consistency is required. Most commentators acknowledge that some IFs should be reported [155] but some concerns are still expressed, suggesting that it might not yet be the time to return IFs. On the other hand, supporters of returning IFs have argued that patient autonomy, beneficence, and a duty of care strengthen the obligation to return IFs. The main arguments in favour and against are summarised in tables 3 and 4.

Table 3: Main arguments supporting return of IFs from clinical sequencing

Main arguments supporting the return of IFs from clinical sequencing	
▪	Beneficence and non-maleficence require the return of IFs because patients might have access to early treatment and/or preventive measures [33, 156]
▪	IFs might concern life-threatening conditions and, thus, disclosure might save a patient's life [28, 157]
▪	IFs might end the diagnostic odyssey [158, 159], especially in rare diseases [26] or cases where other tests have failed to produce results [20-22, 26, 32]
▪	IFs might allow prenatal and pre-implantation interventions [159]
▪	Return of IFs will promote patients' autonomy [156, 160]
▪	Return of IFs to minors will enhance minors' autonomy even if they only affect parents or siblings [160]
▪	IFs might affect more people than the patient and, additionally, they might benefit from the disclosure [160]
▪	IFs might help patients and/or their families to plan for the future [156, 161]

Table 4: Main arguments against return of IFs from clinical sequencing

Main arguments against the return of IFs from clinical sequencing	
▪	Return of IFs is a very time- and labour-intensive process [156, 162, 163] and if patients change their minds the process will become ever more complex [156]
▪	It may be difficult to assess variants if there is no family history of that condition [34]
▪	IFs might not have clear clinical significance [25, 164]
▪	It is necessary to clarify variants' pathogenicity before returning IFs [25, 29, 164]
▪	There may be limited understanding about genomic tests and variants [25, 165]
▪	Interpretation of genomic data remains a challenge [157, 166-169] and clinicians might not have the ability to interpret and return variants [158, 166, 169-171]
▪	Interpretation remains particularly time- and resource-consuming [17, 26, 172]
▪	If IFs are to be returned, there may not be enough geneticists and genetic counsellors available to cover the demand [173]
▪	There are technical difficulties including false positives [16, 28], incomplete coverage and accuracy lower than 100% [28, 174]
▪	It is difficult to specify patients' preferences in advance due to the limited understanding of potential findings [170, 173]
▪	Returning IFs might shift the focus away from the patient and the original diagnostic indication [36]
▪	IFs might affect more people than the patient, and their preferences are not known [175, 176]
▪	Current consent practices might not be adequate to cover clinical sequencing and IFs (long sessions, lack of consensus about what should be included in the consent forms, difficulties in informing about all possibilities etc.) [16-18, 164, 177-180]
▪	There is a lack of stakeholder input to demonstrate what each group wants and needs [25, 157, 166, 167, 181, 182]

2.5.2.2. Practical procedural processes

It is interesting to note that although numerous practical concerns have been expressed (see table 4), a consensus seems to be emerging from the literature that IFs from clinical sequencing should be returned. However, commentators consider that several issues require further discussion before deciding that IFs can be systematically reported when discovered in clinical sequencing. These issues include: current practices and available guidance; the informed consent process and pre and post-test counselling; the type of results that should be returned; and the person most appropriate to return them.

A substantial number of commentators report that current feedback policies vary according to the setting which provides the clinical sequencing, i.e. clinical [167], laboratory [183], or according to the country (or the State, for the USA [155]). In a similar way, differences are observed across laboratories and companies offering sequencing regarding reimbursement practices and insurance coverage [184, 185] and, currently, the cost of most tests is covered by patients. They ask for clear

guidance [167, 186, 187], a framework for the interpretation and reporting of findings [188] and, if possible, for standardised processes that could make the feedback process easier [137, 189]. If clinical sequencing and the return of IFs are integrated into the clinical routine, a standardised process could ensure quality and minimise disparities [29, 189].

Several commentators have expressed concerns about current informed consent processes. They also discuss potential pre-test counselling that could be in place in the future to cover the discovery of IFs. They suggest that an informed consent document containing the core elements and covering all possibilities would have to be lengthy and, hence, inevitably be difficult to read [177, 183]. In the same way, a pre-test counselling session where all possibilities would be discussed would be impractically long [190]. Regarding available informed consent documents, empirical studies report that they rarely mention the potential of discovering IFs, therefore, this suggests the patient's preferences might not have been determined during pre-test counselling [191]. Commentators express fears that even if patients are informed beforehand they might not completely understand the potential implications of the findings [190]. Therefore, they suggest that the current consent process and informed consent documents might not be appropriate for clinical sequencing and that other models, apart from the traditional informed consent model, should be sought [163, 191-194].

Another issue raised was that findings might affect other people than just the patient and, consequently, the preferences for other family members should also be considered. Lucassen et al suggested a familial approach especially when clinical sequencing is conducted with children [195]. They were also concerned about whether patients would inform their family members about findings that could also affect them [194].

Apart from reporting specific variants which might be the current practice [183], two approaches are so far discernible about the type of findings that should be returned. One approach, favoured by ACMG and other scientists, suggests that specific variants should be reviewed, included in a list and those returned to patients. Having a list of results would ensure consistency and would protect laboratories and clinicians from liability [36]. At the same time, a list is seen as something that would enhance patients' autonomy as it would be easier to choose what to receive from an explicit list [160].

The second approach would be to categorise results into groups and return them according to the group to which they belong. The most commonly discussed way of categorisation was suggested by Berg et al who grouped variants into three bins according to their clinical validity and utility (as explained above) [136]. According to this approach, the reporting of results would depend on the bin

into which they are grouped. Several commentators have referenced Berg's "binning system" and consider it to be a convenient and scientifically valid way to make feedback decisions [137], thus making it one of the prevailing strategies. What seems to be shared across the two models is that a consensus about the return of medically actionable results is emerging, while there is currently no agreement about other types of results.

Finally, another issue frequently raised concerns who the appropriate person is to return IFs. Commentators suggest that if IFs are to be returned, this should be done by a competent person (who has usually received formal training or is extensively experienced). Clinical geneticists and genetic counsellors have been suggested as appropriate people. Clinicians, in general, have also been suggested as appropriate but several concerns have been expressed about non-specialised clinicians' ability to understand genomic data, interpret results and lead the feedback process [165, 169, 171, 196-198].

2.5.3. Empirical studies

Usually, the theoretical discussion precedes empirical studies and this sequence is also observed in this case. Although the theoretical literature presented above is not exhaustive, the number of publications discussed exceeds 30, while at present only fourteen empirical studies reporting different stakeholders attitudes have been published. It is worth noting here that at the beginning of this project, of the 14 studies presented below, only five were published, while the remaining nine were published while this project was taking place. From personal communications and as-yet unpublished data, it is expected that more empirical studies will be published in the next couple of years significantly enhancing the current, limited evidence. To facilitate analysis, studies are divided into studies reporting professionals' attitudes (seven), studies reporting patients and lay people's attitudes (five) and two more that report attitudes from a mixed group of professionals, the general public, and the patients or parents of children who have experienced genetic testing.

2.5.3.1. Professionals' attitudes

Nine studies (seven studies reporting only professionals' attitudes and two more reporting professionals and other groups' attitudes) have been identified to date investigating professionals' attitudes. The professionals represented include clinicians or clinical geneticists, lab-geneticists, genetic counsellors, and non-genetics providers (nurses etc.). All studies were published between 2012 and 2015 and the majority come from the USA (six studies were conducted in the USA, one in Canada and two in Australia). The sample size (10-760 participants) and the methodology used (phone interviews, online questionnaires, semi-structured interviews and focus groups) varied considerably across studies.

The majority of professionals in these studies said they would report information for serious and medically actionable conditions [32, 199-202] for adult patients [200, 201, 203]. There was no consensus about providing findings for untreatable but serious conditions, carrier status, adult-onset conditions, multifactorial conditions and results that were not medically actionable (i.e. with treatment or preventive measures available) [32, 201, 203]. In these cases, some professionals believed the choice should be left to the patient [201, 203, 204], while others preferred a more paternalistic approach where professionals would decide what to offer [205]. In a mixed study with professionals, patients and parents, the authors concluded, considering the diversity of opinions expressed regarding the IFs that should be returned, that categories or lists produced by professionals might not be adequate to reflect the needs and values of parents and patients [32].

Professionals with previous experience of disclosing IFs have expressed concerns about patients' ability to fully understand the information provided [200, 205]. They suggested that if IFs are to be returned several criteria should be met. These include sharing experience between professionals, additional counselling at a later time [200], and greater communication between clinicians and laboratory professionals [200, 202] to ensure a bi-directional communication, thus, increasing both parties' knowledge and experiences.

The lack of clinical utility of ES/GS and concerns about their own ability to interpret and feedback results were seen as factors preventing genetic counsellors from offering these tests to patients [169, 204]. Further training, counselling courses, courses on bioethics, more time spent with patients, and good communication between healthcare professionals, laboratories and patients (potentially facilitated by genetic counsellors) could help them better manage IFs and ES/GS tests [169, 202, 204]. Regardless of the concerns expressed, genomic tests were seen as beneficial for patients and, therefore, healthcare providers seemed to prefer them, on the basis that they improve the diagnostic rate [202].

2.5.3.2. Patients' and lay people's attitudes

Seven studies (five plus two) were identified investigating lay people's, patients' and parents' attitudes. All studies were published in 2013, 2014 or 2015 and come from the USA or Canada. The sample size (18 -200 patients and lay people) and the methodology used (consent forms analysis, semi-structured interviews, and focus groups) varied across studies. An attempt to synthesise the evidence from this very heterogeneous group of studies is presented below.

Lay people thought that they should have control over returns of findings and decide on the findings that should be returned to them [32, 205]. They also reported that they considered non-specialised physicians as not being capable of interpreting results [205]. There was a consensus among parents

and lay people that patients should be responsible for tracking developments and re-contacting clinicians about their original sequencing as new genomic knowledge emerged [205].

Yu et al compared attitudes of African-American and non- African-American parents toward the return of individual results from GS [206, 207]. They reported that African-American parents were less willing to receive IFs and had less trust in professionals compared to non- African-American parents [206]. For non- African-American parents, actionability was understood in a broader sense and they asked for results that would be useful to them even if not medically actionable [207]. The majority wanted results both for themselves and their children [207] and were in favour of shared patient-physician decision-making [207].

Two other studies revealed that patients and parents were in favour of receiving IFs and that they were also willing to receive findings for carrier status of recessive disorders, predisposition to later-onset disease, and predisposition to increased cancer risk [32, 208]. At the same time, evidence from one study where healthy individuals described their experience after receiving results from genomic tests suggested that genomic results, even if unanticipated, have usually a neutral effect (53.9% compared to 19.2% who reported having a negative effect), thereby suggesting there seems to be no significant psychological harm from disclosure [209].

Finally, patients with Lynch syndrome (hereditary non-polyposis colorectal cancer) from another study, reported that the benefits of receiving all possible results generated from ES outweighed the undesirable effects. They considered that even when dealing with cancer, IFs could be manageable [210]. The majority (63%) wanted to receive all possible results and they preferred receiving these results from a genetic counsellor (compared to 21% who preferred receiving them from a clinician). Patients seemed to value results even if they are not medically actionable, as it would allow them to plan for the future (financially and psychologically) and would help them understand how it would affect their lives (e.g. retirement and reproductive/family planning) [210]. All patients stated they would inform all relevant family members about the results. The majority (84%) said they would disclose all ES information to family members while the remaining 16% only wanted to share results that were medically actionable [210]. Interestingly, some patients did not consider ES as much different from other predictive medical tests that can guide effective medical management. Patients expressed “nondeterministic understandings of genetics”, i.e. the perception that if a genetic condition is identified symptoms of the condition will appear. The majority felt that they could act upon IFs, for example, by changing their medical management or adjusting their lifestyle choices [210].

2.6. Summarising the available literature and identifying the gaps

There are two different strands of literature concerning the return of results from research and from clinical settings but several arguments and issues raised are shared across these settings. Literature about RoR from research suggests that although there are a number of theoretical and practical barriers, a shift is observed toward RoR. Although most stakeholders accept that results might have to be returned, the practicalities of the process and the type of results to be returned still remains a matter of debate.

The literature concerning the return of IFs is still limited and mainly includes theoretical papers, but I have gathered the following as conclusions. Commentators appear to be sceptical about returning IFs and the practicalities of providing such feedback, yet there is a strong move towards the return of results. Lay people and patients who appear to ask a greater range of results, but professionals, as commentators, are sceptical and would prefer to return only medically actionable results. This mirrors the tension previously discussed between the constitutional rights to information and emphasis on the importance of individuals making autonomous choices as to their healthcare, while professionals still lean towards acting in the best interest of the individual. Professionals are uncertain about the level of autonomy that should be granted to patients to make their own choices as professionals believe patients may lack the knowledge to fully understand the results. At the same time, they (professionals) also question their own ability to interpret results. Patients and lay people also raise doubts about non-specialised clinicians' ability to understand genomic results and they would like control over their results. Offering patients a choice in the context of genomics was seen in my review of the literature as both important and feasible, but a general lack of confidence appears to be preventing professionals from enthusiastically supporting the return of IFs and ES/GS, although they acknowledge the potential benefits of their integration into their clinical routine.

More evidence is accumulating suggesting both the usefulness of clinical sequencing as a diagnostic tool, as well as a shift toward the return of IFs as shown by the limited empirical data currently available. Because of this shift, professionals need specific guidance to support their practice. No matter how challenging establishing such a mechanism might be, I believe there is no excuse at the moral level to ignore patients' preferences and beliefs [211-213]. I do not argue that practical matters should not be taken into account, as such a claim would render the approach unrealistic and unfeasible. Nevertheless, I do argue that our moral principles should be the ones guiding our approach, and in this case, supporting and defending patients' choice is the guiding principle. Therefore, I feel it is important that if patients want results, then the issues surrounding this process

need to be examined and guidance created. However, so that the guidance is useful and appropriate, more empirical evidence is needed to shed light on stakeholders' actual needs, concerns and views. Data, such as the data presented in this thesis, can be used to inform the direction that guidance should take. In this case, informal recommendations in the form of points-to-consider are prepared and presented in chapter 9. The preparation of these points was guided not only by the traditional bioethics principles, as those were defined earlier in this chapter, but also by human rights and the UN Declaration of Human Rights [214] which have been suggested as more actionable and robust [215, 216].

Investigating stakeholders' attitudes is urgent and timely. Lay people and patients' views should be considered, to determine their needs and formulate guidance accordingly. However, because of the time and resources available, I chose to examine professionals' attitudes for this work. Professionals' unwillingness to use clinical sequencing should be studied as well as investigating what they consider as barriers. Only by resolving these issues can clinical sequencing and potentially useful IFs be used in patients' best interests. If professionals' concerns are disregarded, they might remain reluctant of using exome and genome sequencing and patients might never gain access to a diagnostic tool that, as evidence suggests, could be revolutionary. Focusing on professionals' attitudes should also show how any guidance created would be able to act as a working framework and support the integration of clinical sequencing and the return of IFs. Guidance should start being developed at both national and international level, and professionals' insight will be required in the preparation of those guidelines so that they could be widely acceptable in practice. This was the model used by the ACMG. Once guidance is created, it can then be presented to and discussed with lay people and patients to further improve it.

2.7. Aim of the study and research questions

Theoretical papers suggest that, even though there is a move towards returning IFs, there is a general reluctance amongst professionals when discussing the integration of clinical sequencing into the clinical setting. The literature also revealed a significant scepticism amongst professionals concerning the type of results that could be returned and the practicalities of the process. However, the empirical evidence is limited.

I decided to see whether this scepticism was true amongst professionals in Greece, the UK, and the US and explore in more detail what could help professionals overcome any reluctance. I formulated the following research questions to guide my interviews with professionals:

- a) Can you tell me the processes through which individuals or patients access genetic testing and clinical sequencing in your country and are there any barriers that might make the process difficult, or any best practices that you feel facilitate the process?
- b) In what ways do the existing legal governance mechanisms concerning genetic testing and clinical sequencing in your country support or hinder the process, and do you believe they can be improved?
- c) Have you personally returned results through clinical sequencing and/or IFs to a patient, and if so, how did that experience shape your attitude towards the practice?
- d) Can you describe what mechanisms were in place at your institution and/or nationally to support you if you do need to return results and IFs and how they worked?
- e) If you experienced difficulties, can you suggest mechanisms that you believe would have helped you provide better support for the patient and improve the experience?
- f) Can you tell me your thoughts on whether results or IFs should be given to a family member and about any experiences you've had with this?

CHAPTER 3: METHODOLOGY

3.1. Chapter outline

This chapter sets out the methodology I employed and is presented in multiple parts. Following an overview of the study, I describe the theoretical and methodological framework underpinning my approach, and consider the options available for conducting the study. I then present the methods chosen and my rationale behind these choices. In the next two sections of this chapter, I focus on the specific steps followed for each part of the project, the key decisions made and the challenges faced during the process. In the final section, I consider approaches to judging the quality of research of this type, which will be further discussed in chapter 9.

3.2. Overview of the study

This project was organised into two distinct parts. The ultimate goal of this project is to provide support for Greek geneticists, and therefore I believed acquiring an in-depth understanding of their professional attitudes and needs was essential. As identified in the literature review, professionals' attitudes are under-represented, hence, I chose a qualitative approach to allow me to conduct an in-depth investigation into their perspectives and experiences. The first phase aimed at investigating and comparing the views of experts from three different countries: the UK, the USA and Greece and I used in-depth interviews for this cross-national comparison. Greek experts were invited to offer their insights regarding the existing situation in Greece but also regarding future actions that could improve the provision of genetic and genomic tests. As Greece has a relatively short history in using genetic tests for diagnostic purposes, I chose examples of models of health services from two other countries with longer histories (the USA and the UK). I also studied the background of these three countries specifically concerning the use of genetic tests and clinical sequencing. In the interviews with experts from these countries, I investigated the existing situation in each country and asked their attitudes regarding current and future feedback practices (see chapter 4). I used the data from the interviews to provide evidence that could suggest best practice that could be adapted for and adopted in Greece.

In the second part, I conducted a survey of Greek geneticists, aimed at investigating their attitudes toward clinical sequencing and the return of IFs. A quantitative methodology was used and an online questionnaire was sent to all Greek geneticists registered in the two genetics associations currently existent in Greece. The qualitative and quantitative parts of this study were combined in an effort to gather enough evidence to support the preparation of points-to-consider for Greece, thus making this a mixed-methods study.

As the goal was to collect perspectives from genetics and genomics professionals, I chose several subgroups with different backgrounds and formal education to include in my analysis. For the first part of the project, experts included clinical geneticists (CG), lab-geneticists (LG), genetic counsellors (GC) and experts with a legal and/or bioethical background (LB) (for the definitions of the specialties included please see appendix 1). For the purpose of this project, all Greek clinicians specialised or with extensive experience in genetics are referred to as clinical geneticists. Additionally, lab-geneticists, genetic counsellors and experts with a legal and bioethical background are classified as non-clinicians. Given that Greece does not have recognised genetic counsellors, clinicians and lab-geneticists act as genetic counsellors and provide counselling and follow-up support. All Greek clinicians and the three Greek lab-geneticists interviewed reported that they also provide genetic counselling in addition to their other professional duties.

For the second part of this project, the generic term “geneticist” is used (see chapters 7 and 8) to refer to all Greek members of the two associations that completed the questionnaire, regardless of their formal education.

In chapters 8 and 9 I use the term “Greek professionals” to refer to both Greek experts from the interviews and Greek geneticists who participated in the survey.

For the definitions of the different specialties mentioned, please refer to appendix 1.

3.3. Broad Methodological Approach

3.3.1. Cross-national study

Analysing an event or a process that takes place within a country, while comparing the way that this same event or process takes place across different countries, is described as a cross-national study and is a commonly-used research strategy. In this approach, researchers compare a phenomenon in a systematic way, examining similarities and differences between different countries [217]. It is a valuable research approach, which enables generalisation of findings, helps validate interpretations from single-nation studies, forces revisions of interpretations by taking into account cross-national differences that cannot be revealed via single-nation studies, and raises questions about the generalisations made in single-nation studies [218]. Recently, globalisation and decreases in the cost of travel have made cross-national research easier while the development of online research methods has further facilitated this type of study.

Researchers follow this strategy in an attempt to produce, modify or confirm a generalisation or even a theory. By collecting data from more than one country, they broaden their scope [217]. Particularly if they compare data from their own country to data from other countries, the comparison allows them to limit some prejudices associated with pre-existing ideas about a system that are usually formulated through personal experiences or the literature [217].

For health-related studies, cross-national methodology has been used and has been seen as a very productive research strategy [219] as it enables a broader range of comparisons, thus not limiting comparisons to a single nation [218]. Using a cross-national methodology to study health systems also serves in limiting preconceptions that researchers have either in their professional capacity or through personal experiences, especially when studying the health system in their own country. As researchers have their own experiences, especially from the healthcare system in their country, studying more than one country at once may help minimise their biases and help them to be more objective.

This type of research also allows for a “better comprehension of the problems marked by multiple influences in an era of accelerating international transformation” [217: p.626]. It also allows for a critical approach to categories that are universally applicable such as genetic testing or issues that are related to the online domain – such as direct-to-consumer (DTC) genetic testing - that are international. With the appearance of DTC genetic testing, a new era of health services has been created. Genetic testing has become more accessible to individuals who are no longer patients but consumers. In parallel, developments in the fields of genetic and molecular biology as well as

developments in bioinformatics have made people more aware of the availability of genetic and genomic testing. New methods have been introduced and genetics has become more and more integrated into the clinical process. The level of integration can be assumed to differ but there are only a limited number of studies exploring the specific ways in which availability and awareness of genetic/genomic testing are similar or different between countries. As guidance is being drafted at a national and international level, cross-national studies might show where similarities and differences in practice lie. At the same time, cross-national studies will be necessary to provide evidence for the creation of international guidance as evidence from only one country would be inadequate to demonstrate overarching principles.

This study represents a cross-national piece of research across Greece, the UK, and the USA investigating different stakeholders' attitudes towards the return of IFs from clinical sequencing.

Greece was chosen as the main focus for both personal and professional reasons. My previous experience of working in the Greek health system made me interested in investigating professionals' practices further, and being Greek made me want to help Greek medical professionals in any way possible. Greece is a country in which clinical sequencing is currently offered, but there is no available guidance or any other supportive mechanism to provide a framework for managing IFs although clinical sequencing is expected to be more integrated in the future. Moreover, from anecdotal data and personal communication, it seems professionals struggle to handle IFs at the present time. A very limited number of studies (two as of April 2015) [220, 221] have investigated topics relating to genetic tests in Greece and, currently, there is no form of official records or any official body regulating genetic tests (see section 4.4.1.). This gap in the literature, combined with a personal interest to both gain a better understanding of the existing situation and to attempt to help Greek professionals, were the reasons for my choice.

I chose the UK as it represents a country in which there are regulations for most available health services, including clinical sequencing. Existing policies and oversight bodies are designed to ensure a good quality of the service provided. Furthermore, the existence of general practitioners (GPs) acting as gatekeepers for the health system could provide an interesting model that could inspire similar arrangements in Greece. The availability of clinical sequencing, combined with the existence of several professionals considered as experts, were among the reasons for this choice.

Finally, the USA was an "obvious choice". The publication of recommendations from the ACMG in March 2013 made the USA the perfect country to investigate, as it was the only country with a working framework for clinical sequencing at the start of my study. These recommendations created

a considerable debate despite being produced by a recognised body and by researchers considered as international experts. Therefore, carefully considering the US experience could provide helpful insights. Additionally, most of the experts in the area (apart from the ones from the UK and Canada) are located in the USA and their experience was expected to prove valuable.

Both the UK and the USA are countries with strong traditions in the governance of genetic testing and Greece, which is just beginning to apply these technologies, could learn from them. Lessons could be learnt from their experiences (both positive and negative) and the preparation of recommendations could be informed by those from the UK and the USA, albeit in a modified form to fit the Greek context.

3.3.2. Mixed-methods study

A mixed-methods study can be described as any study combining more than one research method for the collection and analysis of data. The methods included might be different qualitative or quantitative [222] or a combination of both [223, 224]. The decision of which methods to combine is guided by the research questions and the objective of the study and is usually taken at the beginning of a project, but can also be altered later if a more appropriate method is found [223]. The objective of such a combination is to obtain knowledge about the issue studied which is broader or could not have been obtained by using a single method [225]. Additionally, mixed-methods approaches allow the researcher to ask both confirmatory and exploratory questions, hence verifying and generating theory in the same study [226].

More specifically, several methods have been combined under the umbrella of mixed-methods. The most commonly used approaches include the combination of a) interviews with focus groups; b) interviews with observations [227] both combining different qualitative methods, and c) interviews with surveys, which is the combination of a qualitative and a quantitative component. The first approach would allow the in-depth investigation of an issue usually combining individuals' experiences with further insights about how people talk and interact as a group regarding that issue [223]. The second approach would provide different types of information, non-verbal elements (e.g. body language, behaviour), for example it would offer an insight on what people may say they do alongside what they actually do in practice, and it would allow one to make observations people would not think to mention or are not aware they are doing. Additionally, observations would allow the study of an issue within its social environment [223]. Lastly, the third approach would permit the in-depth investigation of a topic with an insight on the same issue of a larger number of participants belonging to the same or a different sub-sample [222, 223]. Although, as mentioned, mixed-methods might refer to the combination of different qualitative or quantitative methods, it is usually used to

refer to the combination of a qualitative with a quantitative approach [224] as demonstrated in the following definition (page 526):

“[m]ixed methods is defined as research in which the inquirer or investigator collects and analyzes data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or a program of study” [228].

Regardless of its potential usefulness, as described above, the combination of qualitative and quantitative research has also received significant critique. Although a detailed discussion of the potential problems falls beyond the scope of this thesis, underlining the main concerns might allow a better understanding of this research approach. It has been argued that the main problem with mixing two approaches is the lack of clarity regarding the purpose, design and contribution of each method as well as the analysis of the results and the inference of conclusion from the combined results. Careful consideration and fully recognising each method and its contributions at every step of the process would limit this problem and would permit a better evaluation of the study [232,234]. Additionally, another issue emerges in mixed methods studies if the two approaches are fully integrated rather than parallel or sequential, which allows each element to follow its “requirements” [235]. In those fully-integrated studies, the need for clarity and consistency becomes even more compelling. Moreover, other concerns include the “uneven” combination of methods which weakens the results produced, for example in cases where few interviews might be used to supplement quantitative data and reinforce conclusions; and the difficulty of combining results coming from small purposive samples (usually used in qualitative methods) with large and randomly picked samples (usually used in quantitative methods). Once more, clarity and transparency allow for better interpretation of the results [233,234]. Some issues were discussed concerning the problems with mixing methods and even more have been raised in the literature. Nevertheless, for this project, I decided to choose this mixed-methods approach as I considered it to be appropriate for my research questions and the ultimate goal of producing points that could support all geneticists in Greece. Aiming at minimising the potential problems emerging from combining qualitative and quantitative elements, I have described every step of the process in detail, explained the rationale behind every decision made and have done so in a transparent and clear manner. Furthermore, I have kept the two elements separate and only in the interpretation of results and the inference of conclusions, I have, after careful consideration, combined the outcome of the two approaches.

There were several reasons for me to use a mixed-methods approach. Methods are typically mixed in this way in order to harness the complementary strengths of each approach to produce data of greater explanatory power than that which would have been produced by quantitative or qualitative

component alone [229, 230]. This typically manifests through the addition of breadth and/or depth to a study, the collection of complementary information [225], or the validation of findings [231]. It has been suggested that, especially for studies including health-related issues, mixed-methods can be a useful approach [229, 232] as this incorporates a “multi-level approach” allowing the study of complex systems consisting of different stakeholders with different perspectives [230].

Decisions about how to mix methods typically involve consideration of two main issues: a) the relative timing and b) the weight of each component. Components might take place concurrently or sequentially and they might have equal or different weight (e.g. one being the primary and the other the secondary) [223, 230, 233, 234]. A range of different combinations of methods have been described and it falls beyond the scope of this thesis to describe all possibilities (at least 12 different combinations and different designs have been described [235]) especially since it has been argued that creating a complete taxonomy of mixed-methods is impossible [226].

For this project, I chose a sequential exploratory strategy [226, 230]. The first phase involved the collection and analysis of qualitative data, followed by the second phase of quantitative data collection and analysis that builds on the results of the first qualitative phase [229]. Here, I chose to combine these two methods to explore perspectives, learn more about the issue under discussion and potentially to generalise qualitative findings to a slightly different sample. Aspects of experts’ attitudes were identified in the qualitative component and were then associated with geneticists’ insights from the quantitative findings; both were then used to inform the emergence of points-to-consider.

A sequential approach was chosen for two reasons. First, at the beginning of the study the area was underdeveloped and an exploratory phase using qualitative work was seen as crucial before being able to proceed to the quantitative stage. Second, as Teddlie and Tashakkori have argued, a concurrent approach, although potentially very powerful, is particularly difficult for inexperienced researchers, especially if working solo as I was [226]. A sequential approach is easier to conduct by a solo researcher as the two elements are kept separate and the study unfolds more slowly allowing conclusions made on the basis of the results of the first part to lead to the formulation of questions, data collection, and data analysis for the second part [226, 236].

The literature often suggests that the quantitative phase should precede the qualitative [226, 236]. However, in this case, as the focus of this project concerned a new and underexplored area when the project started, there was very little literature available which could be used to guide the development of a quantitative phase preceding the qualitative. For that reason, I chose to conduct

the qualitative element first as it was necessary to map the landscape before being able to proceed with any quantitative work.

The underlying rationale for me using mixed methods in this way was therefore to support “instrument development” [237, p. 633-634], as the qualitative part was used to help inform the development of the questionnaire and generate more meaningful closed questions. Data gathered from both methods were employed to acquire a more complete picture of different stakeholders’ views and both were used to support the development of points-to-consider, thereby facilitating the “completeness” of the project [237, p. 633-634]. Mixed-methods were also used here to add breadth to this study. The qualitative part was used to map the existing framework in each country, to investigate different policies and different ways of managing findings. Additionally, experts’ input suggested alternative and better practices that could be implemented in the future. I then used the findings from the qualitative part, and the comparison between the countries, to inform the creation of the questionnaire.

3.3.3. First phase of the project

The first phase of this project consisted of in-depth interviews with experts working on clinical sequencing. A qualitative approach was used to help map both what is currently happening in each country and what experts believe should happen. Understandings, opinions, and experiences were discussed during semi-structured interviews with professionals considered as experts. These were mainly experts in genomic testing but some experts with different backgrounds (bioethical backgrounds, and public health backgrounds) were also interviewed to complete the sample. The process followed in this part of the study is presented in detail in section 3.4.

3.3.3.1. Why use qualitative methodology?

Qualitative research is a strategy emphasising in-depth investigation rather than the quantification of data. It is usually based on the inductive approach to the relationship between theory and research, it is often used to generate a theory (theory-grounded) and embodies social reality as a construction that changes constantly and depends on people’s perceptions [237, 238]. The sample used is usually not representative, nor random, and results are usually not generalisable. The strengths of a qualitative methodology include a flexibility of design and the ability to gain understanding in areas that have not been explored sufficiently (or not at all) [231], as in this case, and specifically, in the case of Greece.

The use of qualitative research is often associated with the generation of a theory. Commonly, the broad literature is first reviewed, gaps are then identified and some general research questions are formulated. In the present study, following the review of the literature, two main conclusions were

drawn. First, there is an increasing interest in disclosure of IFs and, second, the attitudes of most stakeholders are not known. Most of the limited studies available have been conducted in the USA and Canada and no-one, to the best of my knowledge, has attempted to compare the situation and attitudes between different countries. This lack of empirical evidence, combined with the lack of official records and evidence about the availability and the existing situation in each country, were the reasons why I chose a qualitative approach. For this investigation, approaching experts from the domain of genetic and genomic testing and conducting interviews was considered an appropriate information-gathering process. Asking open questions and genuinely attempting to understand the perspectives of participants was the most appropriate means through which to investigate people's experiences, their problems and potential solutions.

3.3.3.2. Why use interviews?

The most commonly used methods in qualitative research are in-depth interviews, focus groups and observations. Although other methods are also used for qualitative research, such as documentary analysis or diary-based methods, extensively reviewing the full range of qualitative methods falls outside the scope of this thesis as these methods were not seen as appropriate for this project. Typically, interviews are used when the researcher is seeking information on individual experiences from people regarding a specific issue. Interviews could be seen as a "one-way dialogue", a conversation with a purpose [223]; where the researcher has limited understanding or knowledge about the research area, and desires to investigate further [239]. Interviews are used to capture sensitive issues that require confidentiality [223], while they are also used to acquire an insight into people's personal or professional experiences.

Focus groups are discussions between a number of individuals (usually six to ten) that have been pre-selected for their characteristics [223]. They could be described as an interactive discussion among participants focusing on a specific issue. They are used when the researcher seeks to identify a range of issues but is also interested in observing the interactions between the group and the discussion between the members.

Observation is a method through which the researcher systematically observes a location (or several locations) with the intention of recording the interactions between people and their behaviours in that environment (usually their natural environment). Observations are used when the researcher wishes to investigate a new area, wants to describe a context or explore social norms, behaviours and non-verbal actions and interactions [223] as observation "enables the researcher to describe existing situations using the five senses" [240].

I chose to use interviews because I was seeking information on personal and professional experiences. Some initial questions were identified through the literature review and the goal was to further investigate these questions and elaborate on experts' attitudes. Focus groups were considered but not chosen as they lack confidentiality and are not ideal for seeking personal experiences. Furthermore, due to the limited number of experts in each country, focus groups would have been difficult, if not impossible, to organise logistically. Finally, discussing practices and experiences in a group context might have discouraged experts from sharing views that might be controversial and/or about which they were unsure [241]. Observations were also considered but since clinical sequencing is taking place in more than one location simultaneously, it was considered impractical. Observation would be inadequate, if used on its own, to provide insights into people's experiences and to elicit their views. Neither would it facilitate the understanding of what experts think practices should be. Additionally, due to the relative infrequency with which experts deal with IFs, trying to do observational work would have been impractical, especially for a single-handed Ph.D. student.

Face-to-face interviews are presented as “... enabling a ‘special insight’ into subjectivity, voice and lived experience” [242: p.314]. Interviews are typically used to collect experiences, understandings and the views of participants [229] and through them more detailed information can be produced compared to less in-depth methods, while a better understanding of questions asked is ensured [243, 244].

Interviewing has many advantages considered crucial for this study. Interviews could provide detailed background about why respondents give the answers that they do, allow elaboration of respondents' opinions, and obtain values, motivations and experiences. They can be customised to individual respondents and thus provide tailored responses, especially on complex and/or sensitive issues [245].

In this study, acknowledging experts' tight schedules, time seemed an important factor that needed to be taken into consideration. In a similar way, the possibility to customise questions was also considered as a crucial advantage as the sample was expected to be relatively heterogeneous (because of the different backgrounds of experts approached). As the topic of return of IFs from clinical sequencing is relatively new and there is only a limited literature on the subject, conducting interviews to gather information regarding what is happening in each country was considered the most appropriate way to proceed. Furthermore, in Greece currently, there is no legal or governing framework to provide support when IFs are found (see 4.4.). In this way, the only way to effectively investigate the Greek context was to go directly to experts and ask them about their experiences.

Although a very useful methodology, interviews do have certain disadvantages. They are time-consuming and can produce tremendous volumes of data for coding and analysis, thus, making them more challenging to analyse [243, 244]. This has resource implications and may limit the sample size that can be targeted. Interviews may also be sensitive to interviewer bias and even the physical appearance of the interviewer may promote this. Data could differ between interviews if slightly different versions of the questions are asked and, compared to other methodologies, the cost is higher [245]. Finally, interviews do not necessarily provide information on what people actually practice, they only give people's accounts of what they do.

Acknowledging the disadvantages noted above, I took certain measures to limit the impact of these. The same interviewer, the researcher i.e. me, conducted and analysed all interviews, thus limiting interviewer bias. Slight differences among interviews are not considered a problem in this case as it was within the scope to include experts with different backgrounds to enrich the data. Finally, people's accounts of the existing situation in each country were combined with evidence from the literature review to minimise biases due to such self-assessments. The challenges faced during interviews are discussed in detail in section 3.4.4 and 3.4.5.

3.3.3.3. Why use interviews with experts?

In contrast to lay people, experts are considered those who possess "contextual knowledge" [246] or those who possess an "institutionalized authority to construct reality" (Hitzler, Honer and Maeder, 1994 in [247]). In scientific research, an individual is addressed as an expert because the researcher assumes that this person has certain knowledge on a topic, usually due to extended education or previous experiences which are not possessed by others in the field. This characteristic is the reason why expert interviews were conducted with the aim of discovering and describing this knowledge [247]. According to the research objectives, the researcher decides who could be interviewed as an expert, but this choice is not solely left to personal judgment as it is also related to the "recognition of an expert as an expert within his own field of action" [247].

Expert interviews can serve to establish an initial orientation in a field that is either substantively new or poorly defined as a way of helping the researcher to develop a clearer idea of the problem or as a preliminary move in the identification of a final interview guide. It has been suggested that talking to experts in the exploratory part of a project is a more efficient and concentrated method of gathering data, while conducting expert interviews can serve to shorten time-consuming data gathering processes [248], which, as mentioned above, is one of the main disadvantages of gathering qualitative data. Experts are expected to have a clearer idea of the existing practices, thus

limiting the number of interviews required. Additionally, expert interviews offer researchers an effective means of quickly obtaining rich information.

In this study, I used exploratory interviews to “provide orientation” [246]. Exploratory interviews help to structure the area under investigation and develop a clearer idea of the problem. The experts were used as a complementary source of information to the existing literature and data from these interviews was used to inform the design of the questionnaire administered to professionals. Both sources were then used to inform the development of the points-to-consider.

3.3.4. Second phase of the project

The second phase of this project consisted of an online questionnaire distributed to all registered genetics professionals in Greece. A quantitative approach was used to investigate professionals’ attitudes and needs. Questions about experiences, criteria, intentions and needs were included in the questionnaire as well as questions regarding future feedback practices. In Greece, there are currently two professional associations concerned with genetic and genomic tests. All registered members of these associations were approached and invited to participate in the survey. These professionals included mainly clinicians working on genetic tests and lab-geneticists. Data produced were used, in combination with the data from the interviews, to inform the development of the points-to-consider. The steps followed in the second phase are presented in section 3.5.

A qualitative methodology was considered for this element but was considered inappropriate. This is because the total number of Greek geneticists is approximately 200, therefore conducting interviews with them was considered impractical due to the time and cost barriers involved. Additionally, as some preliminary questions were formulated through the interviews and the literature review, it was considered more important to attempt to collect a larger sample and have a representative sample of Greek geneticists rather than investigating their attitudes in depth.

3.3.4.1. Why questionnaires?

Quantitative research is a research strategy focusing on “quantification in the collection and analysis of data” [237: p.35]. Questionnaires are usually used to test hypotheses or a theory but can also be used to explore associations and even investigate attitudes of a group for which some information is already available [237].

The most commonly used methods in social science quantitative research are structured interviews and self-administered questionnaires. A structured interview is a strategy to ensure the interview takes place in a more standardised way than in an unstructured interview, minimising the differences between interviews. Structured interviews take place face-to-face or over the telephone

(or through the Internet) but in both cases a detailed list of questions is prepared and followed in the same way across interviews. Questions should be read in the exact wording and order every time to ensure consistency, and are usually specific [237].

Self-administered or self-completion questionnaires are completed by participants themselves and could take place face-to-face, by post, or, increasingly, over the Internet. The order of questions usually remains the same, while most questions are closed. Compared to structured interviews, questionnaires are usually shorter, cheaper and they have fewer open questions. Additionally, as there is no interviewer present, participants are less likely to be affected by his or her characteristics [237]. On the other hand, questionnaires have several disadvantages compared to structured interviews. The most important disadvantages are that there is a risk that questions may not be answered, response rates may be lower and no clarifications can be sought [237]. For postal questionnaires a response rate of over 60% is considered acceptable [237]. For online questionnaires, the response rate is usually lower than for paper questionnaires [249, 250] and varies between 20-47%. No systematic data were identified on response rates for this type, possibly because online questionnaires are a relatively new methodology, therefore, it remains unclear what the acceptable response rate is. However, that seems to be dependent on the sample size [250].

I chose to use questionnaires for this project for predominantly practical reasons including lower cost, a quicker process, that they could be administered from a distance, and easier data analysis. In addition, as professionals would be asked for their attitudes, it was considered essential for them to be able to reply to the questions in their own time and space. No sensitive information was requested but, for busy professionals, being able to complete a questionnaire at their own convenience was seen as important.

3.3.4.2. Why online questionnaires?

The Internet has been used as a means to administer questionnaires since the mid-1990s [251].

Online questionnaires can be administered either through email, where the questionnaire is either attached or inserted as plain text or through a webpage. A webpage is usually used to host a questionnaire that has dynamic characteristics and might be interactive (include videos, music or other visual enhancements).

Using online tools, and specifically online self-administered questionnaires, has many advantages compared to postal questionnaires. These include the low cost, lack of geographical limitations, lack of specific time constraints, flexibility in the approach used to collect data, and the ability to expose respondents to almost any type of audio and visual material [245]. Apart from this, the potential improved representativeness of the targeted population and relatively good quality of data [252]

also make this a valuable tool. Other studies have reported higher levels of self-disclosure in cases where there was visual anonymity using computer-mediated communication (CMC) [253]. Visual anonymity creates a “*stranger on the train*” experience [254] where self-disclosure is made easier through relative anonymity and the social cost of disclosure is further reduced by CMC-anonymity while people tend to focus more on their own attitudes and emotions [253, 255]. Although this was not considered to be a problem in this project, anonymity was seen here as an additional method of encouraging participants to share their experiences and attitudes.

Online questionnaires were the strategy chosen mainly due to their flexibility, low cost and lack of geographical limitations. Although no sensitive information was asked, ensuring anonymity was considered crucial for this study as professionals were asked to express their attitudes.

Confidentiality was therefore an important concern and was fully ensured with the use of an online questionnaire.

The main concern about using online questionnaire is that it inevitably targets only people with access to the Internet. Other concerns include the difficulty of estimating response rates and ensuring that the person recruited is actually the person completing the questionnaire [245, 251]. Another potential limitation concerns sampling. In this case, due to the specific sample chosen, these concerns were minimised. The limitations noted above were not seen as problematic for this study as the target group was professionals with a high level of education, had access to online sources and had a potential professional interest in the study. Additionally, because the number of registered professionals was known beforehand, response rates were relatively easy to estimate.

3.3.5. Ethical considerations

For this project, Ethics Approval was sought and granted by the University of Leicester College of Medicine and Biological Sciences Ethics Subcommittee.

After the preparation of the research plan, ethical issues were considered. Neither part of the project raised any particular ethical issues as the aim was to seek professionals’ views and only their previous experience and their opinions on the topic were to be discussed. No sensitive topics were discussed and no personal information was asked apart from information regarding their professional identity during the interviews and some general demographics asked for in the questionnaires (age, educational level, and family status).

An invitation email was sent to potential participants for both parts of the project. Written informed consent was sought prior to the interview and, with participants’ permission, interviews were audio-recorded and transcribed verbatim. All possible actions were taken to ensure confidentiality. The

audio recordings and transcribed interviews were only accessed by the researcher and the study supervisors.

Regarding the questionnaire, as it was anonymous no particular ethical issues were raised. The only issue was the access to potential participants' email addresses. To avoid having to email participants personally, which would have given the researcher access to their personal details (names, addresses, email addresses etc.), the two associations in Greece were contacted and asked to invite their members to participate in the study. An invitation was sent to the two associations, including the link to the questionnaire, who then forwarded it to their members.

Audio recordings of the interviews and data from the questionnaires were kept on a secure hard drive at the University of Leicester until the end of the study and were password-protected. All data will be deleted at the end of this studentship to preserve participants' confidentiality.

3.4. Qualitative stage step-by-step

The qualitative stage of the study consisted of 30 in-depth interviews with experts from Greece, the UK, and the USA. I conducted and transcribed all the interviews verbatim after receiving the participants' consent.

3.4.1. Sampling

For the first stage of the study, purposive sampling was used. Interviewees were explicitly selected to increase the likelihood of generating appropriate and useful data [231]. Professionals were deliberately selected on the basis of expertise in their field. Experts were invited according to their experience, as evidenced through their published work on genetic and genomic testing and conference presentations at a national and international level. The sample was chosen with the knowledge that it was not representative of the general population [245]. As suggested elsewhere, sampling was designed to achieve maximum variation [256] in terms of experiences with genetic and genomic testing, thus, experts with different backgrounds were selected.

Sample size usually depends on the aim of the study and, occasionally, sampling decisions might have to be made opportunistically if there are only a limited number of potential participants [231].

The sampling for this stage was purposive as the goal was to approach professionals with very specific characteristics, i.e. extended experience with genetic tests and, specifically, with clinical sequencing. A small number of experts were first identified through their published work in this area

and then, due to their limited number, snowballing was used to increase the sample size. As suggested elsewhere, a small number, between 6 to 12, might be potentially adequate to achieve saturation for applied work on a narrow research question. Saturation can develop fairly rapidly for studies where the aim is to understand perspectives and experiences among a group of individuals [231, 257]. The total target sample size for my study was between 25 and 40 experts. Within this sample, sub-samples could be identified; for example, the sub-sample of clinicians from all countries or experts with a legal background. This sampling approach illustrates the kind of “mixed-sampling” strategies that are suggested elsewhere and which are used in practice “... to generate information-rich cases” [231]. To meet the sample size parameters for this study, approximately 15-20 experts were contacted from each country, with the hope that 10 from each would be willing to be interviewed.

More specifically, I identified four experts from each country based on their experience and then used the snowball technique to identify other experts. With the help of the experts primarily identified, more professionals were contacted to clarify their area of expertise. The snowballing technique involves the researcher contacting a few appropriate respondents and then asking them to refer people they know personally (colleagues, friends, relatives, acquaintances) or other qualified people [245]. Interestingly, when the initially identified group of experts were asked to refer colleagues that could be seen as experts, the majority of them suggested experts with what they regarded as “opposing views” as they considered this to be more interesting and beneficial for the project.

Sixty-five experts were contacted in total. Thirty-six experts agreed to be interviewed and, due to schedule and location barriers, 31 interviews were ultimately organised and took place. With the participants’ consent, thirty interviews were audio- recorded and transcribed verbatim; one further expert was interviewed but did not want the interview to be recorded, and this interview was excluded from the analysis. Interviews with Greek experts were conducted in Greek while interviews with UK and US experts were conducted in English. Interviews typically lasted 30-60 minutes and were all conducted by the researcher for consistency and practical reasons.

The first group of experts was initially identified through the literature review. These experts each had several papers on clinical sequencing and IFs published and/or were working in organisations dealing with IFs from clinical sequencing.

3.4.1.1. UK

Nineteen experts were invited to participate. Apart from the original four experts, fifteen more experts were contacted through snowballing. Of the nineteen UK experts contacted, eleven agreed

to be interviewed. More specifically, three genetic counsellors, four clinical geneticists, two lab-geneticists and two professionals with legal and bioethics background were interviewed.

3.4.1.2. USA

Twenty-six experts were contacted and ten of these agreed to be interviewed. Saturation was achieved after the sixth interview but four more interviews were conducted as they had already been planned. In total, ten interviews were conducted and, of these, four were with clinical geneticists, two with genetic counsellors, two with experts with a legal and bioethics background and two more with experts with a bioethics background.

3.4.1.3. Greece

Twenty experts were invited to participate from Greece and 10 interviews took place. Saturation was achieved after 8 interviews but two more interviews were conducted as they had already been scheduled beforehand. Three clinicians, five lab-geneticists and two professionals with a legal and bioethics background were interviewed. All the clinicians interviewed, and three out of five lab-geneticists, were also involved in providing genetic counselling as part of their duties.

3.4.1.4. Reflections on sampling and data saturation

Contrary to quantitative sampling that aims at “count[ing] opinions or people”, qualitative sampling aims at exploring the variety of perspectives and “different representations of an issue” [258]. It is the richness of information that it is of importance and hence, the number of participants greatly varies and depends on the objective of the project [258]. In addition, the researcher should also consider practical issues, such as time and resources available, and be pragmatic in his or her goal for the sample size. However, two concepts have to be considered, adequacy and appropriateness [259, 260]. The sample size has to be “large enough to assure that most or all of the perceptions that might be important are uncovered” but at the same time not too big or too large so as to be repetitious [261](p.2). Given that sample adequacy is the goal, saturation is reached, as Bowen argues when “[d]epth as well as breath of information” is achieved [262](p. 141).

Data saturation is a concept that has been greatly accepted and expected by social scientists [263]. Generally, saturation means that the collection of data should continue until there is no new data collected or until there are “fewer surprises and there are no more emergent patterns in the data” [258, 264]. Contrary to theoretical saturation which is the point where “categories are fully accounted for, the variability between them are explained and the relationships between them are tested and validated and thus a theory can emerge” ([231] in [264], saturation as understood here has a more practical meaning.

Saturation has been applied in a variety of qualitative research projects as a measure of sampling adequacy [262, 263]. Nevertheless, it is not an unproblematic concept [264]. Apart from the fact that it might have different meanings in different contexts, as mentioned above, another objection raised regarding saturation is its limited transparency [264]. Determining when saturation has been reached is particularly difficult especially given the limited practical guidance available [262, 263]. Hence, doing so in a transparent way becomes even harder [264, 265]. Acknowledging this difficulty and aiming at achieving transparency, at a realistic level, both the number and the length of the interviews are described in detail; in addition, saturation is used here in its general definition as the point where no more patterns are emerging in the data. It has been argued that the number of the emerging themes could potentially be infinite and thus saturation would be impossible as every person and his or her ideas are unique. Additionally, in deductive approaches, where the researcher start with an idea and tries to confirm it [264], saturation might be even harder as the researcher does not know the themes that could emerge. Despite that, in research there is usually a research agenda and realistic goals that will be pursued which guide the data collection [264]. Also, in this case, which resembles a more inductive approach where data is collected to explore an issue, this focused approach helps in defining areas that should be covered within which saturation can be achieved.

In relation to this project, I decided to interview a subset of experts from each country. The sub-groups presented a relatively homogenous perspective on the topic investigated; therefore, similar themes arose within all the interviews and the analytical themes were not significantly modified after the interviews. As it will be discussed later, there were more similarities across sub-groups with the same background than with the same country of origin but even across all sub-groups there were no particularly significant differences observed. Choosing upfront the number of potential participants was a challenge for me as it was unclear how large a sample would be necessary for data to be saturated [264, 266]. At the outset of the study, I had anticipated that I would require between 8 and 15 experts from each country to be able to produce some meaningful results. This range was chosen based on suggestions and experiences of fellow students and tutors and pragmatically by the time and resources available. An estimate of the sample size was expected by university requirements as part of the ethics approval process, which contradicts the concept of data saturation as discussed above which should be determined after and not before the analysis [264, 266]. In the end, I found that this estimate was accurate in order to reach saturation within each group and after 7 to 8 interviews, in average, I had collected adequate data to produce meaningful results.

3.4.2. Designing the topic guide and choosing the questions

I created a draft topic guide based on the findings that emerged from the literature review and through discussions between myself and my supervisors. I identified the research questions presented in section 2.7. through the literature review that revealed gaps and areas without consensus. I then chose questions that I felt would help me explore these areas in more detail, in a way that would guide but not constrain the interviews. For example, as the literature showed that professionals appeared reluctant to use clinical sequencing and wanted to rely on targeted one, I specifically asked them about that. Similarly, as the literature suggests disagreements regarding the different types of results to be returned, I included a question investigating experts' attitude towards the different results.

As the sample was heterogeneous, the topic guide was individualised further in some cases. In particular, to interview the experts with legal and bioethical background, the topic guide was slightly altered to adjust to participants' area of expertise and gain insight into specific information needed (e.g. availability of guidance in each country). Similarly, slightly different questions were asked to Greek experts regarding counselling since there is no formal counselling process in place. For Greece, the draft topic guide was translated and pre-piloted to test the accuracy of the translation and the meaningfulness of the questions for the Greek context. The topic guide was submitted as part of the application for ethics approval. A generic topic guide is included in Appendix 2.

3.4.3. Piloting the interviews

I piloted the draft topic guides with two members of the University of Leicester staff with similar backgrounds to the intended study participants. The pilot interviews lasted slightly longer than the estimated time for the actual interviews. The first pilot interview lasted 55 minutes and the second lasted 110 minutes. The pilot interviews lasted longer, as expected, as at several points the "participant", apart from answering the questions, made comments regarding improvements to the wording of the question.

After the interview "participants" were asked to comment on the interview process and the topic guide and make any other suggestions they considered appropriate. The draft topic guide was reviewed and revised after the pilot to enhance the clarity of questions and the order of the questions was revised to facilitate the flow of the discussion.

3.4.4. Conducting the interviews

Before starting, I introduced my background and the scope of the study. Given my diverse background as a biologist with a bioethics specialism and working experience in a hospital, most

experts expressed their relief that we would be able to “speak the same language”. They acknowledged that there would be no need for explanations when talking about genetic testing and genetic conditions and they considered that as an important benefit and a good starting point.

Conducting cross-national research is not an easy task; an important issue is the language, as researchers often face linguistic difficulties while interviewing. Interviewing in a foreign language, even for researchers that are able to understand the language and interact with it competently, is difficult unless the researcher is completely bilingual. This can lead to errors being made in the interpretation of data. Terms used in different languages in a similar way can be mistakenly interpreted while the main error consists of making “linguistic and conceptual equivalences too quickly” when translating [217: p.627].

To minimise the language barrier, interviews with Greek experts were conducted in Greek, while the remaining interviews, with UK and US experts were conducted in English. Interestingly, most Greek experts used several English scientific terms, as there are no corresponding terms in Greek. Although acknowledging language as a potential barrier, I was comfortable using English to conduct the interviews with UK and US experts, as this language is so commonly used in the scientific community that it is considered to be the *lingua franca*. Additionally, as English is the language used in the literature, I was already familiar with the terminology and so language presented few, if any, problems. On only one occasion did an interviewee use a word that I did not recognise – (s)he then realised this and explained it. Almost all the interviewees commented on my ability to communicate and interview them in English and considered that I was fluent. Therefore, to the best of my knowledge, language was not a barrier, although this possibility is acknowledged.

3.4.4.1. Reflections on conducting the interviews

Most interviews were conducted during regular office hours at the interviewee’s place of work. Five of the interviews in the US were conducted at a conference, which I was also attending. Most interviews lasted over 40 minutes and time passed quickly as experts seemed interested in the topic. Interestingly, although the literature describes conducting interviews as a difficult process, for me, the preparation before the interviews and the process of contacting experts and arranging meetings was more difficult than the interview itself. A common understanding of all terms used and a familiarity with the literature in this area undoubtedly helped but the main factor was the fact that most experts were approachable and willing to help. In all but one case, they were willing to spend as much time as required even if that exceeded the estimated time that was stated in the information leaflet.

I was constantly oscillating between “insider and outsider” positions trying to combine insights from both positions’ benefits to acquire the best possible in-depth account. “Moving in and out of similarities and differences within and between interviews” could be perceived as a more useful strategy than adopting either the position of insider or outsider [267: p.54].

“Wearing the hat of the insider”, as a biologist with a diverse background in medical science and medical ethics, allowed me to “speak the same language” with interviewees. Not having to explain scientific terms and genetic conditions allowed interviewees to feel comfortable and reply to questions or develop their thinking.

On the other hand, wearing the “hat” of the outsider, as a young researcher or even “just-a-student” occasionally, allowed me to elicit detailed responses and ask questions that someone with the same status as the interviewee may not have felt comfortable asking. Although my previous studies and professional experience combined with a good understanding of the literature provided me with a good level of familiarity with the topics, on more than one occasion I intentionally “played down” my knowledge and drew attention to our differences. Most of the questions asked focused on interviewees’ attitudes as experts and, on several occasions, experts were reluctant to answer saying something like “I don’t know” or “that is a very difficult question”. In cases like these, instead of giving them alternative answers to facilitate the discussion, I would say something along the lines of “I know, but you are the expert and that is why I am asking you”. This approach seemed to encourage the interviewees to express their opinions openly without fear of being judged.

On the contrary, in cases where our similar level of understanding of the science was emphasised, interviewees had a tendency to take for granted aspects that they considered as shared knowledge. This limitation was mainly observed with USA experts where the interviews were conducted while the ACMG annual meeting was taking place. Because both researcher and interviewees had attended the same meetings and presentations, some issues were overlooked and not analysed in detail, especially when the interviewee was one of the speakers and he or she had already expressed his/her opinions in public. Unfortunately, in these interviews some issues might have been neglected as some questions were not asked for fear of appearing uninformed or as not having paid attention to the conference presentations. However, all efforts were made to minimise this issue. Clarifications and examples were asked for in several cases and interviewees were encouraged to expand on their presentations.

Finally, although my personal understanding and knowledge allowed me to develop a good level of communication with interviewees, my professional identity did not completely match the

professional identity of any of the interviewees. This relative distance allowed me to be critical both during the interviews and the analysis of the data. Nevertheless, while acknowledging that we shared some previous experiences, I made a conscious effort, when needed, to maintain this distance and not assume a particular interpretation of the data deriving from the interviews.

3.4.5. Analysing the interviews

The first step of any analysis is familiarisation with the data set to acquire an overview of the material gathered [222]. Since I collected the data and transcribed the interviews, I already had a good understanding of the key issues and emergent themes. In this case, further familiarisation involved listening to the interviews more than once and rereading transcripts.

Moving on to the analysis itself, the most commonly used methods for analysing interviews are content analysis, thematic analysis, framework analysis and constant comparative analysis [237, 268-271]. Other methods for the analysis of qualitative data more broadly include discourse analysis and conversation analysis [272], however, as mentioned earlier, an extensive discussion of social research methods falls outside the scope of this thesis. Instead, I focused on the most commonly used methods for the analysis of interview data. I explain the different options available before explaining and justifying my decision to use a constant comparative approach.

Coming from different traditions, content analysis, thematic analysis, and framework analysis are all possible analytical approaches that were considered but not ultimately chosen. Content analysis introduced into the social sciences around the 1980s, was initially developed for use in communication sciences. It is a process during which both the content and context of documents (videos, music or any other material recorded in some way) are analysed [273]. The researcher focuses on how the themes identified are presented and treated as well as how often they occur [274, 275]. Then these themes are associated with pre-defined variables such as gender [274]. It has been often used for the analysis of media documents as it provides a structured approach where the frequency of certain patterns (e.g. words, phrases, images) is counted [276]. It is often used as the analytical approach in health-related research when attitudes of different stakeholder groups are under investigation (e.g. [277-279]). Although content analysis is particularly useful for the analysis of a large dataset, it has been criticised as too subjective, for not adequately focusing on the conceptual meaning and thus misrepresenting data [276], and for not being appropriate for projects with exploratory character [273] such as this one.

Thematic analysis often seen as the foundational method for qualitative analysis [280] refers in general to the analytical strategy wherein a dataset is interrogated and themes are identified, analysed and reported while being reconstructed aiming at capturing certain concepts [280] [228].

Thematic analysis is a descriptive strategy facilitating the discovery of patterns within a qualitative data set that aims to describe the overarching themes emerging. It is often used without subscribing to any pre-existing theoretical framework and it has often been associated with, or claimed to have derived from grounded theory, i.e. the analysis aiming to generate a plausible theory of the phenomena that is grounded in the data [280, 281]. The analysis starts without pre-defined themes or themes that are anticipated [237, 268, 271, 282] and is open to the themes emerging from the data collected. This approach is data-driven and the themes identified may bear little relation to the questions asked of the participants [280]. It is commonly used for the analysis of interviews and focus groups in psychology-related studies [280] and is also a widely used methodology in health-related studies (e.g. [283-285]) due to its flexibility which makes it easily adjusted to the project. This type of analysis was not chosen as I considered that my previous exposure to the literature and my familiarisation with this area would not allow for such an open-minded approach. An extensive literature review was conducted and a topic guide was used to facilitate the interviews and, therefore, a clear data-driven analysis was not possible for this project.

Framework analysis was developed for applied research in cases where the goals of the study are set in advance and are pre-shaped usually during the literature review. This approach, which is often used in applied social policy research was developed in the UK by a research institute (SCPR - Social and Community Planning Research) aiming at exploring important aspects of society in order to influence social policy [286]. It is code-driven and is usually used when there are clear themes identified during the preliminary stages or when timescales are short and there are existing findings that need to be linked to the analysis [287]. Framework analysis reflects the accounts and observations of the people studied but starts deductively from pre-set aims and objectives [286, 287]. A framework analysis was also considered to be inappropriate as it was seen as overly constraining. A code-driven approach where the primary goal is to build the analysis around the initial codes identified during the literature review [282] would have limited the analysis and would have led to possible neglect of interesting themes that emerged during the interviews that had not been pre-identified.

Constant comparison analysis is a data-driven method that is based on the constant comparison that characterises the categorisation, coding and drawing inferences from the data [231, 288, 289]. The comparison makes it possible to answer questions that have arisen in preliminary stages, previous analysis or reflections on previous data without being constrained by them, while at the same time allowing “themes” to emerge from the data. It is often used in health sciences as it facilitates comparative studies among different samples (e.g. [290-292]) as well as exploratory studies (e.g. [293, 294]). In this case, a constant comparative approach was taken and comparisons included

comparison within a single interview, between interviews within the same group (e.g. different professional background, different country), and interviews from different groups. A constant comparative approach was used as, although I had a draft topic guide and areas that I needed to cover during the interviews, I did not want this to constrain my analysis. Data from the interviews were used to generate codes that were shifting throughout the process. Inductive and deductive elements were included in the analysis and themes and sub-themes were developed and iteratively revised. The process was dynamic and highly interactive [231, 237, 270].

More specifically, as the literature review and the preparation of the topic guide preceded the analysis, some initial codes had already been formulated. The first analysis included the formation of a range of codes that described the general working framework. This first version of the coding framework was too descriptive and heavily rooted in the topic guide. Most codes created were virtually identical to specific questions or categories of questions outlined in the topic guide which was seen as too constraining. Transcripts were read again and, this time, the initial coding frame, generated from the research questions acted to guide, but not constrain, the emergence of themes. New parent and children codes were generated. Some of these new codes were newly defined by the responses of the interviewees (figure 2).

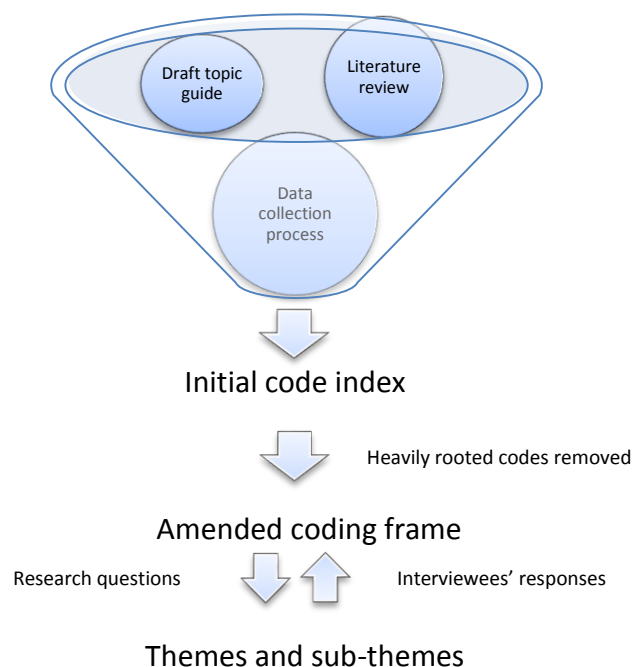


Figure 2: Analysing the interviews

The Greek interviews were the first ones analysed as they were the first ones conducted. However, since the focus of the analysis was to illustrate the similarities and differences of the evidence across countries, I revised the coding framework after the remaining interviews were conducted and finalised it after the completion of all interviews. The majority of the codes identified were shared across countries but, intentionally, one code (and several sub-codes) was used to include all country-specific characteristics that were identified in only one country.

To prepare the amended working framework I started by trying to identify recurring themes. As mentioned above that took place originally using the Greek interviews and was later updated after the completion of the UK and USA interviews. Initially, I identified important themes, such as attitudes, motivations and views. Once these themes were identified, I began to develop the framework by drawing upon the themes identified but also the research questions and the draft topic guide used. Subsequently, themes were re-organised and grouped under a small number of broader themes that were included in the framework. Minor themes I identified were grouped under broader themes and were positioned as sub-codes. Labels and short descriptions were added to the broad themes to facilitate the process. To finalise the development of the framework, I searched for connections between themes and I kept the number of broader themes as small as possible to avoid confusion. Having developed the framework the next step was for me to go back and apply it to all the interview transcripts, a step known as coding. That involved me reading every sentence and paragraph of the transcript and deciding what it was talking about and then categorising it under the matching theme. Different codes were grouped under the major themes identified and depending on the part of the interview, a number of important themes might be mentioned one close to another, including numerous codes; or a long part of the interview might refer to one topic, hence only one theme might be identified. I analysed all the interviews but, to maximise the rigour of the analysis and to ensure the quality of the codes produced, one of my supervisors independently coded two interviews. We then compared notes. The coding framework that I produced was used as the final framework for the coding of all other interviews.

To illustrate the process I followed a section of the framework prepared is shown in figure 3. Furthermore, in figure 4 is presented a section of a transcript and the themes that emerged from that section based on the framework presented in figure 3.

1. Definition of IF

- 1.1. Definition
- 1.2. Appropriateness of the term / alternative terms
- 1.3. Agreement / Disagreement with ACMG definition
- 1.4. Appropriate term to be translated in Greek

2. Nature of findings compared to results from other tests

- 2.1. Same / Different
- 2.2. Reason

3. Current situation

- 3.1. Legal documents / available guidance
- 3.2. How often clinical sequencing is used?
- 3.3. How often IFs are discovered?
- 3.4. What is returned?
- 3.5. Who returns them / available support
- 3.6. Patients reactions

4. Why IFs are difficult

- 4.1. Lack of clear framework
- 4.2. They challenge the traditional models of providing health services
- 4.3. They are different from other medical information although previous experiences with other tests could provide some help
- 4.4. They concern other people apart from the patient
- 4.5. Interpretation is still challenging
- 4.6. Might cause stigmatisation
- 4.7. Other concerns

Figure 3: Section of the framework used for the coding of the interviews

The text that follows is a small section of an interview with one of the experts. In the following figure (figure 4), each colour relates to a different code and the numbers in the second column link back to the coding tree presented in figure 3. The expert is describing what is currently happening with IFs, what choices patients have and what their reactions are according to his/her experience. Some details have been changed to preserve anonymity and some small passages have been removed for reasons of space.

That's a good question. I think people, well it's not presented as a choice. The bin 1, they are very rare but we have returned a few. And people don't seem unhappy with them. [...]	3.1. 3.6.
So for the whole idea of incidental people have mixed feelings and responses to what that means. Ranging from what scientists mean, which is that it is incidental from the original diagnosis to thinking it's unimportant, to thinking it's somehow a little bit we were hiding it. They are a little bit skeptical or suspicious about it. People have very different responses. And I think people don't like the term a lot. They would rather have a term like additional or secondary but then if you say secondary that kind of mean that it is less important and I can be really important. On the other hand once people have it explained they understand it better. But generally this term is a ridiculous term. [...] So it's the whole thing that came out with the ACMG guidelines. What does that mean that the laboratory has it and has to read it. And if that if they are going to set their bioinformatics to look for it then that feels like an action they are taking and that the sequencing doesn't necessarily produce the results if someone doesn't do something. So there is this real philosophical thing on when do you know something. Mixed up with the understanding of what the technology really does. Many people who hear about this, including myself, we have no understanding of the technology and then we try to learn about the technology and then even the explanations we are getting about the technology really varies. Then you hear the analogy about having a whole body CT and that analogy has broken down. But in any case that as a clinician who has been working with genetics they want to be as all the other clinicians. They don't want to be special, they don't want to be different. They say that if we have this information that as the radiologists who see something in the CT, we should return them. And that's something that everybody agrees. But not everybody agrees with the ACMG list. And in our case we don't have these 56 in our bin 1. We had to create a much narrow list. We wanted to have findings for conditions that have interventions that are acceptable and are highly affective and we have a lot of knowledge about it, so we only have 17 mutations. So this idea that there is an expert group that made a list with which everybody would agree is crazy too. So anyway from all these different aspects, the controversy has been	1.1. 3.6. 1.1. and 3.6. 1.1. 3.6. 1.1. 1.2. 4.7. 2.1. 1.2. 3.4. 1.2. 1.1.

Figure 4: Section of a transcript coded based on the framework presented in figure 3.

The analysis of transcripts was facilitated by the use of the NVivo10 software. NVivo is a commonly-used software package for the analysis of qualitative data. This type of software, included in the computer-assisted qualitative data analysis software (CAQDAS), makes analysis faster and more efficient as it automates much of the process [231, 237]. Interpretation is, in this way, much easier as nodes (the NVivo term for codes) can be organised and re-organised more than once while the researcher is trying to make sense of his or her data.

To avoid losing the narrative flow through the use of NVivo, I read and reread the interview transcripts more than once during the analysis process. Additionally, although transcripts were produced, I listened to the interviews more than once even after transcription. My final listening

occurred before finalising the analysis to ensure that codes had been produced and interpreted in context. Finally, the use of the software makes the coding process transparent, thus, allowing different researchers to work independently and compare the codes produced, an approach used here to independently code two interviews and ensure the robustness of the codes produced.

As mentioned above, I identified several themes through the analysis. All but one theme is presented in chapters 5 and 6. The remaining theme concerns the return of results to minors. I have chosen not to include this theme in the analysis as the data collected was inadequate to draw firm conclusions regarding how and which types of results should be returned to minors. There was no consensus among experts and neither the country nor the background seemed to influence their views. As interviews were already exceeding the allocated time, I chose not to elaborate on this topic as it was obvious, from the first couple of interviews, that experts did not have a clear idea how this complex matter should be approached. It is my belief, however, that this topic is critical, and should be the sole focus of another project as numerous concerns have been raised regarding the return of results to minors. The heterogeneity observed among experts does not allow for a synthesis here and, therefore, I decided not to include this theme.

To protect participants' anonymity while allowing the association of their quotes with their professional background, quotes from the interviews (presented in chapters 5 and 6) are tagged using an identifier. This identifier includes each individual's country of origin and professional background. To demonstrate the format of the identifier, an artificial example is presented below:

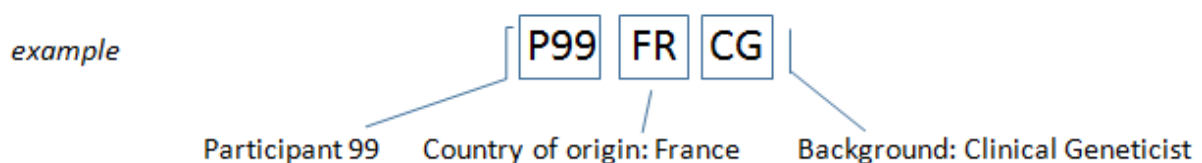


Figure 5: Illustrative example of identifier used to tag quotes for the interviews

3.4.5.1. Reflections on analysing the interviews

The analysis of the interviews was facilitated by the fact that I had conducted all the necessary preceding steps, i.e. completion of the literature review, drafting of the topic guide, conducting and transcription of the interviews. Hence, I had acquired a very clear idea of what each participant was saying even before starting the analysis. The main barrier I had to overcome was exactly that familiarity with the data. Taking a step back and listening to the interviews again without preconceptions was the main challenge faced. This difficulty was overcome by allowing a considerable amount of time to pass before finalising the analysis. Transcripts were produced

immediately after each interview to make transcribing easier, especially in cases where there was background noise. However, I delayed the analysis to allow time to distance myself from the interviews and to be able to listen to them again, thus, attempting to keep my preconceptions to a minimum.

3.5. Quantitative stage step-by-step

The quantitative stage consisted of a 22-item survey distributed to all registered genetics professionals in Greece. Apart from two questions, all others were closed questions and could be answered with either Yes/No/I don't know or with a 5-point Likert scale (Strongly Agree to Strongly Disagree). The questionnaire was then uploaded to the online platform SurveyMonkey® to facilitate access by survey participants.

The English version of the questionnaire can be found in Appendix 2.

3.5.1. Sampling

In Greece, there are two associations of geneticists. All registered members of both associations were invited to participate in the survey. To avoid duplication in cases where professionals were registered in both associations, potential participants were notified that the invitation was being sent to all members of both associations and potential participants were asked to complete the questionnaire only once. No further measures were taken to avoid double responses.

3.5.2. Design of the invitation

The literature suggests that the design and content of the invitation might affect response rates, therefore, I put a lot of effort into preparing the invitation to help solicit the best response rate I could [295]. I prepared the invitation according to the design format suggested by Fan & Yan, while I also took advice on the design was taken from several textbooks [e.g. 251].

The invitation included the name of the organisation, the title of the online survey, the scope of the survey, the URL of the web-site and information about the researcher. Contact details were provided in case potential participants were interested in asking me questions, wished to request further information about the study, or wanted to send a comment. The available literature suggests that the invitation should be kept short with only necessary information to encourage potential participants to read it and participate in the study. For this purpose, a University profile page was created and a link was provided in the invitation. Potential participants could access the webpage to

read more about the study if they wished. In the profile page, I provided information about the study, the supervisory team and also provided my short biography. These helped me show possible participants that this was a legitimate study and that they could believe that they were contributing to important research. The invitation was written in Greek and English. An English version of the invitation can be found in Appendix 2.

The level of personalisation of the invitation has been identified as a predictor of response rates [295]. The easier and most efficient tactic to personalise an invitation is to use a personalised greeting [296]. Nevertheless, as mentioned earlier, for confidentiality reasons, I chose not to personally access the contact details of potential participants but to ask for the two associations to mediate my communication with Greek geneticists. A personalised greeting was, therefore, not possible. Instead, all potential participants were greeted with their generic professional title i.e. “Dear Geneticist”.

All participants were informed that they belonged to a small group of selected individuals invited to participate to share their professional expertise. It has been argued that such a strategy increases response rates as it makes potential participants feel part of a chosen group [295].

Finally, all potential participants were notified that their email was obtained through the genetics association to which they are registered to avoid concerns about access to their contact details. At no time did I want any to feel that their private information had been shared inappropriately.

3.5.3. Pre-notifications, Reminders, and Incentives

Although the usefulness of pre-notification emails has been suggested in a systematic review conducted by Fan & Yan investigating ways to increase response rates, I chose not to use these in this study. Taking into consideration that the sample consisted of busy professionals, I was concerned that increasing the number of emails might be seen as an annoyance and discourage professionals from participating, and, therefore, no pre-notification emails were used.

Using reminders has also been considered as a factor increasing response rates [295]. In this way, a group of professionals could be reminded of the invitation and given a choice to participate if their busy schedule did not allow it when initially invited. Following the suggestion of Crawford et al [297], a first reminder was sent seven days after the initial invitation (the reminder note can be found in Appendix 2). As the response rate seven days after the first reminder was low (23%), a second reminder was sent ten days after the first reminder.

Offering incentives, usually monetary, is used as another way to increase response rates in all forms of surveys [298]. However, although considered, incentives were not offered in this case. The goal of

this project and the intention to produce points-to-consider that could enhance their professional practice were discussed in the invitation and presented as a non-monetary incentive. It was considered that potential participants' professional interest would be adequate to encourage them to participate in the study even without having the expectation of any other incentive.

3.5.4. Designing the questionnaire

As reported elsewhere [295], two factors that concern the development of the questionnaire seem to affect response rates: the content and the presentation of the questionnaire.

Studies sponsored by academic or government institutions are usually seen more positively and generate higher response rates [295]. The authorship and sponsorship of this questionnaire were discussed in the invitation email. Additionally, I used the logo of the University of Leicester in the design of the questionnaire to ensure that participants would know that the study was supported by an academic institution.

Furthermore, the fact that only specialised professionals were invited to participate was considered as a benefit and facilitated the design which was prepared based on that specific group's knowledge and understanding. From the evidence collected through the interviews and my analysis of that data, I came to the conclusion that professionals would welcome any initiative to help them deal more effectively with the return of IFs. Therefore, I believed that those invited to complete the questionnaire would see some potential personal benefit from doing so and that this would therefore positively influence response rates.

The first step in designing a questionnaire involves the researcher becoming familiar with the topic under investigation and the identification of the relevant issues. In my case, I developed this knowledge both during the first phase of the project, i.e. the qualitative phase, and during the development of the questionnaire. Moreover, I continued to review the literature throughout the project. As suggested in the relevant methodological literature, an important part of generating the preliminary information needed to develop the questionnaire was the set of interviews completed with experts who had extensive knowledge and interest in the issue [299]. From my analysis of the data I collected, I decided on the issues I wished to pursue and outlined them in a draft questionnaire. To help me prepare the draft questionnaire, I attended a topic-specific workshop offered as part of the Courses in Applied Social Surveys organised by the UK Institute of Education on Designing Effective Web Surveys. The workshop offered me an opportunity not only to acquire a deeper understanding of questionnaire design but also to have hands-on experience as part of the workshop involved formulating and testing questions within the group.

When preparing the draft questionnaire I took two factors into consideration: questions' clarity and comprehensiveness [299, 300]. I tried to word questions using simple but not simplistic terminology [301, 302], and tried to keep them as short as possible [302, 303], as the length of the questionnaire is one of the most important predictive factors of response rate [304]. I attempted to avoid ambiguities by ensuring questions were written to focus on only one topic at a time and in such a way that would elicit the desired information [299] and the same was done when providing multiple choice answers. For example, in the question asking which different types of IFs should be returned, I chose to offer numerous alternatives in order to have the respondent focus in on one characteristic at a time.

Both during the workshop and during the drafting of the questionnaire I gave a lot of thought to the response categories as these can potentially indicate to the responder my bias which might influence their choice [301, 303]. For example, as Stopher has suggested, rather than asking if students study adequately which would make the "yes" response appearing to be the most "desirable" it was preferred to ask how long students study. Similarly, providing response categories using a scale of 30 minutes, 30 minutes to an hour, etc. to a question on students' study per day might suggest a recognition that students study as little as half an hour per day [303](p.184). Similarly, rather than asking a question and providing open space for a free text answer, studies have shown that it works better if the participant is asked to mark one of a range of possible responses. This is because people seem to feel more comfortable responding in this way, especially when sensitive or controversial issues are under investigation [303] or issues for which there are no widely accepted answers.

There are different options for constructing response categories in questionnaires and three of the most commonly used were drawn on for this questionnaire:

- a) A yes/no/don't know form
- b) A 5-Likert scale (from Strongly Agree to Strongly Disagree)
- c) A multiple-choice stated response

I chose Yes/No responses, for example as in the questions focusing on geneticists' awareness of IFs, for their simplicity and clarity and I provided an "I don't know" alternative acknowledging that they might not have the necessary knowledge or experience to respond to a question or that they might not feel comfortable answering.

Another common form of response category is a scaling question where a statement is provided and respondents are asked to indicate on the scale provided the strength of their agreement. Responses might be provided as labels (e.g. strongly agree) or as numbers with only the ends of the scale being labelled (e.g. 3 in a 10-point scale)[302]. Labels appear to be preferred as numbers might be confusing and less specific [303]. The number of positive and negative categories should be equal to ensure a balanced scale and avoid biasing the participant [302, 303], and a neutral response is provided to express either indecisiveness or no opinion [302]. Both 5-Likert and 7-Likert scales are commonly used. It has been suggested that a 7-Likert scale could be a better choice in some cases as it may be more accurate and provides a wider variety of views, hence increasing the probability of accurately capturing people's opinion [305]. In this case, however, I opted for a 5-Likert scale. The rationale for this choice was that I did not know whether Greek geneticists would be sufficiently experienced to allow them to have a very specific view on the kinds of questions for which this response category was used. My findings from the qualitative phase revealed the rarity of clinical sequencing and even some ambiguity amongst experts regarding its implementation in Greece. I therefore decided that using a 7-point scale might add to the confusion while a 5-point would provide adequate alternatives without making questions too complicated.

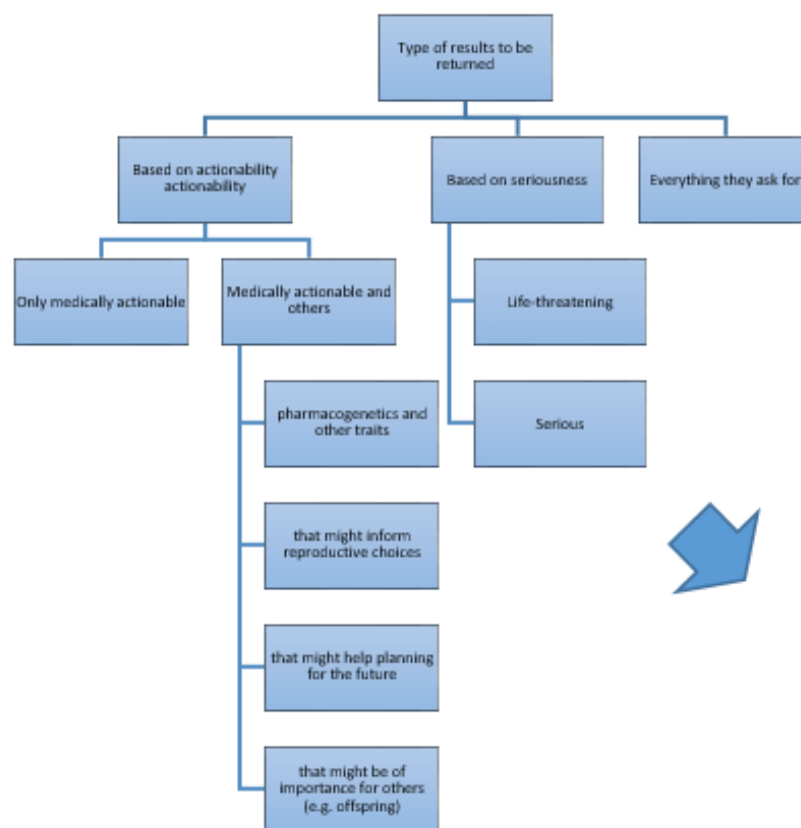
The final type of response category that I used was stated response questions. These pose a hypothetical scenario and provide stated responses as alternative answers, asking the responder to indicate which of the responses he or she agrees with [306-308]. This format is widely used in cases, such as this one, where preliminary data have been collected on a mapping expedition (or another research step) and possible scenarios and possible answers have been identified or in cases where the questionnaire is about a well-researched topic [308].

I developed these questions to allow me to look even deeper into the attitudes of the Greek geneticists on issues, such as available and desired infrastructures to support feedback and concerns and benefits from the use of clinical sequencing, where I wanted a bit more detail and their personal insights. Ideas about the wording and order of the questions were taken from other questionnaires in related areas (e.g. Genomics England - Ethics and Genomics Survey [12]) and the broader literature about administering and developing questionnaires (e.g. [13, 14]). An illustrative example can be found below (figure 6). Using an example code that emerged from the data analysis from the first phase (interviews) it demonstrates how I used the codes and sub-codes help me prepare specific questions and specific response categories in the questionnaire. For example, as shown in figure 6, in the interviews the experts expressed a wide range of different opinion on which specific results should be returned. This is an important point in developing policy, so I felt I needed to

examine it more closely. I used the sub-codes shown here as response categories in question 6 of the questionnaire (see appendix 2). The participants were asked using a scale ranging from Strongly Agree to Strongly Disagree to indicate their attitude toward each of the type of results.

To make the completion of the questionnaire easier, questions were organised into six sections, each representing a specific theme. Section 1 included some general questions regarding IFs and the possibility of discovering them in genetic and other tests; section 2 included questions seeking professional attitudes toward return of IFs; section 3 grouped questions investigating attitudes toward clinical sequencing and IFs; section 4 grouped questions about how to regulate clinical sequencing and IFs; section 5 grouped questions on personal attitudes toward getting tested and receiving IFs and, finally, section 6 was made up of demographic questions. For the English version of the questionnaire, please see Appendix 2.

As the length of the questionnaire is among the major predictors of response rates for online questionnaires [295], as mentioned earlier I made an effort to keep the questionnaire as short as possible. Available evidence suggested that thirteen minutes or less to complete is considered as the ideal length for an online questionnaire [295]. The original version of the questionnaire needed approximately 15 minutes and was, therefore, I considered it too long. I revised it, removing some questions and rearranging others so that the second version of the questionnaire required approximately 9-11 minutes.



SECTION 2 – RETURN OF UNRELATED FINDINGS AND PROFESSIONAL ATTITUDES

6. For the following categories, please say if you think patients should be able to choose to receive information on unrelated findings.

"I think patients should be able to receive information about conditions that are..."

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
life-threatening and preventable/ treatable					
life-threatening and not preventable/ treatable					
life-threatening, late-onset and preventable/ treatable					
serious (but not life-threatening) and preventable/ treatable					
serious (but not life-threatening) and not preventable/ treatable					

Figure 6: Example of code emerged from the interviews' analysis that was used for the preparation of a question for the questionnaire.

All draft versions of the questionnaire were produced in English to allow revisions and iterative development with the support of my supervisors. Only the final version was used for the preparation of the Greek version of the questionnaire. Instead of translating the English version, I re-wrote the questionnaire in Greek with the English version as a guide [309]. The use of the target language, i.e. Greek, was taken into consideration and several expressions only used in Greek were introduced to achieve a faithfulness to the context rather than a simple translation of words. The questionnaire was double-checked for accuracy by three independent colleagues with a background in Greek languages (linguistics, ancient Greek etc.). The text was checked for its grammatical, stylistic and semantic characteristics and compared to the original English version.

3.5.4.1. Reflecting on designing the questionnaire

As mentioned above, I invested considerable thought and effort developing the questionnaire as well-considered content would not only increase the response rate but also provide better answers to the research questions. My preparation of the questionnaire was guided by my research questions and informed by the literature review and the findings from the interviews. Closed questions were chosen to keep completion time to a minimum as this was considered crucial for increasing the response rate, although a small number of opportunities were provided for free-text answers in order to allow participants to provide personal responses and additional data.

The process of developing the questionnaire was less complicated than I expected. The workshop I attended provided practical guidance and proved to be particularly helpful, as were the references and the supporting material provided. The literature suggests that simple and clearly worded questions greatly facilitate questionnaire analysis and therefore it was time-consuming to transform the complicated matters that emerged from the literature review and the first phase of this project into short and simple questions. Nevertheless, as mentioned earlier, familiarising with the topic and the emergent issues through the previous steps of the process greatly helped me design the questionnaire. The main challenge I faced was deciding which questions should be included. The findings from the interviews revealed numerous issues that I thought were important to raise among Greek geneticists. However, as the length of the questionnaire had to be kept short, a number of questions were eliminated. In section 3.4.5. I explained how the limited data collected regarding the return of results to minors was not analysed and not included in the thesis. Therefore, these questions were not included. Similarly, other issues that could emerge during sequencing (such as misattributed paternity or other IFs discovered during prenatal tests) were acknowledged but not included in the questionnaire in an attempt to keep it short and consistent.

In addition, another issue that emerged through the design of the questionnaire was its translation into Greek. As mentioned already, in Greece, as genetic and genomic tests have only been recently introduced, and there is no set terminology for different techniques, different types of tests and other terms concerning the tests. Therefore, in more than one case, I chose a Greek term that could convey the message better and, for reasons of clarity, also provided the English term.

The difficulty of translating text, especially scientific texts, has been discussed elsewhere. Several necessary characteristics have been considered for translators [309, 310]. Translators should:

- a) have a complete understanding of both languages;
- b) be familiar with the area of the study undertaken;
- c) be up-to-date with linguistic developments;
- d) translate from a language to their own native language
- e) be able to write using an easily understood vocabulary;
- f) know and understand the original author's audience and intentions and be able to translate so that the new audience will be able to understand the text in a similar way

I believe I met all the criteria noted above, particularly the fact that I wrote both the original text (questionnaire) and the translation. This helped me ensure that the different language versions were as close as possible in meaning. As mentioned earlier, three people were asked to read both versions and suggest changes where necessary and the Greek version of the questionnaire was reviewed and revised accordingly.

The only issue that emerged was the translation of the term “incidental findings”. In order to be consistent, I wanted to use the same term in the interviews and the questionnaire but there was no consensus among either experts or Greek geneticists regarding a term that would more accurately describe these kinds of findings.

3.5.5. Piloting the questionnaire

I piloted the draft questionnaire with a convenience sample (Ph.D. students and colleagues). Five people piloted the English version and five people piloted the Greek version. The final version was also piloted to establish the time needed to complete it. The participants in the pilot were asked to comment on items they found difficult or confusing. All comments were reviewed and I revised the questionnaire accordingly.

3.5.6. Analysing the questionnaire

I downloaded the response data from the questionnaires from the SurveyMonkey webpage and exported to SPSS (version 20) for statistical analysis. Descriptive statistics were produced to summarise the answers.

On questions using a Likert scale, when a significant difference was observed between “Strongly Agree” and “Agree” (or “Strongly Disagree” and “Disagree”), all categories were kept and analysed. However, when there was no particular difference, the two categories were collapsed into one i.e. “Agree” (or “Disagree”) to facilitate analysis and interpretations.

All frequencies reported reflect the valid percent, i.e. missing data has been already excluded. Participants were allowed to miss out individual items, and, therefore, the sample size varied across questions. However, as most participants replied to all questions, no particular, significant variations were observed.

3.5.6.1. Reflecting on analysing the questionnaire

Unfortunately the number of geneticists that completed the questionnaire only allowed for descriptive statistics. My intention was, if possible, to conduct a basic statistical analysis and interrogate the data looking for associations between different factors.

Literature suggests that to conduct a meaningful statistical analysis the general rule for the sample size is that it should be 10% of the population under investigation unless it exceeds 1000 participants in which case a more complicated calculation is needed as increasing the sample size above 1000 might not offer a more representative result [311, 312]. However in smaller populations, to allow such an analysis and get meaningful results the literature suggests that the minimum sample size should be 100 [312, 313].

In this case out of the 204 Greek geneticists that were invited to participate, 52 completed the questionnaire. Attempting to do statistical analysis with this sample size would mean that the estimated confidence interval would be above 10 which would make any result not representative. For example, with a confidence interval of 10, if 40% of the respondents chose an answer then we would be able to be “sure” that if we had asked the same question on the entire relevant population, between 30% (40-10) and 50% (40+10) of participants would have picked that answer. Having a confidence interval that is that high prevents really meaningful results because, in this example, there is a significant difference between a third of people choosing an answer and half of people choosing one.

Since a formal statistical analysis was not possible, descriptive statistics were conducted and tables and pie charts were chosen to present the frequencies of each response. Tables and figures are used to facilitate the presentation and interpretation of the results [314].

3.6. Reflecting on the quality of the research

This project consists of a mixed-methods study that includes a qualitative and a quantitative component. In both phases of the research, I explored complex issues encountered by genetics professionals. The findings and conclusions of this study could inform clinicians, health care providers, policymakers and consumers of genetics services. As poorly designed studies could lead to “inappropriate application of research in decision-making, health care, health policy and future research”[315] (p. 349) there is the need for establishing clear and comprehensive criteria to judge the quality of the research [231, 315, 316].

There has been a long-standing debate among researchers around the criteria used to judge the robustness of qualitative work which has been often regarded as unscientific, non-representative or too subjective [315, 317-319]. Numerous checklists have been published describing an exhaustive list of criteria to be used to report qualitative research, but as this debate falls beyond the scope of this thesis, no detailed discussion will be presented here. Nevertheless, as this project has a qualitative component from which I have drawn significant conclusions for my work, I will describe the criteria that could be used to judge the quality of the qualitative phase of this research.

I will use the list created by Tong et al. produced based on a systematic review they conducted looking at 22 available checklists (also known as the COREQ checklist)[315]. According to Tong et al. there are 32 criteria that could be used to assess the quality of qualitative work based on how a study is reported. These are divided into the following three domains: (i) research team and reflexivity, (ii) study design and (iii) data analysis and reporting.

Domain I centers on the personal characteristics of the researcher and their relationship with their participants. Tong et al note that in order to reduce possible bias the researcher should clearly inform the interviewees of their credentials and occupation and interest in the research, in order that participants can take these points into consideration when answering questions. I provided my credentials (Ph.D. student at the Health Sciences Department at the University of Leicester) in the information sheet that was sent before the interviews. Moreover, at the beginning of each interview I briefly presented my background, experience, and training as well as a short description of the project and its goals. As I had no previous relationship with the vast majority of the interviewees, to help establishing a relationship, a webpage was created providing more information about the

researcher, i.e. me and the project. The link to the webpage was included in the invitation letter sent to all experts invited to participate and it was also available through the University of Leicester official website. These actions hopefully enabled my participants to better understand me and my goals for this research

Domain II concerns study design and consists of four sub-domains: (a) theoretical framework, (b) participant selection, (c) setting, and (d) data collection. I made some initial decisions regarding the theoretical framework before the beginning of the interviews but my final decisions were made after the completion of the interviews and are described in detail earlier in this chapter (see section 3.4.5). My sampling methodology (purposive combined with snowball sampling), method of approach (face-to-face interviews), sample size (thirty interviews transcribed and analysed) and non-participation are described in detail in section 3.4.1. As far as the setting is concerned, interviews took place in private rooms at the expert's workplace without other people present. I have described the sample with as many details as are allowed in order to avoid their potential identification given that the interviews have to be anonymous. With respect to data collection, I piloted the interviews beforehand, prepared a draft topic guide which I only loosely followed, and audio recorded interviews with participants' consent. I did not make field notes and the interviews lasted approximately 40 minutes. The steps followed are described in details in sections 3.4.1.-3.4.5.

Domain III includes the points about data analysis and data reporting. I coded all of the Interviews and two interviews were independently coded by a second researcher to increase credibility. A section of the coding tree is provided as well as an example of the coding of a section and the software I used, i.e. NVivo. Participants did not provide feedback on the findings but I sent the papers produced as a result of this project to the participants who had declared their interest in seeing them during the interviews. Participants' quotes are presented in chapters 5 and 6 to illustrate the themes that emerged and major and minor themes are presented and discussed in detail in chapters 8 and 9.

No strict reporting criteria exist regarding the quality of quantitative methodology and specifically questionnaires, contrary to other types of research such as qualitative research (see above) or randomised control trials [320]. This lack of structured guidance might lead to poor quality of data and misleading conclusions [321]. Given this gap, in this section, I provide a synthesis of the available data coming from various sources describing the process of designing and judging the quality of a questionnaire.

Preliminary steps include the familiarisation with the literature and the clarification of the information the study aims at generating [322]. As suggested, I used a qualitative approach first to

explore the topics and map the territory [322]. The literature review also reveals whether other published and validated questionnaires exist that have investigated the same topic, which saves time and labour [322]. In some research areas such as research on depression or stress, standardised questionnaires are published [323, 324] that not only facilitate the preparation of a project but also allow comparison among different groups [325]. For the questionnaire to be valid when used in a different study than the one for which it was created, the closed responses provided should “reflect the full range of perceptions and feelings that people in all the different potential sampling frames might hold” (p. 1313) [322]. In this case, no published questionnaire was identified covering the topics that I was interested in. Furthermore, as there were specific questions that had emerged through the qualitative phase, a new questionnaire was prepared. Nevertheless, as mentioned earlier (see section 3.5.4.) ideas were taken from other published questionnaires that supported the preparation of this one.

For the instrument created to be of good quality it has to be both reliable and valid [322]. The validity of a questionnaire is dependent on whether it measures what is supposed to measure. A common mistake leading to invalid questionnaires is the attempt to measure actual practices when in reality they measure perceived ones. In this case, although the majority of the questions concerned professionals’ attitudes, this issue was minimised but not eliminated. It remained an important challenge as some of the questions were intended to measure actual practices. No observations are available for this or other similar groups thus it is impossible to judge whether the self-reported practices actually reflect the actual practices of this group. This remains a limitation that has to be acknowledged. Regardless of all the measures taken to minimise this problem, only further research and especially on-site observations might provide insight on the actual practices.

Moving on to the reliability of the questionnaire, that depends on the consistency of the results produced when the same questionnaire is used over time and is applied in different samples. Reliability is increased when a questionnaire is standardised, i.e. “is written and administered so all participants are asked the precisely the same questions in an identical format and responses recorded in a uniform manner”(p. 1313) [322]. In this case, it is hard to judge the reliability of my questionnaire as it was only used once and in one specific sample. As using it in another sample was beyond the scope of this thesis, the only measure I could take to limit this problem was to pilot the questionnaire before administering it. In the pilot, I asked participants to elaborate on the reasons why they chose certain answers and, as their responses were a result of their differences of opinion rather than different interpretations of the question, the questionnaire was considered to be reliable at that level. It is worth acknowledging here that the piloting and pre-testing of a questionnaire could involve more stages than I implemented. For example, iterations of the questionnaire could be

tested more than once with a small pilot group and/or a different group. Nevertheless, these measures are usually taken for questionnaires addressed to large samples and are administered by larger groups of researchers. For this project, given the sample size (maximum 204 participants) and the expected response rate (around 80-100 responses) piloting the questionnaire once and with one group of people was considered as adequate as [303] I also could have increased internal reliability by including two or more similar questions within the questionnaire [303]. However, for the questionnaire I decided it was more important to keep it as short as possible in order to encourage people to complete it [304] so no additional questions were asked. Nevertheless, if I were to distribute the questionnaire again and to a larger group, I would consider ways to increase its reliability.

Additionally, two more factors can be used to judge the quality of a questionnaire: a) the quality of the questions and b) the transparency during its design, analysis and the drawing of conclusions. To prepare worthwhile questions that can indeed answer the questions of interest, the researcher has to move from hunch to conceptualisation and create a specific question essential for his or her research [326, 327]. Questions can be used to describe a situation, investigate the causes of a phenomenon, solve a problem, test or re-test a hypothesis, seek new knowledge or seek clarification on an existing problem [326]. A good question (or set of questions) could support the creation of a strong (explicit or implicit) theory [326]. As in the case of my work, I wrote questions referring to my findings from my qualitative phase, and the results add to the existing scientific knowledge on this topic. My questionnaire, and this project in general, is not only an effort to describe a representation of different groups' attitudes but also to engage in the development of an instrument, here points-to-consider, aiming at facilitating real-world practices and therefore I made it as specific as possible. Finally, a questionnaire, as most forms of research inquiry, can be judged by its transparency, i.e. the clarity of explanation for all stages of a study [237]. Transparency across the study not only makes the judgement of the quality possible but also allows replication of a study in different samples (populations, settings, etc.) and generalisation across studies [326, 327], hence increasing its reliability (see above). Transparency also opens the research to scrutiny and criticism by revealing all stages undergone and the rationale behind all choices made. Criticism of work, when taking place with good intentions and is productive, is crucial to scientific progress [237, 326]. My questionnaire is available for others to use to replicate my findings or to create their own questionnaires for their study. Overall, regardless of the criticism concerning the use of questionnaires to gather data on complex issues, I found it relatively easy to design and administer and I believe that in combination with the findings from the qualitative component, it produced interesting and useful results and offered an insight into Greek geneticists' views. Although using quantitative methods might be

challenging, and inappropriate for some cases, especially for under-explored areas, I found the questionnaire to be beneficial and an important addition to the data collection.

In this chapter, I have described every step of the project accompanied with the rational for every choice made. It is my intention by being transparent to open myself and my work to criticism but also to allow other researchers to replicate (after adjusting for country and sample specific characteristics) my approach in different populations and more importantly different countries. Genetic tests are expected to be more widely used in the near future, hence the call for sample-specific but also comparative projects.

Finally, I will discuss the quality of the mixed-methods approach chosen. Expanding on what has been discussed in section 3.3.2., mixed-methods approaches have numerous supporters in the last decade [226, 229, 230, 236] and they are recognised as a viable alternative to using purely qualitative and quantitative methodologies [328]. Nevertheless, several aspects including their definition, possible designs and conclusions drawn, are still challenged by academics and social researchers [328, 329]. Supporters of this strategy argue that mixing methods has something more to offer than qualitative or quantitative methods used independently as it allows addressing exploratory and confirmatory questions on the same time [226]. Contrary, opponents have expressed concerns regarding the validity of the findings and the design of the study. More specifically, what is particularly hard about judging the quality of mixed-methods studies is that the validity of the findings from each component has to be judged both independently and as combined. Although there are overlapping areas, some aspects are unique to each methodology and on top of that conclusions might be weak as implementing two different types of procedures to answer the same question is particularly difficult if not impossible [329].

Despite that, it should be noted that in the case of my research the findings from each component were not inconsistent with each other which would have made their analysis challenging. My findings were, as will be discussed in chapter 8, consistent with a great degree and the limited number of differences observed could be attributed to the different levels of expertise among the two groups. However, this is only an assumption and cannot be proven scientifically, at least not in the course of this project. Hence, in claiming to be transparent and producing a study of good quality, this limitation needs to be noted. Likewise, in an attempt to bridge the gap, I compared, contrasted and interrogated the two data sets not only independently but also in relation to each other and I was able to produce inferences as a result of the mixed-methods approach. This approach, suggested by Tashakkori and Teddlie, is known as “integrative framework” and has led to the articulation of nine criteria for design quality and interpretative rigor [328](p.113). These criteria

include: a) the design suitability, b) design adequacy, c) within design consistency, d) analytic adequacy, e) interpretative consistency, f) theoretical consistency, g) interpretive agreement, h) integrative distinctiveness and i) integrative efficacy. I have fulfilled the first three criteria of design suitability, design adequacy, and within design consistency earlier in this chapter where I described the research methods chosen together with my rationale for each choice. I cover analytic adequacy and interpretative consistency in the second half of the thesis, i.e. results chapters (chapters 5-7) and conclusions chapters (chapters 8 and 9). Theoretical consistency and interpretive agreement are covered in chapters 2 and 8 where I discuss the available literature in an open dialogue with the findings of this study. Finally, integrative distinctiveness and integrative efficacy are covered in chapters 8 and 9.

Finally, in section 3.3.2. I briefly described the available alternatives and it becomes clear that there are numerous combinations that fall under the umbrella of “mixed-methods”. This variety asks for the quality of mixed-methods studies to be judged according to the objective of the study [328]. In my work, I used mixed methods to achieve both completeness, confirmation and instrument development. A good mixed-methods study should offer a more complete understanding of the issue under investigation, each component should be used to add and validate findings from the other and both components should be used to support the development of guidance or in my case, points-to-consider. I believe I have conducted a good mixed-methods study as my findings from the qualitative phase revealed experts’ attitudes and numerous issues that should be investigated. I used these findings to inform the preparation of a questionnaire, the results of which confirmed the issues discussed, suggested alternatives and provided further insight on genetics professionals’ views. I used both sets of findings to develop the points-to-consider.

CHAPTER 4: BACKGROUND FOR EACH COUNTRY STUDIED

4.1. Chapter outline

Whilst undertaking the literature review, it became apparent to me that there were significant differences across the three countries in the way that genetic tests are offered; the approaches used to return results and in the existing framework. As recognising these differences is important in the interpretation of my findings, this chapter, therefore, examines and describes the currently existing processes and legal context within each country.

In order to understand these processes, I adopted a systematic approach to investigate each country. These investigations are presented in the first three sections of this chapter. The approach was built on the literature review (presented in chapter 2) and involved three stages as follows; (a) conducting an extensive search to identify the aspects of the different healthcare systems that impact on clinical sequencing and the return of incidental findings; (b) applying the literature to draft flow-charts broadly describing how access to genetic tests is organised in each country; (c) showing the charts to the experts interviewed and using their input to validate and finalise the charts. These charts then provided a clear summary of the literature pertinent to each country. This ensured a common understanding between myself and the experts from the context within which genetic tests are offered. Subsequently, these enabled me to identify mechanisms through which clinical sequencing could be implemented and potential results could be returned. The final section of this chapter provides a comparison between the three countries in terms of the access procedures and the legal context.

Given that the discussion of IFs originated in the USA, I start my description with the USA and, subsequently, move to the UK and then to Greece.

The last section of this chapter (section 4.3.), in combination with findings from chapter 5 and 6, have been published in the paper *Incidental findings from clinical sequencing in Greece: reporting experts' attitudes* [Gourna et al : 330]⁵, an abstract of which can be found in Appendix 3.

⁵ Gourna E. G., Armstrong N., and Wallace S. E., Incidental findings from clinical sequencing in Greece: reporting experts' attitudes. *Journal of Community Genetics*, 2014. 5(4):383-93.

4.2. Background for the USA

4.2.1. Health care services and access to genetic tests

Access to health services in the United States is significantly different and more complicated than in other countries. What characterises the US health care system is the variety of approaches used across different states, clinics, and even across companies offering genetic and genomic tests. This variety is hard to summarise and it falls outside the focus of this thesis to describe the landscape of genetic testing and clinical sequencing in the US in depth. However, to align with equivalent sections (4.2.1. and 4.3.1), this section provides an overview of the framework within which clinical sequencing is offered.

Current oversight is carried out by several bodies (figure 7, [331]) such as the Food and Drug Administration⁶ (FDA)[332], the Center for Medicare and Medicaid Service ⁷(CMS)[333], the Department of Health and Human Services ⁸(DHHS)[334], and the Federal Trade Commission ⁹(FTC)[335]. The lack of federal oversight has led to great variations between individual states regarding the regulation of genetic and genomic tests [41].

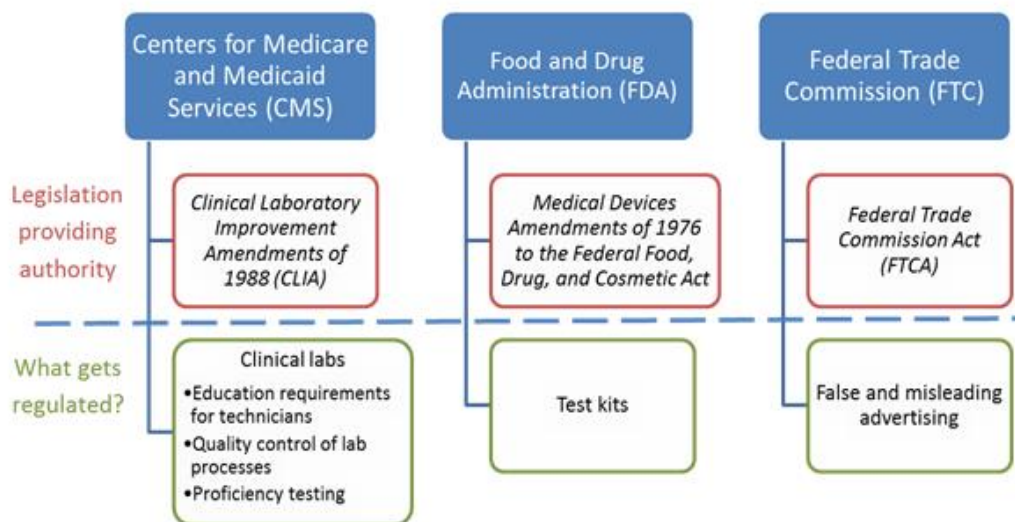


Figure 7: Federal regulation of genetic tests [331]

⁶ The FDA is an agency within the U.S. Department of Health and Human Services responsible for “protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices”

⁷ The CMS is a center that includes Medicare, Medicaid, the Children's Health Insurance Program, and the Health Insurance Marketplace, all providing public insurance schemes to US citizens

⁸ The HHS is the government's principal agency for protecting the health of US citizens and “providing essential human services, especially for those who are least able to help themselves”

⁹ The FTC is the Federal Committee for the protection of consumers, including consumers of genetic tests

Even within the same state, different clinics have different policies concerning access and availability of genetic testing, which makes the US system incredibly complex. Additionally, while the CMS regulates clinical laboratories, it does not consider whether the tests performed are clinically meaningful. After concerns were expressed, the FDA was put in charge of regulating tests based on their clinical utility. The first test was regulated in 2013; previously, most tests were laboratory-developed and not regulated [336]. FDA is expected to publish regulation sometime in 2014-2015, which should help to fill this regulatory gap and better ensure patients' health and wellbeing. Currently (last checked in April 2015), the publication of their guidance has not yet taken place [337, 338].

Figure 8 shows the expected generic path for obtaining genetic test information, taking into account the diversity of healthcare provision in the USA. The flow-chart was created based on the available literature and experts' input. The great variability observed in the US, across States and providers, did not allow me to prepare a detailed representation as I did with the flow-charts for the UK and Greece. Capturing all potential paths would have made the graph very difficult to follow and, therefore, unhelpful. To avoid this, I chose to present a generic path broadly showing how genetic tests are accessed in the US.

An individual with a genetic condition or at risk of a genetic condition could ask his/her health provider for information and a referral to a genetic professional. Genetics professionals include clinical geneticists, genetic counsellors, and genetics nurses. According to the National Human Genome Research Institute (NHGRI), universities and medical centres often have affiliated genetic professionals, or can provide referrals to a genetic professional or genetic clinics [46]. The clinical geneticist will decide, according to his or her professional judgement, whether to order a genetic or genomic test. All genetic test laboratories must be certified according to Clinical Laboratory Improvement Amendments (CLIA). Any results arriving from another laboratory (e.g. research-based laboratory) have to be validated through a CLIA certified laboratory before the clinical geneticist is able to return them to the patient. According to the condition for which the patient needs a test, or according to the clinic or the state, a clinical geneticist might be supported by a specialist physician (e.g. an oncologist if a genetic test is positive for colon cancer) and/or a genetic counsellor [46].

The cost for such a test is covered, depending on the insurance coverage of the patient, by the insurance company and/or the patient [339]. The cost for a single genome sequencing is approximately \$9,000 while for a parent-trio (testing the child's genome and its parents) it goes up

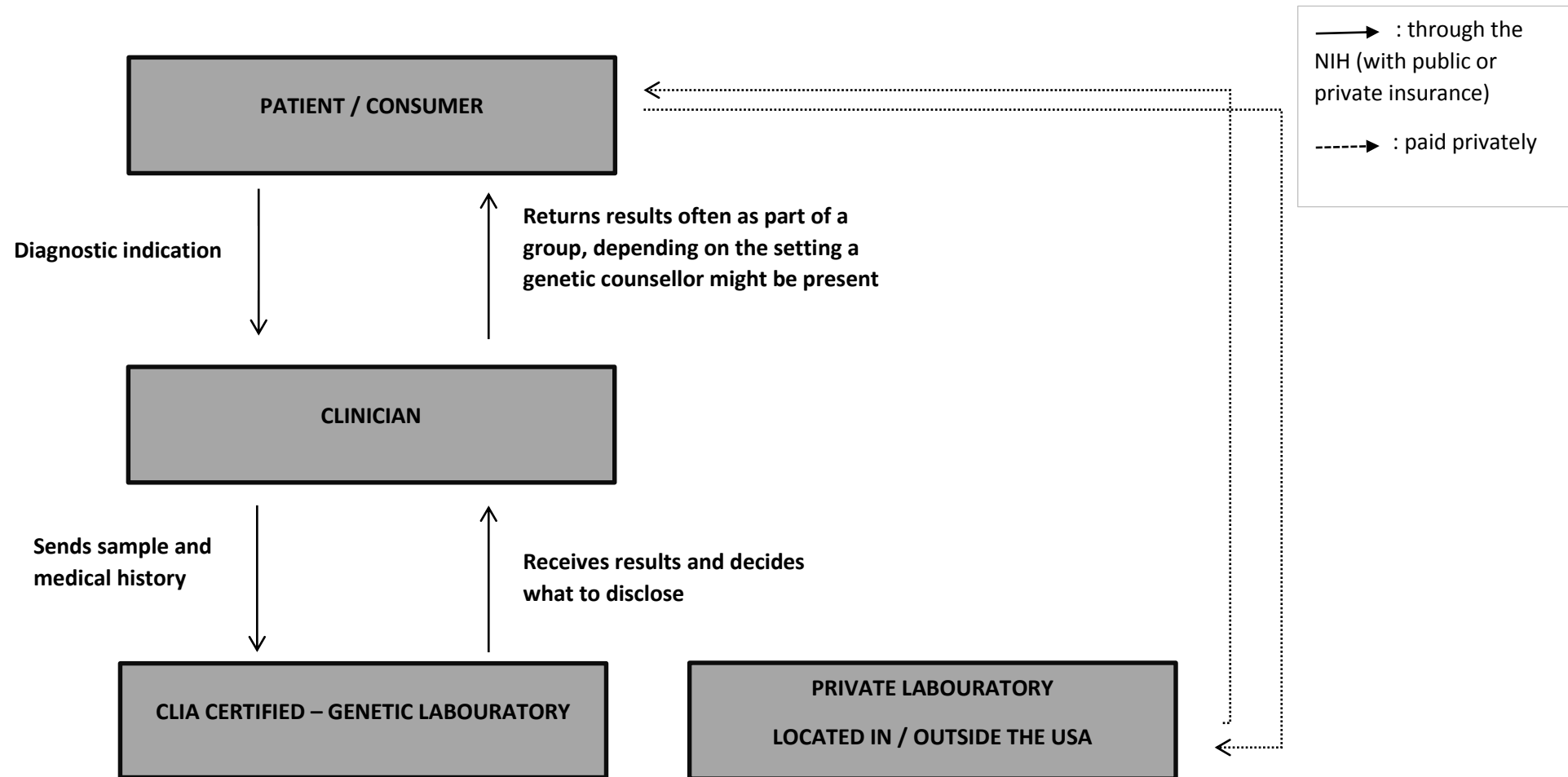


Figure 8: Access to genetic tests in the USA

to \$18,000. To this should be added the cost of the interpretation (approx. \$5,000) [340].

Depending on the company's policy, direct billing of insurance companies might or might not be allowed, and this may require the patient to have received pre-approval before proceeding to the test [340].

Alternatively, an individual could access genetic or genomic tests "over the counter" i.e. through a private laboratory located inside or outside the USA. Nevertheless, in several states, Direct-to-Consumer genetic tests (DTC) are prohibited [341]. Recently the FDA ordered the DTC testing company 23andMe, which had not received FDA approval, to stop offering their health-related genetic reports, produced from their saliva-based test, due to the potential harm to patients [342].

An illustrative example of the variety that is observed across the US can be observed by a simple online search. A list provided by the University of Kansas Medical Center provides information for 23 genetic centres, clinics and departments across the USA [47], while a search in the web-base of GeneTests.org, an American medical genetics information resource, reveals over 120 clinics offering a variety of genetic tests in the State of California alone [48].

4.2.2. Legal background and non-binding documents

Currently, there is no law at a federal or state level covering the return of IFs from clinical sequencing. However, in a clinical setting, failure to inform patients about clinically actionable results might generate negligence suits. Examples of such liability could be derived from negligence actions related to research settings, such as biobanks [3, 4, 343, 344] and failure to inform patients about available and innovative "medical developments" [345]. Negligence suits include both malpractice and ordinary negligence actions [100, 346]. The interpretation of the duty of the clinician to feedback could be supported by such laws. In a similar way, this legislation could also provide a framework for "... potential legal liability a clinician might face for failing to identify and disclose such findings" [154: p.70].

There are a limited number of cases that have been settled outside of court and an even smaller number of court cases about clinicians' duty to disclose IFs [154]. The eight cases identified concerned IFs from imaging techniques, and no case about IFs from clinical sequencing has been found [346]. However, from this literature, it seems that liability could be claimed against clinicians failing to feedback IFs if such a discovery could have prevented or changed the health outcome [346].

As mentioned earlier, a very strict legal framework exists for laboratories providing genetic tests to patients. All laboratories that report specific results for the diagnosis, prevention or treatment of

any disease to patients should have acquired a CLIA certification [347]. Findings that are discovered through research protocols before being returned to patients have to be validated in a CLIA-certified laboratory.

The use of genetic test information in health insurance and employment is regulated by the Genetic Information Non-discrimination Act (GINA) that was signed into law in 2008 [348]. The Act prohibits discrimination in health coverage and employment based on genetic information.

Regarding legally non-binding documents, the main document setting the ethical framework within which IFs from clinical settings should be dealt with is provided by the Presidential Commission for the Study of Bioethical Issues. In their report, they describe the “Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts” [154]. According to the Commission, three recommendations should be taken into account when IFs from the clinical setting are to be returned. These recommendations cover (1) Consent in the Clinical Context; (2) Empirical Data in the Clinical Context; and (3) Clinical Judgement in Managing Incidental Findings. Apart from those, “...respect for persons, beneficence, and justice and fairness” should also guide feedback [154: p.9]. The consent process should be done in a comprehensive way, absolute and relative risks should be communicated and the patient should be informed about the possibility of IFs, while the clinician should respect the patient’s preferences about whether or not they wish to receive IFs. In the report, empirical studies are encouraged to focus on patients’ attitudes, while studies about economic aspects (cost-effectiveness etc.) of the tests are also seen as necessary. Finally, the last recommendation suggests that clinicians should, using their personal and professional judgement, order and conduct “... only tests and interventions necessary for addressing health concerns related to their patient” [154: p.70].

4.2.3. Approaches to returning findings from clinical sequencing

As described above (figure 8), access to genetic and genomic tests is granted through a referral from a clinician. The test is performed and once the referring clinician receives the lab-report with the findings, (s)he will contact the patient and communicate the results. The type of results to be offered differs widely depending on the clinician and the laboratory that performed the tests.

More specifically, in the US, ES and GS are available through several laboratories according to GeneTests [49], however, the most frequently used commercial labs are Medical Genetics Laboratories at Baylor College of Medicine (personal communication and experts’ opinions), Ambry Genetics and GeneDX [50]. Depending on the laboratory, they may follow the ACMG list for reporting IFs and they may also report other medically actionable results if requested [349, 350]. Additionally, they report variants for late-onset conditions to minors that might be medically

actionable for their parents. A clear policy exists in some laboratories against returning late-onset, non-actionable results [351]. Patients are encouraged to receive genetic counselling before and after the test and are allowed to opt-out of receiving IFs [339]. All results are included in the report returned to the patient and his/her family through the ordering physician. In some laboratories, the patient has the option to request an “expanded report” (but always through the referring physician) that would include “deleterious mutations and unclassified variants in genes unrelated to the disease phenotype” [351]. Alternatively, other laboratories offer two reports. The first report (an illustrative example by Ambry Genetics is presented in figure 9, [195]) includes only diagnostic-related findings while the second report, which includes secondary findings, is produced at a later date [352].

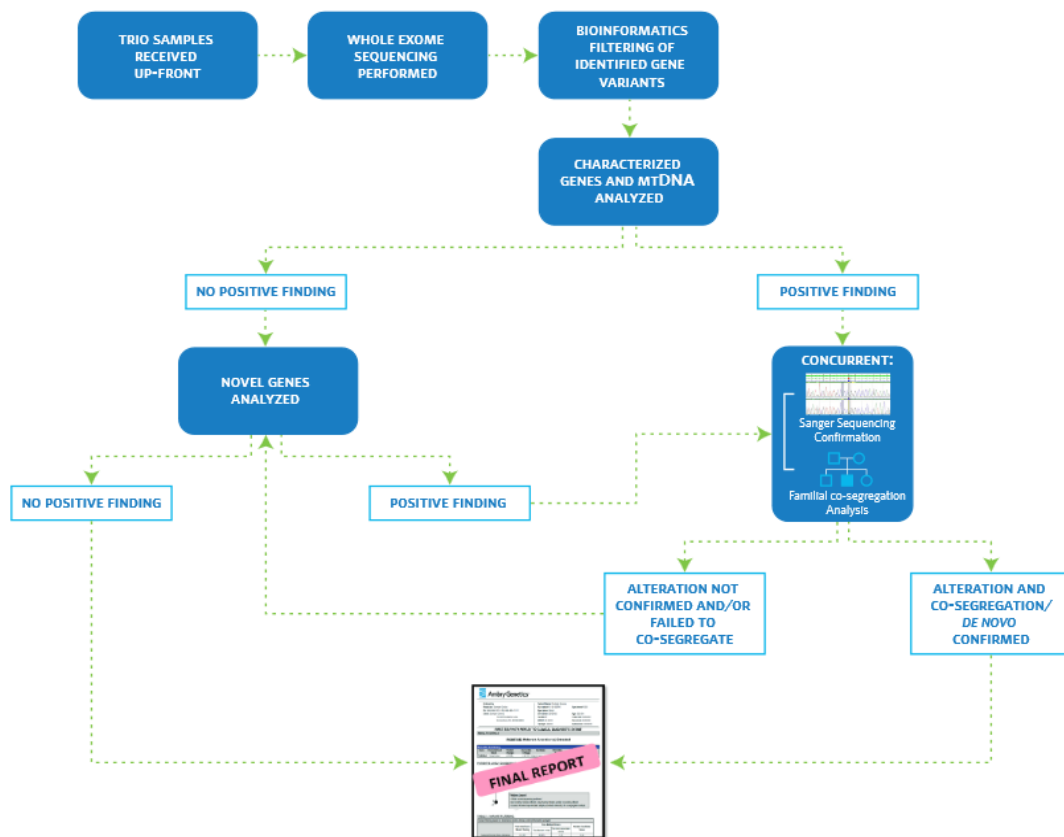


Figure 9: Process for Whole Exome Testing as described by Ambry Genetics [352]

4.3. Background for the UK

4.3.1. Health care services and access to genetic tests

Currently in the UK, patients mainly access genetic tests through the public sector, i.e. the National Health Service (NHS). An individual in need of a genetic test or advice about a genetic condition can ask for information from a GP who acts as a gatekeeper for all health services. Alternatively, if the individual is seen in a hospital, (s)he could speak to their specialist, or their specialist may recommend a test for them, based on a diagnosis. In either case, the individual will be referred to a Regional Genetics Service (figure 10). NHS genetics services include a range of clinical, laboratory and screening services, which are delivered by a network of 24 integrated Regional Genetics Services (RGS) across the UK and in a number of specialist centres around the country [353-355]. Most clinics are associated with university departments.

According to the British Society for Genetic Medicine (BSGM,) the main preconditions why an individual could be seen in a Medical Genetics clinic are:

- A person with a known genetic condition in the family, wanting to know the risks to themselves and/or their children.
- Parents of a child with difficulties which may be due to a genetic condition, referred to see if a diagnosis can be made.
- A person with a strong family history of cancer, wanting to know if they are at increased risk, and, if so, what options they have.
- A person with a known genetic condition wanting specialist advice about the condition.
- A person with a possible genetic condition in the family wanting to know if a diagnosis can be made and, if so, the risks involved and their options.
- A pregnant couple who receive an abnormal test result, wanting to talk about what the result means, and what options are available. [353]

If none the criteria mentioned above is not met, the individual will not be eligible for an NHS genetic test. In that case, the individual might seek to pay for the test privately if (s)he still wishes to proceed with the test. For example, a person without a strong family history of cancer or without a suspected gene identified in any relatives would be able to have the test and cover the cost personally. The cost for such a test would range from around £2,000 to £3,000 [356]. However, no official record of private laboratories providing genetic tests in the UK is currently available, probably because most health services are offered through the NHS.

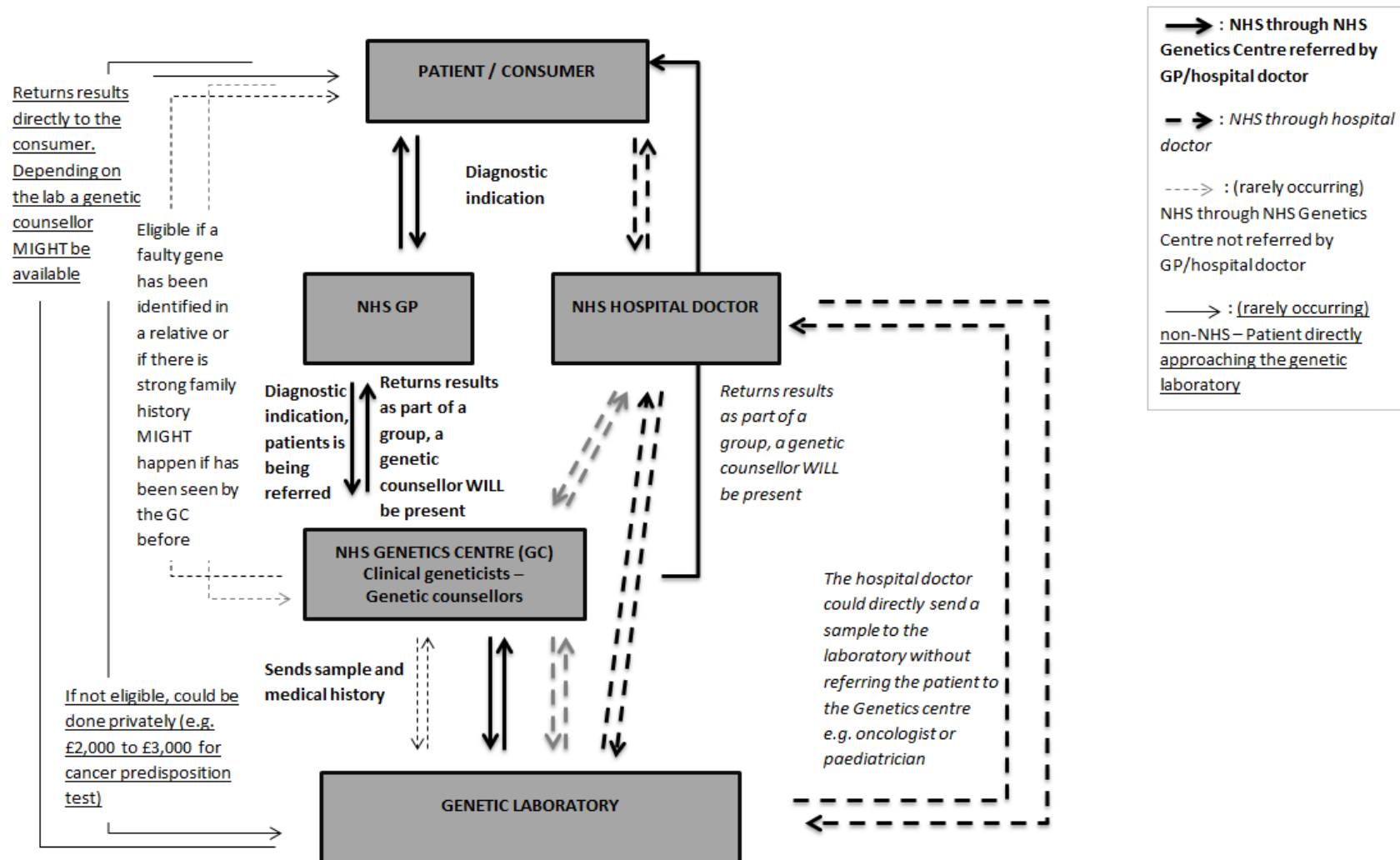


Figure 10: Access to genetic tests in the UK

In the UK, the process of accessing genetic tests in the NHS is very clearly set out. After the individual is referred to the regional Medical Genetics clinic, (s)he will be seen by a genetic counsellor or a clinical geneticist, depending on the condition and particular circumstances. The first appointment is usually used for the specialist to gather all available information about any relevant medical and family history. A second appointment usually includes a medical examination (if needed) and the actual genetic test. A follow-up appointment might be offered either with a genetic counsellor or a clinical geneticist. Finally, individuals receive a letter summarising what has been discussed, and they might also have the choice to ask for a copy of that letter to be sent to their GP or another specialist [357].

A range of genetic tests is offered in all regional genetics service clinics. Patients are usually referred to their closest clinic unless they require a specialised test only performed in a few specific clinics. For example, in the Nottingham Regional Genetics Service Clinic, the tests provided include chromosome or DNA tests, and testing is conducted to identify carrier status, diagnosis, pre-symptomatic testing or predictive testing, pre-natal and pre-implantation genetic diagnosis [357]. More specifically, available tests might include disorder-specific tests (e.g. test for polycystic kidney disease), single-gene tests (e.g. test for DYT1) or panel tests (Cystic fibrosis) [358].

In each clinic, there is a team with different specialities. These specialities usually include clinical geneticists, genetic nursing specialists, and genetic counsellors. Depending on the clinic, more specialities might be included. For example, in the Northern Genetics Service Clinic, located in Newcastle and covering the North East and Cumbria region, the clinical genetics team is also supported by a neuropsychiatrist, with special expertise in Huntington's disease, and a neurogeneticist, with special expertise in mitochondrial disease [25].

4.3.2. Legal background and non-binding documents

As discussed earlier, there is currently no law regulating genomic tests or IFs. Some, albeit limited, guidance is provided through guidelines or recommendations prepared mostly by independent professional bodies such as the PHG Foundation, the AGNC. Currently, IFs, are regulated through existing laws concerning genetic data and genetic tests in general.

Use of personal data is legislated according to the UK Data Protection Act. All health-related data, including that produced by clinical sequencing are, according to the Act, "sensitive personal data" (Article 2:e). According to this Act, personal data is regulated if it "relates to a living individual who can be identified" (Article 1:1) either from this data alone or in combination with other information. Data that is unidentifiable is not regulated by this Act [359]. However, concerns have been expressed that this Act is not adequate to cover data deriving from ES or WS since, even if samples

are anonymised, individuals could still be identified [354]. Sequencing data could be considered as sensitive data according to the Act, if it is considered as data revealing health-related information, but, since it is not specifically mentioned, the professional responsibilities are not clear [354].

Under the Data Protection Act, access to health records can be granted or refused by the data controller. Data access could be refused if it is "likely to cause serious harm to the physical or mental health or condition of the data subject or another person" [360: article 5]. Based on this, access to someone's health records, even by members of the family, might be refused by the data controller. However, patients' health-related information might be disclosed, under the Health and Social Care Act 2012, if it is of sufficient public interest to do so [359].

There is no general law protecting against discrimination based on one's genetic make-up. The use of genetic data by other parties (e.g. by employers) is guided by the recommendations of the Information Commissioner's Office. This guidance restricts employers from asking for pre-employment genetic tests without justification [361] and this limitation is also expected to apply to data deriving from ES and GS tests [354]. Additional guidance regarding access to genetic test results comes from a collaboration between the UK Government and the Association of British Insurers (ABI). This includes a Moratorium that will be in place until 2017, which allows consumers to take out substantial amounts of insurance without having to disclose adverse results of predictive genetic tests [362, 363].

4.3.3. Approaches to returning findings from clinical sequencing

Considering the flow-chart (figure 10), it becomes apparent that in the UK access to genetic and genomic tests is granted through the NHS. A GP or a hospital doctor will refer the patient (or the individual) to the Genetics Centre which will then take charge of the process [356]. Once again, the return of results follows a similar but reversed path.

As there is currently no specific guidance describing the type of results that will be offered in the UK, patients are managed on a case-by-case basis. The clinical geneticist (potentially in collaboration with the lab-geneticist and the genetic counsellor) will decide what to offer based on the patient's needs and preferences. Personal characteristics (e.g. family status) and family history might influence the clinical geneticist's approach.

4.4. Background for Greece

4.4.1. Health care services and access to genetic tests

Currently in Greece, patients have access to genetic testing through both the public and the private sector (figure 11). If an individual has either a diagnostic indication of a genetic condition, a family history of a genetic condition, a gene associated with a genetic condition, or a family member with the condition, then the individual can consult a physician who will refer the individual to a specialised clinic or one of the available genetic laboratories. In the public sector, it is currently unclear what proportion, if any, of the costs will be covered by health insurance.

Alternatively, an individual can go directly to one of many private laboratories, located in most cities in Greece, and ask for available genetic tests [364]. The cost of the test will be fully covered by the individual unless he or she has private insurance, which may cover part or all of the cost.

The vast majority (92.3%) of test requests to private laboratories come directly from patients as no referral is needed [221]. According to the Hellenic Association of Medical Genetics (HAMG) [365: content in Greek], there are currently ten public laboratories providing genetic testing. These laboratories are mainly located in Athens (seven out of ten), while other public laboratories can be found in Thessaloniki, Patra, and Ioannina (major cities in Greece). Most of the public laboratories are linked to a university hospital. These laboratories offer a variety of genetic tests ranging from molecular cytogenetic tests to predictive genomic tests. The Choremio Research Laboratory was the first laboratory founded in Athens in 1965 and was originally part of the first paediatric clinic of the University of Athens. It started offering molecular tests in 1982 and since then a number of genetic tests have been used for research and diagnostic applications [366].

There are no official records about private laboratories providing genetic tests and numbers can only be estimated. According to HAMG (content in Greek), there are at least eleven private genetic laboratories, while, according to a nationwide study conducted in 2011, there were at least 18 private laboratories offering genetic tests in Greece. These laboratories comprise the majority of the genetic testing industry in Greece [221]. They are mainly located in Athens (14 out of 18) and most offer molecular genetic analysis for inherited disorders (92.3%), followed closely by classical and/or molecular cytogenetic testing (84.6%), and predictive genomics (76.9%) [221]. As of 2011, the majority of the genetic laboratories were found to offer genetic tests for less than €300 [221]. According to this study, all private genetic testing laboratories used the services of an expert providing genetic counselling who was either a permanent member of the staff or an external collaborator.

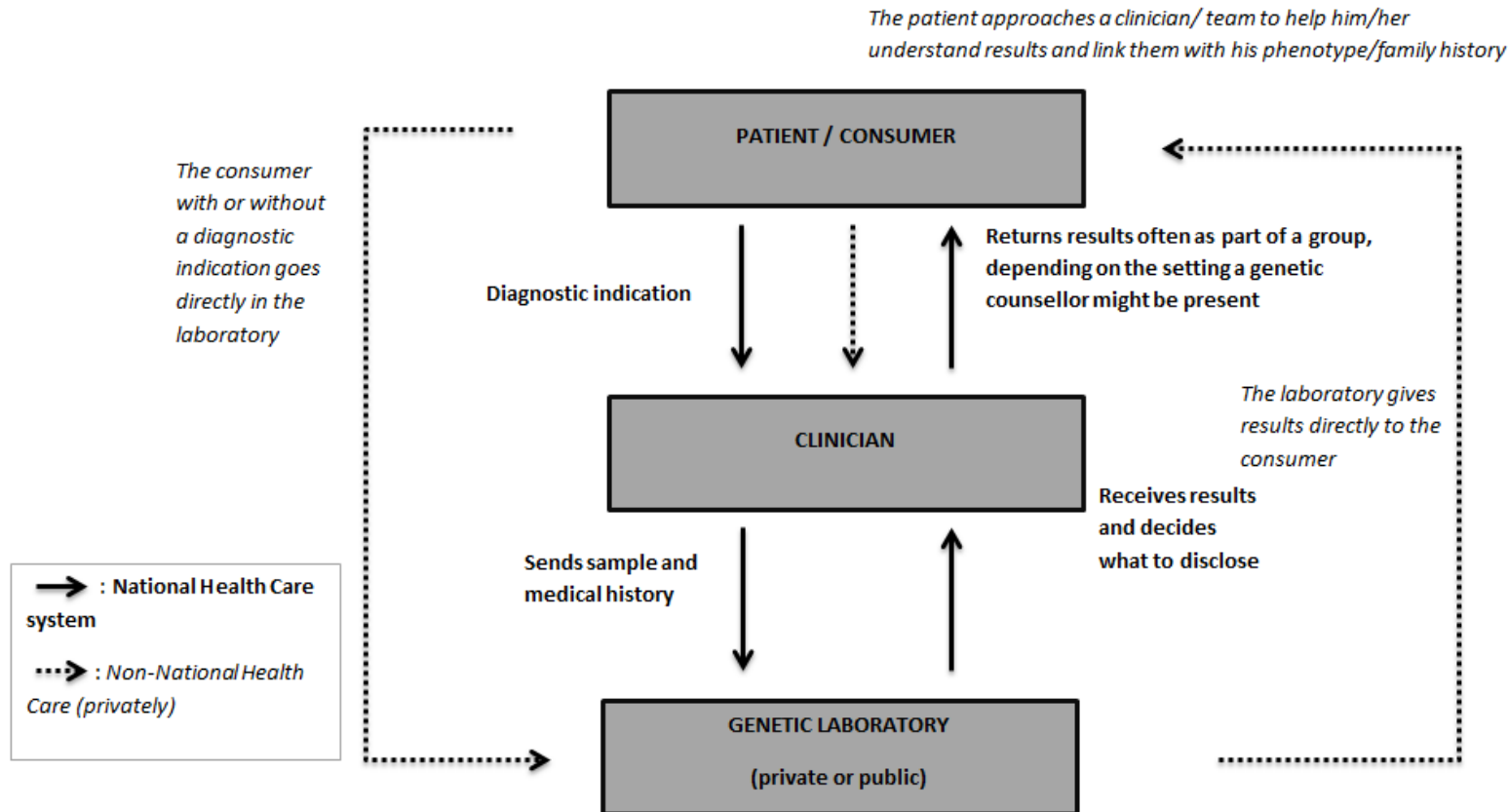


Figure 11: Access to genetic tests in Greece

The majority (84.6%, as reported by HAMG) of genetic testing laboratories have an International Organization for Standardization (ISO) certificate, and could be considered as accredited. However, fewer than 20% of them have been certified for the provision of genetic testing services specifically (with ISO-15189 and/or ISO-17025) [221]. This fact highlights the lack of a governing body to oversee and certify private laboratories in Greece, according to international standards.

No genetics-related medical specialty is recognised by the state. More specifically, neither the specialty of clinical geneticist nor the specialty of lab-based geneticist is recognised. Professionals working in genetic and genomic testing have gained their expertise either abroad, where such formal training is available, or through working in this area for many years. There is also no recognised speciality of genetic counsellor. This role is taken on by clinicians and lab-based geneticists who provide this service as a part of their clinical relationship with their patient.

Currently, in Greece, there are two Genetics Associations, HAMG and Hellenic Society of Medical Genetics (HSMG). In 2013, HAMG had 180 registered members. These included clinicians, dentists, biologists, and biochemists working in genetics [365: content in Greek]. HSMG has 42 registered members (as of December 2014), and the vast majority of the members are clinicians. An attempt to promote the establishment of medical genetics as an independent medical specialty was organised by the HSMG in 2011 but although it was discussed in the Hellenic Parliament in 2012, the attempt failed as the law establishing the specialty was never put to a vote due to the political and financial situation [367]. To date, this issue remains unresolved.

4.4.2. Legal background and non-binding documents

In Greece, there is no specific guidance of any type regarding IFs and clinical sequencing. Genetic testing in Greece is regulated by the legal framework that applies to health services as a whole. The rights of users of genetic services are currently being regulated as patient rights which apply to all healthcare areas. According to Law number 2472/1997 concerning the use of personal data [368], all health-related data is considered sensitive and can, therefore, be collected, stored or processed only by the Hellenic Data Protection Authority and only with the individual's informed consent. Any institutional guidance on sharing personal data between doctors and their patients reflects international codes of practice such as UNESCO's Universal Declaration on the Human Genome and Human Rights (1997) [369] and the International Declaration on Human Genetic Data (2003) [370].

Regarding the return of results, the Oviedo convention, integrated into Greek legislation with law number 2619/1998 [371], states that "[e]veryone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be informed shall also be respected". Tests which are predictive of genetic diseases or which serve either to identify the

subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease shall be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling.

One of the reasons there is no guidance for clinicians is because there are no organisations formally responsible for the creation of good practice guidelines. Clinicians rely on the Law concerning Medical Ethics (number 3418/2005) [372] for general guidance regarding their duties toward patients and their families. According to this law, physicians are responsible for developing a relationship of mutual trust with their patients and respecting their wishes and beliefs. The physician has an obligation to share the truth with the patient. (S)he shall inform, fully and comprehensibly, the patient on the true status of his/her health, and the content and results of the medical act proposed. The goal is that the patient may shape a complete picture of the medical, social, and economic factors and consequences of his/her condition and proceed towards a decision. The physician shall respect individuals' wish not to be informed. In these cases, the patient has the right to ask the physician to inform another person (of the patient's choice) instead. This person will then be exclusively informed of the condition and the content of the results. The physician shall not disclose confidential information to others unless the patient has requested this. The duty to respect and preserve medical confidentiality shall not cease with the death of the patient.

Even when non-legally binding documents are included, there is limited guidance available to cover aspects of genetic testing. In 2001, the Greek National Bioethics Commission issued a statement that addressed the collection and management of genetic data rather than types of genetic tests and issues deriving from them. According to this non-legally binding statement, individuals have the right to receive all results of genetic testing of medical, diagnostic or preventive nature but could also choose not to be informed [373].

4.4.3. Approaches to returning findings from clinical sequencing

In Greece, there is no established framework for offering genetic and genomic tests. As a consequence, the return of results is managed on a case-by-case basis. Results are usually returned through the ordering clinician, who also acts as a genetic counsellor (potentially in collaboration with a lab-geneticist), and the type of results offered are determined by him/her. The patient then decides what to receive in cases where a discussion has not preceded the test.

4.5. Comparison across countries

In the USA, genetic and genomic tests are used more frequently. A great variation is observed across states and clinics and laboratories offering the tests. This variability makes the synthesis of data collected here particularly difficult. The lack of legislation covering this specific topic is also observed here but guidance by professional bodies, such as the ACMG, and the Presidential Committee provides a more complete framework compared to other countries. In the UK, genetic and genomic tests are mostly offered through the NHS via Regional Genetics Service Clinics. Although there is no topic-specific law and guidance is limited, a process has been agreed by the professionals involved and no significant variability is observed across regions ensuring the provision of a consistently good level of service across the country. In Greece, genetic and genomic tests are offered although there is no set framework for their provision. The cost, the insurance coverage and the professionals involved in the process remain unclear, especially taking into consideration that there are no recognised specialties of clinical geneticist or genetic counsellor. Regardless of the absence of topic-specific legislation or guidance, ES and GS are gradually becoming integrated into the clinical setting, as demonstrated by the existence of over 200 registered Greek geneticists.

Moving from the US to the UK and then to Greece, a decrease is observed in both the frequency in which clinical sequencing is used and the availability of topic-specific guidance. The situation in the US is characterised by variability, but the presence of the ACMG as a supervisory body and the fact that there is more guidance than in the other countries, potentially encourages the use of exome and genome sequencing. In the UK, a framework is currently under development and there is an established network of Genetics Centres and, therefore, clinical sequencing is expected to be used more frequently in the future. Finally, in Greece the rarity of clinical sequencing can explain, and be explained at the same time, by the lack of any legal or procedural framework. To facilitate the integration of exome and genome sequencing several aspects of the process should be clarified including insurance coverage; potential results to be offered; availability of supporting infrastructure and the establishment of protocols concerning who is responsible for leading the decision making and feedback process.

4.6. Summary

This chapter has provided a description of the legal and procedural processes relating to clinical sequencing and IFs undertaken within the three countries under study. This has enabled me to identify the important differences between countries that are expanded upon in the final section. The production of the flow charts facilitated discussion between myself and the experts, thus, enabling the differences to be highlighted.

The differences observed between the countries suggest that guidance from one country cannot be applied to another country without significant adjustments. The absence of a detailed process to access genetic tests in Greece compared to the UK and the US means that the provision of such tests is much less organised. Moreover, this lack also suggests that examples of best practice in this regard might be sought from other countries. These examples might come from the UK or the US as these countries have a long tradition of genetic tests and the associated governance. Nevertheless, these examples should be adjusted to the country-specific characteristics and this is why professionals' attitudes are important because such attitudes are likely to inform the direction that guidance should take and to suggest ways to adjust examples of best practice and integrate them into the Greek context. This chapter acts as an introduction to the following three chapters where the collected data is presented. Building on the existing situation in their countries, experts were asked to describe their experiences within their healthcare system and suggest changes that could facilitate the provision of clinical sequencing that could be country specific or, as we will see, shared across countries.

CHAPTER 5: RESULTS FROM THE INTERVIEWS – CHALLENGES ARISING FROM THE USE OF WHOLE EXOME SEQUENCING AND THE MANAGEMENT OF INCIDENTAL FINDINGS

5.1. Chapter outline

This chapter presents the findings from the initial interviews. Here, I focus predominantly on the challenges arising from clinical sequencing and the existing situation in each country as described by the experts interviewed. The chapter is organised into four sections representing two major themes that emerged from the interviews. Findings from the interviews are extended in the following chapter where I focus on the type of findings that should be returned and best practice for the future.

Aiming to establish a deeper understanding of professionals' perspectives, I chose a group of experts who could provide insights on how clinical sequencing is provided; what, if any, results are returned; and what practices could improve the provision of results from exome and genome sequencing. I chose in-depth interviews to collect data as the literature review revealed inadequate empirical evidence reporting professionals' needs and concerns. Furthermore, I believe empirical evidence is needed to demonstrate the direction guidance should take and ensure that a comprehensive framework is created, thus allowing patients to have better access to exome and genome sequencing if seen as beneficial. I used the evidence collected and presented in this and the following chapter to inform the preparation of a questionnaire addressed to Greek registered geneticists (chapter 7) and to provide evidence for the preparation of points-to-consider for the Greek context (chapter 9).

I have presented the results thematically and each theme is divided into sub-themes reflecting the analysis of the interview data. I have divided the results and reported them separately in chapters 5 and 6 to facilitate reading, as having all of them together would have resulted in an impractically long chapter.

The findings reported in this and the next chapter have been published in the paper *Compare and contrast: a cross-national study across UK, USA and Greek experts regarding the return of incidental*

findings from clinical sequencings [Gourna et al : 374]¹⁰, an abstract of which can be found in Appendix 3.

5.2. Practical reasons why IFs are difficult to manage in the clinical setting

5.2.1. Lack of a comprehensive framework

As previously discussed, the availability of guidance varies across the three countries. All experts interviewed, regardless of their country, confirmed that the lack of a clear working framework makes IF management difficult for all parties involved (clinicians, geneticists, genetic counsellors, patients); this was especially expressed by the clinical geneticists and genetic counsellors who are usually called on to feed results back to patients. All experts reported that IFs are currently rare and they are being dealt with on a case-by-case basis, usually using an ad hoc procedure.

Usually we won't have IFs. Maybe by accident. But if we do we do not have any procedure set to deal with them. P14UKGC

Rarely we would have to deal with something like that [IFs]. If we do, we make a decision based on that specific case. We cannot do anything else. P08GRLG

In Greece, the lack of a recognised specialty of “clinical geneticist” makes things even harder and any guidance prepared will have to take this into account.

There is nothing. Absolutely nothing! No supportive mechanism, no laws. Nothing! Not even a recognised specialty [clinical geneticist]. Every labouratory has, in a best case scenario, done what we have done. We have an ad hoc process to solve problems like that. We all meet [clinicians, geneticists] and discuss case by case. P04GRCG

To understand that, here we are acting as genetic counsellors because we do not have genetic counsellors and doctors do not know what to do. They are asking for our help and sometimes even we do not know what to do. P05GRCG

Interviewees from the USA reported that, after the publication of the ACMG recommendations, laboratories and clinicians were only reporting those results included in

¹⁰ Gourna E. G., Armstrong N., and Wallace S. E., Compare and contrast: a cross-national study across UK, USA and Greek experts regarding return of incidental findings from clinical sequencing. *European Journal of Human Genetics*, 2015. (3):344-9.

that list. This was seen by some experts as a benefit as they considered that the ACMG list could ensure some consistency in the return of results.

We were returning primary results and not worrying at all about secondary results. And there was a period before the official ACMG guidelines that different laboratories had different strategies about IFs. After the ACMG guidelines came out most of the clinical laboratories felt obliged to follow the guidelines. For medical and legal reasons in the USA. So after that everybody fell into step pretty quickly actually with the ACMG guidelines. P22USCG

At least with the ACMG list we have had some consistency. We knew what we would get and what not. P21USGC

What was common across countries and reflected in experts' replies, is the absence of a comprehensive framework, a law or any other legally-binding document that all parties would have to respect.

5.2.2. Data interpretation

Experts, mostly clinicians (six of eleven clinicians, one genetic counsellor, and two non-genetics providers), considered that, for now, they have a limited knowledge of genomics and all risks that are associated with different variants.

I do not think any of us really, really understand what we're into. I mean when we did the whole genome, I never really got my head around how big a genome is. [...] there's millions of variants in there. The cases where it's been successful, it has been fantastic, but there are still cases where we're having to scratch around trying to find an answer. P15UKCG

[W]e are releasing things, calling them [deleterious] mutations while they are not, and potentially we are telling people they are at risk of very dreadful and highly penetrant conditions when the risk might be much lower or even non-existent. I think there should have been a period of time that we should have waited to get this information before and once we have had all this then deliver it. P25USCG

Regardless of their professional background or country of origin, all experts agreed that interpretation is the most challenging part of the test and feedback process.

Anyone willing to spend the money could buy the equipment for NGS [next-generation sequencing] but there are only a few who could interpret results. And that is what

makes the difference. Because we will get so many results, we will have a look and using the specific software we will throw 1998 or 1999 out of 2000. The remaining ones we will see. We will have to think about them and consider the family as well. P08GRLG

A lot of uncertainty. This is a big deal! [...] Knowing what I know about difficulties in interpretation. Because I have seen from a first-hand how difficult it is to interpret it. P11UKGC

They also noted that interpretation can be particularly challenging in individuals without any family history.

[I]t is so difficult to actually interpret genomic data in someone who is unselected for a particular condition is very difficult. So if you find a BRCA mutation in a child who is having a sequencing for intellectual disability and there is not family history of ovarian or breast cancer and there lots of family members in their eighties and they never had breast or ovarian cancer. It's very different to find out what risk is associated with that. So you would say that yes, there is an increased risk but would it be 30%, 50% or 80%? P11UKGC

Experts' concerns regarding their ability to interpret genomic results reflect the fact that their lack of up-to-date scientific knowledge, as scientific papers are being published monthly suggesting new or additional (and potentially different) associations.

5.3. Philosophical characteristics of IFs that make them difficult to manage

IFs deriving from genomic tests are, according to the experts interviewed and evidence from the literature, different from other medical information and should, therefore, be handled differently, with even more caution than other medical tests.

5.3.1. Implications for the health and well-being of family members

What was seen by the experts as the prime factor that distinguishes genetic information from other health-related information was that it has implications for others apart from the person who is tested. They noted that a patient's immediate relatives, mainly their children but other relatives as well, could be directly affected by genetic information.

[I]t is a little bit different I guess. To the extent that genetic information has implications for other family members. I think that is the main difference. Otherwise, I do not think it is different. P27USGC

It has implications for other people that are not in the room! That's the unusual thing. P19UKCG

According to those interviewed, the fact that genetic information affects more people than the patient creates an additional obligation to act in the best interests of family members. This obligation affects both the patient, who might have to inform family members about the results, but also the clinician, who might have to consider informing other family members apart from the patient. Due to this obligation, clinicians felt that they might be more inclined to return IFs.

One of the main reasons for returning information, especially for metastatic disease is beneficence toward family members so there is no reason why I would close that door. The issue is that we should try to engage the patient in the conversation about informing the family. Who and how? So hopefully the patient will be able to judge themselves who is the person to receive this information and then let us know who to contact. P23USCG

Two extreme positions were suggested regarding returning results to family members. Experts with a legal background from Greece suggested that family members might have a legal right to request access to genetic information, especially if this concerns life-threatening conditions.

What is different this time is that family members might even have a legal right to have access to that information. Because it could affect them too. P01GRLB

Family members could always claim that they have a legal right to access this information. It is a genetic condition so it affects them all. P09GRLB

In contrast, experts with a legal background from the UK explained that according to current UK legislation the right to confidentiality prevails unless there is a public interest deriving from disclosure.

If it was for the public best interest to disclose, then an individual wouldn't have the right not to disclose. But if there is no public interest then there is a right to confidentiality. P18UKNLB

The difference observed here demonstrates how although experts' attitudes present many similarities, certain different factors relating to the prevalent situation in each country might call for country-specific guidance.

Contrary to legal experts, clinicians from all countries seemed more interested to protect their own patients rather than their families.

Only the patient. I have no right to inform the family. I have never met them, I do not know them. The patient should decide if and when they want to inform them. P06GRCG

I do not know if we have a right to inform the family. I personally think we do not. Some might say that it might be ok for the clinical geneticists to inform them but I do not know. I wouldn't. P14UKCG

Somewhere in between, genetic counsellors underlined the need to encourage and support patients to share information with their families.

The big question is whether family members should be informed. I think you can't force someone to tell their family about genetics but I think you encourage people, you give them the tools, you give them the information, you give them advice as to how to inform family members and that's as far as you can go here in the US. P25USGC

You can't pick up the phone and call the aunt and tell her. But you could explain the risks to the patients and let them know that they should share this information. P07GRGC

The fact that genetic and genomic data concern more people than the patient was brought up several times within each interview. It is worth noting that any differences were observed between experts with different backgrounds, while no particular differences were observed across countries. Genetic counsellors considered that patients have a moral obligation to share information while legal experts went as far as to say that family members might have a legal right to access to this information. Clinicians seemed to focus more on their patients rather than their family while genetic counsellors were somewhere in between and acknowledged the fact that family members should be informed.

Interestingly, experts from the USA regularly mentioned the fact that patients should be informed in advance about the possibility that information relevant to other family members might be discovered. US experts might be insisting on informing patients in advance more often than other experts potentially out of fear of facing legal problems if they fail to do so. They also suggested that patients should be asked whether they want to share this information with their families, especially in cases where a patient might be suffering from a life-threatening condition.

We have stipulated who they would like to have as their legal-medical proxy and that would be the person who would get these results. P22USCG

[I]f the person who is tested, if the proband is not able to give permission to share the information either because is disabled, decapitated or dead I would hope I would have had the discussion before to know if I should share results with family members but if I hadn't and if I thought it would have been in the best interest of the patient and his family and if it was easy to locate the family members then I would approach them gently with the information , otherwise I do not think I would approach a family member without the expressed wish of the person tested to inform them. P27USGC

Several experts stated that they might be willing to approach the family if the patient had died without expressing any preference, but no-one was willing to approach family members against the patient's expressed wishes.

[D]uring counselling this should be covered and people should be informed that results might have implications for family members but I think that if a patient says "no I do not want to tell my family members" then the answer is no, you cannot inform family members. And I think that that's crucial. I think in that space you can do a lot to urge the patient to inform family members, you can offer to tell them yourself, you can offer to help the patient tell them himself you can offer a lot of stuff but the idea of saying that I

am going to override your expressed wishes and tell somebody something you didn't want to tell them that's not ok, it's not ok. P28USLB

Experts from all three countries suggested that patients might have a moral obligation to share results with their family members as that would give them the opportunity to get tested or receive appropriate treatment sooner.

Learning any genetic information is something you should share. It does not affect only you. People need to overcome their spontaneous reaction of hiding something that is bad and share it. This might make a difference in other people's lives. They might have the opportunity to get tested, follow up even have a treatment. It is a moral obligation. P03GRLG

5.3.2. IFs challenge the traditional practice of consent

The experts interviewed also believed that current practices of informed consent might not be adequate to cover genomic tests and the IFs that could derive from them. Their self-reported limited knowledge about genomic information and the difficulties in data interpretation mentioned earlier combined with the high complexity of genomic information make the current consent process inadequate for a variety of reasons.

Experts described what they understood as the “traditional model of consent.” Whoever is conducting the session informs the patient about all possible outcomes of the test, and the patient expresses his or her preferences at that time. Based on this understanding of consent practice, some experts considered that the traditional model might not be enough to cover genetic tests, both for patients who would be interested in receiving results and patients who, after counselling, decide they would not. Two factors seem to be contributing to this.

Experts believed that providing all information in a pre-test counselling session was very difficult, even unfeasible. A counselling session that covered all possibilities would be lengthy and might create unnecessary anxiety for patients.

I think informed consent would be really difficult to obtain and I think what we need to get is a level of practical consent where actually the patients know enough that they're not surprised when we come back to them finding other stuff, but they do not know so much that the consenting process takes three hours or something. P15UKCG

[I]n a very first clinic that did this in the USA their genetic counsellors came out and said that this takes 8 hours to do pre-testing counselling and that is preposterous. There is no way that could fit in the flow of anything that had realistic volumes of work. P22USCG

Additionally, experts believed that patients might not even be in a position to understand some aspects of the test procedure because genetic information might be too complicated for people without a prior basic knowledge of genetics. They also suggested that patients rely on them for guidance through the process.

Yeah. We just can't do it. I just do not know that you could sit down and really get informed consent from your average patient who hasn't got a concept or a picture of what DNA is, hasn't got a concept or a picture of what a gene is. ... [T]hese are very abstract sort of things, and to then say, 'Well we're going to look at twenty thousand genes or however many it turns out we've actually got and we're going to sequence them and we're going to find millions of variations. Then we'll whittle them.' They go, 'Yeah. Just get on with it doctor.' P15UKCG

5.3.2.1. Alternative models of consent

To overcome the difficulties of time limitations and limited knowledge of genomics, experts suggested alternative models of consent. These models usually included more “practical”, as they understood, consent where patients trust their clinician and let them take some decisions on their behalf and always in their best interests.

Moving one step forward, most experts from all three countries, especially clinicians, considered that patients should trust their clinicians and allow them to act, when necessary, in a paternalistic way. That would give them the freedom to decide whether the patient should or should not be informed about some types of results according to the patient's abilities to understand and handle results and according to their personal and familial circumstances (e.g. results that might affect reproductive choices discovered in a patient that does not have children might not be returned since they do not primarily affect the patient's health). Although patients' autonomy was considered essential, some clinicians considered that a strong commitment to autonomy might be against the best interest of the patient.

Again think about this from a pure human perspective, you have, you know that a young woman with breast cancer that had just been diagnosed, you do her sequencing and you

find she has a predisposition for hypothermia [refers to malignant hypothermia¹¹, [375]] you know she is going to the operating room and you're really not going to give her this information?? If so what kind of person are you?! I mean that you would allow somebody to fall into danger because you felt some pedantic commitment to autonomy?! P23USCG

Clinicians and genetic counsellors seemed to acknowledge that occasionally they are acting in a paternalistic way, but they seemed to consider this as unavoidable.

I think for the most part the family should be able to make some decisions, but as I said there are still some exceptions that my gut feeling says it's just not right. We still need some data in other things and I recognise that this might be a little paternalistic but that's it. P27USGC

We try very hard not to be directive, not to tell people what to do but you might want to be a little bit more persuasive if the condition is very serious and life-threatening. P11UKGC

Autonomy was discussed by experts here and it appears that some experts understand it in a different, more “active” way. In particular, experts with a legal background suggested a more “active” interpretation of autonomy where patients would have to actively ask for information.

Whoever is doing the genetic counselling should provide all the available information. They should let them know that IFs could be discovered. And then it is on the individual's responsibility to ask his doctor if they indeed discovered something. This way we would be sure that the individual actually wants to learn the findings. ... They need to actively participate! [...]He should be the one asking, approaching the clinician. If he does not care to receive this information then that's it. P01GRLB

Moreover, many experts regarded that building trust between the healthcare provider and the patient is crucial and could therefore, if treated as essential for the whole process, facilitate the return of results. A bi-directional decision making could be the basis where communication would replace paternalism and informed consent practice would include something more than simply signing a document.

¹¹ Malignant hypothermia is an autosomal dominant condition that is triggered by exposure to certain drugs used for general anesthesia. If undiagnosed or untreated it can be fatal.

It is important to start developing trustworthy relationships. Even in a country such as Greece where this is not developed enough. We need to start doing it. It's more than just signing a document. There will be of course documents that need to be signed but this is something more. We need to gradually change our mentality. P09GRLB

The aspects described above could be developed as separate models or be included in a revised model with several characteristics e.g. where communication would be more bi-directional and participation more active. In addition to these, several experts considered that as genetic and genomic information affect and inform the whole family rather than just the patient, a familial approach to consent should be incorporated. According to this approach the whole family would be informed and participate in the process.

I mean of course the familial decision-making and the familial context is the thing that sets genetics apart from other risk factors and how to manage the family and reconcile conflicting interests within a family is something that clinical geneticists and genetic counsellors grapple with but are very experienced with ... in some circumstances taking a broader view of consent and involving family members in these sorts of decisions would be a very good idea. P16UKNLB

Experts interviewed suggested that the unique nature of clinical sequencing is challenging the traditional way that health services were provided until recently and that new ways to inform the patient, to encourage him or her to share information with family members and to ensure informed consent, have to be investigated. Additionally, the way that a patient could be supported to be autonomous throughout the process was also discussed. Finally, experts, especially clinicians, seemed to consider that some level of paternalism might be acceptable and some decisions may inevitably have to be made by them on the patient's behalf.

5.3.3. Potential for stigmatisation

Another important issue that experts from all three countries reported was that patients had concerns about stigmatisation if a genetic condition was found in themselves or a member of their family. For example, they reported that their patients are often concerned about marriage prospects if a genetic condition is diagnosed in a family and that that is an important reason why they do not always share information, even within their family.

We are having mothers of teenagers or young adults coming here and they say "... how would we manage to find her a husband if people would know that we have that?" and they do not tell them anything. And then their kids grow up and have kids of their own

and they do not have the chance to use prenatal or pre-implantation diagnosis and they end up having kids with serious juvenile form of these conditions and when they learn that they could have known and could have done something about it they are so disappointed. They would do everything to avoid being stigmatised. We face that very often here [in Greece]. P10GRCG

We have here a large portion of my patient population that are with the orthodox-Jewish community and there is great stigmatisation of having a genetic condition in your family in terms of marriageability and meeting matches and so many of my patients within that community I give them the option and they opt out of getting these secondary findings and I think that that's their right to have that option to do. P22USCG

Concerns about stigmatisation were usually raised in a societal context. Interestingly, experts reported that patients raised concerns about stigmatisation even within their own family. This is one of the reasons preventing them from sharing genetic information with their family members.

They are more interested in protecting their own confidentiality over protecting others. They are worried about what others [family members] will think if they [patients] tell them that "we were diagnosed with that", and they don't. P18UKLB

5.4. Intentions to use clinical sequencing

Experts expressed philosophical and practical concerns regarding the use of clinical sequencing, i.e. preferring to use less targeted tests. The lack of a comprehensive framework, as reported by them but also as identified in the literature review, combined with the other concerns expressed, might affect experts' intentions to offer clinical sequencing. To investigate this assumption, I asked experts to describe their intentions to use clinical sequencing in their current clinical settings.

Most experts from each country said that they would prefer to avoid using GS/ES altogether and in this way avoid the possibility of discovering IFs. All clinicians and most genetic counsellors from all three countries stated that they would prefer to use targeted tests focusing on the condition under investigation, trying in this way to avoid having more information than is needed for the diagnosis.

For me, it is rather simple. If symptoms resemble Huntington's for example I will order a test only for that. I won't start looking around. I won't even use genetic testing unless I have to. I am not saying that it is not useful, because it is, and occasionally we have

managed to diagnose conditions that we couldn't have done otherwise, but if I can use other kinds of testing I would rather do that. With genetic testing you never know what you will get. P10GRGC

Yes [I would prefer targeted tests] and I think that's a general principle of medicine. Do not gather information you do not need. It's a problem. P26USCG

However, a smaller number of experts, mostly lab-based geneticists (four of seven geneticists, one clinician, and one genetic counsellor), considered that ES/GS might be preferable as such tests would be an information-rich resource for patients' health.

For now from a researcher's point of view with whole exome or whole genome sequencing it might be better to have next gen sequencing, you do get a lot of junk as expected, but you also get a lot of discoveries. And because we are at an early stage that's very, very useful. Further in the future once you get certain biomarkers then it might be better to have targeted tests, I think that's the way forward. Because they are easier, quicker and much cheaper. I kind of see a mixture of both. There is a lot of whole genome/whole exome going on right now and trying to limit it down to targeted sequencing. P20UKGC

With NGS you might get a diagnosis that you wouldn't get from anywhere else. So I would use it. That's probably one of our best uses of exome sequencing. 25-30% of the times now according to the data I have seen get an answer from the exome sequencing. When they couldn't get an answer from anything else. P21USGC

Of course, I will use GS if I can. And probably I will find something but that is why the interpretation of results is what matters. P07GRGC

The preference of most experts' towards targeted tests appears to be associated with the numerous concerns expressed. Nevertheless, as they acknowledged the potential usefulness of these tests as a diagnostic tool, it would be feasible to assume that if new scientific knowledge could clarify issues about the utility of the tests, and if there was guidance created and a support system available, they would be willing to use clinical sequencing more in the future.

5.5. Current feedback processes

This section describes current approaches to feeding back IFs across the three countries. As expected, more differences are observed here regarding actual feedback processes across countries than for the practical and theoretical difficulties discussed earlier, as experts mainly discussed country-specific characteristics that are associated with the existing healthcare system in each country.

5.5.1. Differences in the feedback process

In Greece, all results, both diagnosis-related and IFs, are given to patients during a genetic counselling session where the clinician or the geneticist is acting as a genetic counsellor. The results are returned verbally and also in writing.

Here we are acting as genetic counsellors as well. There is no one else to disclose results. Physicians neither can nor want to do it. They know they are not trained for it, and neither are we but since there is no-one else, we have to. P08GRGC

We give results during genetic counselling but we also hand them a report to have it for their personal medical record. P03GRGC

In the UK, there is a more complex system. If an IF is found the result would be validated and then, if available, a multi-disciplinary team (MDT) would be called to decide whether this finding should or should not be reported back to the patient. If an MDT is not available clinicians would discuss results more informally with colleagues and come to a joint decision. Only if no other specialised clinicians are available would the ordering clinician decide alone.

If we do not find the answer to the original clinical question by looking at that list of defined genes, then we need to do the whole exome, then any incidental findings that are felt to be clinically relevant and actionable, are fed back through an MTD which includes clinicians, laboratory scientists, genetic counsellors. P15UKCG

At the moment, it would be individual clinician's decision. So no there isn't anything. It is case-by-case. If some department would find CF carrier status they might not feed it back and others might. There is no kind of consistency in that. P11UKGC

If results were reported back from the laboratory to the ordering clinician or a GP then patients would probably be referred to a genetics centre.

So at the moment what mostly happens is that the ordering physician is somebody who's not a specialist. If it comes back as either definitely pathogenic or "no idea what it is", they get referred to us [genetics centre]. We wouldn't expect non-specialist paediatricians to have that conversation. That would be very much a geneticist's role.

P17UKCG

[F]ollow up findings with people that are more specialised, validate and give it back to the clinician to feed it back to the patient. P20UKLB

Usually, decisions about findings are taken by the clinician, although some initial decisions are also taken inside the laboratory.

If something specific is found we would send it back to the clinician who would feed it back. If it's not specific to the condition for which the test was ordered if it was valid then again we would feed it back to the clinician who would be the one making the choice. It will be up to the clinician to decide what to do. P20UKLB

Lab-people are acting as gatekeepers sometime. This is happening at an earlier stage. If something gets to us we would have a hard time not to return it. We do not like withholding stuff from our patients. P17UKCG

In the USA, as described in chapter 4, different states and different clinics might have completely different policies. After the publication of the ACMG recommendations, experts stated that the general impression was that laboratories and clinicians were only reporting the results listed in that guidance. American clinicians appear to have agreed that the burden to decide what to report (such as the ACMG list) should be put on the laboratories, as it would be very difficult for clinicians to decide not to return a result if they were given it.

[A]fter the guidelines it's up to the clinician but in the USA there is no way that a clinician will receive a report with findings and not return it to a patient. From a legal point of view, all of our results are in electronic records increasingly they are in what we call a patient's portal in which they can get access to their information very very quickly. There is no way if it is printed in a report that you could in my opinion, in the USA, withhold that information. P22USCG

Results are usually dealt with case-by-case, either by the ordering clinician or by a committee, if there is one available.

Clinically we are talking about it mostly case by case. We do not want to judge what the criteria would be to return, it's a little difficult. P23USCG

USA experts expressed their concern that families are left unsupported after the disclosure.

To tell people, family members, what's the risk etc. Nothing is set out for them.

P21USGC

Apart from the opinions discussed earlier about whether and how family members should be informed about IFs, some differences in feedback processes were noted across the countries. Experts from Greece mentioned that they encouraged their patients to inform family members and provided them with contact details about available genetics centres. However, the Greek experts reported the lack of any other supporting mechanism to help families through this process.

Unfortunately, the only thing we can do for families is to let them know that we are here. We are more than willing to sit down with them and explain what was found in their relatives.

But that's the only thing. P04GRCG

In contrast, experts from the UK suggest to their patients that they prepare an open letter that they could give to their family members with all available information and contact details. Family members could then go directly to the local genetics centre and receive information or even get tested.

So we will give a letter to our patient to say, 'A mutation in this gene has been found or an alteration in this gene has been found. You may want to discuss this. See your GP and ask for a referral to your local genetics centre.' P12UKGC

5.5.2. Findings that are not fed back

I have so far discussed what happens to findings that are to be fed back. However, experts also discussed what happens to findings that either the laboratory or the clinicians decide not to return, or that the patient chooses not to receive. Findings that are not fed back are handled completely differently in the three countries studied.

In Greece there is no centralised medical record system; additionally, most hospitals do not have electronic patient records. Therefore, every report is written, printed and added to the patient's file. Patients do not usually have access to these files unless they request a specific report. Consequently, if a finding is discovered but not fed back, the laboratory report would either be destroyed or added in the patient's file with a note that the patient does not wish to receive it.

We might keep it or destroy it. It depends. It's definitely better to destroy it to avoid having someone telling the patient accidentally. P04GRCG

The laboratory record will remain but will be anonymised and an effort would have to be made to link the record back to a patient.

We will keep it but it will be only with a number. The name of the patient won't be anywhere. Once the test is done, we keep them for research reasons not diagnostic.
P03GRLB

In the UK, the report produced would be destroyed if the clinician did not want to feed it back, or if the patient had asked not to receive it. However, the findings would still be in the laboratory records but in most cases would be anonymised.

Well, they're on spread-sheets and they're on web browsers. So they're there. So I mean I could click on my computer and find this, you know, I've got this spreadsheet and it's still sitting- I mean it's anonymous obviously but it's there. I haven't kind of deleted it. P13UKCG

So I can think of a specific example where we've been in that situation, where somebody wanted a predictive test for something and they were to come for their result and prior to seeing them in clinic we opened it so I then know that result, and then they choose not to come to a clinic and they say, 'I do not want to know'. And in that situation we would destroy that report because it's too dangerous if it sits in the notes. It's never been reported back to the patient and then gratuitously a) somebody assumes that they know, and b) somebody gives it to them without due preparation. We'll make a very clear record, 'Patient chose not to come to receive the result. Result destroyed'. They wouldn't get rid of the DNA because we do not get rid of any DNA. P17UKCG

UK clinicians considered that data could be reviewed in the future if more data were available and that is why samples would be kept.

Everything's that found, there's an electronic record kept. There isn't any plan at the moment to periodically review those, but if significant new information came to light, we would have the facility to do that. When they're stored electronically, they'll still be identifiable. So we'll be keeping data files of stuff that is identifiable so that if something does change, we can feed it back if necessary. P15UKCG

However, they also considered that if new variants were identified in the future it might be better, and even cheaper, to do a new test, maybe using a more developed methodology, rather than re-sequencing the same sample using NGS.

[L]ogically if they decide not to feed them back they should keep them because it might be relevant in the future. In reality, it's better to discard them and re-do the test in the future especially if it's easy and cheap. We would choose what to feedback, record what we have fed back and then destroy it and the defence for that is that it's getting so much faster and cheaper to re-do it so if you need it would be easier instead of retrieving it.

P19UKCG

In the USA, clinicians would probably feedback everything included in the lab report, even if it was different from the ACMG list. They would feel obliged and they might be scared of having information of which the patient is not aware. They would ask the laboratory to report only specific results to try and avoid having to deal with anything else.

If it is in the report I get I would have to report it to the patient. It would be too dangerous not to. And I wouldn't feel comfortable either. Knowing something that they do not. So I would rather not know at all. P29USCG

5.5.3. Experts' previous experiences and training facilitate the current feedback process

Apart from the actual practices described above, experts were asked to discuss how they experienced the process of disclosure themselves. Interviews showed that the gap in guidance, as reported, is usually filled by experts' reliance on their previous experiences from other areas of medical practice.

As discussed earlier (see 5.2.) experts believed that IFs from clinical sequencing differ from other health-related information for several reasons. However, clinicians from all three countries also talked about how unrelated and/or unexpected results have been a common phenomenon with all medical tests, meaning that their previous experiences could go some way towards helping them deal with IFs from clinical sequencing.

[T]his is an ancient problem and every time you intervene you might find something that you didn't ask for. P19UKCG

IFs are part of the job and has always been part of the job, so you would have lives saved or lost lives because people misunderstood the meaning of an incidental finding.

P13UKCG

They also considered that their formal training has prepared them to deal with uncertainty.

We're kind of used to doing this as doctors. We do chest x-rays for someone having a cough and we might find that they've got something else. Do CT scans or MRIs and we find other stuff not uncommonly and we just sort of manage it and deal with it and get on with it. I think this will be the same. P15UKCG

And clinical geneticists and people in medicine in general, have been dealing with IFs forever, that's not new and they are very used to it, and the uncertainty that brings

P11UKGC

Previous personal experiences included examples of other tests where IFs could be discovered such as imaging technologies, prenatal tests, cytogenetic and genetic tests in children with developmental delay.

[A]n array-CGH on anything, but if you pick something incidentally then you confirm it and you give it back. That fits with general practice in the moment. It is the same with imaging technologies, if you find something you were not expecting you confirm it and you feed it back. P11UKGC

Judging from their previous experiences, some clinicians considered that new types of findings are more often returned when a test is newly introduced, a fact that might change once sufficient knowledge is acquired. Not knowing what could prove useful in the future would lead them to feedback more results in order to avoid missing something that would be useful to the patient now or in the future. After the accumulation of more knowledge about the value of such findings, professionals may be more comfortable with only returning significant findings.

So when you first see something, you're perhaps more keen to feedback because you're not quite sure what the significance of it and you feel it's important the families have an understanding of that. And then as our knowledge grows and we're more confident that this is not of any clinical significance, then less and less we do report it back to patients because we're operating within a clinical environment where we're being asked specific questions about disease. P17UKGC

Most considered that previous practices could provide examples of how IFs from clinical sequencing should be handled.

Well I think that we have examples to follow and incidental findings arise through imaging and I think the usual practice is to have a multidisciplinary meeting and discuss with, if it's an imaging thing, with the radiographers or radiologist or whatever, and the clinician, and I think that MDT approach would be the one that would be used at the moment. P16UKNP

[T]he equivalent of cosmetic dermatology. So dermatology offers nowadays, there's stuff they'll do for you that your insurance will pay and there's stuff they'll do for you but you have to pull out your credit card before you get it. It's possible that a health system might say, 'Yeah. We could give you that ancestry information. It costs a hundred and fifty bucks or five hundred bucks or whatever. Here's the machine. Put your credit card in.' P26USCG

They say that if we have this information that as the radiologists who see something in the CT, we should return them. And that's something that everybody agrees with. I know it's not the same because of everything we have discussed already but it is a starting point. P25USLB

Experts recognised that genomic data differs from other medical data (see 5.2.) and previous experiences and examples from other disciplines, as described, might provide guidance. However, these are not likely to be sufficient to assist experts in knowing which findings to return.

5.5.4. Coping, regrets and readiness to receive results: patients' reactions to results

As shown in chapter 2 the number of empirical studies investigating lay people and patients' attitudes is still limited but it shows that lay people want IFs reported and the choice to learn about them. When experts were asked to describe their own experience with patients asking (or not asking) for IFs, they reported that patients indeed ask for most available results. Professionals' perceptions regarding their patients' preferences and needs are important as they affect professionals' intentions to use or not use these tests. Furthermore, they provide some preliminary evidence suggesting issues that should be addressed during the preparation of guidance.

Following examples from the literature (see section 2.4.3.1.), experts interviewed for this project were, amongst others, asked to estimate their patients' intentions, abilities to understand and cope with clinical sequencing and the potential to discover IFs. Most clinicians

I interviewed believed that their patients were usually able to handle results even if they were unexpected and unrelated to the original diagnosis.

All I know is that parents, patients and people in general can cope with information. And they want information; I do not think we should patronise them by protecting them from the data. And I think it's ok to say that if we do not know, we do not know. But just to share this journey with them. And not to hide information from them. P11UKGC

Yes, I think they are [able to handle results]. People are extremely resilient and have tremendous resources and strengths and support and are capable of dealing with things. P27USGC

Similarly, having a “label”, i.e. an explanation for their symptoms or characteristics, was considered valuable even if no treatment or cure was available.

[I]t ends the diagnostic odyssey, which in itself is a value. And if you look into what patients say, they are just grateful for having an answer. Even if it does not help P21USGC

The mother was very pleased that we'd made this diagnosis. It helped to explain some of the differences between her two children as well as the similarities. Because of having a label, actually, although there is no cure for this condition, it's been suggested that there's some treatment to manage some of the symptoms. P13UKCG

Experts, regardless of their country, reported that most patients ask for as much information as is available.

They ask for everything. All possible tests. P05GRLG

All I know is, from my own personal experience, that people are very resilient. And they, even really, what seems to be really bad news, they can cope with, if supported and helped with it. That is why I think genetic counselling is very very important. P11UKGC

Experts from all three countries believed that patients are usually able to handle IFs and the uncertainty that comes with genetic tests but there are, at this time, no studies published investigating patients' attitudes after receiving IFs from clinical sequencing. My findings have highlighted this as an area that should be further investigated to reveal whether patients can cope with genomic results. Directly accessing this information, rather than asking professionals' of their

experiences and views, will provide valuable insight on how patients actually think and manage similar situations.

5.6. Chapter summary

In summary, all experts described that, for now, ES/GS is not used very often in the clinical setting and the possibilities and limitations of these technologies are still unclear. Only in the USA, after the ACMG guidelines, there is some subject-specific guidance. In both Greece and the UK, professionals rely on other colleagues for support and help in the decision-making process about whether or not to return IFs to patients. Currently, clinical sequencing is ordered by a clinician and results are fed back to the clinician or the team that ordered it. Some experts reported the existence of support from a genetic counsellor, at some point of the process, while most of them described the lack of a comprehensive framework. In all three countries, the laboratory is partly involved in the decision-making process about what results to return. This usually happens in a more informal way, with laboratory-geneticists participating in the interpretation of results and feeding back to the clinicians only what they regard as clinically significant variants. More similarities than differences were observed among the experts interviewed. This was most marked when comparing clinicians with similar professional backgrounds, irrespective of their country of origin.

The interviews with experts showed that they found the management of IFs from clinical sequencing challenging for several reasons. These included practical difficulties, such as the lack of a clear framework, the limited understanding of genomic information by all stakeholders and difficulties in interpretation. Experts also discussed more philosophical challenges raised by IFs. IFs deriving from clinical sequencing differ from other medical data for three reasons. First, they are shared across families; second, consent forms are inadequate for managing this added complexity; and, third, there is a risk that knowledge of an IF may result in stigmatisation. The current feedback processes vary and appear to be shaped by the healthcare system within each country. Similarly, the availability of any framework and the management of results that are not fed back to patients also differs across countries. In contrast, experts' previous experiences and their opinions about patients' ability to handle IFs seems to be influenced more by their professional background than the country within which they work.

This work is extended in chapter 6, where best practice that could facilitate the management of clinical sequencing and IFs is identified.

CHAPTER 6: RESULTS FROM THE INTERVIEWS – RESULTS TO BE RETURNED AND GOOD PRACTICE FOR THE FUTURE

6.1. Chapter outline

This chapter presents clinicians' views on the types of results that should be offered to patients and the criteria used to make such decisions. Subsequently, I will report the practices that could be implemented in the future to facilitate the integration of clinical sequencing and the return of IFs.

6.2. Which results should be returned?

6.2.1. Actionability and other criteria

A diverse range of responses was given when experts were asked to identify the type of results they considered appropriate for return to patients.

All experts were in favour of returning medically actionable and valid results. Furthermore, experts from the USA and Greece were also willing to return any results the patient asked for as long as s/he had received counselling beforehand. In contrast, experts from the UK seemed in favour of limiting return to clinically valid relevant results.

Interestingly, experts talked about actionability in different ways. For most clinicians, actionability was understood strictly in medical terms, i.e. having a treatment available.

I really believe that we should still be thinking about medically actionable variants instead of variants that the family might think would be of personal utility. P27USCG

You know, personal utility has never been the purpose of medicine. It was never what it is. I think the idea of actionability, as the idea to change treatment, the medical actionability, is the way to go with this. This is the way we think in medicine. P23USCG

Alternatively, a small number clinicians considered that clinical significance could be used as a criterion.

No. I don't think it has to be actionable per se. I think it needs to be clinically significant. Actionable implies you only report stuff that's curable and I'm not necessarily sure that's the case. I mean I would be more careful about whether it had clinical significance.
P17UKCG

Genetic counsellors and experts with a legal background interpreted actionability in a broader sense and were in favour of returning results that could affect future reproductive choices or even results with personal utility for patients, i.e. anything that they would perceive as useful such as findings that could help them plan their future.

So reproductive choice is probably not medically actionable. It's psychologically actionable and we haven't clearly defined it I will say but I think we are thinking that we mean things like where there are screening options or its reaction to anaesthetics.
P14UKGC

Personal utility. People would want to know a lot of things because that would help them make decisions in their lives!! And that would be actionable for them. If they're going to die soon for example. But clinicians won't find that as actionable probably. They will see it as a medical term. P18UKLB

Contrary to the consensus observed regarding medically actionable results, some experts expressed very strong positions as to what types of results should not be returned. The age of onset seemed to influence their attitude and some considered that late-onset non-actionable results should not be returned.

I would not agree with returning late onset non-actionable conditions to children. That is completely off the table. And I am not convinced yet that we should return non-actionable results to adults either. Like Parkinson's, I am still not sure if this would have more benefits than risks at this point. P27USGC

As before some experts had a very strong opinion against returning carrier status¹². They considered that results demonstrating a predisposition should not be returned either as neither was considered as medically actionable. On the contrary, some experts, mainly Greeks, were willing to return carrier status as they found it potentially useful.

We're not feeding that back. We're not feeding back carrier status. P15UKCG

¹² please refer to appendix 1 for definitions

No, no, no, no, no. So nothing like that is a sort of predisposition or where there is that sort of level of contention about its predicted power and validity. P15UKCG

Yes, I know it is not medically actionable, but it [carrier status] be important for the patient. P08GRLB

Most experts considered that results with unknown significance should not be reported as they would cause unnecessary anxiety.

[W]e don't want to have unknown IFs or findings that are not actionable or that they don't have significance and that's not something we want to talk about. P25USGC

For unknown significance findings probably not, if something of unknown significance was found then we would investigate that further and try to find out what it's functional role was and then if it had no functional role we would forget it, if it had then we would incorporate this to validate it further and then perhaps feed that back . P20UKGC

Experts discussed different criteria that could be used to determine the type of results that should be offered to patients. Actionability was a revealing criterion, and medically actionable results were seen as appropriate for return. However, actionability was a contested term as different experts understand and define it differently. Apart from medically actionable results, other types of results, e.g. those with personal utility have been considered for feedback or carrier status, nevertheless, there is no consensus whether such a disclosure would be to the best interest of the patient. There are also differences according to the country, such as returning carrier status, which should be considered when creating points to consider.

6.3. What would constitute good practice?

6.3.1. Guidelines, a law or a list of results

All experts, regardless of their country or their professional background, expressed their need for a clear working framework. However, some differences were observed regarding the type of framework that they thought could or should be created for the future. Depending on their professional background and their country, experts were either asking for guidelines to be prepared, a law to be created, or a list of results that it would be obligatory to return.

Concerning the creation of guidelines, all experts asked for clear guidelines to support all parties involved in the return of IFs.

It would be really useful to have guidelines. I know we don't have guidelines for other more urgent things but this is also important. P09GRNLB

There are guidelines being prepared right now. And that's good because we definitely need them. P15UKLB

Interestingly, Greek experts also considered that a law might be useful to enforce the use of the guidelines as it would have a binding character that could force all parties to comply.

Taking into consideration how things work in Greece I think guidelines might not be enough. Maybe a law would be more appropriate. It would force people to respect it.
P01GRLB

Using the ACMG list of variants as an example, I asked experts whether they would prefer a list of results or more general guidelines. Most experts considered that general guidelines or guidelines describing the criteria to use would be more helpful than a list of results.

I wouldn't ever want a list and I think that may be where we go as a short-term, but list by definition creates rules which are procedural opposed to context dependent and that's the problem. Clinical practice is an art form in the sense that it's not the variant that determines your management, it's the clinical situation. P17UKCG

No, not a list. I would rather have the criteria to help me decide rather than the conditions or the variants. P06GRLG

They considered that a list would have several disadvantages, i.e. could never be conclusive; would be out-of-date very quickly; would not be dynamic; would be subjective as it would require a judgement about which conditions are “worse” than others; and it would be by definition incomplete.

They're just full of problems. There's also, you know, how do you define a list, you know, 'My disease is worse than your disease', or why do they stick with cancer and cardiac conditions on the whole? And as soon as you've defined that list, you've made a rod for your own back. It is a completely mental idea. P15UKCG

I think it's more helpful to have general guidance that sets principles rather than contains a prescriptive list of variants because that will, you know be out-of-date,

knowledge is changing so fast that understanding of conditions and of variants and of penetrance, you know, it will be out-of-date. So for me, you know, the general issues about, I don't know, reasonableness or sort of things that incorporate the clinician using their judgment and their knowledge of the family circumstances and all those sorts of issues are relevant and allow just decisions to be more subtle than just applying a list.

P16UKLB

Clinicians especially were against having a list as they considered that it would limit their clinical freedom and not allow them to base their actions on their professional discretion and make adjustments according to each case they faced.

We have very few absolute rules and I think where possible I would really encourage us not to have a list because a list a) it needs updating, it's not dynamic, and actually I think the management of people is dynamic and I don't think that's list-dependent. [...] but I can tell you there is always an exception and that's a clinical judgement of exception. Whereas if you had a list [...] then you actually lose the quality of what is called clinical practice. [...] I think it's much better to have a broad approach because our knowledge is moving at such a pace. Lists are intrinsically dangerous. P17UKCG

Not a list. We should be able to decide what to do according to the family we have in front of us. We are trained to do this and this is actually our job description. We need support not someone depriving us of our clinical discretion. P04GRCG

Interestingly, only some experts from the USA were in favour of having a list of variants that would be returned. This could be because they are familiar with having a list, i.e. the ACMG list. Those considered that a list would provide some consistency in the health services provided and it would facilitate the feedback process.

But what they are saying is that if there is not some consistency in the information that you get back you could make the wrong assumption along the line. So if you are a counsellor and you don't get back this information, these ACMG variants, you might assume that it was negative. And so for rationality sake, it is better to have some sort of consistent. So the lab should look at that [list] and that directs you to what the clinician should give back. P21USGC

And I really respect what they were trying to do. They used the ACMG [list of variants] as a checklist. So how the physicians are handling it, well if you really have the 56 then the lab can give you enough information and the clinician would know what to do. P25USGC

6.3.2. Counselling and support

As mentioned earlier, several experts argued that existing models of informed consent and counselling might not be appropriate for clinical sequencing, especially ES or GS. They discussed that patients and families should be informed and supported if IFs are to be returned.

Many experts considered that patients are not asking for detailed information about genetics but only want and understand the implications that results might have for them and their family. Clinicians, in particular, considered that patients need, above everything else, an honest approach and need to trust that their clinician is acting in their best interests.

I mean I don't think patients are really looking for a detailed Ph.D. level knowledge of genetics, genetic mechanisms, and disease. I think what they're looking for is honesty and openness and an understanding that you're going to do your best to find whatever it is that's causing their condition and most of the time they'll bite your arm off to try and get that answer. P15UKCG

Probably not! You don't need to understand the science of atherosclerosis just to know that cholesterol of 240 is bad for you. So, what level of hard information, factual information they need to grasp and what context they need to understand it in is what we need to figure out. P23USGC

Additionally, most experts, especially genetic counsellors and those acting as genetic counsellors (as in the case of Greece), considered that patients would get a basic understanding if whoever is informing them is patient and willing to spend enough time with them and adjust the counselling to their needs and characteristics.

Yes, they can understand it but their level of understanding depends on how much time you spend with them, how patient you are and if you can explain things in their level of understanding. P10GRCG

[L]ay beliefs about genetics are very powerful and so you can [...] give them all the risks if they actually don't align with their own personal beliefs they find it very difficult to incorporate it. [...] So when you have one-hour session to try to explain everything, all the science etc. And they had a lifetime of believing something different, it's very tricky. P11UKGC

Many experts, especially from the UK and the USA, underlined the need to be able to provide follow-up to their patients after providing them with results. They considered that deciding to give feedback was unavoidably connected to an obligation to be able to help them after that.

You have what we say they duty or the responsibility of helping them. If you hand them information you are responsible for making sure that it is in their best interest. And part of that means that you can't give information without access to resources. P21USGC

Especially in the UK, most experts considered that to integrate clinical sequencing into the health care service they needed to ensure that patients should be required to attend follow-up sessions. This is how their health system is working so far and they believed that this should continue.

If you feedback findings but then can't offer requisites and care and treatment, then that is an ethical issue. We have an obligation. This is how we do things here. P16UKNP

[I] think there is a lot of scope for causing a great deal of harm if these things are disclosed without the right amount of support. P12UKGC

US experts expressed concerns that the way their health system is organised meant they would be commonly providing results although there is no support for patients after that.

To tell people, family members, what's the risk etc. Nothing is set out for them. P21USGC

All experts regardless of their country or their professional background underlined the importance of genetic counselling. Most of them were in favour of an open and honest approach that would be necessary to try to convey hard scientific data that might be difficult to understand for a patient without previous knowledge of genetics. Many also suggested that spending enough time with a patient might be important while the need to provide them with follow-up was also highlighted.

6.3.3. Resources needed

When discussing counselling, the discussion tended to focus on resources. Especially for the Greek and the US context, experts were worried about access to genetic tests and covering the costs deriving from the test itself, the interpretation and the counselling. Experts from the UK suggested that rearranging the budget to promote prevention rather than treatment would be the best way to handle IFs while maximising limited resources.

...[T]he health gain for the individual does not offset the health cost for the system. So we can sort of incorporate a resource management that in some ways can be defensive but in some ways it can be quite dangerous. It can end up saying, "I know I could save this person's life from dying from ovarian cancer if I would tell them but then I would have to offer an expensive intervention to them and all other people so I won't say anything ". Allocate the budget!! P19UKCG

We have NHS here and that means that we need to make sure we have all the available resources before starting ordering NGS, especially knowing that IFs might come up. We need to find money to deal with patients' needs and support. P17UKCG

On the other hand, experts from Greece expressed their concerns that in a healthcare system with limited resources several steps that could lead to better practices might be considered as a "luxury".

It's not that I don't think this is important but we have so many things lacking right now that I don't know. Maybe this is a luxury. We need to find way to support families but how?! P06GRCG

6.3.4. Who to decide and who to disclose?

What seemed to be an alternative, even in limited-resource healthcare systems, is to have a multidisciplinary team (MDT) deciding about IFs and whether they should be returned. In this way, the burden of the decision could be shared across different professionals, while each one would bring his or her area of expertise, leading (at least in theory) to a better decision.

Have a multidisciplinary team. So that you come to a consensus based on the best available evidence and using the people who are sort of expert in that particular field rather than just thinking you can go and read up about it yourself and then you're the expert. P13UKCG

If you have IFs, especially if they are unusual or serious, I believe you need a team to decide. Having a geneticist or the ordering clinician deciding is not enough. The burden is too big. P03GRCG

There should be a "team approach". The team that is in charge to conduct the test should be also in charge to return results. P03GRLG

Ideally, a multi-disciplinary team should do it. P23USCG

Interestingly, although UK experts seemed to consider it natural to have an MDT in each clinic offering sequencing, Greek experts' opinions diverged on this point. Some would prefer to have an MDT in each clinic while others considered that one MDT could be created and act as an independent body without any connection to the clinics.

Everywhere we provide clinical sequencing, there should be an MDT deciding. P19UKCG

I would like to have an MDT in each clinic. Consisting of the ordering clinicians and other specialities such as geneticists, genetic counsellors etc. but inside the hospital for sure.

To have an idea of what is really happening. P03GRCG

I think that an independent body might be better. That would also save us some money.

Have some that would cover more than on hospitals. In that way, they would be able to be independent and make decisions unbiased. P02GRLG

All experts underscored the importance of having a person who is properly trained for this task but their definitions of "properly" differed. Clinicians believed that they were the most appropriate group, as they considered informing patients about test findings to be part of their professional role, while lab-geneticists and experts with a bioethical background thought that results should be disclosed by a multidisciplinary team. This team should consist of not only clinicians but also other professionals, such as lab-geneticists and clinicians specialised in the relevant condition (e.g. an oncologist if a cancer susceptibility gene is discovered). At the same time, most of the experts questioned the appropriateness of clinicians not specialised in genetics dealing with genetic tests and the results, especially when ES or GS is used. They were of the opinion that non-specialist clinicians lacked the expertise to explain the procedures and to provide appropriate pre and post-testing counselling.

Experts' professional background seemed to influence their answer; clinicians considered that they were better equipped to return results if a team is not available.

Clinicians' job has always been to take care of patients. To inform them about good and bad news. We have been trained to do so. We have a much better understanding of the conditions but also of how the human body works. P10GRCG

The ordering clinician probably. It would be best to be the clinician who had advocated the test and had consented the person in the first place. I think they would have the clearest duty to prevent any harm. And doctors don't only care about the condition you

came in with. Often they don't even know why you came in and the tests they do are often quite exploratory. Even outside the genetic consent. P17UKCG

Clinicians and a small numbers of experts with a different background also suggested that because the nature of genetic information is very complicated for lay people, it might be better to discuss it with a clinician, ideally the treating clinician or someone who has an existing relationship with the patient and his or her family. This would allow the clinician to be able to decide based on each specific case what could be offered and adjust the pre and post-test counselling accordingly.

This is a family that I know personally and in fact have known since the mid-1990s, known at the stage this happened for fifteen years since this child was herself a little girl. And so I felt that this was clinically a very important piece of information for this family [and I returned it]. P13UKCG

In contrast, all the other experts considered that a genetic counsellor might be more appropriate.

A genetic counsellor is better trained to deal with this. P21USGC

I think with what is happening here and from my experience working with genetic counsellors from research I absolutely think that genetic counsellors are best equipped. There are some very well-informed clinicians but clinicians are not always easy to understand. But genetic counsellors that their forte, that's what they do. They explain that very clearly. They are fantastic. P28USLB

An approach where two healthcare providers would collaborate was also suggested by many where a genetic counsellor would return the results together with the ordering clinician.

Well, I think that the physician of the person who got tested or the genetic counsellor or both should be involved. Certainly not the laboratory. It's really contextual. P27USGC

In the UK, there are suggestions that GPs be involved in the process of returning IFs. Most UK experts interviewed considered that GPs should not be involved as they do not have the required training or expertise.

We're very careful about how we're feeding this back, who we were feeding it back to. So we wouldn't go back to the GP. I mean I'd almost pick up the phone and phone the patient myself before I would call the GP. P15UKCG

As an exception, one UK expert considered that although GPs were not trained properly, they could still handle IFs. This expert believed that GPs would understand much more than the patients and they would therefore be in a position to help their patient to acquire a minimum understanding.

The good news is that doctors are very good in rapidly upgrading their knowledge when they need it. Be one step in front of the patient. And patients do understand that doctors are not walking computers. There might be the case that I would have to look up to something and go back to the patient. Doctors should be allowed to update their knowledge and then help their patients. [...] But they are definitely in a better position than patients. P19UKCG

The participation of a genetic counsellor in the feedback process was considered essential by everybody, regardless of their country of origin or professional background.

Genetic counsellors are the best people to disclose and maybe what we need to do is have more genetic counsellors. P18UKLB

Here we are also acting as genetic counsellors as well. There is no one else to disclose results. We would need genetic counsellors to do this work. They would be much better. P08GRLG

According to some experts, the role of a genetic counsellor is crucial to the process but this role is evolving and might have to change to include a more active role if clinical sequencing is to be integrated into clinical practice.

[H]aving time and being able to concentrate on it [is what they need]. [...] they will have to shift more to the area of working with people who have positive results or tests. Rather than explaining informed consent in advance. P21USGC

I think they are really great in educating families but I don't think they do as good job as they can to help them make the right decision for themselves. And helping them guide them through and find their way through the decision-making process. They should be able to do a better job than they do now. P27USGC

Even in cases where an MDT could not be in place, experts considered that the clinician or the geneticist returning results should be supported by a genetic counsellor.

You definitely need a genetic counsellor there. Especially if you can't have a team. The clinician might not be able to provide the necessary support by himself. P05GRLG

Some experts acknowledged the fact that there are not enough genetic counsellors available currently. They suggested that other specialities could be trained to be able to return results even if they do not necessarily have the formal title.

I think it is unrealistic to expect that a genetic counsellor would be attached to every clinic [...] and we don't have enough for that anyway. P11UKGC

Increasingly we need to teach other people who may be called genomicists to do it. They may be other sub-specialities that we have trained [...] to do this. Or we do it but we do not literally do it face-to-face. We need some way to educate the public and the providers. P22USCG

Overall, experts were in favour of having a multidisciplinary team deciding about IFs to be returned and leading the return process. If such a team is not available, clinicians believed that they should manage the disclosure while all other experts considered that genetic counsellors were better prepared for such a task.

6.3.5. When to return results

When discussing the best time to return findings once they are discovered, almost all the experts said that IFs should be returned immediately.

Yes, I would tell them right away. No reason not to. P05GRLG

I don't think why you would wait given that half of these genes are about cancer. What was the point of doing it in the first place if not to return it? Personally, I can't see the logic of waiting. P22USCG

However, some of them qualified their position by noting that, depending on the IF or on the circumstances of the patient, the feedback might have to be postponed.

...[I]f you had a situation where results were potentially related to the reason why you did the test then yes. There is no reason why you would not return it right away. If the result was unrelated when you would wait. P23USCG

Experts discussed cases where the patient is facing a life-threatening condition (e.g. cancer) and something unrelated is discovered while in treatment. They considered that in cases like this, IFs might have to wait until the patient overcomes the current health problem and is in a position to receive unexpected news.

If I discovered something in a cancer patient and it was not related then no I wouldn't return it right away. I would wait. To finish with his treatment. He is facing too much already. I wouldn't want to put more on his shoulders. P04GRCG

6.3.6. Additional ways to improve feedback practice

In addition to all the steps mentioned above, some experts also suggested several improvements that could be made to help all stakeholders involved to deal with IFs.

These included having a bioinformatician to support decision making by providing more detailed interpretation of the data, or a psychologist to help patients come to terms with the results, or to support the process of sharing results with family members.

Interpretation needs technical support, that is, having someone who is good at bioinformatics would make a huge difference. P11UKGC

It would be a great help to have a psychologist to help us. And help the families too. A clinical psychologist specialised to genetic tests. That would make things much easier. P10GRCG

Other suggestions included the preparation of information leaflets for patients or videos that would help patients to come to the pre-counselling session better prepared and with specific questions. That could reduce the time required and help patients get a better understanding of the process.

We need to inform patients and potential users too. An information leaflet would be useful. In that way, they would know some basic things before coming. P09GRLG

A video might be extremely useful as it would help patients come in with specific questions. And we would also make sure that everybody gets the same information. Nothing would be left outside [the consultation?]. P22USCG

Outreach activities, especially targeting specific groups, e.g. patients' support groups, and communication between different healthcare providers would also be beneficial.

I think in Greece we need to start with a dialogue. Not only among professionals. We should invite patients too. A discussion that could provide some data to help a scientific or professional body to prepare guidelines. P09GRLB

As discussed in earlier chapters, experts interviewed here also considered that more empirical research is crucial to clarify people's understandings and needs.

We need focus group or a qualitative study to try [...] understand what they [patients] are using to decide whether something is worth returning. [...] I think that is part of what we would like to figure out qualitatively. I think it's an open question to see if they really need to understand, I mean what do they need to understand in order to make this decision. Do you really need to understand the science? P23USCG

[B]ut most fundamentally I believe we need empiric data to understand how most clinicians, the clinicians that are going to do the follow-up, and most patients, how they would find it most useful to categorise results. I think that's a really important body of work that we need to do. P26USCG

6.4. Chapter Summary

Whilst a consensus emerged across experts regarding the return of medically actionable results, no agreement could be reached regarding other types of results. Many experts considered an approach where only medically actionable results are returned as very restrictive. Experts' background seemed to be a significant indicator affecting their perspectives regarding the type of results that should be fed back to patients. Conversely, their background did not affect the differences observed when experts were discussing the practicalities around best practices and future implementation of clinical sequencing. Differences observed could, however, be attributed to available resources and to the healthcare system of each country.

The next stage of my work was to combine these findings with the available literature and identify the issues that I felt needed to be explored more specifically. I used these points in my questionnaire asking about Greek geneticists' awareness of IFs; their intention to use clinical sequencing; and the actions seen as necessary to facilitate the process.

Building on the research questions presented in section 2.7., following the conduct and analysis of the interviews, I formulated the following research questions to guide my design of the questionnaire:

- i) In what way are Greek geneticists' perceiving clinical sequencing and which are their attitudes regarding its usefulness and the possibility of returning results?
- ii) How could Greek geneticists be supported to offer clinical sequencing and return IFs?

For example, the majority of experts interviewed here were in favour of returning IFs but some only wanted medically actionable results returned, while others would be willing to return other results such as those that could inform patients' reproductive choices. Therefore, I included a question asking specifically which types of results should be returned. I also found that Greek experts were more likely to want to return carrier status information, which differed from those in the other countries. These and other findings from the interviews were directly translated into questions and multiple-choice answers for the questionnaire to provide more evidence and confirm what issues were important and applicable for Greece. These are presented in the next chapter.

CHAPTER 7: RESULTS FROM QUESTIONNAIRES – INVESTIGATING GREEK GENETICISTS' ATTITUDES

7.1. Chapter outline

This chapter presents Greek geneticists' perspectives on the usefulness of clinical sequencing and their attitudes toward the return of IFs. These perspectives are derived from the results of the online questionnaire sent to all registered Greek geneticists. These findings, combined with evidence from the literature and findings from the qualitative phase are used to inform the discussion about the guidance that should be prepared for Greece. Geneticists are those who will be asked to consider and offer, where appropriate, clinical sequencing, therefore, their input was considered vital.

The results are first briefly described and then tables and figures are presented, where necessary, to illustrate agreements and disagreements. The results are loosely presented in the order questions were asked in the questionnaire.

The complete questionnaire can be found in Appendix 2.

7.2. General Results and Participants' Characteristics

As described earlier (see chapter 3), all registered Greek geneticists were invited to participate in an online questionnaire (see Appendix 2 for the translated version of the questionnaire). At the time of the survey, HAMG had over 180 members while HSMG had 43 members.

As reported by the contact person from each association, at the time of the survey, HAMG had a mailing list with 170 contact details for their registered geneticists to whom all emails were forwarded. HSMG had a much shorter list of 34 email contacts. Therefore, in total, 204 Greek geneticists were invited to participate. The number of geneticists that actually received the invitation or the reminders, due to practical barriers (change of email address, classification of email as spam etc.), is unknown as there was no personal communication with participants and the questionnaire was anonymous. The response rate has, therefore, been calculated assuming that all members who had provided the two associations with emails received the survey invitation.

The online survey remained open for two months and at the end of the second month, the survey was closed and downloaded from the server. At the end of that period, 51 geneticists had completed the questionnaire, giving a response rate of 25%. The response rate, although relatively low, was considered acceptable for an online questionnaire (as lower response rates are often observed in online questionnaires, see chapter 3.3.4.1. for more information). This might be attributed to the fact that ES and GS are still considered as novel technologies in Greece. Clinical sequencing is still rarely used and many geneticists might have very limited experience in this area and, hence, they might have considered that they had nothing to contribute. Additionally, as the HAMG (which has the most members) relies on professionals to self-assess their identity as “geneticists”, some of them might be less familiar with ES and GS tests, and, subsequently, considered themselves as not appropriate to provide professional views on the matter.

The vast majority of the responses (48 out of 51) were collected during the first month and only three more geneticists completed the questionnaire in the second month. An increase of responses (eleven responses within 24 hours) was recorded after the first reminder but, after the second reminder, only four more people completed the questionnaire in the 24 hours that followed.

As illustrated below, the majority of participants were females (72.7%) and well educated with 68.2% having a Ph.D. Most geneticists worked in a laboratory or a university (32.6 and 41.9% respectively) and were mainly lab-geneticists and oncologists (23.8 and 35.8% respectively). Participants’ demographic characteristics are presented in table 5.

Table 5: Participant demographic characteristics

Demographic characteristics	%
Gender	
Female	72.7
Male	27.3
Age (years)	
≤30	23.3
31-40	23.3
41-50	25.6
51-60	20.9
61-65	2.3
>65	4.6
Having children	
Yes	52.3
No	45.5
I would prefer not to say	2.2
Workplace	
Hospital	11.6
Labouratory	32.6
University	41.9
Other research setting	9.3
Other (please specify)	4.6
Specialty	
Clinical Geneticist	11.9
Genetic Counsellor*	4.8
Lab-Geneticist	23.8
Oncologist	35.8
Paediatrician	14.3
Other	9.4
Highest degree	
Bachelor's degree (e.g. BA)	9.1
Master's degree (e.g. MSc, MA)	22.7
PhD	68.2

* Greek experts acting as genetic counsellors were grouped according to their primary specialty while only those trained abroad and who had an official title of Genetic Counsellor were included in this group.

7.3. Attitudes towards IFs and medical information deriving from ES/GS and other medical tests

The vast majority of geneticists (over 97%) were aware that IFs could be discovered during clinical sequencing using ES or GS and they were also aware of the possibility of discovering IFs when other medical tests are performed.

They believed a variety of tests could produce IFs including prenatal tests, imaging tests (MRI, scans, and x-rays) and simple blood tests. Results are summarised in table 6.

Table 6: Awareness and attitudes toward IFs from medical tests and ES/GS

Awareness and attitude of participants	%
Awareness toward discovering IFs when using ES/GS	
Yes	96.1
No	3.9
Possibility of discovering IFs from other medical tests	
Yes	94.1
No	3.9
I don't know	2.0
Tests that could produce IFs	
Blood tests	78.0
Prenatal tests	92.0
MRI/ Scan / x-rays	90.0
Other tests	18.0

For Greek geneticists, genetic information was seen as different from medical information deriving from other medical tests (76%), while only 12% of them considered that they were similar (see figure 12).

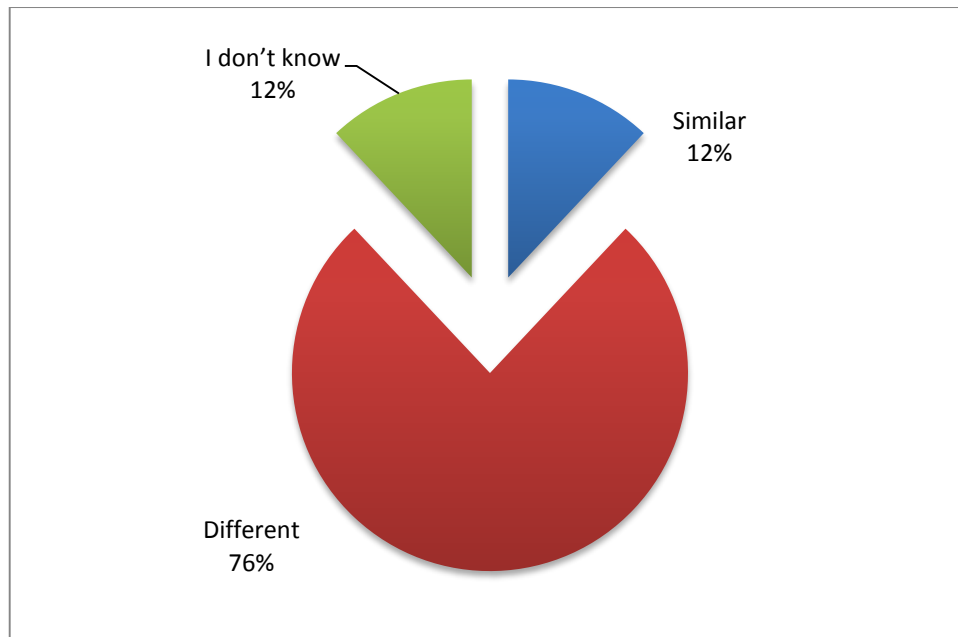


Figure 12: Comparing genetic information to information from other medical tests

Participants were then asked, using an open-ended question, to describe the way in which they considered genetic information to be different. The most commonly mentioned replies received were synthesised as follows: “genetic information does not have a linear relation to phenotype” i.e. carriers might never have symptoms; “genetic information involves more people than the patient” (mainly children and siblings); and “genetic information is more certain than other medical information”. Other reasons mentioned, included genetic information being more complicated; its interpretation being more challenging; it reveals the cause of a condition; and the information revealed requires a stricter framework of confidentiality.

7.4. Types of findings that should be returned

To investigate the criteria that geneticists thought would be appropriate to use when deciding which IFs are to be returned, several types of possible IFs were described. The categories chosen correspond to the descriptions of results that the experts discussed during the interviews and was asked to explore different aspects of actionability. A 5-point Likert-scale (Strongly Agree-Agree-Neither Agree nor Disagree- Disagree - Strongly Disagree) was used to facilitate the data collection and analysis.

Answers and percentages are presented in tables 7 and 8.

Table 7: Types of results to be returned to patients

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
life-threatening and preventable/ treatable	43 91.5%	3 6.4%	0	0	1 2.1%
life-threatening and not preventable/ treatable	20 42.5%	14 29.8%	11 23.4%	1 2.15%	1 2.15%
life-threatening, late-onset and preventable/ treatable	37 78.7%	8 17.0%	0	0	2 4.3%
serious (but not life-threatening) and preventable/ treatable	33 70.2%	11 23.4%	2 4.3%	0	1 2.1%
serious (but not life-threatening) and not preventable/ treatable	18 39.1%	14 30.4%	12 26.1%	1 2.2%	1 2.2%

As illustrated above (table 7), Greek geneticists consider that medical actionability is the most important criterion. Over 92% of them agreed (or strongly agreed) that medically actionable results should be returned, regardless of whether they concerned life-threatening, serious or late-onset conditions. Fewer geneticists considered that non-medically actionable results should be returned; however, the percentage remains high, with 72.3 and 69.5% agreeing that results for life-threatening and serious conditions respectively are appropriate for disclosure.

In a similar way (see table 8), when geneticists were asked to choose other results to offer to patients, pharmacogenetics¹³ [376] were chosen by over 95% of geneticists, followed by information about carrier status¹⁴ relevant to their children or their reproductive choices, with 93.4 and 91.3% respectively, agreeing that carrier status relevant to (patients children or their own) future reproductive choices should be returned. This confirmed comments made during the interviews. The return of not immediately relevant results received an agreement of almost 70% while, interestingly, 23.9% agreed that uncertain results¹⁵ should be returned.

¹³ Genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.

¹⁴ An individual who has a recessive, disease-causing gene mutation on one chromosome of a pair and a normal allele on the other chromosome thus not displaying that trait or show symptoms of the disease.

¹⁵ Results with unclear clinical utility and validity, usually that do not have a clearly demonstrated link to a phenotype or disease.

Table 8: Other types of results to be returned to patients

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
That demonstrates response to different medications or drugs (e.g. statins, anti-depressants etc.)	33 71.7%	11 23.9%	1 2.17%	0	1 2.17%
Tells if the patient is a carrier of a condition that could be relevant to his/her children	37 80.4%	6 13.0%	1 2.17%	1 2.17%	1 2.17%
Tells if the patient is a carrier of a condition that could be relevant to his/her future reproductive choices	34 73.9%	8 17.4%	3 6.5%	0	1 2.17%
Is not immediately relevant to the patient but could be useful later in life (e.g. relating to a very late onset cancer or predisposition to stroke)	19 41.3%	13 28.3%	8 17.4%	2 4.4%	4 8.8%
Is uncertain and cannot be interpreted at the moment	6 13.0%	5 10.9%	15 32.6%	7 15.2%	12 28.3%

Contrary to the experts interviewed in the qualitative stage, Greek geneticists were more willing to return a number of results and did not limit themselves to only medically actionable results. The high percentage of geneticists willing to report non-medically actionable results, especially when they concerned carrier status, might relate to the fact that in Greece two recessive conditions (β -thalassemia and Cystic fibrosis) are highly prevalent among the population. In Greece, carriers of β -thalassemia could represent 5%-14% of the population (depending on the area) [377], while for Cystic fibrosis, 4% of the population is estimated to be a carrier [378]. Greek geneticists' willingness to return results about carrier status, keeping these two conditions in mind, could explain this phenomenon as they might consider this information to be important for their patients; for their own reproductive choices or out of interest for their children. Furthermore, taking into consideration that patients are currently paying for tests themselves, geneticists might consider an ES test as an opportunity for their patient to receive as much information as possible, and, therefore, this might be another reason why they seem so willing to return several types of results, even results that are uncertain.

7.5. Decision making and feedback process

Regarding the decision-making and feedback process, the majority of Greek geneticists preferred to have a multi-disciplinary team (MDT) to assist them, 41 and 31% respectively (figures 13 and 14).

When it comes to decision making concerning which IFs should be fed back (figure 13), lab-scientists and genetic counsellors were seen as appropriate by 17% and 15% respectively and only 8% of geneticists believed that the treating clinician should be making this decision. Eleven percent of geneticists believed that the patient should be included in the decision-making process. Eleven percent of geneticists believed the patient should be included in the decision-making process.

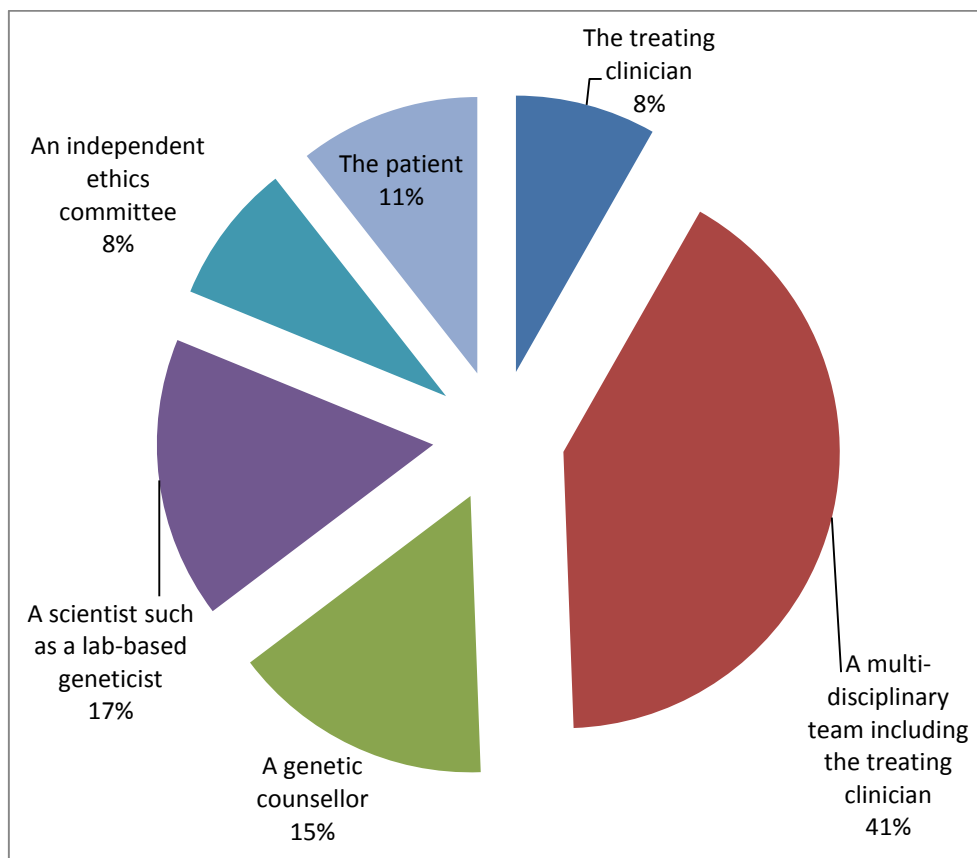


Figure 13: Who should decide about which IFs should be reported?

Regarding the feedback of results, either a genetic counsellor or a lab-geneticist was considered as appropriate by 27% and 20% of geneticists, with 31% preferring an MDT to feedback results (figure 14).

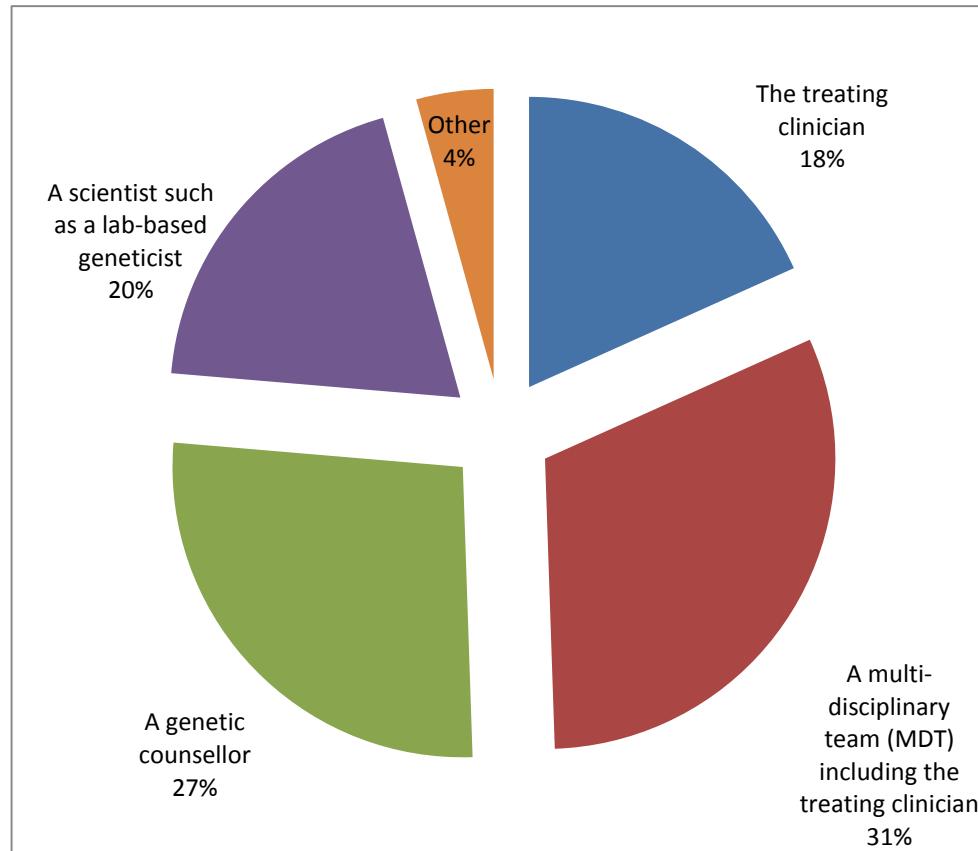


Figure 14: Who should be in charge of the feedback process?

Whilst in the interviews experts were mainly in favour of an MDT to return results, and alternatively (if there is no MDT), a clinician or a genetic counsellor (depending on the background of the expert asked), here, geneticists' perspectives are less clear. They would still like an MDT, but the agreement was far from unanimous. Individuals, such as a lab-geneticist or someone acting as a genetic counsellor, were seen as appropriate people to return results. This divergence could be explained by the fact that the questionnaire focused on the Greek context where MDTs are not available and, potentially, Greek geneticists were being pragmatic and proposed more realistic answers.

Furthermore, it is worth reiterating that almost one out of four geneticists that completed the questionnaire was a lab-geneticist and several of these are likely also to be acting as genetic counsellors to cover the lack of formally trained genetic counsellors in Greece. This might provide

some insight as to why they consider themselves capable of being involved in the decision and feedback process.

Clinicians' perceived lack of understanding of genetic tests might be partly the reason why treating clinicians were not the preferred group to make decisions or return findings. It is also worth mentioning that clinicians receive minimal training in genetics during their formal education (undergraduate studies). Interestingly, a significant number of geneticists considered that the treating clinician, although not appropriate to lead the decision making, should be included in the feedback process. This finding could be predicated upon the existing relationship between the patient and the treating clinician, i.e. geneticists might consider that if there is a relationship in place already, then the treating clinicians might be able to facilitate the feedback as (s)he would know more about the patient and his/her preferences and needs.

When geneticists were asked to describe the best possible way to return results, there was a unanimous feeling that IFs should be returned in a face-to-face consultation (100%). They all considered that this was the most appropriate way to return these findings and only a few of them were willing to accept any alternative method. Only 8.5% would be willing to return IFs over the phone, and only 2.1% would be willing to use a secure online database, post or any other method to return results if face-to-face consultation was not possible.

7.6. Attitudes toward using ES and the possibility of discovering IFs

Geneticists considered that exome sequencing would help them get a diagnosis (82.2%) and generate other medically useful information (66.7%). Interestingly, almost half of the geneticists (45.6%) saw ES as a good opportunity for other family members, apart from the patient, to gain access to information (table 9). Surprisingly, more saw this as a potential benefit than those who considered that the patient would have access to information about himself/herself. This might suggest that geneticists who participated in this study consider that genetic information is shared across the family, and, therefore, that potential benefits should also be shared and they considered this as an important characteristic of clinical sequencing.

Table 9: Potential benefits from using ES/GS

Potential benefits from using ES/GS	%
Will help me get a diagnosis for the primary investigation	86.9%
Will generate medically useful information other than for the primary investigation	67.4%
My patient will learn information that could benefit other members of his family	45.6%
My patient will learn information about himself/herself	39.1%

Although they perceived that ES could have several benefits, they were very concerned about their patients' ability to manage the results (79.6%) and their own ability to interpret results from ES (77.3%). They were also concerned about the high cost of the test (59.1%), which is not surprising given that, currently, the insurance cover for genetic tests is limited, if any exists at all (table 10).

Table 10: Potential concerns from using ES/GS

Potential concerns from using ES/GS	%
My patient might not be able to handle the results	80.0%
I will not be able to interpret results	75.6%
High cost	59.1%
My patient's family might not be able to handle the results	57.8%
It might reveal unrelated findings	44.4%

For more than half of the geneticists (54.6%), their willingness to order ES is affected by the possibility of discovering IFs (figure 15).

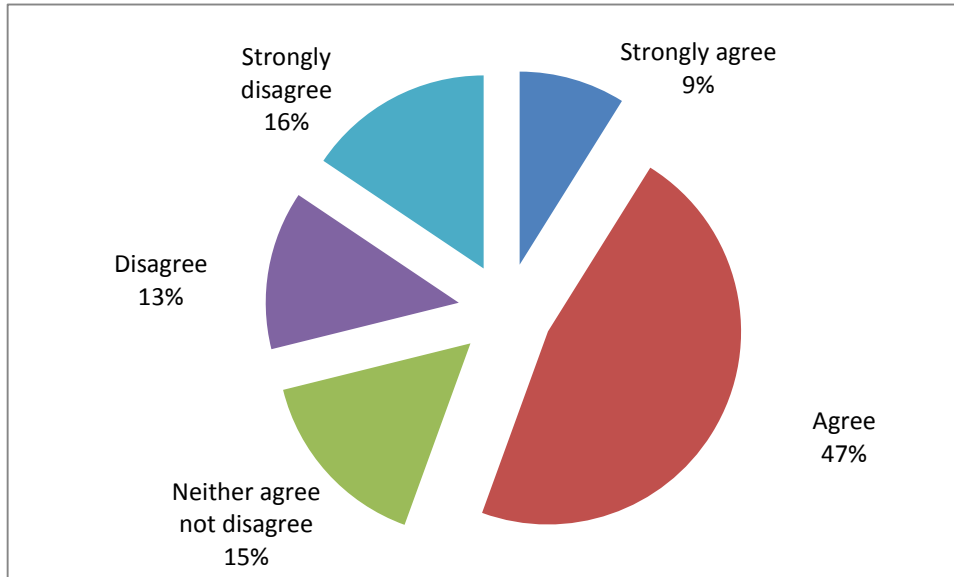


Figure 15: "The possibility to discover unrelated findings would influence my opinion to order an exome/genome sequencing test"

Exome and genome sequencing were considered by Greek geneticists as potentially useful as they could offer information for both the patient and his/her family. However, several concerns were also expressed, such as those listed in table 10 and the possibility of discovering IFs was among them. Although this possibility is only one of the concerns raised it appeared to influence geneticists' intention to order ES/GS tests (figure 15).

7.7. Future actions to support the discovery and return of IFs

Greek geneticists were in favour of receiving recommendations (95.4% agreed or strongly agreed) to support them with the discovery and feedback of IFs. They also considered that a legislation might be useful (72% agreed or strongly agreed), while they thought that having an MDT to support them locally would also facilitate the process (83.7% agreed or strongly agreed).

Table 11: Best way to support professionals when IFs are discovered

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
A law should be created	17 39.5%	14 32.6%	5 11.6%	5 11.6%	2 4.7%
Recommendations should be prepared	28 63.6%	14 31.9%	2 4.5%	0	0
A team of clinicians should be put in place locally to deal with cases one-by-one	6 15.8%	8 21.1%	12 31.5%	8 21.1%	4 10.5
A multi-disciplinary team should be put in place locally to deal with cases one-by-one	24 55.8%	12 27.9%	5 11.6%	2 4.6%	0
Clinicians and others should be required to return only the results on a specified list'	6 15.4%	11 28.4%	11 28.4%	6 15.4%	5 12.8%

“Having a list of results to return” and “having a team of clinicians to deal with cases locally” were the least preferred choices when geneticists were asked to describe what should be done to support them with IFs (table 11).

Greek geneticists preferred to have an MDT consisting of professionals and patients' representatives preparing the guidelines (73.9%) but would also accept the guidelines being prepared by a professional body such as the HAMG or the HSMG (60.9%) or the National Bioethics Commission (60.9%, table 12).

Table 12: Who should prepare guidelines/ or a list of results?

Who should prepare guidelines/ or a list of results	%
A multidisciplinary group consisting of professionals and patients' representatives	73.9%
A professional body e.g. HAMG	65.2%
The National Bioethics Committee	60.9%
Anyone as long as they are created	2.2%
Every clinic/labouratory should create its own	0.0%

Finally, geneticists were asked to choose a term to best describe the term “incidental findings” in Greek. There was no agreement among geneticists as to what would be the most appropriate term. The term “τυχαία” (which translates as “random”), the term “απροσδόκητα” (which translates as “unexpected”), and the term “μη-σχετικά” (which translates as “unrelated”) were the suggested alternatives and they all received between 26-33% (figure 16).

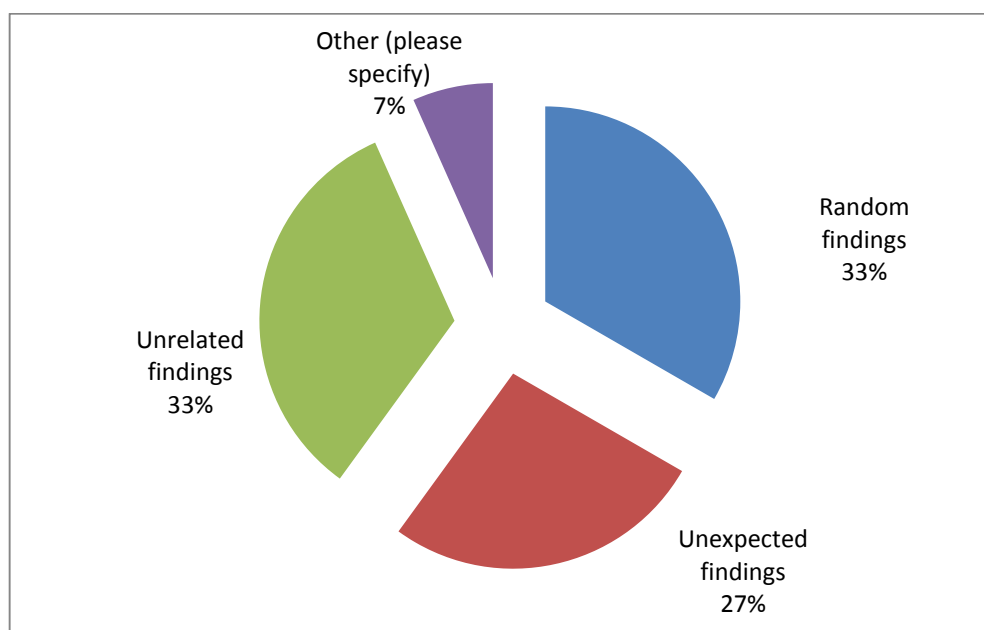


Figure 16: Best term to translate IFs in Greek

Another term was suggested by the geneticists, this was the term “πρόσθετα ή επιπλέον” findings (which translates as “additional or extra”). As observed in the international literature (see chapter 3), choosing one term to describe all type of findings might be challenging. This difficulty is also

illustrated here, where there was no consensus about the most appropriate of a variety of possible Greek terms to use. Some of the Greek terms focus on the unrelated character of the finding in comparison to the primary or diagnosis-related findings, while others focus on their unintentional discovery. Choosing one term might not be feasible, at national, i.e. Greek, or international level.

At this point, it should be mentioned that the term used for the questionnaire was “τυχαία και απροσδόκητα” (which translates as “random and unexpected”). These terms were used in combination to describe IFs as these were the terms suggested during the interviews as the most appropriate.

7.8. Chapter Summary

In this chapter, I have presented the findings from the online questionnaire. All registered Greek geneticists were invited to take part. The term geneticist was used to include all professionals working in the area on and around genetic and genomic tests. Lab-geneticists and oncologists were the most common respondents. The sample was characterised by professionals with a very high educational level, evenly distributed across the age range and mostly consisted of women.

Greek geneticists were aware of the possibility of discovering IFs from ES (and other medical tests) and would be willing to use it in the future as they see it as a potentially useful resource for the patient and his/her family. However, they were reluctant to use these tests as they were concerned about the interpretation of results, patients' ability to deal with the results and their high cost. Furthermore, the possibility of discovering IFs appeared to influence their willingness to use them. In situations where the tests had been ordered, geneticists were willing to return a variety of results. Contrary to evidence from the literature and the interviews, Greek geneticists were willing to return results of personal utility including carrier status or results that could affect patient's reproductive choices. The limited availability and high cost might explain why Greek geneticists seem willing to use the tests to collect as much information as possible.

Greek geneticists focused on their potential usefulness for the future and asked for a clear framework to be created to allow and facilitate such an integration. Moreover, as they saw this as a one-time opportunity for their patients, they would choose to return any results that could be of any use, medical or otherwise.

CHAPTER 8: DISCUSSING THE FINDINGS

8.1. Chapter outline

Chapter 8 discusses the findings of this project, along with their implications. After briefly underlining the particular characteristics of genomic IFs, I move on to the challenges emerging from the feedback process. Concerns raised by the professionals who participated in this project and problems deriving from the discovery of IFs are iteratively discussed with the literature aiming at highlighting potential management approaches. Finally, areas, where consensus was reached across professionals, are presented and the chapter closes with the description of a model that could potentially be implemented in Greece and elsewhere. Details regarding its implementation will be described in detail in the next chapter.

To facilitate the discussion, my results are discussed with findings from other studies and are presented thematically, loosely reflecting the themes emerging from the interviews and the questionnaire. Minor repetitions might be observed as actual and future practices are presented separately to mirror the themes from the interviews. Those who completed the questionnaire are referred to as 'respondents' in this section.

8.2. General thoughts about exome and genome sequencing and the discovery of IFs

The use of clinical sequencing and the management of IFs has been discussed as shown in previous chapters (chapters 1 and 2). Regardless of the concerns expressed, recently published results from the Baylor College of Medicine's Whole Genome Laboratory (one of the leading institutions for genetic tests in the USA) show that ES might prove to be a valuable tool in the diagnosis of patients with a suspected, yet undiagnosed (using traditional tests), genetic condition [8]. Similarly, genetics professionals also see clinical sequencing as a powerful tool that could

provide them with useful information on their patients' health [18]. The interviewees and respondents who participated in this project all considered that clinical sequencing could reveal information that would help them get a diagnosis for the primary indication for which the test was performed and offer them other information about their patients (and their families). Experts discussed cases where clinical sequencing has enabled a diagnosis where other tests have failed to produce results. However, the use of clinical sequencing seemed to be strongly linked, in their minds, to the discovery of IFs, which confirms the existing literature.

Interestingly, this link appears to discourage professionals from using ES, although they all agreed that IFs are not a phenomenon solely associated with genetic and genomic tests. They all acknowledged that other types of tests, such as imaging tests or prenatal tests, had the potential to produce IFs. For example, commentators in the literature have used different examples of tests that could produce IFs, ranging from a simple blood test [37] to radiology tests and Chromosomal Microarray analysis (CMA [379, 380]). Nevertheless, participants and commentators considered that genomic IFs require special consideration as, among others, they both provide information about potential future conditions [35] and reveal information about other family members [17, 18, 35, 178, 381]. One key issue that appears to differentiate genomic IFs from other IFs is to find ways to include and share this information with family members [17, 18, 35, 93, 102, 178, 200].

For the time being sequencing is not used very often and IFs are rarely discovered. The frequency of exome and genome sequencing varies across countries, reflecting country-specific characteristics, availability of equipment and awareness of its potential by healthcare providers. However, the accumulation of evidence suggests beneficial outcomes when using ES and lower costs are leading toward the most frequent use of ES in the clinical setting. However, my research has shown that while experts use their previous experiences and practices to help them with this issues, these are not sufficient to fully guide the management of genetic and genomic IFs.

Therefore, I believe that there is a need for a clearer or more comprehensive framework, and its creation should be prioritised. Furthermore, I also found that topic-specific training, offered to all healthcare providers directly involved in clinical sequencing, and potentially be expanded to all medical specialties, would help clinicians to develop a better understanding of the uses of genetic and genomic tests [17, 18] and encourage them to use them for the benefit of their patients.

8.3. Feedback process and challenges deriving from the return of IFs

8.3.1. Concerns deriving from practical difficulties related to exome and genome sequencing and their IFs

I found that the discovery of IFs, and particularly their return, created numerous issues for experts, deriving not only from the nature of the results themselves but also from constraints imposed by the frameworks available for them to use. Two major issues were raised by professionals related to their perceptions about challenges deriving from ES and return of IFs.

First, the experts interviewed reported concerns about their understanding of genomic information. Greek geneticists, similarly to other professionals [204, 382] and lay people [383], raised concerns about their limited understanding of genomic information and their lack of training to keep them up to date with new advances in the genomic era [384]. This self-reported questionable readiness [18] might affect the integration of genomic tests into the clinical settings or even harm patients if clinicians offer inappropriate tests, or if they do not offer tests that could provide patients with a clearer and quicker diagnosis. Nevertheless, to the best of my knowledge, before my study there was no empirical data published investigating or evaluating clinicians' knowledge (especially for non-specialised clinicians) about genomic information, common misunderstandings and their ability to interpret genomic results.

Second, both experts and Greek geneticists discussed the challenges of the interpretation of data and expressed their concerns in this regard. All groups, except lab-geneticists, openly talked about their fears regarding the use of novel tests that they do not fully understand nor are able to interpret. Challenges in the interpretation of genomic tests reveal the need for further research that would allow clear associations between variants and phenotypes [136, 385, 386]. An interesting example can be drawn from a paper on the return of results from research that could also be relevant to clinical sequencing. Kocarnik and Fullerton have noted that current recommendations do not take into account pleiotropy¹⁶[387]. As one gene might be responsible (or associated) with more than one phenotype, these phenotypes might be categorised into different categories. This would make the classification even harder since the same variant might

¹⁶ the phenomenon according to which one gene might influence multiple, potentially unrelated phenotypic traits

be classified under bin 1 [136], and, therefore, considered as reportable for its association with one condition, and, at the same time, under bin 3 for another, which is not reportable. This example illustrates that the better scientists become in interpretation, the more chances there are of discovering pleiotropic findings. Ignoring such mechanisms might lead to an incorrect diagnosis, thus causing patients to undergo additional treatment or treatment for the wrong condition, adding in this way one more challenge to the feedback process [387]. This recent publication underlines how clinical practices should not be based on the mistaken idea that we fully possess a complete knowledge of genetics and genomics. It demonstrates that due to the limited understanding of genomics, as mentioned by experts, several issues might be disregarded and might gradually emerge, thus creating more problems with data interpretation and results management. Additionally, yet unpublished studies reveal difficulties in defining which mutations are deleterious as mutations that appear benign in one population might be shown to be deleterious in another [personal communication]. Accumulating evidence shows that genetics and genomics are not usually as “clear-cut and highly determinative” as have been portrayed by public beliefs and the media [164] and exposes difficulties in creating a list of deleterious mutations that should be fed back in a bid to minimise lawsuits and be up-to-date.

Creating ways to ensure that new knowledge is circulated quickly and efficiently could help to avoid such problems. International consensus, international collaborations [35] and open access publications and databases might prove helpful in avoiding such issues (see 8.5). This will be especially important for Greek clinicians where resources are limited. This recent publication by Kocarnik and Fullerton also demonstrates that any guidance produced will have to be updated regularly to keep up with scientific discoveries. Following the ACMG’s suggestion, guidance might even have to be updated yearly to ensure that it will be up-to-date and reflect current scientific knowledge. The need for an annual update of guidance would lead to the need for continuous training for clinicians and other healthcare providers involved. Professionals will need to be up-to-date with new variants and newly discovered associations and a model where they are only trained once is insufficient nowadays to keep up with the fast pace of scientific developments. Any guidance created will have to incorporate this need and ensure a high quality of service is provided by supporting continuous education through seminars, meetings and inter and intra-disciplinary communication. Based on this, I believe that is important for me to include points about continued education and training in my points-to-consider.

8.3.2. Theoretical, ethico-legal and social concerns deriving from the familial nature of genomic data

Adding to the more practical concerns mentioned above, several concerns have been raised of an ethico-legal-social character. These concerns will shape the theoretical principles upon which guidance and regulation are going to be built and will provide ideas for best practice in the future.

What seemed to be crucial for all participants in my study was that IFs from clinical sequencing could have implications for the health and wellbeing of patients' family members, as genetic information is shared across the family. Genetic and genomic tests are seen to reveal information that is "personal yet at the same time often familial" [178, p.5] and those who participated in my study saw that as is a major difference from other medical information.

8.3.2.1. Potential for stigmatisation and discrimination based on genetic and genomic data

A number of experts interviewed expressed concerns that patients might be discouraged from using clinical sequencing, receiving IFs, and particularly sharing results with family members out of fear of being discriminated against or stigmatised. The literature has discussed potential discrimination and stigmatisation due to genetic findings in patients. In particular, potential discrimination and stigmatisation have been discussed in other studies about receiving results from clinical sequencing [200, 205], or participating in research [80]. However, the experts interviewed here mainly focused on their patients' fears of being stigmatised within their own family rather than within society, which has been little discussed [175, 388-390]. They reported that this is a very important reason why patients are reluctant to share these results with their family members.

Stigmatisation has been discussed in several contexts (e.g. mental health or health insurance [391-394]) and specific cases have been elaborated such as the issues deriving from stigmatisation in relation to disclosure of HIV status [395-405]. Examples could be drawn from this literature when strategies about feedback are considered in populations where stigma might be more common in order to encourage the use of diagnostic tests and minimise stigmatisation of diagnosed individuals. Regarding stigmatisation within the family, there are limited steps that could be taken. During informed consent and counselling sessions patients should be supported to understand the implications that genomic results may have for their family members and should be encouraged to share where necessary. That is why relevant points have been introduced in the points-to-consider presented in the next chapter. An alternative way to encourage communication within

the family without exposing sensitive information could include the anonymisation and then the sharing of results [178], although, due to the nature of genetic information, this might be particularly challenging. For the time being, it remains up to the patient to make the final decision. Guidance, such as my points-to-consider, will have to take this into consideration. Professionals should ensure that patients understand the potential implications that test results might have for their family members, taking into account patients' personal, religious and other beliefs.

8.3.2.2. Is there an (legal) obligation for professionals to share genomic results with family members?

From this familial nature of genomic information, a number of obligations might emerge. But what, if any, are the legal obligations of healthcare providers? Experts told me that, for now, their obligation is limited to informing patients in advance about the potential for IFs being discovered and asking for their preferences regarding sharing options.

Concerns were expressed regarding the expansion of providers' obligations and, especially, regarding informing family members of the discovery of health-related IFs in the absence of (or contrary to) patients' expressed preferences. Examples coming from other medical areas make these concerns very realistic. There are court cases in the UK, as previously discussed, that begins to raise the possibility of an obligation on clinicians to inform family members of genetic diagnoses. Persons of interest (family members or partners) have legal access to test results in cases of HIV patients in the USA and Canada [406, 407]. Similarly, as a practice to protect the public interest, even overriding patient's confidentiality, most countries, including Greece and the UK, have a list of infectious diseases that, when diagnosed, the clinician has an obligation to file a report on regardless of the patient's preferences [372, 408]. For the time being, there are no legal actions to suggest such a right in the context of genetic tests. Nevertheless, such a precedent should be regarded when discussing obligations toward sharing of results as such legal cases might be used to resolve litigations. Furthermore, official recommendations issued by the Australian government provides "a lawful pathway for health practitioners to make disclosure of genetic information to genetic relatives notwithstanding refusal by the patient to consent to such disclosure" [409: p.217] that other countries might follow. According to this, the healthcare provider could override a patient's desires and disclose genetic information to a patient's genetic relative only to lessen or prevent a serious threat to his or her life, health or safety [410]. Although approaching genetic relatives would happen without the patient's consent, the relative would only be notified that (s)he should seek advice from a doctor because a genetic condition was

identified in the family. The relative would not be informed of the condition nor the person carrying it. Before reaching that point, the healthcare provider is urged to try and get the patient's consent. Despite the fact that, for now, the guidelines are not legally binding, providers can "... avoid actionable complaint by following them closely"[411].

The example mentioned above remains an exception, as there is no similar guidance at a European or international level. Nevertheless, a step in that direction was made, at an advisory level, by the General Medical Council (GMC) in the UK. The GMC, acknowledging relatives' interests in accessing results, noted that, although confidentiality of patients should be respected, there is the possibility of breaching it to share genetic results, if, in this way, serious harm for relatives could be avoided [178, 412, 413].

Fears of liability have been expressed, especially amongst US experts, in cases where the disclosure could have prevented or changed the health outcome [414]. This suggests that health professionals might be justified in actively informing a patient's family [415]. Additionally, according to the ASHG, the breach of confidentiality might be acceptable for findings of serious, preventable or treatable conditions for which early detection might reduce risks [175].

Considering the evidence above, it could be claimed that a shift might start appearing where others who might be potentially affected could have a legal right to access genetic and genomic information. For now, these examples are limited; however, if similar cases are observed in other countries, and other laws are introduced, then the obligations of all stakeholders involved would have to be re-evaluated. Professionals' obligations, especially if legally binding, should be clarified for all contexts as fears of litigation might influence professionals' willingness to use potentially helpful tests or share potentially helpful results.

The variety of international approaches presented here demonstrates the complexity of this problem and a potential shift of practice. The principle that genetic and genomic data is shared across the family is respected by all; nevertheless, the specific obligations deriving from this seemed to differ, revealing the need for further research on this area. Practices will have to ensure that patients are aware of the potential complications of the results, not only for themselves but also for their families. For the time being, professionals' obligations are limited to informing their patients about the implications and encouraging them to share as appropriate,

and any guidance I prepare will have to include mechanisms to support professionals need to convey this important message.

8.3.3. Concerns regarding informed consent and counselling process

8.3.3.1. Clinical sequencing challenges traditional informed consent process

Due to all the difficulties deriving from the use of ES and the possibility of discovering IFs, experts considered that ES represents a modern challenge for health services. Its implementation is expected to affect the healthcare system in general. In particular, experts interviewed for this project believed that clinical sequencing and IFs challenge the current consent practices where the patient is offered all choices and decides about everything beforehand. Such a model might not be adequate to cover genomic tests and the IFs that could derive from them. Several reasons were discussed to explain this potential restriction.

First, the limited knowledge about genomic information and the difficulties in data interpretation noted earlier, combined with the highly complex nature of genomic information, might render the current consent process inadequate. For example, it is unclear what information should be offered to patients, especially when potentially relevant variants do not have very well-determined associations but are judged as important regardless of that. In such cases, this limited understanding would make it hard to organise a well-structured and clear information session as even providers face difficulties making the complexity of the genomic data understandable.

Second, as geneticists from the survey pointed out, genetic and genomic information does not necessarily have a linear relation to phenotype. Therefore, discovering a variant does not mean that a condition is going to be manifested. Third, it should also be acknowledged that the provider might not be in a position to predict all possible results and inform stakeholders in advance.

Similarly, (s)he might not be able to inform stakeholders about all potential results, as such an endeavour would be extremely time-consuming and might not be helpful to patients with limited knowledge of genetics. And fourth, due to the familial nature of genetic information it is difficult to know how patients might decide to communicate potentially useful results to their relatives and record these preferences in advance.

As a principle, patients should not and cannot be expected to consent to all potential results whose number might be infinite [35]. In general, genetic and particularly genomic tests make it harder to keep a balance between providing sufficient information and providing too much, thus, risking overloading the patient with information (s)he cannot handle [164]. If professionals are

unable to provide all information in advance, or if such a process is not feasible for other reasons e.g. due to time and resources limitations, then it is not surprising that the informed consent practices might have to be reconsidered [111, 136, 194, 416-418].

Illustrating these difficulties, experts suggested that patients often rely more on professionals and their professional opinion than try to form their own when they are unable to understand. Furthermore, it has been claimed that patients, similar to research participants, do not always read carefully, if at all, the consent forms provided nor do they always understand the information presented during the informed consent procedure [419, 420]. Long documents written in a complicated, scientific language may further discourage patients [421, 422]. They prefer to allow their clinicians, especially if they have an existing relationship with them, to make some of the decisions on their behalf. While this is a traditional way to practice, it places a huge burden on clinicians who are not confident regarding their level of knowledge, as has been discussed.

8.3.3.2. Is it time to consider alternative consent practices?

Concerns expressed by the experts I interviewed and Greek geneticists inevitably led me to question them about the need for new informed consent practices. They suggested that new ways to inform the patient, to encourage him or her to share information with family members and to achieve informed consent have to be investigated. Additionally, the ways that a patient could be supported to make their own informed decisions, rather than only relying on their clinician, throughout the process were also discussed.

The available literature has suggested that the traditional practices are inadequate to cover clinical sequencing [183, 194, 200, 204, 387, 416, 417] and several alternative models have been presented. These alternatives include, among others: (a) a short informed consent where only core elements would be presented (and signed for) accompanied by an interactive web-based information system for managing results “in a convenient, confidential, and personalised context that is responsive to their value system” [156, 183]; (b) a preference-based informed consent document with menu-like options or findings categorised in different ways [50, 416]; (c) a generic or broad consent [423]; and (d) a generic consent allowing the physicians to make some decisions on behalf of patients [417]. Additionally, it has been discussed that consent should include patients considering the implications for their relatives and providing “an agreed path” to share results, especially if these could modify relatives’ risk of morbidity or mortality [178]. For the time being, none of these alternatives seems to be preferred, by the participants of this project or

others, as shown in the literature, to replace the current informed consent practice, as they all raise further issues than they solve.

Nevertheless, participants of this project appeared to favour a model incorporating elements of different alternative approaches. They were inclined toward a more “practical” consent, combining elements from items (b) and (d) presented above, where patients can express preferences regarding specific types of results that they would like to receive and where patients would trust their clinicians and let them take some decisions on their behalf and always in their best interests. Clinicians, and clinical geneticists especially, seemed to consider that some level of paternalism might be acceptable and that some decisions would inevitably have to be made by them. They were in favour of a broad consent with a “hint of paternalism” that would allow them to make some decisions according to their professional judgment. They recognise that such an alternative would raise the possibility of “... a potential conflict between patient autonomy and clinical paternalism” [167, p.6], yet might still provide a way of balancing the two.

The discussion expanded to include experts’ understanding of autonomy. Other commentators have, in the past, discussed how informed consent should be the result of an active process involving a “bidirectional communication of medical facts and patients’ values” [37, p.368]. Whoever is informing the patient possesses the technical and clinical knowledge while the patient, based on his or her experiences and personal beliefs, makes the final choice [37, 424]. Interestingly, legal and bioethics experts interviewed for this project went one step further and discussed autonomy in a more “active way”. They suggested that patients should be responsible for seeking their results, rather than professionals having the obligation to seek out patients. According to my knowledge of the literature, this is the first time that experts have suggested such active involvement of patients in the feedback process.

Finally, some of the experts I interviewed generally preferred a preference-based consent process where patients would be allowed to choose some results according to the categories presented. Interestingly, although most commentators in the literature have expressed strong objections to aspects of the ACMG guidelines as they consider that they undermined patients’ autonomy (e.g.[25, 50]), opinions in favour have also been expressed. According to Vayena et al., the ACMG guidelines might enhance patients’ autonomy as they provide them with “... a fuller menu of worthwhile options from which patients can make life-shaping (including life-saving) choices” [425, p.1].

Ideally, before recommending alternative models of consent, I should be considering whether existing practices are seen as appropriate and helpful by the users of the tests, i.e. patients. As this project has focused solely on experts and professionals rather than patients, I cannot present any primary data for this group. However, in order to gain some insight, I asked participants in my study to describe their experiences with patients. Although the majority of Greek geneticists were worried about their patients' ability to handle these results, experts from all three countries seemed to consider that patients are usually able to handle IFs and the uncertainty that comes with genetic tests. This approach, where professionals were asked to assess their patients' abilities has been used elsewhere, and found that patients would like most available results, regardless of their source (clinical or research setting [C. Eng in [158], [143, 148, 380]) and only a minority would opt out of receiving IFs [158, 208]. Commentators have suggested that patients and parents welcome results, even for conditions for which there is no treatment or intervention available, as they value a diagnosis in other ways [426]. For example, when there is no treatment available, having a diagnosis might help patients avoid certain medication or unnecessary and unhelpful therapeutic options [426]. To the best of my knowledge, there are currently no empirical studies investigating patients' and families' satisfaction regarding consent process for clinical sequencing. This is a gap in the literature that needs investigating and the results of such studies should be taken into account when creating guidance.

8.3.3.3. Counselling and support for patients

Thinking about informed consent inevitably led to the issue of counselling and support for patients and families, and this was also seen to need re-evaluation. Experts discussed how patients and families should be informed and supported if IFs are to be returned. All experts, regardless of their country or their professional background, underlined the importance of genetic counselling. Most of them were in favour of an open and honest approach to convey complex scientific data in an accessible way for patients without previous knowledge of genetics. They also suggested that spending dedicated time with a patient is important, as is the provision of appropriate follow-up.

Pre and post-test counselling would provide the necessary support and would offer an environment where patients would be able to express their preferences in advance [167, 201] and be seen as a whole family [164, 201]. Specialised healthcare providers, usually genetic counsellors (with or without a specific area of specialisation [427]), play an important role in this process. Furthermore, depending on their needs, patients might develop different relationships with their

clinicians or genetic counsellors so that the patient's preferences should be taken into consideration [197]. Nevertheless, there is concern about whether current health service provision allows patients to develop a long ongoing relationship with their physician because of restraints on the number of appointments or length of appointments [346].

Commentators have expressed concerns about having lengthy counselling sessions. It is suggested that the use of clinical sequencing would require very long sessions, over 5 hours, making it impractical for providers, and with questionable utility for patients [423]. However, this contradicts my findings where the experts interviewed suggested that spending sufficient time with patients would make a difference although they did not specify what was 'sufficient.' Therefore, it is unclear whether simply lengthening counselling sessions would be adequate to ensure the amount of support needed or whether other alternatives might have to be considered. Extremely lengthy sessions would be impractical and difficult to integrate into a busy clinical routine. Ways to limit the time needed could include pre-counselling steps such as providing written material, videos, or case studies to patients before the counselling session. Such a process would allow patients to gain an initial idea and a basic knowledge of the test they were going to have and have the time to raise questions that they could then discuss during counselling. Finding the right balance between providing enough information to help a patient to make an informed decision and providing too much information that it becomes counter-productive [423] is another challenge that needs to be faced before ES and GS can be fully integrated into the clinical setting. At this time, I can only recommend that counselling should be seen as an integral part of the process and should be organised in a way to support patients and their families.

8.3.4. Intentions to use clinical sequencing

Experts' intentions to use clinical sequencing were discussed in detail. They seemed to consider ES as a useful tool but, due to the practical, technical and theoretical challenges (as described above), the majority of the experts interviewed seemed to prefer to avoid all this by using targeted tests instead. This strategy is common among clinicians (or clinical geneticists) both from my sample and from other studies [50, 150, 428]. Moreover, in my sample, clinicians interviewed (from all countries) as well as Greek geneticists were in favour of using targeted tests and leaving ES as a "last resort". Only the lab-geneticists interviewed considered ES to be an information-rich resource that justifies its use regardless of the challenges it raises.

No study comparing attitudes of clinicians to attitudes of lab-geneticists was identified through the literature review. However, it might be a safe assumption to make that the difference observed between them in this study could be attributed to their different backgrounds and formal education. Lab-geneticists are likely to be driven by their scientific interests more than clinicians, as the latter may be more focused on securing a diagnosis for their patient in the most straightforward way. Moreover, non-specialised clinicians in particular, might feel uncomfortable using novel tests, such as exome and genome sequencing, contrary to lab geneticists who might feel more familiar with these tests. These assumptions, based on the attitudes reported here, might explain the preference towards targeted tests. Targeted tests might be seen by clinicians as a safer option as they have been used more widely and for longer, compared to ES or GS tests. The views of clinicians from this study confirm what has been found in other studies and commentaries [50, 150, 428]: that when targeted tests are available, professionals would prefer to avoid ES or GS [36, 65]. They all suggested “prudence” when using clinical sequencing, and stated that IFs should be avoided until there is a better scientific justification for its use [150].

This negative attitude towards the use of less targeted tests might change in the near future as new knowledge is acquired regarding the possible benefits of using exome and genome sequencing as a diagnostic tool [8]. Nevertheless, if this does not happen, I believe that serious concerns are raised regarding the consequences of this unwillingness and, thus, the limited employment of useful tests. Developing and improving these tests is not a worthwhile investment of time or money if clinicians are reluctant to use them because of their reported difficulties in understanding genomic information. On the other hand, refusing to consider all alternatives might deprive patients of getting a diagnosis sooner, and potentially more cheaply, due to their clinician’s reluctance or even unwillingness to use ES or GS. Further training might help clinicians be in a position to fully exploit all available tests for their patient’s benefit. This may include continuous education to allow them to be trained to follow new developments and help them implement them into their clinical routine. This point needs to be made in guidance to help secure available training and support for clinicians, as well as other healthcare providers.

8.4. Process Issues in Returning Results

8.4.1. What results should be offered to patients?

Regardless of the concerns described above, and the resulting reluctance to order exome and genome sequencing for patients, my participants were in favour of returning some findings if they were incidentally discovered. Informed by the literature, I asked both my interviewees and respondents questions regarding the return of medically actionable and other non-medically actionable results. The literature suggests a unanimous agreement that medically actionable results should be returned to patients, and this was also the finding of this project.

It is noticeable that on a continuum of possible results (with medically actionable results at one end and results of unknown significance at the other), the literature presents agreements only for the extremes: medically actionable results should be returned, while variants of unknown significance should not. For most commentators everything in between is a “grey area”. National and international organisations such as the ACMG, ASHG, and the ESHG have suggested that medical actionability is the criterion that should be used [69], while Berg et al have used that same criterion to divide all results into three bins and return them accordingly [136]. However, defining medical actionability seems not to be an easy task. Experts in my study and elsewhere [18, 379] have openly said that actionability might differ depending both on the context in which it is being used and the personal beliefs of the person involved. Kranzt & Berg in a recent publication underlined the difficulty in defining medical actionability and suggested crowdsourcing as a way to produce widely-accepted categories [429]; while Goddard et al, acknowledging the difficulties in choosing actionable IFs to be returned, suggested an “...evidence-informed method to determine when to qualify when to report incidental findings from next-generation sequencing technologies” [137, p.1].

Interestingly, although professionals seem to have a hard time agreeing on a definition of actionability, the available literature suggests that lay people and patients seem to understand actionability in a less strict way and this seems to be shared across different patients and lay groups. The limited number of available studies on public and patients’ attitudes suggest that more results are desired: results with personal utility are requested by research participants [430], patients [158] and lay people [431]. These perceptions, although they need to be investigated further, might suggest that for patients and lay people the notion of actionability might be closer

to personal utility than the medical understanding of actionability, typically adopted by professionals. Medical actionability, although an important, and for now, a prevailing, criterion is not the only one; personal utility and planning for the future seem to be equally important for patients and lay people and might have to be considered when results are offered. These differences need exploring as agreeing on a definition of actionability might help Greek clinicians be more able to know which results to return.

No conclusion could be reached regarding other types of results to be returned as different views were expressed. I found a scepticism across my sample of experts regarding the return of non-medically actionable IFs, which again supported the available literature. Contrary to lay people and patients, professionals seem to adopt a more conservative approach. However, as discussed, Greek professionals seemed much more willing to return a plethora of results. Among Greek geneticists, the number of those in favour of returning several other types of results was particularly high and, contrary to other professionals [167, 201], many were willing to return even IFs of unknown significance. I was unable to study this further in this project but will take this willingness into account when developing my points-to-consider.

Apart from medically actionable results, other suggested results to be returned were pathogenic findings [113, 164, 432]; findings for early onset conditions [23]; findings that are life-threatening; findings that could affect future reproductive choices; findings with personal utility [433]; and findings that could benefit other family members (usually offspring) [425]. Finally, an alternative could be to adopt an open approach where patients would be allowed to choose and receive all the results that they want, even results about carrier status [156, 208, 416, 417]. Such an approach is also reflected in the existing policies in several of the major providers' policies in the USA [183] and seemed to be particularly welcomed by Greek professionals.

The lack of agreement regarding non-medically actionable results might suggest that specific aspects of guidance might have to be left blank and professionals allowed to use their professional discretion to adjust to the context, rather than attempting to find a universal rule and apply it in all settings and circumstances. However, general guidelines could help professionals make decisions regarding actionability but also will help to ensure a level of consistency across practice. Guidance, in any form it might take, should be dynamic allowing case-specific characteristics to be taken into account.

8.4.2. Who should be in charge of the decision-making and feedback process?

Another topic that was seen as important by all participants was the person or body to take charge of the decision making and feedback process. The experts I interviewed and professionals from the survey were in favour of having an MDT deciding which IFs to be returned and how to conduct the feedback process. This is not surprising in the case of Greece as there is currently no such type of framework. The limited available help for Greek professionals could come from the Greek National Bioethics Commission, but as this only acts as an advisory body, it is unable to provide practical guidance. What is surprising is the fact that both UK and US experts also asked for support from an MDT, as this support should already be in place in several UK and US major hospitals. Multi-disciplinary teams dealing with problematic cases exist in some UK and US institutions and, in clinical settings, they usually take the form of a Clinical Ethics Committee (CEC). Nevertheless, even if in place, these committees are mostly seen as entities dealing with consent issues, end-of-life-decisions, and withholding or withdrawing treatment [434-436]. Hence, genetics experts and professionals might not consider them as appropriate to provide the necessary assistance when it comes to genetic and genomic tests. Furthermore, there is some limited literature also suggesting that even in cases where such structures are available, healthcare providers, primarily clinicians, hardly make use of them [434, 437]. The reasons suggested include limited awareness of the available services, failure to recognise a problem as ethical, and unwillingness to include others in solving what is seen, mostly by clinicians, as “their own problem” [434, 438]. These observations might encourage the reconsideration of the available models of CECs and, potentially, the creation of a different model that could address issues raised by these new technologies. This new type of committee or team, in any form it might take, might have to focus on offering more practical guidance than that which a CEC is, by definition, expected to deliver, i.e. ethical guidance. If CECs are to be replaced, a new model might be helpful to provide an amalgamation of support of practical and ethical guidance, thus, covering most potential cases. Lastly, another factor that requires consideration is the status of the decisions made by the committee (or MDT). Questions regarding the legal and political authority of the committee and whether its decisions were legally binding would need to be examined.

In the absence of such an infrastructure, the clinicians I interviewed considered that they should manage the disclosure while all other experts considered that genetic counsellors were better prepared for such a task. Contrary to what has been discussed elsewhere [384], my clinicians

considered themselves as capable of filling the gap that the absence of an MDT would leave. Interestingly, this also contradicts the doubts they expressed about their self-reported limited understanding of genetic and genomic data. This contradiction could be explained if two factors are considered. First, the sample of clinicians interviewed for this study consisted of expert clinicians (or clinical geneticists) with considerable experience in genetic and genomic tests, rather than the non-specialised clinicians that other studies might have involved. Clinicians interviewed in this study might feel able to provide crucial support to their patients, but this does not necessarily reflect all clinicians' ability. And, second, the first choice of the majority was to have an MDT leading the process, showing that a multi-disciplinary group of professionals might be more appropriate compared to a single person, even if that person is an expert.

8.4.3. Timing of return of results

I also asked questions during the interviews regarding the most appropriate time to return results. Most experts believed that results, if appropriate for feedback, should ideally be returned when discovered, but that exceptions might have to be made to fit with patients' and families' needs. Results might have to be kept and returned at a later time after the predominant problem, for which the test was ordered, is resolved [36] or until the person having the test decides to receive them, e.g. a teenager asking to receive them when they are older [439]. Once more, it seems the experts in my study prefer that recommendations, although providing a framework, should not be prescriptive. A flexible approach would allow professionals to adjust to their patients' needs. The timing of the return of IFs is one of the areas that should be partly determined on a case-by-case basis according to the patient's particular circumstances, e.g. primary condition, family situation, and preferences and could be done by an MDT.

8.5. A framework for the conduct of clinical sequencing and the management of IFs

Several questions, both from the interviews and the questionnaire, focused on what professionals felt the process should be in the future that would facilitate and improve the integration of ES into the clinical setting, particularly in relation to the management of IFs. Hence, this section of the discussion is of great importance as most suggestions are summarised here, illustrating the direction that points-to-consider for Greece could take.

8.5.1. The process for creating a comprehensive working framework to guide practice

Current guidance (and/or regulations), as Lucassen and colleagues have suggested [178], is individual-centred and it is a challenging task to apply this to genetic and genomic tests that produce familial information, i.e. a group-centred context. More specifically, as experts from the interviews I conducted noticed (even in the US), although the ACMG guidelines provide a framework helping labs and clinicians [380, 428, 432, 440], feedback processes vary greatly across states or even across clinics/labs. For Greece and the UK, guidance is less specific and professionals clearly want more support before exome and genome sequencing are integrated into the clinical routine.

As presented in Chapter 6 experts variously requested that a) guidelines be prepared, b) legislation be enacted or c) a list be provided of results that it would be obligatory to return. The need for the first option – general, as well as more specific guidelines – is described by many commentators, e.g. guidelines for IFs for mitochondrial disease [441]. At the same time, there are many who express concerns about the process through which guidelines may emerge. The need for transparency while preparing guidelines to encourage public trust, the need for a multi-disciplinary approach, and the use of evidence and external reviews have all been mentioned [93]. Additionally, as is discussed below, guidelines need to take into account current professional consensus [25] and the current situation in each country. As very efficiently described by Burke et al., there is a need for a “...robust dialogue among stakeholders to define a pathway to normatively sound, evidence-based guidelines...” [25, p.854]. Different stakeholders need to be included and engaged in the process including representatives from patients’ groups [25, 35, 442], clinicians, geneticists and others.

Regarding the possibility of enacting legislation, Greek experts suggested that, at least in the Greek context, legislation might be more appropriate than guidelines. Interestingly, and to the best of my knowledge, this alternative has not been discussed elsewhere. ES and GS are newly introduced testing methodologies and are changing very fast, therefore, legislation might not be appropriate as it would fail to “keep-up” with technological and clinical advancements. Legislation might be required at some point in the future to respond to the needs arising from the full integration of ES/GS into the clinical setting. It could also help with the potential of a rising number of legal cases if such arise. The case law on this is very young and so far existing examples derive from IFs from the research setting (see chapters 3 and 4). At a later date, when there will be hard scientific evidence available and variants for disclosure will have been determined, legislation might be helpful but it is doubtful whether enacting legislation now would be worthwhile. Apart from this, especially for the US context, the diversity observed across states would make the preparation of legislation quite challenging.

While legislation may not seem a viable alternative for some, nevertheless, whether what will be created will have a legally binding character or not should be judged at a local level to ensure that it complies with the particular needs and reflects country-specific characteristics of the healthcare system. Among Greek professionals, legislation was considered as a viable alternative as its legally binding character might ensure compliance. However, previous examples, such as that of the Greek law 3305/2005, have shown that even a law might not have adequate power. According to this law, based on European standards (Directive of the European Parliament and the Council of Europe recommendation (2004/23/EC)), a Greek National Authority for Medically Assisted Reproduction (NAMSR) [443] was to be created. This body would have been responsible for oversight of all assisted reproduction units, provide accreditation and ensure compliance with regulation. NAMSR was created in theory in 2005 but after two years of struggling without support or funding, its members resigned. This left the area of assisted reproduction without any oversight mechanism, thus allowing illegal and unethical practices to occur in a country seen as an attractive “medical destination” due to the lower cost of assisted reproduction compared to other European countries [444: content in Greek, 445, 446]. This example demonstrates how a piece of Greek legislation would not guarantee compliance if it did not reflect professionals’ practice and society’s norms [447, 448] and, especially, if it was seen as an attempt to “... impose foreign processes within Greek reality” [448: p.823]. Simply introducing a legally-binding document would

fail unless the necessary infrastructure was also created and consensus was built among Greek professionals.

Finally, regarding the alternative of having a list of results, the ACMG list was used as an example and experts were asked to comment on whether they would prefer having a similar list or more general guidelines. Professionals did not necessarily see a list as being restrictive of their professional judgment, and some (mainly from the US) welcomed such a possibility as they thought it would provide consistency of practice across clinics.

Many acknowledged that the ACMG list (which includes variants with well-established links with clinical diseases, available screening or surveillance, prophylaxis or treatment) represents a “... very good starting point for deliberation” [25: p.857]. Nevertheless, several arguments against having such a list have been presented. The production of a list suggests that some variants have been considered as more serious than others and the ones not included would not be investigated. Nevertheless, current scientific evidence has demonstrated that other variants might be of equal significance even if they have lower penetrance simply because they might be highly actionable [25, 136]. Additionally, as underlined even by the authors of the ACMG list, a list could never be complete and would need constant updating [10]. Other results might also be of interest to patients (e.g. pharmacogenetics or carrier status) [25], while a list was also seen by many as a type of screening [25, 442, 449]. Previous examples of screening for genetic-associated conditions have demonstrated that alternative approaches (a family-history approach) might be more useful and that screening might lead to unnecessarily invasive tests and follow-up [37, 450]. Moreover, several countries have very specific and relatively strict rules applying to screening programs. Finally, a list would have to include variants with very clear clinical utility and validity. Judging from the reactions towards the ACMG list [25, 37], which was prepared by leading scientists in genomic tests, such a task would be particularly difficult. While the number of difficulties grows, it becomes obvious that such a task would be even more challenging for Greek geneticists who have limited experience and no support. Therefore, the list would need help to come from international colleagues who have the resources to assess, validate and periodically update information about variants and their associations with genetic conditions. Therefore, I do not believe a list would be the right decision for Greek professionals.

8.5.2. Additional support that could facilitate the process

A way to support professionals, as suggested by experts interviewed here, would be the development of genetic databases where healthcare providers, as well as researchers, could share their findings regarding new variants and new associations discovered with each other. This would have a beneficial effect if laboratories were granted access [451], thus facilitating clinical sequencing in general and the interpretation of results more specifically. As commentators and experts from the literature have suggested, databases might support professionals by limiting the difficulties they face when trying to “keep up” with the rapid advances in genomics. Mainly UK and US experts considered these databases as a useful resource. Greek experts rarely mentioned that they could access databases to get the support they need. Limited awareness of such initiatives or fear that such access would require funding could be potential reasons explaining this difference.

Furthermore, when experts were asked to describe other ways to facilitate the process, several improvements were suggested including bioinformatics support for the interpretation and filtering of results and psychological support for the patient and their families. Correspondingly, commentators ask for ways to acquire a better understanding of variants and their clinical implications. This could happen with either the development of a “... comprehensive and diverse centralised resource to provide curated information on pathogenicity for clinical use” [113, p.631] or a combined effort from professionals and patients [166]. Additionally, the development of a publically available registry of genetic tests and laboratories performing the test might be useful [157], especially for resource-limited health systems such as Greece. Training and continuous education for clinicians and other healthcare providers [17, 35, 217], web-based tools to educate patients and lay people and to manage patients’ preferences [452], and development of mechanisms to filter results according to patients’ preferences [71] are also included in a long list of potentially useful tools, often used in other settings, e.g. DTC tests. Finally, the majority of commentators underline the need for more empirical research on stakeholders’ attitudes and needs [25, 167]. Having access to such resources would only be of benefit to Greek clinicians.

8.5.3. More funding is needed

Finally, a topic that inevitably emerged from the interviews, both when discussing challenges about clinical sequencing and when discussing future practices, was the availability of funding. ES and GS are novel technologies requiring new and expensive equipment and specialised staff to

perform the tests and interpret results, for example, clinicians' time to conduct or participate in the feedback process, and the time and cost of all the follow-up that could potentially be needed. Counselling and interpretation are time and labour intensive [25, 102, 134] and, depending on the context, funding might have to be secured or re-allocated from other services. Additionally, there is the fear that, with the current incomplete scientific evidence, the return of IFs might create the need for follow-up that would be expensive and might cause unexpected harm, increasing the costs even more [40, 453]. The desire of others (relatives) to know if they also have the clinically significant variants [164], would again increase the cost and time required of professionals. Although the actual cost of the tests themselves has vastly decreased in recent years, it still remains unclear what the total cost of equipment and labour is. Systematic research is needed to investigate exome and genome sequencing cost-effectiveness compared to the improvement of the diagnostic rate [454]. Such a calculation will help support any approaches to the Greek government requesting additional funding.

8.6. Moving one step forward – Instead of a conclusion

It is obvious that the preparation of guidance is not an easy task and a one-size-fits-all model might not be appropriate. Furthermore, the different approaches discussed, usually between clinicians (and clinical geneticists) and non-clinicians, i.e. all other specialities, suggest that different forms of guidance might have to be created at a professional and at a national/local level. Alternatively, guidance prepared might have to be the result of a multi-tiered approach where different sections would be addressed to different groups of stakeholders.

I argue that a top-down approach [455] would not be helpful in the case of clinical sequencing and IFs management for Greece. The example of the original ACMG recommendations, where a guidance document was produced and imposed on the setting, illustrates that the collection of strong empirical and scientific evidence needs to precede policy creation, as that policy has not been universally accepted even in the US. The "... assimilation of genomics into the public health..." remains a challenge [456: p.225] and the integration of genomic tests into the clinical setting is not an exception. I believe what is needed for Greece is: (a) scientific data investigating the clinical utility of clinical sequencing and suggesting cases where genomic tests would be

useful, e.g. to improve diagnostic rate, or produce diagnosis at a lower cost, (b) clearly established access and feedback mechanisms, (c) empirical evidence demonstrating different groups (professionals, lay people, patients) and sub-groups (clinicians, genetic counsellors etc.) needs, (d) a clear understanding of how different stakeholders interact and (e) establishment of immediate and long-term objectives in relation to the uses of clinical sequencing and IFs. Based on this foundational evidence, best practice and guidance (or perhaps regulations in the future) can be developed.

More specifically, I believe the creation of multi-tiered guidance should follow the following pattern. The would be ***practical specialty-specific guidance***, prepared by and addressed to specific professional groups, e.g. an association of lab-geneticists could prepare best practice for interpretation of variants for lab-geneticists, but also for the use of others. This pattern could be followed by other groups. In this way, each profession would have a set of practical recommendations to guide their specific practice, ensure consistency at their level and reflect a consensus among professionals with the same background. If there are several similar groups, recognising the potential differences in practices between them and aiming at minimising the potential conflict that could emerge, communication between similar professional bodies should be encouraged. At the second tier would be ***guidance to establish effective collaboration across groups on the specific topic***. Clinical sequencing and the management of IFs are multi-disciplinary areas where different professionals cross paths, therefore, their interactions and collaboration should be facilitated by the description of best practice. This guidance should be the result of cross-disciplinary discussions and based on elements found in the practical guidance produced at the professionals' level. Finally, the third tier would consist of ***formal guidance and, potentially, at a later time, regulation on the specific topic***. Before formal guidance is produced, other stakeholders' input should be sought to ensure that all parties' needs are taken into consideration [456]. Professionals with an ELSI background should have a major input, and the same would be true for representatives of industry and patients' organisations. Moreover, lay people and patients' direct input would be equally important. The inclusion of a broad range of stakeholders would ensure a diversity of points that, if used in a transparent way, could lead to the preparation of widely accepted guidance. I believe this would facilitate the integration of clinical sequencing, protect both patients and professionals, involve decision makers and engage scientists in "... good science..." [457].

The generic model described here could be seen as a bottom-up approach [455] where simpler and more practical pieces are used to give rise to a more complex whole, and in this case, one more widely applied to the whole system, i.e., Greece. It is my belief that this approach, if allowed by available infrastructure, would be most appropriate.

8.7. Chapter Summary

Clinical sequencing is seen as a potentially useful diagnostic tool. Nevertheless, unclear obligations regarding the return of IFs, combined with the lack of a clear framework and support, lead professionals to consider it useful at a more theoretical level for the time being. If issues emerging from its potential implementation are resolved, and guidance is produced to provide a comprehensive framework, then clinical sequencing might actually prove to be highly useful and improve health services. Any guidance produced would have to be dynamic to keep up with scientific developments and, yet, adequately structured to ensure a consistent level of good practice.

Contrary to what has been discussed elsewhere, participants in this project were in favour of a practical consent process where the patient would have the choice of receiving different categories of findings while, at the same time, (s)he would allow the healthcare provider to make some initial choices on his/her behalf. The patient would be at the centre of the approach suggested and would be supported through extensive counselling to be responsible and to actively seek results. Both the patient and providers would be supported by an MDT that was cited by the majority of participants as the most appropriate structure to lead the decision-making and feedback process. These, then, are key facts on which I will build my points-to-consider.

Different notions of actionability among professionals suggest that although it is a useful criterion, guidance should not be based solely on it. Offering choices to patients and supporting them to make informed decisions were seen as more important and any guidance produced would have to incorporate their understanding of actionability, partly as personal utility, as well as professionals' stricter interpretation as medical actionability.

The qualitative and the quantitative phase of my project provided evidence that demonstrated that preparing one set of guidance might be challenging unless it was multi-tiered and catered for

the needs of different groups. This approach might be more feasible if a bottom-up approach were adopted.

Findings from my study suggest that several principles are shared across countries and, therefore, I have used examples found in other countries, and especially in the UK and the USA that were studied here, in the preparation of a framework for the Greek context. However, country-specific characteristics would have to be taken into consideration and models adjusted accordingly to ensure that whatever is produced would be applicable in the Greek clinical context. Therefore, at this point, only a point-to-consider can be developed. Yet it can be an important part in the creation of guidance for Greece, which I will discuss in the next chapter.

CHAPTER 9: POINTS-TO-CONSIDER FOR GREECE

9.1. Chapter outline

This final chapter focuses on the Greek context. I have taken the findings from this project, as discussed in chapter 8, and combined them with evidence from the literature and adjusted them to fit the Greek context. This final discussion provides the background to the informal recommendations, i.e. points to consider, for Greece. I provide an evaluative discussion of the findings that are the basis of the points to consider, explaining how different data were used for the points raised. Following the points-to-consider I provide some reflections on the conduct of the research and how my experiences and decisions influenced this piece of work.

The final part of this chapter is dedicated to the reflections about the strengths and limitations of this study. In addition, I identify the remaining gaps in this area and provide suggestions for areas that need further research.

9.2. Greek-specific points-to-consider

As I argued in the previous chapter, the challenges emerging from the implementation of ES and GS and professionals' reluctance to use them, both suggest that, for the time being, the integration of sequencing into the clinical setting will happen gradually and in parallel with other scientific developments. Subsequently, I suggest that a generic model, using a bottom-up approach, as the one I described in section 8.6., would prove to be useful for the preparation of guidance as it would allow the co-evolution between guidance and the collection of evidence.

This bottoms-up approach would need to be adjusted for Greece, as there are no specialty-specific professional bodies, e.g. for lab-geneticists, who would be the most logical to manage the process. The existing professional bodies only have an advisory role and do not, to the best of my

knowledge, produce recommendations nor do they develop best practice documents. Therefore, adjusting the model presented earlier to Greece means that the first two tiers would have to be combined and professional bodies, including a variety of specialties such as the HAMG, would need to work together toward producing a document with both practical and theoretical aspects. To this end, the points-to-consider presented below, will be offered, after the completion of this project, to the two professional associations of Greek geneticists (HAMG and HMSA), to the Hellenic National Bioethics Commission and to the School of Public Health to act as a basis for future development, acting as the background document to facilitate the creation of combined tier 1 and 2 guidance on clinical sequencing.

9.2.1. Returning results in the Greek context

Regarding the type of results to be returned to patients, I suggest that Greek clinicians use a model of Berg's binning system that I adapted specifically for the Greek context (see table 13). The bins should be used not to constrain the results offered, as described in the literature, as discussed above, but to facilitate informed consent, counselling, decision-making and the feedback process. It could also be used to track which results patients and clinicians return.

Greek professionals were almost unanimous in believing that medically actionable results should be returned to patients, therefore, this should be used as a primary criterion. These results, referred to as "bin 1", should be offered if incidentally discovered but patients should be informed about this possibility during counselling and should also be encouraged to share them with their family members.

Clinicians should also discuss with patients whether they wish to have results that are either about life-threatening or serious conditions but are not actionable, or are about less serious conditions but which could be of personal or reproductive importance. In a similar way to other information that could inform reproductive choices, carrier status might help people inform their children and take measures to avoid having a condition by using prenatal or even a pre-implantation genetic diagnosis. The examples of β -thalassemia or cystic fibrosis would be included in "bin 2". As these two recessive genetic conditions are very common in Greece, this could be the reason why Greek geneticists were so willing to return carrier status if discovered incidentally. Patients would be able to understand the potential benefits and limitations of knowing this information more easily than other conditions. The potential disclosure of results from "bin 2" should be discussed and a shared-decision between the genetics professionals and the patient should be made. If patients

are unable or unwilling to make this decision, then genetics professionals, in collaboration with a clinician (who, ideally, already has an existing relationship with the patient), could, if asked by the patient, make this decision on his or her behalf. If such an alternative were chosen, the process of decision making should be well-documented, and include the decisions of both parties; the patient would be asked to explicitly consent in writing and the report should be included in the patient's records.

Table 13: Proposed Greek system for “binning” of incidental findings from exome or genome sequencing

(adapted from Berg et al [136])

	Criteria	Clinical Validity		Unknown Clinical Implications
		Clinical Utility	Personal Utility	
Genes	Bins	Bin 1 Medically actionable	Bin 2 Non-medically actionable but potentially important for the patient	Bin 3 All others
	Examples	BCRA 1/2	Carrier status for cystic fibrosis or β -thalassemia	
	Return Practice	Reportable	Reportable	Reportable ¹

¹ Inform the patient of the discovery. The patient should be responsible for seeking future advice as to the usefulness and the updates of VUS.

“Bin 3” would, as Berg suggested, include variants of unknown significance (VUS). The patient should be informed about this possibility as well, and should be able to choose to receive these results. Interestingly, Greek clinicians were more willing than their colleagues from other countries to return results of uncertain significance. Significantly, in Greece, where patients would have to cover the cost of the tests themselves, professionals seemed prepared to offer most results. An assumption could be made here: Greek geneticists might be willing to use ES to acquire

as much information as possible (even unclear results) out of fear that due to the high cost, which was a major concern, their patients might not be able to afford another test in the foreseeable future. They might, therefore, be more accommodating of the idea to use the test performed to access information even if not immediately useful or interpretable. However, understaffing problems combined with other practical limitations such as time restrictions, difficulties in keeping track of and re-contacting patients etc., would most likely make it impossible for the laboratory or the clinic to follow-up on all patients with VUS. Therefore, if the patient chooses to receive VUS, it should be his or her responsibility, as proposed by the experts interviewed here, to follow-up and re-contact the geneticists to ask whether new discoveries related to his/her results have been made. This could happen regularly, potentially on an annual basis, and in cases where something new has been discovered, the patient could then arrange an appointment with the genetics professionals concerned to decide how to proceed. Given that the results from the sequencing would be available and no re-sequencing would be required (unless seen as beneficial), this potential annual update would, on a patient's request, include a review of available databases to investigate whether the VUS discovered have been associated with anything new. If future scientific developments require it, then re-sequencing could be conducted.

This approach reflects clinicians' ideas about the return of medically actionable results, genetic counsellors' ideas about a shared decision-making model, and experts with legal and bioethical backgrounds' ideas about a "more active" autonomy where the patient has a responsibility to contact and ask for updates.

9.2.2. Results interpretation and databases

To facilitate the interpretation of variants, especially those belonging to bins 2 and 3, access to national and international databases would be required. The important role that databases could play in facilitating professionals' interpretation of results has been discussed among commentators, in other studies and by experts interviewed for this project. Yet, as noted earlier, Greek professionals did not spontaneously mention this. Potential reasons might include a limited awareness of such initiatives in other countries. Alternatively, it might also be explained by an awareness of the limited resources available, i.e. knowing that if these databases would require some form of monetary registration. They would be unable to afford access due to the limited funding that most research or clinical institutions have in Greece.

Many are in favour of the establishment of “... databases archiving high-resolution genome-wide datasets and integrating evolving phenotypic findings” [86, 102: p.359, 118] that would be used both for clinical and research settings [17]. The need for free, public access databases has been seen as a way to move forward toward the creation of a public resource to organise and evaluate variants discovered and support the interpretation of variants [458, 459]. These types of initiatives could come through governmental bodies such as the National Human Genome Research Institute that created the Clinical Genomic Database (CGD) [460]; major universities in the USA (e.g. Harvard Medical School, Boston [458]) or in Europe (e.g. Leiden Open Variant Database)[461]; or other funding bodies (e.g. Wellcome Trust Sanger Institute) [462]. The CGD, which is freely accessible, offers associations between genes and conditions and aims to provide support for the use of clinical sequencing as “part of active medical care” [346]. If genetics professionals are made aware of initiatives like these and are willing to contribute to their further development, then eventually an international database could be created where newly discovered variants and associations could be uploaded, helping professionals from all around the world. Genomic data interpretation would be greatly facilitated and clinical sequencing would perhaps be seen as the useful tool that it is, rather than a resource of questionable usefulness, as it is seen by many today. If such a resource is made freely available, countries such as Greece, with limited resources, would be greatly supported.

9.2.3. Counselling

In Greece, counselling and support for families are one of the greatest challenges that has to be overcome to facilitate genetic sequencing. Although current legal documents, e.g. the law for Medical Ethics [372], acknowledge the need for counselling and even require it for every genetic test performed, the lack of a state-recognised specialty of genetic counsellor illustrates how insufficient measures have been put in place to ensure that counselling is indeed offered to patients. This has resulted in counselling being left to the discretion and abilities of the clinicians or other healthcare providers such as lab-geneticists or clinic directors. With limited resources, usually understaffed, and time constraints imposed in settings that offer more services than they should according to their “job description”, Greek geneticists offer counselling as part of their other professional obligations. In spite of their efforts, while adequate to cover the current limited demand, it is doubtful that this could continue if ES were used more often in the near future. Specific and well-organised efforts should be made on behalf of the state to offer specialised training to those already involved in the counselling process and to create specific programs for

the training of new professionals. This training could take the form of a specialty for clinicians and continuous education and specialisation for other genetics professionals, e.g. geneticists and biologists. As discussed, in 2011 HSMG was created to “put forward the establishment of Medical Genetics as an independent medical specialty” (translated from Greek) [367] but no action has since been taken and the issue remains unsolved to this day, leaving genetics professionals’ needs unmet. Building on this initiative, the discussion needs to be re-opened and actions have to be taken to push the matter forward and initiate the lengthy process of public deliberation and, eventually, the establishment of recognised specialties. It is hoped that a strong emphasis on this issue in the points-to-consider will underline the importance of this issue.

9.2.4. Multi-Disciplinary teams

Having an MDT leading the decision-making and feedback process was seen by my experts as the best way forward. However, regardless of the efforts made, establishing MDTs in Greek hospitals has been mostly unsuccessful [463]. The current situation is unknown, however, anecdotal evidence from expert witnesses report that some hospitals have ethics committees mainly consisting of clinicians but dealing solely with research protocol approval. Therefore, I believe that the formation of MDTs to assist healthcare providers in the event of ES and discovery of IFs should be put on the table for discussion. It remains unclear whether this should be a team or a committee based in each setting offering genetic and genomic tests or whether it should be an independent committee covering more than one setting (clinics or hospitals), or a local one covering a whole area, e.g. city. Different countries provide models of local, national or university-based committees with advisory, legally binding (or not) rules that could provide useful examples [464-468]. The committee (or MDT) that would provide the necessary support for Greek geneticists should be neither only advising nor strictly guiding but something in between. I believe a committee with flexibility and reflective judgement is needed to translate guidance into practice and to deal efficiently with emerging new cases.

9.2.5. Need for funding

In Greece, experts noted that ES and GS are expensive and there are insufficient numbers of people trained to perform the test and interpret the results. Additionally, counselling, support for patients and families, and follow-up tests require even more funding. As described by the expert participants in this study, ES is still rarely used and the high level of resources required is one of the reasons explaining this observation. This is particularly true for Greece. Resources do not

dictate what should be done; they do, however, dictate what can be done. Currently, most genetic tests are paid for by patients themselves, posing an unbearable weight on them and limiting the use of these tests to those who can afford them, thus, creating health inequalities. While re-allocating the health budget might be feasible for the UK, it could not be easily applied in Greece where the limited budget and personnel is affecting all aspects of the health services.

Designing a model that would require unlimited resources in time and money would help no-one. Proposing ideal situations, while an interesting and challenging mental exercise for academics and researchers, do not in any way help patients and professionals seeking support. Hence, my points-to-consider are prepared with the Greek context, with its limited resources in both personnel and finances, in mind.

As discussed earlier in this chapter, it is clear that a policy of the “one-size-fits-all” type is not appropriate for the return of IFs from clinical sequencing as there are so many perspectives and contributing factors that need to be taken into account. Taking this into consideration, the goal of this project has been to produce informal recommendations based on expert evidence. I hope that these points will provide a preliminary working framework for any Greek body (professional or legislative) seeking to prepare guidance, in any form this might take. It is my intention for these points-to-consider to provide a structured framework to help professionals, while at the same time, be adequately dynamic to allow professionals to use their discretion to adjust the decision making and the feedback process to their patients’ needs and circumstances.

9.3. Moving towards points-to-consider for the return of IFs from clinical sequencing

9.3.1. Preparing for the points-to-consider – A summary of the results of the research

Up to this point, I have presented the data collected for this project through interviews with experts in genetic and genomic tests from Greece, the UK, and the USA and through an online survey completed by registered Greek geneticists. Regardless of their different levels of experience, both groups represent genetics professionals and are those who would be involved in performing or ordering ES and GS and returning any IFs discovered.

Their previous experiences with genetic and genomic tests and the fact that they are the target audience for this study were the reasons they were invited to participate here. Investigating their attitudes and needs was seen as important before the preparation of points-to-consider for Greece. As they would be the ones using the tests and potentially seeking guidance from the points-to-consider, it was considered crucial that their input was sought and that their attitudes and opinions were reflected here. It is for this reason that this section of the thesis focuses on using this input to inform the preparation of points that could be considered whenever a genetics-related body or organisation decides to proceed in preparing formal recommendations or guidelines to support the implementation of clinical sequencing and the feedback process of IFs.

Greek experts and Greek geneticists were asked to offer their insights to inform the creation of a list of considerations that attempts to reflect a professional consensus and mirrors the Greek situation. At the same time, country-specific characteristics have been taken into account to ensure that the recommendations produced will not simply be a transfer of practice from another country but will be created according to the Greek context.

As requested by the expert interviewees, and echoed in the literature, the points-to-consider presented below have emerged through a transparent process, which also adopts a multi-disciplinary approach and incorporates professionals' input. These points-to-consider, although they are evidence-based, should not be considered as formal guidance. Rather they are intended as starting point for those seeking to create guidance, in any form that might take. Taking into consideration the need to include other stakeholders, primarily patients and lay people whose input is absent here, the points-to-consider presented should be treated with caution as they echo only professionals' attitudes and needs. Nevertheless, I believe that with this thesis I have provided adequate evidence to initiate the discussion and demonstrate areas that require further research.

9.3.2. Developing the points-to-consider

Policy making is by definition a complicated and labour intensive process which becomes even more complicated in the genomics context because of the complexity of genomic data, the insufficient current knowledge we have and the constant changes altering our understanding [469]. In general, developing points-to-consider follows a similar process to developing guidelines or any other form of guidance. Prior to presenting my points-to-consider, I will explain the process I used to develop them.

Points-to-consider and guidance are developed to outline desired outcomes and the process needed to achieve them. The multiple steps required in the creation of the guidance reveals the complexity of the process. Apart from the time, developing guidance is also a very labour intensive process, which is why they are usually prepared by groups of people rather than individuals [470, 471].

The first step is to define the area and the scope of the guidance, in this case, clinical sequencing. Once the area is defined, evidence is collected, and assessed, including identification, synthesis, and interpretation of the data. At the same time the potential stakeholders who have an interest in the resulting guidance should be identified [470, 472].

Once evidence is collected one needs to assess whether it should be included. Issues to be considered include the generalisability of the evidence collected, for example to what degree evidence from a small project such as this one, coming from a small sample, may be generalised to meet the needs of a wider population. In my case, my evidence was limited to the judgement and experience of genetics professionals and no other stakeholders' input was sought. Thus, it is expected that the points-to-consider created here are more likely to be susceptible to bias and led by professionals' interests. Given that this was the original scope, no measures were taken to limit these biases. However, the process was made as explicit as possible to increase transparency and avoid misconceptions. Also, the points-to-consider are flexible enough that other stakeholders' views can be reviewed and included at a later time. The resource implications and feasibility of interventions also have to be considered when creating formal guidance [473]. Cost-effectiveness analysis should take place and resource constraints of the healthcare system, including time, staff, and equipment should also be taken into account [470]. Modern policy making requires

transparency and public participation as that will provide the guidance with greater value [474, 475] and would increase public trust [476].

Input for the preparation of the points-to-consider came from three sources: data identified from the literature review (discussed in chapters 2, 8 and 9), empirical data collected specifically for this project describing genetics experts and geneticists' attitudes and suggestions (presented in chapter 5-7), and last, but not least, expected norms found in policy making (discussed in chapter 2). For example, both experts and geneticists discussed the potential usefulness of clinical sequencing as well as their reluctance to use it due to its currently-perceived limitations. This concern is echoed in point 1 (sub-points i-iii). In health-related policy-making literature it is widely accepted that counselling should be an integral part of the health services provision, as well as that patients' personal beliefs should be respected. This point was also among the findings from the empirical data collection and are echoed in points 2i and 2ii of the points-to-consider. I have worked throughout to ensure that the findings that came from the literature review and the empirical data collection are included when they aligned with the principles guiding this project.

While these examples appear to show a linear relationship, that is incorrect and misleading. Points-to-consider \neq Literature review + Empirical evidence + Policy making norms. That would be too simplistic. My description is only an attempt to schematically represent the process that I followed, inspired by similar attempts presented elsewhere [477]. Yet, to move from the descriptive level described above (genetics experts and geneticists' attitudes and suggestions) to the more normative level of developing points-to-consider, an important component is missing, personal choice. My personal views and principles have inevitably influenced this project, although I have tried to be impartial in research practice. Every step represents a choice made and every choice made and every conclusion drawn should be seen as "a dynamic system of recurring inferences" [477](p.27) that represents not a linear sequence but a circular iterative process. Subsequently, before presenting the points-to-consider, I will briefly discuss the underlying principles I believe guided my work.

The ethical norms pertaining to human research and clinical practice trace back their roots to the Nuremberg Code. As I discussed in chapter 2, principles such as autonomy, beneficence and choice have dominated the discussion. These principles have also been guiding policy and practice for many years; however, today a new, more holistic approach has been introduced. This relatively new ethical, legal and social implications (ELSI) approach [478, 479] and its evolution

(ELSI 2.0)[480] call for the “core bioethical principles” i.e. autonomy, justice, beneficence, and non-maleficence, to be adapted to the needs of genomic science [481]. I agree that an individual-based autonomy model is inadequate to respond to the complexity of genomics, because it is predictive but uncertain and because of the familial considerations. Because the realities of practice have to be considered, solidarity (working together when groups’ aims might be different) has to be introduced to encourage research and allow collaborations [482, 483] and critical reflection on the scientific developments and their (potential) implications. Once more, flexibility is crucial to allow policy-making to follow the scientific advances and ensure ethical compliance [481, 484]. But this does not mean we cannot work to create systems that will allow patients to choose how they want to manage their health information.

I, of course, do not claim that in this single handed Ph.D. project to have offered the answers to all the practical, methodological and ethical questions raised so far. I do believe however that I have contributed significantly to the literature, through the papers I have published on early parts of this research and by preparing a points-to-consider that could lay the ground for a systematic discussion in Greece regarding clinical sequencing and IFs. I have done so in a transparent way that will allow others to take on the discussion from this point. In doing so, my experiences, principles, and values have unavoidably influenced not only the methodologies used but also every question asked and every decision made along the way. I am a strong supporter of autonomy and free choice, and I also have the perhaps naïve belief that patients can be supported and informed to make decisions for whatever is in their best interest. Nevertheless, as a biologist, it would be impossible for me to disregard the inherent complexity and familial nature of genetic and genomic information and the difficulties raised by those characteristics, for example, on how to share information with the patients’ relatives. In a similar way, I cannot neglect the uncertainty and incomplete understanding of genomics and the incredibly fast pace of the scientific developments. These are serious considerations that have to be taken into account and discussed systematically before any formal guidance takes a form that would guide practice in the clinical setting and would affect different stakeholders. I have tried to reflect these difficulties in an impartial way.

Although a supporter of autonomy, in exceptional cases I would be willing to accept some sort of “good medical paternalism” [485] where a patient would ask for the healthcare provider to help him or her make a decision if unable to make it himself due to severe illness, cognitive load,

limited, if any, understanding of the intervention and its implications. The autonomous agent, i.e. the patient, recognising the limitations of his knowledge or decision-making ability, is willingly asking for help from another more experienced and knowledgeable agent. I see this as an enhancement of autonomy rather than a barrier and I consider that helping that patient to be showing support to them, rather than paternalism, a term that usually has a negative connotation. These three factors – the familial nature of genomics, our expanding yet still incomplete knowledge about it, and the fact that patients actively seek support from physicians – are the reasons why I once more underline how important it is for the guidance created to be dynamic. This is crucial as it will allow guidance to co-evolve with scientific developments, adjust to circumstances of each particular case, fill the gap in the asymmetry of knowledge between patients and physicians and show respect by avoiding harm for the person and his relatives.

9.3.3. Points-to-consider for the return of IFs from clinical sequencing

Purpose and Interpretation

1. **Purpose.** The purpose of these points-to-consider is to provide support to genetics professionals in Greece regarding the use of clinical sequencing, and specifically of exome and genome sequencing, and the management of incidental findings discovered during the test. Furthermore, these recommendations seek to provide points for consideration for bodies preparing formal guidance for the Greek context.

Its primary goals are to:

- i. Serve as a preliminary framework until the preparation of formal guidance.
- ii. Detail ways in which the welfare, rights, and interests of stakeholders involved in the clinical sequencing, including professionals, patients, and their families, can be protected and promoted.
- iii. Provide evidence of professionals' needs and attitudes towards clinical sequencing and management of IFs.
- iv. Reveal areas that require focused research.
- v. Encourage discussion among all potential stakeholders.

2. **Interpretation.** Without ascribing any formal meaning or taking the form of formal guidance, these points-to-consider should be interpreted in good faith and are to be understood as a whole. Although examples of other countries have been used for the preparation of the recommendations, the recommendations are developed and are relevant only for the Greek context.

II. Foundational Principles

These points-to-consider seek to provide a preliminary framework and offer support to stakeholders, mainly professionals, involved in the clinical sequencing and management of IFs. The foundational principles guiding the recommendations are:

- i. Respect for individuals and their families
- ii. Foster trust between professionals and patients (and potential users of clinical sequencing)
- iii. Promote health and wellbeing of all parties involved
- iv. Improve healthcare services and advance scientific knowledge

POINTS-TO-CONSIDER

1. Using clinical sequencing and managing incidental findings

- i. Clinical sequencing is a potentially useful diagnostic tool; nevertheless, due to the current incomplete knowledge regarding its limitations and its potential findings, alternative tests (such as single-gene tests or gene-panel tests) should be considered first.
- ii. If alternative tests are unavailable or fail to produce results, clinical sequencing should be used in the best interests of the patient.
- iii. Primary findings should be reported to the patient. Secondary findings should not be actively looked for but should be reported, if incidentally discovered, according to the patient's wishes, as expressed during counselling.

2. Counselling and informed consent process

- i. Counselling should be an integral part of the process and mechanisms should be put in place ensuring that standard procedures are followed.
- ii. Counselling should be adjusted to the patient's abilities and pre-existing knowledge. Lay language should be used and scientific terms should be simplified, if seen as necessary. Personal and other beliefs (e.g. religious beliefs) should be respected.
- iii. During counselling and the informed consent process the patient should, among other issues, be informed of the limitations of the clinical sequencing, the possibility of discovering IFs and their potential implications for him/herself and/or his relatives.
- iv. During counselling and the informed consent process the patient should be encouraged to declare his/her wishes regarding receiving (or not) IFs relevant to him/herself and/or his/her relatives.
- v. During counselling and the informed consent process the patient should be encouraged to declare his/her wishes regarding disclosure of IFs discovered to his or her relatives.

Under exceptional circumstances the patient should be allowed, during counselling and the informed consent process, to request the help of a healthcare professional to assist with the decision-making regarding IFs for him/herself and his or her relatives.

3. Types of results to be returned

- i. Medically actionable results should be returned, according to the patient's preferences, if discovered incidentally.
- ii. Non-medically actionable results, including carrier status, should be considered for feedback by a competent body, e.g. a multi-disciplinary team (see article 5) and returned according to the patients' preferences and which best serve his or her health and wellbeing.

4. Training and continuous education for healthcare providers involved in clinical sequencing

- i. Healthcare providers should receive further training on genetic and genomic tests.
- ii. The specialties of clinical geneticist and genetic counsellor should be recognised by the state and specialised training should be offered to those wishing to enter the specialties.
- iii. To encourage genetic-oriented knowledge, courses about medical genetics and related areas should be introduced into the medical training curriculum.
- iv. To encourage the involvement and raise the awareness of other professionals involved in the provision of genetic and genomic tests, courses focusing on genetics should be introduced to the curriculum of other faculties, e.g. Biology, Nursing.
- v. Efforts should be made to facilitate the continuous education of healthcare providers ensuring that they are able to follow the scientific advances in the area of clinical sequencing.

5. Creation of Multi-Disciplinary Teams

- i. Multi-Disciplinary Teams (MDTs) should be created to support the management of IFs.
- ii. An MDT should seek to:
 - a. Ensure consistency, by gradually developing a step-by-step process while, at the same time, have the flexibility to encompass case-specific characteristics
 - b. Allow professionals to develop their specific area of expertise
 - c. Assist in pre and post-test counselling, follow-up and support for patients and families
 - d. Be in a position to collaborate with both private and public hospital/clinics and laboratories offering genetic and genomic tests
- iii. If an MDT is not available:
 - a. Results should continue to be returned from the laboratory to the treating clinician who would decide what to offer/return to patient based on his/her preferences as expressed during pre-test counselling

- b. Ways to include lab-geneticists in the decision making and feedback process should also be considered, as they are more aware of scientific developments and test limitations than other healthcare providers

6. Preparation of formal guidance

- i. Formal guidance should be prepared, in any form that might take, to assist professionals in the provision of clinical sequencing and management of IFs and to best serve patients' health and wellbeing.
- ii. Any organisation preparing this guidance, such as the National Bioethics Committee, a professional body (such as the Hellenic Association of Medical Genetics or the Hellenic Society of Medical Genetics), the Department of Health or any other competent body, should act according to professionals' consensus and reflecting the needs of patients and lay people.
- iii. Empirical research is needed to provide evidence of patients' and lay people's needs and attitudes before the preparation of formal guidance.
- iv. Guidance should be dynamic and easily updatable. Due to the current developments, guidance should be regularly updated (ideally yearly) to reflect the current scientific knowledge. A dynamic mechanism should be in place to allow the integration of new scientific developments.
- v. Guidance should be dynamic, allowing for professionals' discretion, and adjustable to case-specific needs.
- vi. Existing limited resources need to be taken into consideration when formal guidance is created.

The points-to-consider presented above demonstrate one possible direction policy making could take. Nevertheless, although evidence-based, these should not be used to replace formal guidance. For guidelines to be produced consensus needs to be developed among different stakeholders and a deliberate system of widely accepted principles needs to be created to guide decisions and ensure consistency in practice. In this way, such guidance will garner the acceptance of professionals and be seen by the public as trustworthy. For consensus to be developed, numerous techniques could be used. These alternatives include a Delphi technique, the nominal group consensus model and other models such as the ones developed by the NIH (Glazer in [486]). These models provide participants with a structure within which policy development could be

conducted. For example, a policy-Delphi could be used, using an informed group or a group of experts to whom preliminary evidence would be presented and, based on responses given, consensus would be gradually developed. The points-to-consider presented here could be the basis for such an approach [487].

The input of different stakeholders' and the development of moral principles are, of course, valued, but there is an urgent need for practical guidance in the clinical setting to ensure a high-quality provision of services and the protection of patients; therefore, practical guidance might need to be prioritised. I acknowledge that such an approach would require a very well-structured and organised infrastructure, with different professional associations in place. In Greece, the required infrastructure is not particularly well developed or organised; nevertheless, with the preliminary evidence prepared and presented here, a network of professionals could easily be set up and maintained without the need for extensive resources. After the development of guidance prepared by and addressed to professionals, resembling tier-one and two of the model presented earlier (see chapter 8.6), draft recommendations could be prepared for deliberation and other involved stakeholders could be included.

Such a process would be lengthy and labour-intensive but could create a dynamic, yet structured, framework, ensuring that all stakeholders involved are respected and protected and that their obligations and rights are clear. Moreover, the strength of such a model is that this structure could be adapted and adopted by different countries as the majority of principles guiding the process are not country-specific.

9.4. Reflecting on the conduct of the work

This final section of the thesis is based on my personal experiences when undertaking this project for my doctoral thesis. My purpose is to present a description of my experiences with preparation, data collection and data analysis for all stages of my thesis. It outlines my thinking and working processes involved in conducting the interviews and the questionnaire and subsequently attempting to generate the points-to-consider based on the findings of the quantitative and qualitative components. I believe that my own reflections of the process could explain areas where my research was influenced by my own views and the decisions I made along the way.

Furthermore, in this final section, it will also be shortly described my development as a researcher and the choices I could make if I was starting this whole project from the beginning. My hope is that this can help others interested in conducting similar projects.

To gain a deeper understanding of the topic, I believed it essential to begin this journey with an extended literature review. This review helped me identify the research questions I was interested in and the ways in which I would approach my work. It also revealed the areas I needed to develop if I wanted to conduct a project of high quality and produce worthwhile results. Inevitably, my background as a biologist rather than a social scientist, was often, in those early stages, more of an obstacle rather than a benefit. It quickly became obvious to me that I needed to cultivate a variety of skills including but not limited to conducting and analysing qualitative and quantitative research. Aiming at filling this gap, I spent the first six months exclusively on my training. I attended numerous seminars and workshops and I used most of the remaining time reading both about my topic, i.e. incidental findings, and different approaches to social sciences.

At this point, and trying to be honest to my reader, I need to fully disclose that although I spent so much time reading, I am still not a social scientist. I am confident that there are various books and articles out there that I could have read and I did not because of time limitations or simply because I chose to read something else instead. For these reasons, and being realistic, I also need to acknowledge availability as a factor guiding my choices. The University library offers the possibility of requesting and borrowing books from other libraries, however, I was mainly focused on the literature available on the library or online. I only ordered a small numbers of papers and a handful of books. The vast majority of my readings were found in the library of the University of Leicester. This first period of my thesis helped me become who I am today and looking back the only thing I would do differently would be to perhaps extend this period. I need however to admit that when I started reading papers on the topic, especially the papers that immediately followed the publication of the original ACMG guidelines, I quickly became overwhelmed and I started being impatient. Maybe I even felt overly confident that what I had read was enough to start and that available support would be adequate to help me throughout the process. Therefore, although I went back to the literature and to my numerous textbooks several times during the conduct and writing of this thesis, what I could have done differently is be more patient. Reading the literature about the return of incidental findings from clinical sequencing captured my full interest right away. The first time I read the (original) ACMG guidelines I was so impressed and troubled that I

was really looking forward to getting out in the real world, talking to people that knew the area and learning what they thought about it. Also having a very strong personal view on the ACMG guidelines and specifically against forcing patients to receive results unavoidably made me impatient to talk to experts and see if it was only me thinking that this perspective would create more problems that it would solve. This, in combination with the limited available empirical evidence, were also the main driving factors that influenced my decision to use interviews as my first approach.

Feeling nervous about the prospect of conducting interviews in person with established professionals, I nevertheless started contacting genetics experts. I began with the ones who had published papers on incidental findings or who had expressed a certain opinion (in favour or against) the return of IFs. I was extremely surprised when the majority of the people contacted replied to my email. I had thought that busy and well-recognised doctors and academics would not reply to an email sent by an unknown Ph.D. student but I was pleasantly surprised. Motivated by their friendly replies I organised several interviews. Quickly it became obvious that I had too many questions in mind that I was aiming at asking during the interviews. In my first email, and in the information sheet I had sent to the potential participants, I had stated that interviews were estimated to last approximately about 20-30 minutes. And that was my honest expectation. During the first 3 or 4 interviews I knew with certainty that I had been too ambitious. The interviews lasted much longer and even in cases where the length of the interview exceeded one hour, some of the questions were not covered. Experts had set opinions about the issues under investigation and allowing them time to elaborate and discuss their reasons inevitably meant that some questions had to be skipped. At that point and having observed experts' difficulty in expressing a clear and comprehensive opinion about the return of IFs to minors I decided to exclude those questions. From that point onwards, I only focused on IFs discovered in adult patients. I, together with all the other students attending the seminars on interviews, had been warned that interviews usually last longer than expected as people tend to discuss the topics they are interested in rather than answering specific questions. I had been warned and I had done my best to have clearly defined questions to avoid such issues. However, experts elaborated more on those questions that were either directly related to their expertise or experience or the ones they considered the most challenging. In that way, I ended up with very long replies to some of my questions and very short ones, or even one-word answers to others. Unfortunately, time did not allow me to ask more questions and elaborate more on some areas. Each interview was unique

and each interviewee chose to focus on slightly different areas of the same topic regardless of my efforts to cover every aspect in the same amount of detail. I intentionally allowed some interviewees to expand as they wished without of course forgetting the remaining questions. They usually discussed their personal attitudes and practices in more details when they were allowed to guide the discussion. Looking back, I think I would have chosen a much smaller number of questions and I would have focused on them rather than trying to cover as many areas as I could in the limited time available.

I transcribed the vast majority of the interviews myself and thus I was feeling very confident that I knew what each interview was about. Feeling energised by meeting and talking to all those interesting people who were willing to share their thoughts with me I started analysing my interviews right away which proved to be a mistake. Although analysing the interviews as I was conducting them allowed me to remember each interviewee clearly, made transcribing them more easily and have that feeling of still being in contact with each person, it also prevented me from developing an overall feeling about the interviews as a whole. Some of the themes initially identified were heavily rooted in the questions from the topic guide and I was not allowing myself to get some distance and see what people were actually saying. My interpretation was unavoidably influencing their sayings. It took me some time to realise what I was doing and it was only then that I stopped the analysis, completed the remaining interviews and forced myself to take some time before going back to the analysis. When I eventually did, I had to delete all that I had initially done and start over. I re-read all interviews and I started identifying themes from the beginning. What I would have certainly done differently, if I could start over, would be to wait until all interviews were completed before starting the analysis formally. But I assume that part of becoming an independent researcher is making your own mistakes and learning from them. Although warned, I had never expected the amount of data generated by the interviews and how labour-intensive analysis would be but at the same time spending so much time working on the interviews allowed me to develop a better understanding of experts' attitudes, hence I consider that time well spent.

As with the development of the topic guide, I started working on my questionnaire with some basic questions in mind. While doing the literature review, and more intensively, while conducting and analysing the interviews some questions started developing in my mind. Experts seemed to share general attitudes and differ in some of the details. For example, the majority were in favour

of returning incidental findings but some only wanted medically actionable results returned, while others would be willing to return other results such as those that could inform patients' reproductive choices. These findings from the interviews were directly translated into questions and multiple-choice answers for the questionnaire (see chapter 3). With the questionnaire I wanted to investigate whether the general attitudes I was observing in my interviews would be present in a slightly different sample. Of course the questionnaire was also populated with some general questions but in general the theme was kept consistent as the area I was intending to cover was very similar to the one covered in the interviews. As before, some issues were not included in an effort to keep the questionnaire short and easy to complete. The questionnaire was designed and amended numerous times before and after being piloted and finalised. When its length and clarity were considered appropriate by the group piloting the questionnaire, myself and my supervisors, the questionnaire was sent to the two Genetics Associations. Looking back what I would have done differently was that I would have chosen to offer the "Other" choice to more questions. I believe that because I was the one conducting both stages of the project, sometime I was heavily rooted in my questions and the findings from the interviews that, for some questions, I only offered the choices that were raised during the interviews. Providing space for genetics professionals to express an alternative that was not previously mentioned might have yielded interesting results. Nevertheless, as there was no plan for follow-up and questionnaires were anonymous even if there was something new mentioned there would be no way explore it further.

Moving to the administration of the questionnaire, I thought that having the questionnaires anonymous might encourage more professionals to participate and to express their honest opinions without the fear of being judged. This was the reason why I chose to send the questionnaires to the Genetics Associations and have them mediate all my communications with their members. This choice, although reasonable at the time, potentially came at the cost of a low response rate. Not having the possibility of sending more emails to the potential participants or personalise my invitations and reminders might have contributed to the low number of responses as a personal invitations has been found to be an important factor increasing response rate (see chapter 3). However, this would have required me to have access to personal data held by another body, so I considered it more ethical and easier to have the Associations send them on my behalf. Furthermore, knowing some people at each association made it easier to ask them to send the one invitation and two reminders (which I wrote myself). When I started, I had thought that

more people would be interested in participating in my study. I was thus quite disappointed by the response rate. If I knew the response rate would be low I would have had to have more interviews, possibly structured interviews rather than the questionnaire. However, such an alternative would have required many more resources and be time intensive as it would require my physical presence in Greece. The questionnaire proved to be a useful resource but I am assuming that having, for example 30, more interviews with geneticists might have been an equally, if not more, information-rich source.

The low response rate from the questionnaires set in motion a different course of actions that I had planned. I was expecting, and hoping, to have a higher number of responses, one that would allow a basic statistical analysis. Nevertheless, with 52 responses I had to adjust and only use descriptive statistics to try to make sense out of the data. This was proved to be quite hard as some assumptions had to be made along the way in an attempt to explain different responses and draw inferences from the replies. Looking back, I do not think I could have done anything differently, as the number of responses collected did not allow for any different type of analysis.

Last but not least, the most challenging phase of this project was the preparation of points-to-consider. Earlier in this chapter I have described in detail how and what principles were guiding the development of the points-to-consider. Being reflective along the way was particularly challenging as some of the choices were made at a less conscious level and it was often hard to distance myself and separate the findings from my own biased judgement. It has been even more challenging to document and report this process here. Moreover, often I also had to overcome personal dilemmas. For example, as an advocate of autonomy and free choice myself, it was hard to accept that occasionally patients might not be able to make a choice for themselves. At the same time, as a biologist it was obvious sometimes that if I had difficulty understanding all the potential implications of clinical sequencing, lay people with no previous knowledge of genetics, often uneducated, confused and stressed would face more difficulties. In cases like that what helped me was reading other more experienced people's opinions. Often, I found other scholars that had similar concerns and had made suggestions with which I agreed. These are the ones that took me a step forward and these are among some of the ones referenced here. It would be very easy to say that the points-to-consider only reflected experts and geneticists' input. Simply remaining at that descriptive level would indeed be simpler, but it would also be misleading. As mentioned earlier, it is important to acknowledge my own position and values. I do not subscribe

to a naïve view that the researcher simply describes other people's attitudes or gives voice to his or her participants. My position, arguments, and principles have inevitably influenced what I have selected, edited, reconstructed and of course what the conclusions of this thesis are. However, throughout this project, I have been transparent as to the decisions made and the rationale behind them and I believe that the approach chosen matches what I wanted to know and that all my decisions are acknowledged and justified.

9.5. Strengths and limitations of this project

9.5.1. Strengths

This study has a number of advantages that derive from its methodological approach and its findings and it also suggests there are positive implications for the future integration of clinical sequencing and management of IFs.

This study is the first to compare across countries professionals' attitudes regarding the usefulness, awareness, and intention to use clinical sequencing and attitudes towards the return of IFs. The comparison revealed more similarities than differences across countries demonstrating that overarching principles are shared among professionals and go beyond the characteristics of each healthcare system. As clinical sequencing is expected to be used more often in the future, comparative studies are needed to demonstrate the direction national and international guidance should take. This work was the first step and has shown that examples from other countries, with longer traditions in health governance, could be used and could facilitate the preparation of guidance in countries with limited resources and experiences in novel technologies. Rather than "re-inventing the wheel", studying examples of other countries could inform the preparation of guidance as it would, as in this case, suggest practices that could be transferred as they are and practices that would require adjustment to fit different contexts. Furthermore, as the process of preparing points-to-consider for Greece has been described in detail, the example of this project could be used by other countries with similar healthcare systems to Greece after adapting this process to adjust to their specific characteristics and needs. In this way, more countries could develop guidance in a shorter time while a minimum level of consistency would be ensured as guidance would be built on the same overarching principles.

For this project, two methods (qualitative and quantitative) have been used. The combination of the methods has served to increase participation and enable a better comparison across countries, while enriching and allowing triangulation between the findings. At the same time, the mixed methods used have validated the findings and have revealed common attitudes among groups of professionals.

The strengths of the qualitative phase of this project mainly derive from the choice of in-depth interviews as the method of data collection. In-depth interviews, which usually lasted about an hour, provided a rich source of information because participants were given the opportunity to

talk about their real, concrete experiences which incorporated the past, present and anticipated future. Especially for Greek experts, this project provided them with the opportunity to describe a valid and realistic picture of the Greek situation, which is little known outside Greece.

Furthermore, another strength of this study is its quality. As described in section 3.6. a COREQ checklist was used to assess the quality of the qualitative work and all 32 points included in the checklist were covered. The use of the checklist and the verification of all the points that are covered increases the transparency of the research methodology used and provides what is described as the “theoretical possibility of the reader being able to duplicate the study” [315](p.356). It is my goal, by using the checklist, to facilitate a critical analysis of the work conducted here and to add to the debate in favour of those supporting the qualities and efficiency of qualitative research.

Other strengths derive from the quantitative phase of this project. Relatively new methods of research, such as online questionnaires, were used and were proven to be useful. Choosing online questionnaires provided me with the opportunity to contact and collect data from professionals who I would have been unable to reach in other ways due to practical barriers (time, distance, resources). Moreover, all registered Greek geneticists were invited to participate and contribute with their input, subsequently providing a possibly representative sample of geneticists working on clinical sequencing. Assuming that the geneticists who replied to the questionnaire are the ones interested in genomic tests, either because they offer them already or because they expect they might in the future, then the generalisability of the findings here are likely to be good and findings from the questionnaires could potentially be generalised to all Greek geneticists.

Finally, from a Greek perspective, this study offers insights for which there is currently very limited literature available. The points-to-consider prepared here can be to facilitate the preparation of formal guidance in Greece. It is my intention, after the end of my doctoral studies, to share the points-to-consider produced with the National Bioethics Committee, translate them into Greek and make them accessible to Greek professionals through the two genetics associations. In this way, the results of this project will have practical implementations and will provide insights into professionals’ attitudes.

9.5.2. Limitations

As discussed above, this study has a number of original contributions and strengths. Nevertheless, as with every study, it inevitably also has limitations. These limitations are acknowledged in this section in an attempt to facilitate future research in this area.

The first limitation of this study concerns language. All research was conducted in two languages, Greek and English, and potential losses of meaning in translation should be acknowledged. Efforts were made to minimise this possibility as numerous people were called upon to verify the translations, in both linguistic directions. Greek native speakers with formal education (undergraduate and postgraduate studies) in Greek and proficiency in English were used to double-check documents translated from English to Greek while English-native speakers were asked to check the accuracy and quality of documents produced in English. All tools used (topic guide for the interviews, questionnaire, invitation, reminders) were piloted and their wording, vocabulary, and clarity were checked. One limitation that I could not overcome was the translation of the term “incidental finding”. Although all experts and Greek professionals were asked for their input regarding the translation, no consensus was observed, potentially reflecting the disagreement of professionals from around the world regarding the most fitting term to describe these type of findings.

The relatively small number of experts interviewed for the qualitative phase of this project could be a potential limitation. The small number might limit the generalisability of the views collected here. However, the area is currently under development and, hence, the total number of professionals, and in particular of those that could be seen as experts, is a relatively small population to start with. Especially for Greece and the UK, the number is limited and interviewing a larger number of USA experts, where greater numbers could potentially be found, would have created an imbalance across countries and was, thus, considered as not beneficial for the purposes of this study. Nevertheless, the sample was diverse as intended, and, therefore, a range of attitudes is presented here. Additionally, as saturation was achieved in each one of the sub-groups, it is my belief that the insights offered here present a wide range of different views on the issues raised and, thus, provide a good reflection of the existing situation. Furthermore, as experts suggested (through sampling using snowballing technique) colleagues with opposing views, I collected data on a variety of attitudes. The attitudes of other experts, especially for UK and US experts, were represented through the literature review that was incorporated here to provide

additional evidence. Regarding the interviews, although in-depth interviews offered a rich data set, interviewees were describing their views on the situation rather than the situation itself. Acknowledging this, the interviews would have been further enriched if accompanied by observations of genetic testing practice but the rarity of the ES tests and other constraints (time, money and distance) did not allow such an approach. This could, however, be an interesting area for future research, once exome and genome sequencing becomes more common.

Concerning the quantitative phase of the project, the relatively low response rate was the main limitation. Although within the acceptable range for online questionnaires, the response rate did not allow formal statistical analysis of the data and, therefore, no clear associations could be produced. The response rate achieved could be explained by the limited use of exome and genome sequencing in Greece at the current time and professionals' limited experience and expertise, potentially discouraging them from sharing their opinions. Besides this, another limitation was that I was unable to calculate an accurate response rate as the number of geneticists who received the questionnaire remains unknown. Hence, the response rate could be higher if the number of questionnaires received was lower than 204, which is the total number of registered geneticists in the two Greek associations. Finally, as questionnaires were self-completed, the accuracy of the information collected relies on professionals' honesty and knowledge of the area. As mentioned earlier, other methods such as observations could be used to increase the accuracy of the evidence collected.

9.6. Future research

I have, in this study, successfully filled in some of the gaps identified during the literature review, such as providing more empirical evidence on professionals' attitudes towards the integration of sequencing in the clinical setting and feedback of IFs or the type of results that are to be returned. Similarly, I have also made suggestions as to how traditional bioethical principles can be integrated into this context to support better practices and guidance. However, a number of areas that remain under-investigated and require further research. I have identified three major areas that I believe call for more empirical evidence.

First, there is a lack of empirical data regarding lay people's and patients' attitudes regarding the use of clinical sequencing and management of IFs. Lay people and patients should be approached and their needs, intentions, and their awareness should be investigated, among other factors. Similarly, their understanding of genetic and genomic information should also be sought. These groups could be studied together, however, I believe it might be more helpful if approached separately as studies from other areas have revealed that patients might have different concerns and needs compared to healthy individuals that face the possibility of sickness only as a hypothetical scenario. The latter, i.e. patients, have experiences not only regarding their existing condition but also regarding their relationship with their clinicians, the healthcare system and might also have been exposed to other factors such as counselling, receiving results etc. and, hence, are in a different position than lay people as potential patients. Regardless of the approach chosen, both groups should be asked about their intentions to use clinical sequencing, their intention to receive IFs, the types of IFs that they would like to receive as well as the process through which they would like to receive their results. Their opinions about sharing these potential results with their family members should also be investigated to show if additional measures have to be taken to encourage patients and lay people to share genetic and genomic results. As mentioned during several of the interviews, research is needed to explore not only these groups' attitudes but also the factors influencing their decisions.

Second, clinicians' and other healthcare providers' abilities to be involved in the process should be investigated. Their understanding of genetic and genomic information would inform the type of training and further education that might be needed to help professionals deal with this complex

issue. If research reveals limited understanding, as suggested, then specialised educational material and training in the form of seminars or intensive courses could be prepared, tailored to the needs identified.

Third, different stakeholders' attitudes after receiving results could provide insightful input that would greatly improve guidance and help its preparation. In most cases, stakeholders are asked hypothetical questions and, therefore, answers received reflect their theoretical reactions. However, the reality might differ and gaining access to patients' and professionals' input after receiving or returning results would show if current processes are sufficient and how they could be improved to best serve patients' needs and preferences.

One more area in need of further evidence is genetic counselling and informed consent practices. As discussed in previous chapters, concerns have been expressed regarding the appropriateness of the traditional informed consent process and counselling to cover clinical sequencing. Research is needed to show whether such claims are true and if so, to demonstrate new models and practices that could be implemented to assist the process.

Finally, I believe that the use of clinical sequencing and the return of results to minors needs additional attention. Preliminary data collected through this project was inadequate to support any conclusions. This topic is of great interest and needs to be investigated separately.

9.7. Conclusion

Empirical evidence collected through this project, verified by the literature review, reveal that in Greece there is currently no framework regarding the management of clinical sequencing and the return of IFs to patients. This absence leaves all decisions to genetics professionals' discretion. As these professionals feel unsupported, they ask for guidance to help them ensure the provision of a good level of health services. In this project, evidence from experts and genetics professionals from three countries was collected and used to prepare points-to-consider specifically for the Greek context. These points-to-consider aim at providing a preliminary basis upon which formal guidance could be created.

The points-to-consider include both issues that touch on ethical norms such as the need for extensive counselling as a reply to basic human needs seeking support, and practical issues, for example, the need to recognise a medical specialty of clinical geneticist and genetic counsellor. These, combined with a scheme resembling Berg's binning system, could guide the management of clinical sequencing and the return of IFs until formal guidance is produced and at the same time inform the creation of this guidance. As scientific developments are moving at a fast pace, I believe that a bottom-up approach is the most appropriate for the preparation of formal guidance and the empirical evidence collected for this project, based the points-to-consider that I have prepared. Such an approach would show patients that their rights to make their own choices have been respected, yet there is support for them if they choose to seek expert assistance. Such guidance will help healthcare professionals provide the best treatment possible, while recognising that they too need support. Guidance created in a transparent fashion will show all stakeholders that it is built on the best practices available and will enhance stakeholders' trust in clinical genetic services.

APPENDIX 1 – GLOSSARY

Definitions for different specialities mentioned in the text

Geneticist: The general term used to include all professionals, with different backgrounds and formal education, being specialised or working closely on genetic and genomic tests.

Clinician: The general term used to describe all individuals with medical training. This individual has usually direct contact with the patient. For the purpose of this project, this term will be usually used to refer to medical doctors usually not specialised in genetics.

Clinical Geneticist: The individual who has received medical training and is specialised in genetics, i.e. the diagnosis and management of hereditary disorders. For Greek professionals, as there is no recognised specialty, therefore, this is not their format job title, this term will be used to refer to medical doctors that have either received their specialty abroad or that have extensive experience working on genetic and genomic tests and are therefore specialised “by experience”.

Lab (oratory) Geneticist: The individual who has studied Biology or another related field and has specialised in genetics, and is working on the laboratory conducting the sequencing and participating in the data analysis.

Genetic counsellor: The individual who has received appropriate training (usually a Master of Science) and is able to provide genetic counselling. Depending on the country (s)he must have been certified by a competent body.

“The genetic counselor determines whether a condition in the family may be genetic and estimates the chances that another relative may be affected. Genetic counselors also offer and interpret genetic tests that may help to estimate the risk of disease. The genetic counselor conveys information in an effort to address concerns of the client and provides psychological counseling to help families adapt to their condition or risk” [488].

For Greek professionals, this term will be used to include clinicians and lab-geneticists offering counselling as part of their other professional obligations. That person, since there is no recognised specialty in Greece, could have received the specialty abroad or by extensive experience.

Non-clinicians: For the purpose of this project this term will be used to describe all other professionals, healthcare providers or not, who have not received a medical training and are involved with genetic and genomic tests in another way, i.e. lab-geneticists, genetic counsellors, professionals with legal and bioethical background.

Other potentially useful definitions

Allele: “An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Though the term allele was originally used to describe variation among genes, it now also refers to variation among non-coding DNA sequences [488]”.

Carrier: An individual who has a recessive, disease-causing gene mutation on one chromosome of a pair and a normal allele on the other chromosome thus not displaying that trait or show symptoms of the disease [489].

Exome: “That part of the genome that corresponds to the complete complement of exons of an organism or cell” [490].

Genome: “The genome is the entire set of genetic instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cells' mitochondria. Each set of 23 chromosomes contains approximately 3.1 billion bases of DNA sequence” [488].

Heterozygous: “Heterozygous refers to having inherited different forms of a particular gene from each parent. A heterozygous genotype stands in contrast to a homozygous genotype, where an individual inherits identical forms of a particular gene from each parent” [488].

Homozygous: “Homozygous is a genetic condition where an individual inherits the same alleles for a particular gene from both parents” [488].

Mutation: A mutation is a change in a DNA sequence.

Pharmacogenetics and Pharmacogenomics: The general term used to describe the study of genetic variations in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects. Used interchangeably with the term pharmacogenomics which also investigates the role of acquired and inherited genetic differences in relation to drug response and drug behaviour through a systematic examination of genes, gene products, and inter- and intra-individual variation in gene expression and function [491].

Phenotype: “The observable physical and/or biochemical characteristics of the expression of a gene; the clinical presentation of an individual with a particular genotype” [489].

Genotype: “The genetic constitution of an organism or cell [489]”.

Recessive: Describes a trait or disorder requiring the presence of two copies of a gene mutation in order to express observable phenotype [489].

Variant: An alteration in the normal sequence of a gene. This alteration might be significant, non-significant or unclear.

APPENDIX 2 – SUPPLEMENTARY MATERIAL

In Appendix 2 will be presented all supplementary material used for the interviews and the questionnaire. These include:

- a. Information Sheet sent to all interviewees before the interview. A printed version was also handed to all of them at the beginning of each interview.
- b. Consent form signed by all interviewees
Two copies of the consent form were signed by both the researcher, i.e. me, and the participant. One copy has given to the participant and the other copy was kept secure until the end of this project.
- c. Generic draft topic guide used for interviews
- d. Invitation, forwarded, though the Genetics Associations, to all registered Greek Geneticists
- e. Questionnaire
[It should be noted that the website SurveyMonkey© was used for the upload of the questionnaire therefore the version presented here has been modified to fit the page and document format.]
- f. Reminder, forwarded, though the Genetics Associations, to all registered Greek Geneticists

It should be noted that all documents are available in both Greek and English versions (and could be provided upon request). Only English versions are presented here.

Participant Information Leaflet

**Project Title: Incidental findings in clinical sequencing****Thank you for reading this information leaflet.**

You are being invited to take part in a research project. Before you decide to participate it is important for you to understand the scope of the research.

Please take time to read the following information carefully and ask me if anything is unclear or if you would like more information.

Purpose of the research

I am conducting a study for my PhD that is looking into incidental findings (IFs) from clinical sequencing using Next Generation Sequencing (NGS). The first part of my research, in which you are invited to participate, will include interviews with professionals, considered as experts in their field. These interviews are conducted for information-gathering purposes in order to inform future research (part 2 – questionnaires). My work will be comparative and it is looking into professionals from Greece, the UK and the USA. The main aim of my research is to get a better understanding of the situation in each country. I will investigate previous experiences with IFs and NGS and identify professionals' views on the matter; compare these across the three countries and identify issues that will facilitate the creation of a questionnaire that will be applied to young lay people.

Why have you been chosen?

You have been chosen to participate in this research because you are considered as an expert in genetic testing and I think you can help me with my study.

However, you do not have to take part in this research if you do not want to. If you do decide that you would like to take part, you can withdraw up to the point of publication of my thesis. If you do decide to take part, you will be given this information sheet to keep and you will be asked to complete a consent form.

This study is being supported and funded by the University of Leicester. It has been approved by the University of Leicester College of Medicine and Biological Sciences Ethics Committee.

Please turn over



Participant Information Leaflet

**Participating**

If you decide that you would like to take part in this research, I will arrange an interview at a time and place of your convenience. It may be possible that we can do the interview over the telephone. In the interview I will ask you about your opinions and experiences of genetic testing in general, NGS and incidental findings and what you expect in the future. The interview will take around 20 to 30 minutes and I would like your permission to audio record it. The transcripts will be kept secure at the University of Leicester.

Confidentiality

All actions will be taken to ensure that your identity is not revealed:

- The audio recording and transcribed interview will only be accessed by the research team. Audio recordings will be deleted at the end of the research.
- No personal data will be linked to the interview data. With your permission, I would like to record your general job title. Anything that you have said that might identify you will be removed or changed in the published findings.
- Quotations from the interview may be used in the research report or resulting publications but you will not be identified.

Results of the research

If you would like to receive a summary of the results of the study, please provide me with your email address and I will send the publications resulting from this work.

Contact for further information


If you would like further information please contact myself or another member of the research team:

Elli Gourn
Department of Health Sciences
University of Leicester, Leicester LE1 7RH
eg202@le.ac.uk

Supervisory Team
Dr Susan Wallace, Supervisor sew40@mail.cfs.le.ac.uk
Dr Natalie Armstrong, Supervisor na144@le.ac.uk

Thank you for taking the time to read this information sheet.

This study is being supported and funded by the University of Leicester. It has been approved by the University of Leicester College of Medicine and Biological Sciences Ethics Committee.

Consent Form		 University of Leicester	
<u>Project Title:</u> Incidental findings in clinical sequencing.			
Please read each statement and initial the box if you are in agreement:			
I have read the participant information sheet and have had time to ask any questions or ask for further information.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
I understand the scope of the research and what my role is going to be.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
I understand that taking part is voluntary and I can withdraw from the research at any point.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
I understand what will happen to the interview data and the actions that will be taken to avoid identification.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
I agree to have the interview audio recorded.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
I agree that anonymised quotations from this interview can be used in the thesis and any resulting publications.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
I am happy for my general job title to be recorded.	Yes <input style="width: 40px; height: 20px;" type="checkbox"/>	No <input style="width: 40px; height: 20px;" type="checkbox"/>	
I agree to supply my email address in order that I may receive findings of this study. Email:	Yes <input style="width: 40px; height: 20px;" type="checkbox"/>	No <input style="width: 40px; height: 20px;" type="checkbox"/>	
I agree to take part in this research.	<input style="width: 40px; height: 20px;" type="checkbox"/>		
Participant name:	Participant signature:	Date:	
_____	_____	_____	
Researcher name:	Researcher signature:	Date:	
_____	_____	_____	
<p>Thank you for taking the time to participate in this study.</p> <p>This study is being supported and funded by the University of Leicester. It has been approved by the University of Leicester College of Medicine and Biological Sciences Ethics Committee.</p>			

Project Title: Incidental findings in clinical sequencing.

1. General questions

- What is your job title?
- How would you define “incidental findings” (IFs)?

2. Regulations and guidelines

- Do you know if there are specific regulations about returning IFs to patients?
- If yes, what type? (law, guidelines etc.)
- If no, to your best knowledge, are there guidelines or any other supporting system to help clinicians if IFs are discovered?
- Is there a specific regulation/ procedure in place in your lab/clinic?
- Any problems with implementing them?
- Do you have a committee that would be able to assist?
- If yes, could you please tell me a little bit about it?
- What kind of supporting mechanism do you think should be in place?

3. Personal questions – previous experiences and attitudes

- Have you had any experience with IFs so far?
- If you did, how did you handle it?
- What would you consider in deciding whether or not to inform the patient/their family about the IF?
 - ✓ Actionable vs not actionable?
 - ✓ Mendelian or simply associated with a certain condition?
 - ✓ Not related to the patient but could be useful to his family?
 - ✓ Other?
- What concerns, if any would you have, regarding returning or not returning IF?
- If you decided to return the IF
 - ✓ Who to? To the patient or his family?
 - ✓ When? Should they wait after the end of the cancer treatment?
 - ✓ Who should disclose it? Oncologist? GP? Other?
- In what way should results be returned? (verbal/written, by mail/email/face-to-face)
- What happens if patient dies? Should findings be disclosure to his family?

Questionnaire



The questionnaire is anonymous. All answers will remain strictly confidential.

The completion of the questionnaire will take you approximately 10 minutes.

Thank you for taking the time to complete the questionnaire and replying with honesty.

For questions or further information about our research or feedback about the questionnaire please contact: Elli G. Gourni (eg202@le.ac.uk)

SECTION 1 – GENERAL QUESTIONS

1. Are you aware that when conducting a whole exome or whole genome sequencing for a diagnostic indication, findings that are unrelated to that diagnostic indication could be discovered?
 - a. Yes
 - b. No
 - c. I don't know
 2. Do you consider unrelated findings as an issue deriving exclusively from genetic/genomic tests?
 - a. Yes
 - b. No
 - c. I don't know
 3. If not, do you think that any of the tests mentioned below could produce unrelated findings (please check all that apply):
 - a. Blood test
 - b. Prenatal test
 - c. MRI/ Scan / x-rays
 - d. Other (please specify):
 4. Would you consider that comparing to information deriving from other medical tests, genetic information is:
 - a. Similar
 - b. Different
 - c. I don't know
 5. In which way different? Please specify:
-

SECTION 2 – RETURN OF UNRELATED FINDINGS AND PROFESSIONAL ATTITUDES

6. For the following categories, please say if you think patients should be able to choose to receive information on unrelated findings.

"I think patients should be able to receive information about conditions that are..."

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
life-threatening and preventable/ treatable					
life-threatening and not preventable/ treatable					
life-threatening, late-onset and preventable/ treatable					
serious (but not life-threatening) and preventable/ treatable					
serious (but not life-threatening) and not preventable/ treatable					

7. "I think patients should be able to receive information that..."

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
demonstrates how they might respond to different medications or drugs (e.g. statins, anti-depressants etc)					
tells them if they are a carrier of a condition that could be relevant to their children					
tells them if they are a carrier of a condition that could be relevant to their future reproductive choices					
is not immediately relevant but could be useful later in life (e.g. relating to a very late onset cancer or predisposition to strokes)					
is uncertain and cannot be interpreted at the moment					

8. Who should decide which types of unrelated findings to offer to patients? (please check all that apply)
- a. The treating clinician
 - b. A multi-disciplinary team including the treating clinician
 - c. A genetic counsellor
 - d. A scientist such as a lab-based geneticist
 - e. An independent ethics committee
 - f. Patients' representatives
 - g. The patient
 - h. Other (please specify)
9. Let's assume a patient has given consent to receive unrelated findings discovered during clinical sequencing. How should this information be delivered? (please check all that apply)
- a. Face-to-face consultation
 - b. Telephone consultation
 - c. Email
 - d. A secure online database
 - e. Post
 - f. Any of the above - I don't think the way makes a difference
 - g. Other (please specify)
10. Who should feedback these results? (please check all that apply)
- a. The treating clinician
 - b. A multi-disciplinary team including the treating clinician
 - c. A clinician
 - d. A genetic counsellor
 - e. A scientist such as a lab-based geneticist
 - f. An independent ethics committee
 - g. Administrative staff e.g. secretary
 - h. Other (please specify)

SECTION 3 – ATTITUDES TOWARD WHOLE EXOME/GENOME SEQUENCING AND IFS

11. Please say if you agree with the following statement.

"The possibility to discover unrelated findings would influence my opinion to order a whole exome/genome sequencing test?"

Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree

12. "I believe the benefits from ordering a whole exome/genome sequencing test is that ... (please check all that apply)
- a. Will help me get a diagnosis for the primary investigation
 - b. Will receive medically useful information other than for the primary investigation
 - c. My patient will learn information about himself
 - d. My patient will learn information that could benefit other members of his family
 - e. Other (please specify)
13. "My concern about ordering a whole exome/genome sequencing test is that ... (please check all that apply)
- a. I will not be able to interpret results
 - b. It might reveal unrelated findings
 - c. My patient might not be able to handle the results
 - d. My patient's family might not be able to handle the results
 - e. The high cost
 - f. Other (please specify):

SECTION 4 – MANAGING THE USE OF WHOLE EXOME/WHOLE GENOME SEQUENCING IN THE CLINIC AND UNRELATED FINDINGS

14. Please say if you agree with the following statements.
 "To support professionals when unexpected findings are discovered ...

	Strongly agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
A law should be created					
Recommendations should be prepared					
A team of clinicians should be put in place locally to deal with cases one-by-one					
A multi-disciplinary team should be put in place locally to deal with cases one-by-one					
Clinicians and others should be required to return only the results on a specified list					
Other (please specify):					

15. If recommendations or a list had to be created who would you think would be the most appropriate group to do so:
- a. a professional body e.g. HMGH
 - b. the National Bioethics Committee
 - c. Every clinic/labouratory should create its own
 - d. A multidisciplinary group consisting of professionals and patients' representatives
 - e. Anyone as long as they are created
 - f. Other (please specify)

SECTION 5 – TRANSLATING THE TERM INCIDENTAL FINDINGS (IFs) IN GREEK

16. Which term would you consider most appropriate to translate in Greek the English term "Incidental findings";
- a. Απροσδόκητα ευρήματα [Translated as unexpected]
 - b. Τυχαία ευρήματα [Translated as random]
 - c. Μη σχετιζόμενα ευρήματα [Translated as unrelated]
 - d. Άλλος (παρακαλώ διευκρινίστε) [Other (please specify)]

SECTION 6 – DEMOGRAPHICS

17. Are you currently working in:
 - a. A clinic
 - b. A laboratory
 - c. University
 - d. Other research setting
 - e. Other (please specify)
18. Are you a:
 - a. GP or Primary Care Physician
 - b. Clinical geneticist
 - c. Genetic counsellor
 - d. Diagnostic lab scientist
 - e. Oncologist
 - f. Radiologist
 - g. Gynecologist
 - h. Nurse
 - i. Other (please specify)
19. How old are you?
 - a. <30
 - b. 31-40
 - c. 41-50
 - d. 51-60
 - e. 61-65
 - f. >65
20. You are:
 - a. Female
 - b. Male
21. What is your highest degree?
 - a. High school graduate
 - b. Undergraduate studies
 - c. Post – graduate studies
 - d. PhD
 - e. MD
22. Do you have children?
 - a. Yes
 - b. No
 - c. I would prefer not to say

Thank you for taking the time to fill the questionnaire.

If you are interested in receiving the findings from this study please provide us with your email below:

For questions or further information about our research or feedback about the questionnaire please contact:
 Elli G. Gourna (eg202@le.ac.uk)



1 Sep 2014

College of Medicine,
Biological Sciences And Psychology
Department of Health Sciences
2nd Floor, Adrian Building
University Road
Leicester LE1 7RH
UK

**Invitation for "Investigating Professionals' Attitudes toward
Return of Incidental Findings from Clinical Sequencing" Survey.**

Dear Medical Geneticist,

You have been invited, as a member of the [Name of the Association], to provide your expert opinion about Return of Incidental Findings from clinical sequencing. As the purpose of the study is to prepare recommendations seeking to support geneticists, your participation is vital in order that your views are fed into the creation of the recommendations.

This study is part of a PhD programme conducted at the University of Leicester, looking at Professional Attitudes toward Incidental Findings from Clinical Sequencing. The aim of the study is to get a better understanding of Greek Geneticists' needs and concerns and to prepare some recommendations that could support professionals when IFs are discovered. Further information about me and my study could be found in: [Elli G. Gourni](#) [link]

The completion of the questionnaire will take approximately 10 minutes.

The questionnaire is anonymous and all replies will remain confidential. No sensitive information will be sought. With your permission, we would like to record some demographic information (age, job title etc.) but you can choose to not answer any questions you wish. You can withdraw from this study at any time by closing the browser window. No data will be retained until you click the submit button.

The following link will take you to the questionnaire:

https://www.surveymonkey.com/s/IncidentalFindings_GreekGeneticists

Thank you for taking the time to complete the questionnaire.

Your time and opinion is greatly appreciated.

Ms Elli G. Gourni
PhD Researcher
[Department of Health Sciences](#)
[College of Medicine, Biological Sciences and Psychology](#)
University of Leicester
Tel: 0116 252 2267 Email: eg202@le.ac.uk

For questions or further information about our research, feedback about the questionnaire, or to receive our findings; please contact: Elli G. Gourni (eg202@le.ac.uk)



8 Sep 2014 [and sent again on the 20 Sep]

College of Medicine,
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Department of Health Sciences
2nd Floor, Adrian Building
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Leicester LE1 7RH
UK

**Reminder for participating in the "Investigating Professionals' Attitudes toward
Return of Incidental Findings from Clinical Sequencing" Survey.**

Dear Medical Geneticist,

*Last week you were invited to participate in our survey investigating Genetics Professionals attitudes toward
Incidental Findings from Clinical Sequencing.*

If you have already completed the questionnaire please accept our sincere thanks.

If not, could you please take the time and complete it today?

*As we are trying to prepare recommendations for Medical Geneticists, your views are valuable, in order that
recommendations reflect your attitude and that are to be proven useful.*

Please find below the link for the questionnaire

https://www.surveymonkey.com/s/IncidentalFindings_GreekGeneticists

Thank you for taking the time to complete the questionnaire.

Your time and opinion is greatly appreciated.

Ms Elli G. Gourni

PhD Researcher

[Department of Health Sciences](#)

[College of Medicine, Biological Sciences and Psychology](#)

[University of Leicester](#)

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For questions or further information about our research, feedback about the questionnaire, or to receive our findings; please
contact: Elli G. Gourni (eg202@le.ac.uk)

APPENDIX 3 – ABSTRACTS OF PUBLISHED WORK

1. Incidental findings from clinical sequencing in Greece: reporting experts' attitudes.
Gourna E. G., Armstrong N., and Wallace S. E.,
Journal of Community Genetics, 2014. 5(4):383-93.

Unprecedented progress in sequencing technologies and decreasing cost have brought genomic testing into the clinical setting. At the same time, the debate in the literature concerning the return of incidental findings (IFs) has made this an important issue internationally. These developments reflect a shift in genetics that will also affect smaller countries, such as Greece, that are just starting to implement these technologies and may look to other countries for examples of good practice. Ten in-depth interviews were conducted with Greek experts in clinical sequencing. Previous experiences and attitudes toward IFs and clinical sequencing were investigated as well as views on the existing policy regarding managing genetic information generated through testing.

Interviews were analysed using thematic analysis. All participants reported the lack of any legal or other supportive mechanism. IFs are currently managed at a “local” level, i.e. within the clinic or the laboratory in an ad hoc way. All participants thought that clinically valid and actionable IFs should be returned, but always with caution and in respect to patients’ wishes, although several experts reported returning IFs according to their clinical discretion. Experts reported that most patients ask for all tests available but they felt that more counselling is needed to understand and manage genetic information. Due to the lack of any supporting mechanisms, professionals in Greece, even those with established experience in the field of genetic and genomic testing, have difficulties dealing with IFs. All experts agreed that it is now time, before the full integration of genomic testing into everyday clinical practice, for guidance to help Greek physicians work with patients and their families when IFs are discovered.

2. Compare and contrast: a cross-national study across UK, USA and Greek experts regarding the return of incidental findings from clinical sequencing.

Gourna E. G., Armstrong N., and Wallace S. E.,

European Journal of Human Genetics, 2015. 24(3):344-9.

Return of incidental findings (IFs) from clinical sequencing has become a hotly debated topic over the past year. Efforts are being made by several bodies to provide guidance at both national and international levels; however, no studies comparing attitudes of experts across different countries have been published so far. Our goal was to investigate attitudes towards the return of IFs from clinical sequencing across UK, USA, and Greek experts. Thirty in-depth interviews were conducted with genetics and genomic experts with different backgrounds. Our study revealed more differences when experts were compared according to their professional background than their country. General principles guiding the decision-making and the feedback process were common across all experts but the details of integrating these tests might vary as different professionals reported different needs and attitudes.

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