FACULTY OF MEDICINE
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Disclosing incidental and secondary findings in clinical genomics.

Professional practice, patient experience and ethical reflection.

Marlies Saelaert

GHENT
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FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

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Ghent University, Faculty of Medicine and Health Sciences
Thesis submitted to fulfill the requirements for the degree of Doctor in Health Sciences

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LIST OF ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
AGNC	Association of Genetic Nurses and Counsellors
AMA	American Medical Association
Bioethics Commission	Presidential Commission for the Study of Bioethical Issues
CCMG	Canadian College of Medical Geneticists
CMG	Centre for medical genetics
CNV	Copy-number variant
ES	Exome sequencing
ESHG	European Society of Human Genetics
FDA	Food and Drug Administration
FG	Focus group
GUS	Gene of unknown significance
IF	Incidental finding
IPA	Interpretative phenomenological analysis
IRD	Inherited retinal disease
ISFs	Incidental and secondary findings
MRI	Magnetic resonance imaging
NGS	Next generation sequencing
P	Participant
PHG	Public Health Genetics
SF	Secondary finding
VUS	Variant of uncertain significance
WES	Whole exome sequencing
WGS	Whole genome sequencing

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PART 1 BACKGROUND

Chapter 1 – INTRODUCTION

Prologue

When Prometheus had stolen the divine fire from heaven and taught mankind about the infinite potential uses of this magical new phenomenon, Zeus was filled with wrath and anger because of this betrayal. Instead of immediately punishing Prometheus himself, Zeus decided to first unleash his fury upon the shameless creatures of men that dared to try to mimic the Olympians. As a first step in his plan, a girl of stunning beauty, modelled after the examples of Aphrodite, Hera, Demeter and Athena, was sculpted from clay moistened by his saliva. Each of the gods conferred upon her a talent or accomplishment and therefore she was called "All-Gifted" or Pandora. Zeus decided to grant her one more gift, being a jar filled with secrets. "This jar", Zeus said to Pandora, "is your wedding gift. However, it is purely decorative and it contains nothing of interest. You are never to open it." Pandora sincerely promised she would never do so.

Hermes took Pandora by the hand, led her to the house of Epimetheus, the brother of Prometheus, and introduced her as Epimetheus' wife to be. Pandora and Epimetheus lived a happy life, but nevertheless, every now and then, Pandora was tickled by the jar she kept on a shelf in their bedroom. Zeus' remark that the jar was empty and contained nothing of interest triggered her curiosity and made her think that it might, instead, contain something of great interest, something of value and power.

One night, after a party Epimetheus had organised for Pandora, she could no longer control her curiosity and she opened the jar. Flying and flapping shapes buzzed from the jar, screaming and howling in her ears. Pandora felt a shooting pain, cried out in fright and horror and closed the lid of the jar to seal it again. The cloud of wailing creatures clawed the air and flew away over the town, the countryside and the entire world. The names of these creatures were, for instance, Hardship, Lies, War and Pain. Deceit, misery and pain had arrived on earth and they would never leave again.
What Pandora did not know was that, when she hastily closed the jar again, one creature was left behind and imprisoned forever. Its name was Hope.

(Paraphrased of S. Fry, *Mythos.* (1))

1.1. Next Generation Sequencing and its clinical implementation

On April 14th 2003, thousands of co-operating scientists presented the result of what had been a tremendous effort (2). That day, the endeavour of sequencing a human genome, including its 20 000 to 25 000 genes and three billion DNA base-pairs, had been completed (3). This Human Genome Project had required about 13 years of work and costed about 2,7 billion dollars (3-5).
Technologically, the Human Genome Project was primarily achieved by means of classic Sanger sequencing which sequences DNA in a serial manner (6). Since the realisation of the Human Genome Project, technology has evolved enormously. More recent sequencing technologies called Next Generation Sequencing (NGS) allow for the massively parallel sequencing of a vast number of genes or large numbers of genomic regions (7-9). Because of this simultaneous sequencing, NGS-based techniques are much more efficient and cost-effective than Sanger sequencing for deciphering the full genome or large panels of genes (6).

1.1.1. From panels to exomes to genomes

NGS is a suitable technology for clinical genetic testing and it can be applied in testing strategies with different scales (10-13).
The use of targeted disease-specific gene panels, ranging from a few to hundreds of genes, is a first application of NGS technologies (10, 14). In this approach, a distinction is made between the sequencing of raw data and the analysis of a disease-specific panel of genes which is assumed to hold the relevant clinical information (15). Targeted NGS-based panel testing is a convenient approach in a diagnostic “phenotype to genotype” context where the patient has a clinical phenotype and/or a family history that is indicative of a specific (monogenic) disease (10, 13, 16). Currently, targeted panel testing may still be preferred as a time-efficient and cost-effective first line testing procedure for many monogenic diseases (14, 17, 18). When using exome-based panel testing, this also holds the possibility of flexibly reanalysing the raw data when new candidate genes for a condition have been identified (12).
A second application of NGS technologies is whole exome sequencing (WES). WES interrogates all protein-coding genes which accords with approximately 1,5% of the whole human genome (19, 20). In a diagnostic context, WES is a suitable testing strategy when a patient has an undiagnosed rare disease, a negative family history of disease or a phenotype that is indicative for a condition with a high genotypic heterogeneity (i.e. a condition that may be caused by (likely) pathogenic variants in many possible disease genes) or with an unknown inheritance pattern (13). Also when targeted panel testing did not reveal a definite genetic diagnosis, WES can be performed (21). Mendelian (monogenic) diseases are mostly caused by pathogenic

variants in the exome and hence WES represents a testing strategy for most monogenic conditions (10, 19). For some conditions, especially those with a complex or unknown genetic background, it has been suggested that WES is more cost-effective than targeted panel testing (19).
Finally, NGS allows for whole genome sequencing (WGS). In 2007, the genome of James Watson was sequenced in a few months using this approach (22). Ever since, both the turnaround time and costs of WGS have decreased steadily (7, 20). Sequencing a human genome can nowadays be realised in a few days for a little over one thousand dollars (3, 5). WGS proved to be a suitable testing strategy for complex conditions such as developmental delay or intellectual disability (14, 23, 24).

For each case of clinical genetic testing of monogenic conditions, the most convenient application (targeted panel testing, WES or WGS) should be considered (14, 25). An efficient use of NGS-based strategies should avoid a disproportionate accumulation of tests and should aim for the highest diagnostic yield (i.e. the highest identification of disease-causing variants and molecular diagnoses) in the shortest time and at the lowest cost (14, 25, 26).
In this dissertation, NGS-based panel testing mainly refers to exome-based panel testing, which will be indicated as (clinical) exome sequencing or clinical ES. When referring to NGS technologies, this covers the techniques of ES, WES and WGS.

Europe is currently developing a "1+ Million Genomes Initiative", in which an international collaboration aims for the sequencing of more than one million genomes accessible for research and personalised medicine by 2022 (27). Initiatives like these illustrate that the decrease in required resources, the fast turnaround time and the increased accuracy of ES, WES and WGS have strongly stimulated the application of NGS in clinical routine medicine (3, 16, 25, 26, 28, 29).
NGS-based strategies are promising for various reasons in different clinical domains. While avoiding the financial cost, psychological burden or even medical harm of a series of negative, targeted tests, one single NGS-based test may reveal the underlying genetic predisposition of ever more conditions and hence realise a higher diagnostic yield (10, 14, 16, 30-32). NGS-based testing can enable a more detailed clinical diagnosis and prognosis and realise a better understanding of disease. Consequently, targeted drugs and optimal therapeutic strategies may be provided that are tailored to a person's specific genotype, attempting to target a specific disease gene or mutation by means of gene therapy (10, 25, 33, 34). This way, NGS technologies contribute to the realisation of personalised or precision medicine as a complement to a more general "one size fits all" approach (19). In people with a family history of a genetic disease, NGS-based testing can be used for risk assessment, which may allow for preventive, reproductive or therapeutic interventions in affected persons (35, 36).

In a reproductive context, NGS-based testing can reduce the recurrence of severe monogenic conditions to future children, for example by means of preconception carrier screening for recessive conditions or by means of a prenatal diagnosis or preimplantation genetic testing (37, 38).

1.1.2. Challenges

When the genome of James Watson was sequenced in 2007, the majority of the sequenced data could not be associated to a biological function and could not be interpreted in terms of disease risks (39). Twenty (likely) pathogenic variants were identified but during the counselling session, very little could be said about these variants' exact meaning (40). This situation still reflects some major challenges in NGS-based testing techniques, namely the (pathogenically) uncertain and/or dynamic interpretation of results and the counselling of patients (19).

a. Interpretative uncertainty

More than a decade after the sequencing of James Watson's genome, the interpretation of NGS-generated data remains a demanding endeavour. The function of many genes is still unknown and disease may be caused by a complex interplay between multiple genes and environmental factors.

An important challenge in the interpretation of genomic data is caused by the large amount of variants of uncertain significance (VUS) that are identified by ES/WES/WGS (31, 41). VUS may be identified in known disease-causing genes and in genes of unknown significance (GUS) and are results for which scientific knowledge and literature currently provide insufficient evidence or contradictory information to decide on their clinical and pathogenic significance (42, 43). VUS (or class 3 variants as they are referred to by the American College of Medical Genetics and Genomics) are not an interpretation problem unique to NGS-based testing but the scale of potential VUS in ES/WES/WGS is, compared to single-gene or chromosomal testing, enormous (13, 44). In fact, most NGS-based test results will be VUS and hence these results have been called a "plague" (19, 45). As described by Hoffman-Andrews, NGS-based testing has resulted in a book of life of which we can read the alphabet but of which we do not always understand its vocabulary and grammar (35).

The complex analysis of NGS-generated data and VUS creates a substantial interpretative uncertainty in clinical genomics (19, 31, 46). Specific recommendations for the reporting of VUS are currently not available and laboratories are stimulated to develop their own protocols (41, 43). Because of this lack of general guidance, laboratories may report results differently (43). Even within one laboratory, professionals may report VUS differently, since the

pathogenic classification of variants has been described as partly subjective, even when classification guidelines are used (43).

The pathogenic uncertainty in VUS inherently complicates disclosure and counselling practices. VUS may be reported from the laboratory to the referring clinician to avoid the missing of a (future) potentially pathogenic result or in respect of the clinician (43, 47). However, the reporting of results with an ambiguous disease-causing effect is not without risk (21, 31, 48, 49). The result may be over-interpreted by the clinician and subsequently reported to the patient, which may result in unnecessary follow-up consults or inappropriate medical interventions (13, 19, 37, 43). A noteworthy example of over-interpretation is found in a study that reported surprisingly high rates of bilateral mastectomy in women who were informed about a VUS in a breast cancer susceptibility gene (35). However, such an intervention may only have survival benefit for women with a pathogenic variant in a hereditary breast cancer susceptibility gene, for instance the *BRCA1*-gene or *BRCA2*-gene (35).

VUS illustrate how, despite decreased costs of NGS-based testing *in se*, data analysis, interpretation and validation may still require a considerable amount of time, effort and financial resources (19, 25).

Further research, professional and interdisciplinary collaboration and large genomic databases are required to address the problem of pathogenic and interpretative uncertainty (14, 19, 30, 31).

b. Raw data, reanalysis and recontacting

Genetic variants' pathogenic classification is a flexible and dynamic process (31, 50). As scientific knowledge about disease-associated genes and genetic variants evolves over time, VUS and other sequencing results may be reinterpreted and VUS may turn out to be pathogenically significant or benign (41, 51). It has been indicated that reanalysis, even if 12 months after the initial analysis, may increase the diagnostic yield (41). Also the evolving phenotype of a person, changes in a person's family history of illness or important life cycle junctures such as pregnancy may clarify or increase the relevance of (perhaps initially unreported) variants (50, 52). This pleads for recontacting practices and the provision of follow-up consults (31). Recontacting patients may offer significant benefits for their (and their relatives') health, psychosocial wellbeing or reproductive plans (53). Accordingly, patients have expressed the desire to be recontacted when new information is available and they would consider it a sign of high quality care (53, 54).

However, recontacting patients may also cause anxiety and (financial) worries or be perceived as an intrusion of privacy (53). Moreover, it may be questioned whether practices of reanalysis and recontacting are feasible, since they would significantly add to the burden and responsibility of genetic professionals (7, 53, 55). Professionals have acknowledged the value

of a periodical re-evaluation of sequenced variants but they also mentioned that the required time and financial resources are lacking (50, 53). Consequently, most genetic centres have no routine activity of reanalysis and recontacting and an international study of informed consent forms showed that the issue of reinterpretation was addressed in less than half of them (41, 53).

To this day, data reanalysis and the recontacting of patients are usually considered good clinical practice and moral responsibilities but not legal duties (41, 52, 53, 56). This idea is also reflected in statements that have been published by the European Society of Human Genetics (ESHG) and the American College of Medical Genetics and Genomics (ACMG). A routine re-evaluation of variant classifications and recontacting patients may be ethically desirable but are not duties since these practices are logistically and practically impossible (50, 53). Therefore, patients should be informed that their genetic data are analysed based on the knowledge available at the specific moment of analysis (30, 56).

If data would be reanalysed, there is currently no consensus on who should take initiative for this reanalysis (53, 57). Many healthcare professionals think that they should initiate reanalysis and also lay people do consider this a professional responsibility (30, 43, 53, 58). However, a professional initiative may be practically impossible (if, for instance, the patient's contact details have changed) or inappropriate without prior consent (41, 52). Holding patients responsible may, however, also be problematic since they probably lack the genetic literacy to recontact professionals and ask for reanalysis (43, 52, 55).
Therefore, recontacting is frequently considered a joint venture and shared responsibility between the clinician, laboratory and patient, a position which is also endorsed by the ESHG and ACMG (28, 50, 52, 53, 56, 59, 60). The ESHG, however, warns that a shared responsibility may result in a failure to take any action and therefore should be seen as a pragmatic solution until best practices have been identified (53).

Two important remarks can be made regarding reanalysis and recontacting. Firstly, even though recontacting may be a moral duty, this practice should be considered a *prima facie* duty that should be balanced with other interests (55). Also, for instance, the principle of justice should be kept in mind and patients' potential benefit of being recontacted should be balanced with the required resources to realise this ideal (53). Secondly, guidelines on recontacting may not be able to eliminate the need for case-by-case and context-specific decisions. The decision whether or not to recontact a patient may depend on, for instance, the nature of the newly available information, the balance between professional beneficence and patient privacy, the potential impact on a patient's relatives, etc. (53, 55).

Finally, an important issue associated with the reanalysis of data and the recontacting of patients is the (long-term) storage of raw genomic data and patients' access to these data. Issues concerning the retention and return of un-interpreted data have not received much attention and currently there is no consensus on, for instance, the time and most appropriate place of storage (42, 61).

In Belgium, it is currently not possible to obtain one's raw genomic data when consulting a centre for medical genetics and there is no national database where all these data are stored centrally. Centres also do not share un-interpreted data but only clinical reports with other clinical institutions or professionals. This practice aligns with most other medical terrains. Nevertheless, lay people have expressed an interest in getting access to their raw data (62-64). They consider this access a realisation of empowerment and a way of control (63). It gives them the opportunity to consult other services for a (re)interpretation of the data and to control the sharing of these data (61). Genomic data may be (re)interpreted by other genetic professionals or by third-party interpretation tools (61, 65). These third party interpretation services may provide non-medical information, e.g. concerning ancestry or athletic performance, as well as health-related results including risk estimates for complex diseases or for serious monogenic disorders (66). However, the first scenario (involving medical experts) may burden the public healthcare system or may challenge non-genetics specialists that may be consulted (61, 64, 65). The second scenario (involving (online) third-party interpretation tools) raises questions, also in patients themselves, about data privacy and confidentiality (37, 46, 63, 64, 66). Also the validity of the automated analysis, patients' overestimation of health-related information, the disclosure of this information without adequate counselling and the medical, personal and familial impact of this information are important concerns (61, 64, 66).

Therefore, many professionals are reluctant to provide access to raw data (29, 62, 67). They are worried about the (potentially unnecessary) downstream of follow-up consultations, increasing costs and a subpopulation of "worried well" (62). Nevertheless, they realise that people may consider this a paternalistic attitude that conflicts with their entitlement to these data (62).

Also practical and logistics issues are at stake when patients should have access to their raw data, such as the problematic storage of terabytes of data. One option is to store raw data as part of a patient's electronic medical record but this option has raised data protection and logistics concerns (e.g. regarding costs and required infrastructure) (61). These problems may be solved by private data storage by patients. However, this policy requires a certain degree of genomic literacy and awareness among lay people and may conflict with values of justice and equity (61).

Ultimately, it should be considered, especially in a context of clinical care, how patients' access to their raw data – which may be considered personally uninterpretable data - may contribute to good care and patients' wellbeing (21).

c. Counselling

The complexity and uncertain and/or dynamic interpretation of NGS-based test results are reflected in clinical counselling and informed consent procedures that have become both more important and demanding (68).
In a context of genomic medicine, counselling procedures are characterised by a dissonance between the enormous amount and complexity of possible results and the limits of patients' ability to understand and process this information within the time frame of a counselling session (45, 69-72). Professionals should aim for a clear and streamlined counselling procedure that provides nuanced information without (emotionally) overwhelming patients (69).
It is considered practically impossible to counsel patients about all possible results and disease risks. However, patients should receive some essential information before clinical genomic testing (73). They should be informed and counselled about the benefits, risks, limitations and possible outcomes of clinical genomic testing, about the potential impact and consequences of results, about privacy and confidentiality issues, about the potential relevance of genetic test results for family members and about the responsibilities that may arise from results (51, 60, 62, 74). Patients themselves have also emphasised the importance of adequate counselling and of being prepared for the disclosure of possible results (7, 75).

For several years now, professionals wonder how much information patients actually need to be adequately informed about genomic testing procedures without being overwhelmed (14, 26). The most efficient and comprehensible way of information delivery has been debated, as well as the most effective organisation of pre- and post-test counselling consults (17, 70). The preferred length of a genetic counselling session illustrates the complexity of effective counselling procedures. Whereas patients and lay people would prefer these sessions to be as long as necessary, professionals do not consider this feasible (20, 76, 77). The efficacy of counselling sessions that take "as long as necessary" has also been questioned by patients who experienced counselling as a long and demanding process (70). Therefore, new and alternative ways of counselling that go beyond traditional face-to-face-encounters may be necessary (26, 78, 79). Several ideas have been suggested such as multidisciplinary or communal counselling sessions or the use of online tools (51, 79). Many patients have nevertheless indicated to prefer real-life, face-to-face counselling consults and it is doubtful whether patients are ready for new ways of counselling (7, 51, 63, 80, 81).

A written informed consent form may be useful during pre-test counselling sessions, as it can structure the session, support patients' understanding and reflection and function as a reminder on what has been decided (also for other healthcare professionals) (82). The act of signing a form may also give patients a sense of control and ownership towards the process of genetic testing (82).
There is no consensus yet on what information should be included in an informed consent form (83). Ayuso et al. designed a minimum list of elements that should be addressed in an informed consent form for WES/WGS-based testing, including topics such as the test procedure, the potential risks and benefits of the test, alternative testing possibilities, patient choices, privacy, confidentiality and data storage (84). As a consequence of genetic results' dynamic interpretation and patients' changing context and preferences, consent forms may also address issues of reanalysis and recontacting (32, 51, 57, 71, 85).
Informed consent forms should however not be too long or too complex and they should be formulated in a comprehensible way (38, 76, 82). The requirement of presenting a lot of complex information in an accessible way has raised doubts on the suitability of classic informed consent forms (57, 86-89). Tabor et al. conducted a study in which an informed consent protocol was presented that was almost ten pages long and took up to three hours to be fully explained (90). The addressed participants considered it necessary to receive and understand a lot of information before making an informed decision but they criticised the procedure's length and complexity (90). Alternative informed consent procedures, such as binned or staged consent, have been suggested but no consensus has been reached yet on the most suitable procedure (57, 65). Currently, the use of an informed consent form for clinical genomic testing is not required in Belgium.

1.2. Diagnostically unrelated findings

As clinical genomic tests analyse large regions of the genome, they have the potential to result in an amount of results that is without precedent in medicine. Several (pathogenic) variants can be identified, of which some may be clinically relevant for the diagnostic testing indication (primary, pertinent or diagnostic results), yet others may exceed a person's clinical presentation or phenotype (14, 26, 28, 42, 45, 51). Incidental findings (IFs) or diagnostically unrelated findings that go beyond the initial rationale for testing, may be potentially disease-causing and hence relevant for a patient and/or her family (19, 51, 91, 92). IFs have been identified as one of the most challenging consequences of clinical ES/WES/WGS (10).
Whereas IFs are unintentionally identified, the terminology of secondary findings (SFs) is generally reserved for deliberately pursued diagnostically unrelated genomic results (93, 94).

This deliberate pursuit of additional results may be applied as a procedure of "opportunistic screening" in which an additional list of genes and/or variants is analysed (95).
Before discussing the potential disclosure of IFs and SFs to adult patients in a diagnostic context, the nature and terminology of IFs and SFs will be explained.

1.2.1. The detection of IFs in medicine and genomics

IFs are a well-known phenomenon in other clinical settings and for over thirty years, the terminology has been used for various types of diagnostically unrelated findings, for instance in magnetic resonance imaging (MRI), X-ray tests or primary healthcare consults (8, 83, 96, 97). The terminology has been transferred to the genetic and genomic domain but the analogy between, for instance, radiological and genomic IFs should be made with caution since several differences can be pointed out. Genomic IFs usually do not identify current health problems but reveal susceptibilities, predispositions and future health risks; their discovery does not imply a clinical diagnosis but a future risk assessment (60, 98). Moreover, genomic IFs inherently include inheritance risks and may not only be relevant for the patient herself but also or exclusively for the tested patient's family members (8, 60).
Within the specific context of genetics and genomics too, IFs are not new phenomena, since genome-wide testing by use of conventional karyotyping or molecular karyotyping can also identify diagnostically unrelated chromosome and genomic abnormalities (8). The techniques and sensitivity of NGS-based testing have, however, significantly increased the scale and complexity of genomic IFs (92).
Every human genome holds thousands of variants of which most are benign and attributable to normal genetic diversity. Other variants are located in genes with an unknown clinical relevance (GUS) or are VUS in known disease-associated genes. Three to five variants in every human genome may nevertheless be pathogenic variants that indicate an increased disease risk, such as an increased risk for colon cancer or Alzheimer's disease, or a carrier status of a recessive condition (8, 16, 51, 99). Different estimations have been made about the prevalence of IFs and rates have ranged from 1% to almost 9% of clinical genomic tests that would identify an IF associated with a serious, medically actionable condition (10, 19, 48, 95). These different estimates can be caused by study differences regarding included participants, classification criteria for variants' pathogenicity and included genes, panels or conditions (28). If IFs would only apply to (likely) pathogenic variants that are associated with adult onset and life-threatening conditions for which a medical prevention or treatment is available, such as breast cancer and ovarian cancer, it is expected that such findings will be identified in about 1-2% of European-ancestry persons tested by WES (100). If variants associated with a carrier status of an autosomal recessive condition, for example cystic fibrosis, would be included, probably every case of WES/WGS would reveal IFs (28).

WES and especially WGS inherently hold the possibility to produce a large amount of results and IFs. However, also NGS-based panel testing and clinical ES may identify IFs, since a diagnostic panel can include genes that are associated with different conditions or phenotypes (30, 101). An example is the PID-panel for primary immunodeficiencies that contains the *ATM*-gene, in which pathogenic variants have been associated with an increased breast cancer risk. As ever more gene-disease associations are identified, panels may become larger, which will increase the chance of IFs (42). A current example of a frequently used large panel is Mendeliome analysis, interrogating all genes associated with Mendelian diseases. Finally, bioinformatics filters will analyse larger noncoding regions that exceed the protein-coding parts of a gene when WGS-based instead of WES-based panel testing will be used. Again, this will increase the chance of IFs. Hence, even though the use of NGS-based panel testing or clinical ES only holds a small chance to identify IFs, it is considered impossible to completely avoid IFs (21, 91, 97).

1.2.2. Terminological questions

When testing techniques inherently reveal a large amount of variants and when IFs are unavoidable, it may be contradictory to indicate diagnostically unrelated findings as "incidental" (8, 42). The terminology of IFs may also suggest a sense of triviality, while instead, it may concern life-threatening findings (8, 51, 83, 97, 102). Other terminologies for diagnostically unrelated findings have been suggested such as unsolicited, unanticipated, additional or secondary findings/variants (21, 92, 97, 102). However, most alternatives for the terminology of IFs have been considered equally problematic. Findings may not be unanticipated because of professionals' expertise or because of the associated condition's prevalence in the general population and findings may not be additional or secondary when there is no primary result (51, 97, 103). It was also suggested that different contexts or settings may require different terminologies (103). To this day, no consensus has been reached on the most suitable terminology. This problem was reflected in a study of international consent forms for diagnostic genomic sequencing. While one quarter of the studied forms did not mention the possibility of diagnostically unrelated findings as a whole, the forms that did refer to this possibility, were characterised by a variety of frequently undefined or even incorrectly used terms (91).

Finally, the concept and terminology of NGS-based IFs have been fundamentally criticised because of the active interpretation these results require (104). This active interpretation may raise the question whether all IFs may actually be considered SFs.

When IFs are revealed in radiological tests or when IFs are identified in genome-wide tests such as (molecular) karyotyping, these IFs result from the use of visual images or genetic results that unavoidably cover a broader field of vision than that which is strictly necessary (105, 106). The IFs that are engendered by these technologies have been characterised as truly serendipitous and "impossible not to see" (83). Instead, NGS-based IFs have to be actively looked at and interpreted. This active detection and interpretation does, however, not turn these findings into SFs. IFs are not the result of an intentional and deliberate screening process but merely a consequence and a side-effect of a technology used for a specific, diagnostic goal. Even though some IFs may be anticipatable and even expected when specific panels are used, exhaustive lists of reportable IFs have been dismissed by professionals, as the spectrum of possible IFs is ultimately unknown in advance (68, 86). This fundamental unpredictability can affect the nature and possibilities of pre-test counselling.

In the pursuit of SFs, usually a well-defined list of genes is additionally and intentionally screened and variants are actively sought for; in this way, the spectrum of potential SFs is inherently anticipatable (83, 94, 107). SFs are not merely a side-effect of a diagnostic search but a well-considered and clearly delineated set of additional results that clinicians and/or patients want to receive along with the diagnostic test result because of their assumed clinical validity and utility. The comprehensiveness which is included in the pursuit of a list of SFs cannot be expected or guaranteed in case of IFs. Referring to the analogy with radiological additional findings, genomic SFs may be compared to the performance of an additional X-ray that explicitly focusses on another part of the body than the initial X-ray or to the extension of the scope of a blood test (101, 108). The intentional nature of SFs may again affect pre-test counselling procedures and SFs may be presented as results which are not only instrumentally "looked at" but also purposefully "looked for".

The distinction between IFs and SFs is reflected in the terminology that has been suggested by the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission). The Bioethics Commission suggested a diversified terminology of anticipatable IFs, unanticipatable IFs and SFs (94). Whereas anticipatable IFs are known to be associated with the test (for instance because the gene in which the additional pathogenic variant has been identified, is part of a disease-specific panel), this is not the case for unanticipatable IFs (for instance when new gene-disease associations have been recently identified or when another clinical testing procedure has been performed than expected) (94).

The difference between diagnostic results, IFs and SFs has sometimes been pinpointed as irrelevant, since all results may be equally important for a patient and since all results could be equally part of the purpose of clinical care (8). Even though IFs or SFs may have equally significant consequences as primary results, the existence of diagnostically unrelated findings as a distinct category of results is now generally recognised (94, 105).

IFs and SFs have a strong similarity in a clinical context: both types of results exceed the specific diagnostic indication for which testing has been initiated. In some occasions, when the focus is mainly on the diagnostic unrelatedness of results, it may be suitable to unite both types of results in a common term. However, the differences between IFs and SFs in intentionality, scope, professional and patient expectations and possible counselling procedures suggest a distinct terminology may be preferable. A clear and consistent terminology could avoid confusion in professional and patient expectations, study protocols or reports and informed consent procedures (8, 51, 60, 91, 97, 102, 103).
In this dissertation IFs refer to unintentionally discovered and diagnostically unrelated results (92, 94). SFs denote intentionally and deliberately pursued and diagnostically unrelated results (93, 94). When the focus is on the diagnostic unrelatedness of both types of results, irrespective of their accidental or intentional discovery, these results may conjointly be referred to as "incidental and secondary findings" (ISFs). The use of this overarching term may also be necessary when certain literature refers to unspecified diagnostically unrelated genetic test results.

1.3. Disclosing IFs and SFs

Many types of IFs and SFs can be identified, ranging from findings with a non-medical relevance (e.g. results regarding ancestry or non-paternity) or with an unknown pathogenic consequence (VUS IFs, e.g. a VUS in a gene associated with heart arrhythmia or Lynch syndrome) to findings with a reproductive value (e.g. a carrier status of Duchenne muscular dystrophy) or (medically) actionable findings (e.g. an increased risk for breast cancer or type II diabetes). Actionable genomic findings have been described as increased risks for a genetic disease for which (medical) prevention or treatment is available that could improve the outcome of the associated condition (95). The detection of actionable IFs and SFs may improve a potential condition's prognosis and outcome in terms of morbidity or mortality but also in terms of wellbeing and quality of life (20, 95).

Both the non-disclosure of any IF and the full disclosure of all possible ISFs are considered unviable policies (8, 109, 110). A complete non-disclosure of IFs is considered ethically unjustifiable given the harm it may cause or the potential benefit it may impede (8, 57, 78, 79, 109). Conversely, a full disclosure of all possible IFs and the active pursuit of all possible SFs is regarded as unfeasible in a diagnostic context for logistic, economic and counselling reasons (21, 51, 57). Hence the delineation of reportable IFs and SFs has been an important point of concern among genetic professionals. The appendix provides an overview and summary of

frequently referred to recommendations on the disclosure of IFs and SFs in diagnostic, constitutional WES/WGS in adults.
The next section will present some key strategies and arguments for the delineation of reportable ISFs. Subsequently, professional ideas on the active pursuit or limitation of ISFs will be outlined, as well as suggested policies regarding an optional or mandatory disclosure of results. Finally, the perspective of lay people on the disclosure of ISFs will be described.

1.3.1. The spectrum of reportable findings

a. Binning results

Binning systems are a frequently used system to categorise and select potential ISFs that may be reported. In genomic binning systems, genetic variants are categorised according to their nature and their associated condition's estimated characteristics, such as the condition's medical actionability, penetrance (i.e. the probability that a variant will express the associated condition) or age of onset (45, 91). Overall, predetermined binning systems aim to avoid an information overload regarding ISFs and to support a more comprehensive and efficient decision making process and counselling procedure regarding disclosure (16, 45).

In 2011, Berg et al. already developed a binning system for IFs (45). This binning framework was based on two parameters. The first parameter regarded the IF's clinical relevance or validity (determined by the gene in which the variant is located), the second parameter regarded the IF's pathogenic relevance (determined by the nature of the variant in itself) (45). Based on these parameters and on a variant's clinical utility or actionability, three important bins were distinguished: (i) (likely) pathogenic variants in clinically valid and actionable genes, (ii) (likely) pathogenic variants in clinically valid but medically non-actionable genes and (iii) variants in genes with an unknown clinical validity (variants in GUS) (45).
Bin 1-results were expected to be a rarity, as this bin only includes highly penetrant and (likely) pathogenic variants in clinically valid and medically actionable genes that are associated with monogenic, rare diseases such as Marfan syndrome (45). However, if such results were identified, Berg et al. advised to always report them. Bin 2 included results with an ambiguous clinical utility but with potential personal utility (45). Examples are variants associated with severe but medically non-actionable conditions such as Alzheimer's disease or Huntington disease or IFs regarding a carrier status of autosomal recessive conditions (45). Berg et al. advocated to only report bin 2-findings at a patient's consent and after shared decision making (45). Finally, Berg et al. recommended to never report IFs of the last bin (variants in GUS), nor VUS IFs, not even when these VUS were identified in clinically valid genes (45).

A binning-system may be a valuable framework to structure decisions on result disclosure and counselling sessions. However, the clinical implementation of binning systems, including the framework of Berg et al., may be challenged by the uncertain delineation of specific bins and the ambiguous definition of variants' or conditions' characteristics (62). These problems will be further discussed throughout the manuscript.

b. Arguments for disclosure

Almost ten years after the publication of Berg's binning system, many genetic professionals still support this framework's core ideas and recommendations. In a context of clinical genomic testing in adults, genetic professionals generally support the possibility to return clinically valid and relevant IFs that indicate a significant health risk (17, 51, 57, 60, 111-113). They particularly approve the return of medically actionable IFs, for instance regarding cancer predispositions (51, 83, 86, 109, 114-116). Informing patients about this category of IFs provides the opportunity to take preventive or therapeutic action that may realise a better (clinical) outcome (8, 57, 106). In line with the second bin of Berg et al.'s framework, a considerable amount of professionals would also consider the return of IFs regarding a carrier status of autosomal recessive conditions or regarding pharmacogenetics (10, 79, 86, 109, 115, 117, 118).

Despite the willingness to report particular IFs, genetic professionals are also cautious towards clinical and psychological risks of reported IFs. Reported findings may result in an information overload, psychological distress and clinically harmful interventions (16, 62, 71, 79, 119). In combination with the sometimes uncertain pathogenic significance of genetic results, reported IFs may cause unnecessary anxiety and worries in patients (107, 120). Knowledge of IFs and consequential actions may also induce financial risks or harm, stigmatisation or discrimination (8, 57, 71, 113, 121).
Therefore, genetic professionals are less motivated to report IFs that are related to multifactorial conditions or non-medical issues and IFs that are not highly penetrant, not clearly pathogenic or not medically actionable (57, 83, 109, 122, 123). Only a minority of professionals interprets actionable IFs as results that allow for lifestyle adjustments (71, 121).

In essence, the disclosure of IFs because of medical risk reduction and the non-disclosure of IFs because of (medical or psychological) risks are two sides of the same coin, i.e. the promotion of patients' (medical) wellbeing (96). Hence both disclosure and non-disclosure are grounded in the ethical values of beneficence (preventing or removing harm and promoting someone's best interest) and non-maleficence (not inflicting harm) and in analogous

professional duties (51, 57, 69, 111, 124). In chapter six, these ethical values will be discussed in depth as underlying arguments for specific reporting practices.

Research has suggested that healthcare professionals with different roles may have different perspectives. Clinical geneticists seem to feel less obliged to report a wide spectrum of results and to screen for SFs (125). Compared with genetic counsellors or primary care providers, they are more likely to limit disclosure to medically actionable IFs (86, 109, 112, 123, 126). This may be explained by their specific expertise on genetic test results and their focus on clinical utility, whereas counsellors and primary care providers may be more concerned about social and psychological issues (86, 123, 126). However, in comparison with genetic researchers who have no contact with participants, clinical geneticists are more likely to emphasise their moral duties towards patients and the professional obligation to report clinically significant IFs (127).

1.3.2. Looking for or limiting additional findings

a. Opportunistic screening

Some professionals consider the potential benefit that may be realised by reported IFs to be of such significance that these findings should not be left to chance but actively pursued. This idea was prominently articulated by the ACMG (86, 95). In 2013, the ACMG published its recommendations that advised the active analysis and reporting of (likely) pathogenic variants in a minimum list of 56 genes (later updated to 59 genes) that are associated with 24 conditions (93, 95, 128). The listed genes were deemed to be correlated with highly penetrant, severe or life-threatening monogenic conditions that may stay asymptomatic for a long time and for which medical interventions are available that may prevent or reduce serious morbidity or early mortality (8, 93, 95, 128). The gene list has similarities with the first bin of Berg et al.'s classification system but the ACMG recommendations are more specific regarding the spectrum of reportable results (51).
According to the ACMG, a patient's best interest is achieved most effectively when (likely) pathogenic variants in the listed genes are actively and deliberately pursued as SFs and this in any case of diagnostic, constitutional WES/WGS (i.e. testing by WES/WGS for congenital conditions), irrespective of the specific testing indication and irrespective of the age of the tested patient (95). This deliberate pursuit was defined as a way of opportunistic screening: if the exome or genome is sequenced anyway, it may be a small effort and hence a perfect opportunity to look for some additional disease risks (34).

Most participants of a survey among ACMG members considered the opportunistic screening for SFs as in line with medical standards (129). By setting high standards for reportable results,

an over-reporting of (false positive or irrelevant) results, an overwhelming of patients and a burdening of the healthcare system may also be avoided (130).
Internationally, however, professionals have criticised the suggested practice of opportunistic screening. Genetic professionals raised (and still raise) doubts about the penetrance, expression and disease-predictive value of IFs and SFs in persons without associated symptoms or without a relevant family history of disease (14, 57, 71, 72, 83, 92, 121, 123, 131-133). Consequently, the disclosure of results of which the potential benefits, risks and cost are still unknown, may be interpreted as a violation of the precautionary principle (134). In line with this criticism, the ESHG and EuroGentest do not support the active screening for SFs (8, 91, 92). Also recently published points to consider for laboratories discourage an active search for SFs (56). In line with many professionals' opinion, European policy documents generally advocate (WES/WGS-based) targeted panel testing, the avoidance of IFs and SFs and a diagnostically focussed care in a clinical context (8, 15, 30, 42, 56, 92, 123). This idea was reflected in an international study of informed consent forms which revealed that the potential pursuit and disclosure of SFs was mentioned in only a minority of the analysed forms (91).

ACMG acknowledged the lack of empirical data on the listed genes' clinical validity and utility in persons without symptoms, as well as the insufficient scientific evidence for the potential benefits, risks and costs of disclosure (51, 95, 132). Instead of being entirely evidence-based, the recommendations were partly based on professional consensus (95). ACMG's most recent reaction on the contested clinical validity and utility of diagnostically unrelated variants in asymptomatic people regards a short statement on the application of its recommendations outside the clinical context (135). It says that, even though reporting (likely) pathogenic variants in the listed genes will probably benefit patients and their families, the list of 59 genes is not validated for and should not be applied to general population screening (135).

b. Limiting results, costs and risks

The intentional search for SFs has additionally been criticised because of the additional resources this practice requires (83, 129, 132, 136). The analysis, interpretation and communication of both IFs and SFs will demand extra time, money and human effort and will put an extra burden on professionals and genetic centres, especially in case of difficult variant interpretations (51, 121). This way, a "1000 dollar genome may create a million dollar headache" (137). Costs associated with IFs and SFs should be considered in a broad sense and from a long term perspective, including for instance follow-up consults for identified IFs and SFs, the psychological or family-wide burden of reported results and issues concerning reanalysis and recontacting (57, 127, 131, 132, 138). Generally, VUS IFs are not reported,

which accords with guidelines such as those of the ACMG, since it avoids an unbearable professional burden, excessive costs and a risk of over-interpretation (43, 93, 117). Nevertheless, it complicates the issue of reanalysis and recontacting when new techniques or scientific information become available (28). If VUS IFs are not registered or not reported to clinicians or patients, it is unclear how someone may take initiative in a potential reanalysis. Parallel to the current and more general discussion on reanalysis and recontacting, informing patients about reanalysed VUS IFs seems an ethically desirable but also practically unrealistic practice (8, 50). Current informatics technologies are not yet accustomed to this practice and therefore, priority should be given to the reanalysis of diagnostically relevant results, especially for patients who did not yet receive decisive diagnostic test results (42, 53, 56). In accordance with this idea, Christenhusz et al. currently suggest an "interpretation freeze" of IFs based on the scientific knowledge available at the specific time of testing (69).

The additional costs and burden that may be created by IFs and SFs have raised concerns about the fair and just distribution of limited resources (8, 13, 51, 60, 92, 111, 139). Disclosure policies on IFs and SFs may result in less remaining resources for diagnostic practices and it should be considered whether the potential advantages of reported results can outweigh the costs that are associated with IFs and SFs (15, 26, 92). However, it has also been claimed that if diagnostically unrelated finding are that valuable that they are reported as IFs, these results might as well be pursued as SFs (140). In terms of pre-test counselling, a deliberate screening for a predetermined list of results could also allow to better inform patients about potential findings (141). Wouters et al. stated that it should not be considered unfair to provide patients with additional, potentially useful information; it should rather be considered unfair to leave the discovery of this information to chance (140).

Finally, IFs and SFs will frequently need to be compared with genomic information of a patient's family members to determine the clinical and pathogenic significance of these results. This too requires additional resources and these costs should be integrated in the weighing of IFs' and SFs' potential benefits, risks and costs (48, 142).
Validating IFs and SFs by use of family members' genomic information may also psychologically affect relatives, since they may discover to be a "person at risk" (142). Conversely, when a patient does not want to receive clinically significant IFs or SFs, this decline may indirectly deny an opportunity for risk prevention in family members and hence affect their health and wellbeing (21, 92, 96). Situations like these raise questions about responsibilities towards relatives that may be created by IFs and SFs (8).

c. Minors

Even though this issue exceeds the scope of this dissertation, it should be mentioned that the recommendation of the ACMG to pursue and report SFs in any case of diagnostic WES/WGS, irrespective of the tested patient's age, has been largely contested (95). For decades, the idea had been advocated that genetic tests for adult- and late-onset conditions should be postponed until adulthood if no preventive interventions are available during childhood and that decisions on genetic testing should be driven by the child's best interest (131, 132, 143, 144). The ACMG recommendations, however, advocate the disclosure of predispositions for adult-onset conditions to (parents of) minors because these results may be the only opportunity to inform family members about a genetic risk (128, 130). Critics stated that this implies that a child's future autonomy is surpassed by professional beneficence and by the opportunity to avoid future morbidity and mortality in relatives (95, 128). It has been questioned whether considering the family as the basic unit of clinical care can be aligned with the primacy of a child's best interest and how the valuation of children's genetic information for the benefit of others may be justified (95, 132, 144, 145).

1.3.3. Optional or mandatory disclosure

Internationally, many professionals advocate a patient consent for the disclosure of IFs and many want to respect patients' personal preferences and wish to know or not to know IFs (10, 62, 71, 79, 83, 96, 111, 113, 119, 122). This professional perspective was illustrated in the study of Lohn et al. where genetic professionals spontaneously added patient preferences as an important criterion for disclosure (109).
Not allowing patients an opt-out of IFs has been said to contravene standard medical practice and to infringe upon classic ethical principles such as respect for patient autonomy, the right not to know, shared decision making and informed consent (119, 121, 131, 132, 144, 146). However, several professionals also acknowledged that a patient's choice to opt out of, for instance, severe and medically actionable IFs may be hard or even impossible to respect (57, 115). This remark is in line with Art. 7. § 3. of the Belgian Law concerning the Rights of Patients which states that a patient's request not to receive medically relevant information should be respected unless the non-communication clearly causes a serious health detriment to the patient or third parties (147).

The difficult balance between respecting and declining patients' choices is reflected in the ambiguous attitude of the ESHG and EuroGentest towards an opt-out possibility. They advocate the elaboration of clear protocols on the disclosure of IFs but they simultaneously

recognise the option to report a severe and medically actionable IF against patients' will when rejecting this result might seriously endanger the health of patients or their relatives (30, 92).

Finally, the ACMG guidelines of 2013 prescribed a mandatory reporting of SFs, independent of a patient's preferences (95). This mandatory disclosure was justified by its alleged alignment with established medical practice (for instance in radiology or dermatology), by its avoidance of genetic exceptionalism and by the professional duties of beneficence and care (95, 130, 148, 149). Some authors agreed that mandatorily reported SFs offer more valuable options for life but the recommendation of a mandatory disclosure was mainly the subject of severe criticism (89, 119, 121). As a result of persistent objections from its own members and the genetic community in general, the ACMG allows a patient opt-out of SFs since 2015 (8, 129, 150). This opt-out possibility for SFs is supported by a vast majority of professionals (8, 56).

According to the adjusted ACMG recommendations of 2015, it is not possible to partially opt out of a subset of SFs, as this would make the counselling process too complicated (131, 150). Critics nevertheless advocated the possibility of a selective opt-out since this allows patients to make an analysis of SFs' potential risks and benefits that is specifically adjusted to their personal and family situation and values (79, 129, 131, 151). Moreover, the ACMG still advocates screening for SFs as a routine practice (150). Recommending a practice of SFs as a routine practice with an opt-out possibility and not as a practice based on an opt-in choice may, however, impede patients' informed choices (131). In opt-in procedures, patients explicitly express their consent; in opt-out procedures, patients agree more implicitly by taking no specific action which may result in a lower amount of refusals to consent (152).

1.3.4. Lay people's perspective

For many years, the disclosure of genomic ISFs was mainly considered from a theoretical and professional point of view and this narrow perspective is reflected in international policy documents (8, 28, 51, 98, 132, 145). A systematic review of 2012 could only find four empirical studies on genomic IFs, of which two studies were situated in a research context and two in a diagnostic context (96). Seven years after this review, and particularly stimulated by the publication of the initial ACMG recommendations, a considerable amount of empirical research on IFs and SFs has been realised. Over the last years, this research also paid increasing attention to the perspective of the general population on IFs, SFs and genomic medicine in general.

In Belgium, the King Baudouin Foundation (KBS-FRB) and the Sciensano Cancer Centre recently organised a citizen's forum on genomic medicine. A diverse group of 32 well-informed adults reflected on the most imminent points of concern, including societal, ethical and legal implications of genomic medicine (34, 38). Belgian citizens demonstrated a significant interest in genomic medicine. They expressed a sense of genomic responsibility and solidarity as well as a need for autonomous choices and active control (27). The combination of both interests may result in a wish for a society where genomic medicine advances people's health without discriminating them on medical grounds (27).

Internationally, lay people clearly show an interest in personal genetic information. Various criteria, such as a condition's severity, penetrance or age of onset, may affect people's interest in IFs and SFs but overall, people show a broad interest in these results (29, 37, 46, 76, 153, 154).
Some studies indicated a predominant and almost omnipresent interest in medically actionable IFs and SFs (20, 63, 83, 85, 123, 155-157). A review study indicated that 94% of patients included in the selected research wanted to receive actionable SFs in a diagnostic context (20). A study including young women with diagnosed breast cancer even revealed an omnipresent desire to receive actionable IFs (155). These results are considered to be an opportunity for disease prevention and informed decision making regarding future health risks (63, 75, 158, 159). For some people, the clinical relevance of IFs and SFs could be a reason not to allow an opt-out for these results, as this opt-out could have harmful consequences for themselves and/or family members (160).

Besides, many people would also be interested in medically non-actionable IFs or SFs and this for reasons of personal utility (7, 57, 60, 81, 83, 123, 161). They would like to receive medically non-actionable results because of psychological or reproductive interests (for themselves and family members), altruistic intentions (to contribute to scientific research or future treatments for others), the pursuit of self-knowledge (for example regarding one's ancestry), the possibility of lifestyle changes or the value of knowledge *per se* (29, 46, 54, 63, 80, 81, 83, 123, 155, 156, 159, 162, 163). People also fear to regret the decline of information with a possibly future relevance (161). Even when a finding's meaning may be ambiguous or uncertain, many people would still prefer to be informed and few would refuse the disclosure of diagnostically unrelated results (7, 31, 51, 111). This way, a preference in lay people for the disclosure of numerous or even all possible IFs or SFs has frequently been suggested (7, 51, 161, 164) (48, 60, 164).

Despite this general and broad interest in ISFs, not all people want to receive (all) IFs or SFs and some people have expressed a more selective interest (54, 91, 153, 165). Reasons for

patients' potential decline of IFs or SFs may be related to the possible costs of additional testing, the complexity of results, a focus on diagnostic results, a fear for an information overload or moral obligations towards others and a general distrust in the healthcare system (80, 121, 156). Patients' major argument against the receipt of ISFs is the fear of not being able to psychologically cope with these results and the fear of living with a "presymptomatic patient status" (7, 57, 75, 85, 159). Since it is impossible to unlearn ISFs, their disclosure may result in strong and enduring anxiety and affect one's overall wellbeing (165, 166). All ISFs may be inherently "bad news" but especially medically non-actionable findings, results associated with very severe (and slowly progressive) conditions, results without a clear pathogenic significance (VUS IFs), results that are not health-related and low-penetrance results are considered potentially harmful or psychologically distressing (63, 80, 153, 155, 156, 167-169). Nevertheless, people mainly expect positive effects of disclosed IFs and SFs or they consider worry as a manageable trade-off for the potential benefits of disclosed results (70, 81, 161, 168, 170). The rationale regarding (psychological) harm that may be caused by ISFs is mentioned more frequently by professionals whereas lay people and patients want to decide for themselves on the risks of reported results (54, 57, 62, 63, 70, 83, 99).

People generally stress the importance of involvement and control regarding the disclosure of IFs and SFs and many patients think they should be allowed to have a look into Pandora's box that has been opened by genomic testing (8, 20, 57, 62, 63, 154, 171). People emphasise the values of autonomy, personal choice, ownership and empowerment and they argue that these values may supersede results' medical actionability (51, 54, 57, 62, 63, 76, 121, 155, 160, 162, 171). When people receive more detailed information on IFs and SFs, they may nuance the absolute weight of patient choice but they structurally reject unilateral professional decisions on the disclosure of results (54, 57, 75, 111, 160, 162). This idea complies with the concept of shared decision making where patients and professionals collaborate in medical decision making (168).

People's longing for autonomy and their confidence in psychological coping abilities regarding IFs and SFs have been supported by studies that did not identify feelings of anxiety, distress or regret shortly after the disclosure of medically actionable SFs (166, 172-174).
Without denying people's ability to psychologically cope with IFs and SFs, it should be taken into account whether people's confidence may be affected by cultural expectations of emotional strength (166). Research also warned for the difference between genetic test results' lower psychological impact on people who were known to be at risk and results' more severe impact on people without a suggestive family or personal history (36, 72). This difference may be of particular relevance in a context of presymptomatic IFs and SFs.

1.4. Genomic testing and the opening of Pandora's box

The prologue of this dissertation referred to the myth of Pandora. Several researchers have already used the story of Pandora to illustrate the current evolution in medical genomics and NGS technologies. Horn et al. and Hashiloni-Dolev et al. recalled the mythological character in the context of prenatal genomic sequencing and Townsend et al. and Behr et al. referred to Pandora in the specific context of genomic IFs (62, 175-177).
A study on lay people's use of metaphors in a context of genomic sequencing showed how the reference to Pandora's box is mainly associated with the potential discovery of troubling information (178). The metaphor mainly focusses on an unleashing of results that cannot be controlled and on information that cannot be unlearned (178).
In view of this interpretation, one may wonder whether the myth of Pandora is the best metaphor for the debate on IFs and SFs in current genomic medicine. Should genome analysis and its possible results be perceived as an uncontrollable box filled with risks or may this metaphor require some adjustments?

1.4.1. Revealing the box's content

The myth of Pandora illustrates how genome analysis provides the tools to open Pandora's box. This analysis may engender both diagnostic test results and findings that are no longer diagnostically focussed and temporary relevant but broad, predictive, dynamic and potentially lifelong relevant (78, 80). This way, IFs and SFs may reveal a significant part of the content of Pandora's box without direct clinical indication (21, 42, 92, 163).

IFs, SFs and the opportunity to reveal what is inside Pandora's box may drastically change the nature and organisation of medicine and healthcare. In a clinical context, many if not all patients may discover they carry additional genetic predispositions and they are potential future patients or "pre-patients" who suffer from future multi-morbidity (27, 179).
A society of pre-patients will have to define suitable ways of treating people who carry genomic defects without suffering from the associated disease yet and this in both a medical and psychosocial way (15). Whereas patients with a symptomatic condition may be included in conventional healthcare trajectories, this may not always be the case for people without symptoms yet with a diagnosed predisposition. It is still unclear to which care pre-patients are entitled and whether and how traditional healthcare procedures are compatible with people's pre-patient status (92, 105). Since therapeutic interventions may only be required at an unknown moment in the (distant) future, pre-patients may, for instance, feel better supported by a longitudinal follow-up trajectory than by acute clinical consultations (69, 142).

Analogously, the responsibilities of pre-patients (e.g. concerning lifestyle changes and family communication or towards employees or insurance companies) are still unknown, as well as the potentially required adjustments of professional roles and responsibilities (27, 92, 105). The rights and responsibilities of a genetically at-risk person and the threats of genetic discrimination are definitely worth future research.
Ultimately, the shift from treatment to prediction and prevention and the medical and social group of pre-patients may transform concepts of health and illness and the nature of medicine (27, 38, 107, 179). The potential changes in the organisation and nature of medicine and healthcare may become so big and important that they have been labelled a paradigm shift (105, 179).

An important element in the potential paradigm shift may be the evolution that genome analysis can increasingly offer the tools not only to open Pandora's box but also to manage or even overturn the risks one may discover (as IFs or SFs). Described opportunities of NGS technologies, including personalised medicine, reproductive options or even gene therapy, suggest that opening Pandora's box can arouse not only "flapping shapes" and "wailing creatures" but also opportunities for prevention and recovery. Rather than feeling powerless and being overwhelmed by IFs, SFs and what may still be "bad news" initially, patients may have increasing possibilities to act upon this information and cope with what has been unleashed. As described in the introduction, these possibilities are not necessarily limited to medical actions and can also include personally relevant actions.
The developing spectrum of coping possibilities towards genetic information introduces a part of the myth that has frequently been neglected, i.e. the creature still locked up in the box. IFs and SFs are not only an opportunity to discover additional health risks as the frightening content of Pandora's box, they may also contribute to the release of the imprisoned creature, Hope.

1.4.2. The need for an improved policy and understanding

Are IFs and SFs an opportunity to unleash the creature of Hope from Pandora's box, and if so, how can this release be realised in an effective, efficient and ethical way?
When reviewing this introduction, these questions do not seem to be answered unequivocally (19, 160). To close this introduction, three factors that prevent an unambiguous answering of these questions are identified.

Firstly, there seems to be a considerable divergence between professionals' and layman's/patients' perspective on IFs and SFs. Professionals emphasise duties of beneficence and non-maleficence whereas lay people and patients rather accentuate and expect respect

for autonomy (62, 119). This discrepancy between prioritised values may result in conflicts where the *prima facie* values of professional beneficence and patient autonomy need to be balanced (38, 57, 60, 109, 115, 124).
From a professional perspective, the clinical utility and medical actionability of results strongly affects the balancing of values; the medical benefit that can be realised by disclosure can be a sufficient reason to overrule a patient's autonomy when this patient wants to opt out of a medically actionable IF (51, 57, 76, 106, 111). Medical actionability turned out to be a crucial professional threshold for disclosure (for both results that *can* be reported and results that *should* be reported): the more ISFs allow for medical interventions with a potentially beneficent outcome, the more these findings' disclosure seems to be justified or even required (51, 60, 79).

For patients however, the criterion of medical actionability seems to be less important and values of autonomy, involvement and empowerment may take precedence over this criterion (51, 54, 57, 62, 153, 161, 162, 180). People's preferences regarding ISFs do not seem to follow the division between medically actionable and non-actionable findings and even when results are not medically actionable, people suppose there may be ways to take (preventive) action (7, 153, 165, 170, 171, 180, 181).
Patients' and professionals' different approach of genetic information may explain their divergent perspective on valuable genetic results. Whereas professionals consider genetic data as a source for health information, diagnoses and risk assessments, patients may consider this information from a personal, social and existential perspective (73). Finding common ground between both perspectives has been a challenge for several years now (182).

Patients' emphasis on autonomy and empowerment also indicates another potential adjustments of the myth of Pandora. Some people want to open the box and unleash its full content, not as an uncontrollable event but as an autonomous choice. Others, however, may prefer never to open Pandora's box or to release only the information needed for diagnostic purposes. This way, Pandora's box may transform into a 'lock box', a metaphor that refers mainly to a sense of control and to an intended, relevant and safe use of the box's content (178).

Secondly, there is considerable disagreement between international policy documents and between professional perspectives on the disclosure of IFs and SFs. No consensus has been realised yet on criteria, arguments or values that are decisive for disclosure or on the weight of patient preferences and professional responsibilities (42, 57, 79, 183). In chapter four, the lack of consensus between international policy documents and among professional perspectives will be discussed in detail.

In the context of this introduction, it is particularly important to indicate that in many countries, the discrepancies between policy documents and professional perspectives entail a lack of specific guidance and institutional protocols on the disclosure of ISFs (30, 42, 51, 56, 86, 92, 111, 184). This may result in divergent disclosure practices and policies, in *ad hoc* approaches regarding ISFs and in a violation of the principles of equity and justice (8, 91).
However, not a lot is known about the actual reporting of IFs or SFs and few studies have described this practice in a diagnostic context. In a US-based study of laboratory practices, all included laboratories reported diagnostically unrelated results but a very heterogeneous spectrum of disclosed results was identified (117). Also an international study on laboratory reporting practices demonstrated a large diversity, including practices of not disclosing any IF, reporting medically actionable IFs and actively screening for SFs (118). Additional studies may further outline the application of international and professional recommendations on actual disclosure policies and reveal how professionals' and layman's perspectives are interpreted in clinical practice.

Thirdly, many questions about patients' interpretation of IFs and SFs remain unanswered, despite the increasing research on layman and patient perspectives.
Some previous studies included people without illness experience or patients without genetic testing experience but this kind of research design abstracts patients' clinical context (20, 48). Hence the need for further research on the perspective of people who are actually experienced with illness and genetic testing has frequently been expressed (7, 54, 78, 99, 156, 164, 181). Research that indicated a predominant interest in medically actionable IFs and SFs in cancer patients suggested the hypothesis that disease-specific experiences may affect patients' understanding or preferences regarding IFs and SFs (7, 20, 57, 155, 157, 159). Further research is needed on the interpretation of IFs and SFs by people with other illness experiences (54).
This research should also pay more attention to people's underlying motives for (not) wanting to know IFs and SFs, since little is known about these motivations (145). One study identified an association between a higher educational level and a more selective preference to know ISFs (162) but generally, persons' sociodemographic characteristics have been considered as of no significant impact on preferences regarding IFs and SFs (153, 161, 164, 170). Concepts of (medical) actionability, personal utility, psychological harm and autonomy have been shown to affect patients' interest in ISFs (cf. supra) but other motives may be identified and a more profound understanding of patients' preferences should be pursued.

Answering the question whether and how ISFs may be an opportunity to efficiently and ethically release the creature of Hope from Pandora's box, requires further research on the

issues mentioned above. It is precisely this particular need for further research that will be addressed in this dissertation.

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PART 2 RESEARCH OBJECTIVES AND OUTLINE

Chapter 2 – OBJECTIVES, RESEARCH QUESTIONS AND SCOPE

2.1. Objectives and research questions

The main objective of this dissertation is to examine the practice and perspective of important stakeholders regarding the disclosure and (ethical) meaning of IFs and SFs in a context of NGS-based clinical genomic testing.
These insights may clarify the potential correlations or discrepancies, firstly, between international guidelines and actual practices and, secondly, between the perspectives of different stakeholders. The outcome of this study and the resulting knowledge may inform and support constructive reflection on relevant future policies and contribute to the development of best practices that include various stakeholders' perspectives.

In the realisation of its objective, this study will specifically focus on, firstly, practices and perspectives of genetic professionals and, secondly, patient perspectives and meaning structures. Professional practices and perspectives will be investigated at a national level in Belgium and more particularly in the context of centres for medical genetics (CMGs). Patient perspectives will be obtained from adults with a Mendelian disease who have been genetically tested in a diagnostic context. In both stakeholders' perspectives, a detailed study of subtle elements in practice, policy, experience and (ethical) meaning will be pursued.

The main objective of this dissertation results in two specific research questions:

1. How do genetic professionals in Belgian CMGs report IFs and SFs in NGS-based clinical genomic testing in adults and how do they perceive the (ethical) motives for and consequences of this disclosure?
2. How do genetically tested adult patients perceive the potential disclosure of IFs and SFs and how do they assign meaning to these potential results?

2.2. Scope

The introduction showed that the debate on IFs and SFs covers a broad range of technological, practical, clinical, societal and ethical issues. It is therefore important to precisely define this dissertation's scope and its position in the debate.
This dissertation will focus on IFs and SFs that are revealed by use of NGS-based testing techniques (including clinical ES, WES and WGS) in a clinical context. The dissertation targets situations of constitutional testing for Mendelian diseases (i.e. testing for hereditary conditions that are caused by germline mutations) in competent adults.

2.2.1. The clinical context

The debate on genomic IFs initially has its roots in a research context (1-3). Scientific research is founded on its own principles but genomic testing has been said to fade the distinction between research and clinics (4-7). After negative clinical test results, patients may be referred to a research context without fully realising this change of context; researchers may also be the treating clinician of a research participant (4, 8, 9). It has been suggested that the interface between the clinic and research is inevitable and that both fields should be considered translational fields (5). This would imply dual roles for clinicians, expanded ethical duties for researchers and an increased relevance of clinical and research recommendations (5).

Despite the potentially blurring boundary between the clinical and research context, the introduction of clinical genomic testing raised new questions on IFs, since both contexts are nevertheless characterised by specific aims and principles. Research is hypothesis-driven, aims for generalizable results and advanced collective benefit and may be performed by a researcher who is no physician and has no clinical relationship with the research participant (1, 2, 5, 8-11). Clinical care, instead, is focussed on clinically relevant results and a particular patient's benefit. Clinicians should also respect standards of good clinical practice (1, 5, 6, 8, 9, 11). Their professional duty of care is emphasised by their relation and bond of trust with patients (10, 12). This way, professionals' (clinical and ethical) responsibilities and participants'/patients' expectations can be very different in a research or clinical context (5, 13).
The specific experiences, aims and responsibilities of both stakeholders in a clinical context are the main focus of this dissertation. As a consequence of the central position of the patient in this clinical context, this dissertation will mainly focus on the disclosure of IFs and SFs from genetic professionals to the patient, rather than between professionals.

2.2.2. Inherited retinal diseases

Constitutional testing for hereditary diseases but also somatic testing for acquired diseases, for instance in solid tumour or haematological profiling, can reveal IFs or predispositions for hereditary diseases (14). It is important to realise the different healthcare contexts of IFs that are identified in constitutional testing and IFs that are revealed in somatic testing. Patients who participate in somatic testing may have an advanced disease, pursue effective therapeutic options (instead of a diagnosis) and rarely received pre-test counselling that could have warned for the potential discovery of pathogenic germline variants (14, 15). In this dissertation, the focus is on IFs and SFs that can be identified during constitutional testing for

hereditary Mendelian diseases, more specifically for the testing of inherited retinal diseases (IRDs).

IRDs represent a large group of clinically and genetically heterogeneous eye disorders that are a major cause of early-onset blindness (16, 17). IRDs have an estimated collective prevalence of 1 in 2000, affecting about two million people worldwide (16). IRDs are characterised by a progressive degeneration of rod and cone photoreceptors and/or retinal pigment epithelium and include both isolated conditions (for instance retinitis pigmentosa, cone-rod dystrophy, Leber congenital amaurosis or Stargardt macular dystrophy) and syndromic conditions (for instance Bardet-Biedl syndrome and Usher syndrome) (18-20).
IRDs demonstrate a significant phenotypic heterogeneity, which means that a specific genetic variant can result in a variety of symptoms that are expressed in variable degrees (18). A patient's symptoms may evolve over time and different types of IRDs may phenotypically overlap (18, 20). These factors complicate or preclude the assessment of a specific diagnosis on merely clinical grounds (18, 20). IRDs also demonstrate a tremendous genetic heterogeneity, which means that one specific IRD phenotype may be associated with a large group of genes and variants (18, 21). To date, IRDs have been associated with pathogenic variants in over 270 disease genes (16, 17). This genetic heterogeneity makes WES-based testing a suitable approach for genetic testing.
For most IRD subtypes no treatments are currently available but important progress is currently being made in gene-based therapies for IRDs with Luxturna™ as an example of the first US Food and Drug Administration (FDA)-approved gene therapy (22, 23). In the context of gene therapeutic trials of IRDs, a definite and early genetic diagnosis is particularly important for both minors and adults. In this dissertation, we focus on situations where competent adults with an IRD have been genetically tested mainly because of diagnostic, prognostic and/or potentially therapeutic reasons.

Like in any case of NGS-based constitutional genomic testing, IFs may be identified by genetic testing for IRD. Lee et al., for instance, have reported on the disclosure of an IF in the *BRCA2*-gene and an IF in the *MSH6*-gene in patients symptomatic for IRD but without personal or family history of the IF-associated genetic predisposition (20). The study mentioned no further details on professionals' decision making process concerning disclosure or on patients' perspectives or preferences concerning IFs. In this dissertation, however, these issues will be of central importance.

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Chapter 3 - DISSERTATION OVERVIEW AND METHODS

3.1. Different levels and perspectives within this dissertation

The results section of this dissertation starts in chapter four with a critical study of the debate on IFs and SFs in a context of clinical ES/WES/WGS. Different phases in the international discussion will be identified, as well as the various levels of the discourse.
The 2013 ACMG recommendations will take a central role in this study, as they have intensively stimulated the international debate. The recommendations will be compared with other (Europe, US and Canada based) policy documents and professional controversies will be assessed. The updated ACMG recommendations of 2015 will be introduced as a second phase in the debate in which, however, important points of discussion could not be solved. In parallel with the two phases of the debate, major points of discussion will be orientated at three different but interconnected levels, being a terminology, policy and value level. Subsequently, the intrinsic interaction between these levels and the reciprocal sustainment of unsolved questions will be made explicit. The acknowledgement of this interaction will be emphasised as an important condition for future debates on IFs and SFs that want to transcend artificially isolated problems. Finally, as an additional complement to the debate, the inclusion of a genuine patient perspective will be encouraged.

Chapters five, six and seven present the results of two comprehensive empirical studies that were conducted to answer the central research questions of this dissertation. Chapters five and six will answer the first research question ("How do genetic professionals in Belgian CMGs report IFs and SFs in NGS-based clinical genomic testing in adults and how do they perceive the (ethical) motives for and consequences of this disclosure? "). Subsequently, chapter seven answers the second research question ("How do genetically tested adult patients perceive the potential disclosure of IFs and SFs and how do they assign meaning to these potential results?").

In the interrogation of both professionals and patients, an in-depth examination and understanding of stakeholder perspectives, current and future practices and lived experiences was pursued. Therefore, a qualitative approach was chosen for both empirical studies. Such a qualitative approach allows for rich narratives and a considerable freedom of speech (1). As qualitative approaches are holistic and context-oriented, they aim to analyse the expressed perspectives without reducing their complexity (2). This way, new points of concern and new interpretations of examined concepts may emerge from the data and these may expand or reorient current discussions.
For both qualitative studies, an extensive procedure was developed to ensure the trustworthiness and reliability of the data collection, analysis and reporting. This procedure

combined elements of peer debriefing and a systematic audit trail (3). One co-researcher conducted a secondary analysis of a subset of the data. Subsequently, transcripts, code schemes and thematic structures were intensively discussed.

3.2. Professional perspective

The first qualitative study, focussing on the professional practice and perspective concerning IFs and SFs, did not aim for individual or role-specific views but for the integrated perspective of a group of professionals and is consequently designed as a focus group study (4). Focus groups stimulate discussion and interaction between participants and allow for a co-construction of meaning (4, 5).
Focus group participants were recruited in the eight Belgian CMGs. To encourage an open discussion between colleagues, one focus group discussion in every CMG was considered most appropriate and a representative group of professionals who are experienced with NGS-based genomic testing was pursued for every discussion. Multidisciplinary groups, including both clinical geneticists, clinical laboratory geneticists and possibly other genetic professionals such as genetic counsellors, nurses and bio-informaticians, were aimed for.
In every focus group, a semi-structured interview guide was used. This interview guide was created after a thorough study of the literature and was evaluated by the multidisciplinary team of co-researchers, including an ethicist, a geneticist and a philosopher. The interview guide consisted of open-ended questions and focussed on the return of IFs and SFs to adults, preconditions for disclosure, ideas on future policy, challenges and difficulties, duties of genetic professionals and CMGs, the impact of international recommendations, counselling procedures and personalised healthcare procedures.
At the outset of every focus group, the focus on a context of clinical NGS-based testing for monogenic diseases was emphasised, excluding preconception, prenatal, screening and research contexts. Focus group data were analysed thematically, inductively and unrestricted by *a priori* theoretical concepts (6).

Chapter five presents the focus group study results regarding reporting practices concerning IFs and SFs in Belgian CMGs. Used criteria for reporting will be identified, as well as their sometimes challenging interpretation, application and interaction. This way, the scope of reportable results, now and in the future, will be delineated and the similarities and differences between CMGs will be demonstrated. Also points of discussion and individual disagreements between participants of the same genetic centre will be addressed.
Correspondingly, these study results reflect the extent to which international policy guidelines are actually incorporated in practice and which elements of recommendations are most

feasible and challenging in efficient policymaking. Finally, chapter five discusses how (inter)national guiding frameworks for disclosure should be balanced with patient-specific, case-by-case deliberations.

Chapter six discloses the results of the focus group study regarding underlying ethical values for the disclosure of IFs and SFs. International literature frequently refers to *prima facie* values regarding respect for patient autonomy, professional non-maleficence and beneficence. Chapter six empirically identifies how these and other values are considered in actual reporting practices for IFs and SFs and how potential value conflicts are weighed. Subsequently, the way these values are invoked to support and defend disclosure practices is critically reflected upon. Concepts of genetic literacy, soft paternalism, normative rationality and distributive justice will turn out to be important in this ethical consideration.

Chapter six can be situated within the spectrum of empirical bioethics where ethical issues are not considered from a purely theoretical or *a priori* ethical perspective but also from an empirical approach as "ethics-in-action" (7). In empirical bioethics, the empirical and normative perspective are considered necessarily related and they are integrated in a way which allows a refinement and adjustment of both poles (8, 9). In comparison with a theoretical and more general ethical analysis, an empirically informed analysis is regarded as more sensitive to a particular context and hence more relevant for actual practice (9, 10). A reflective equilibrium or coherence between ethical theory, principles, policy concerns and empirical data (including, for instance, the contextualised experience and perspective of important stakeholders) is pursued (9). This way, the chance to successfully implement the outcome of moral reasoning is considered to be higher (9, 10). Important to mention is the pragmatic and dynamic character of the reflective equilibrium: the equilibrium is merely an attempt towards but never the full realisation of a "better" ethical system; moral problems require constant revision because of an ever-changing social and technological context (10).

3.3. Patient perspective

As a complement to the professional point of view, a second qualitative study was conducted to pursue a conceptualisation of IFs and SFs from the perspective of patients. This study was designed as an interview study and investigated how patients with lived experiences of illness and genetic testing perceive the possible disclosure of IFs and SFs. More particularly, the perspectives of adults who have been genetically tested for an IRD were examined, with a particular focus on the meaning they assign to potential IFs and SFs. The choice for this particular group of participants was guided by these people's lived experience of severe,

chronic and currently untreatable illness and their experience with genetic testing. Participants were recruited in a university hospital and a semi-structured interview guide, also evaluated by the multidisciplinary team of co-researchers, was used. Open-ended questions focussed on participants' lived experience of IRD and genetic testing, the possibility and potential consequences of IFs and SFs and important elements for the interpretation of IFs and SFs from a patient perspective. An interpretative phenomenological analysis was used to examine and interpret the lived experiences of participants and the way they give meaning to the concepts of IFs and SFs (2, 11).
Chapter seven presents the results of this interview study and outlines a context-inclusive interpretation of IFs and SFs from a patient perspective. Three main components will be identified in the meaning structure of IFs and SFs, namely result-specific qualities, lived illness experience and family embedding. These components will be profoundly analysed, as well as the interaction between these components. Finally, some ideas are expressed on the impact of the complex, context-dependent meaning of IFs and SFs on effective counselling strategies for NGS-based diagnostic testing.

As well as chapter six, chapter seven can be situated in the domain of empirical bioethics. However, a more continental approach to empirical ethics is applied in this chapter. This means that explicit attention is paid to patients' embodied singularity and relational context in the consideration of their illness experience (12). Patients' lived experiences are considered essential for ethical and effective healthcare policies and these are analysed irrespective of concepts and principles that are settled in advance (13). The lack in continental bioethics of traditional and normative terminologies (such as autonomy, rights or duties) should not be interpreted as favouring the empirical over the normative but as developing a new vocabulary of the normative in terms of, for instance, embodiment, singularity and interdependence (12).

At the outset of this dissertation, neither the professional perspective nor the patient perspective is deemed to be *a priori* decisive. Knowing and understanding both perspectives on IFs and SFs is considered quintessential to eventually elaborate a relevant and effective policy (14).

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PART 3 RESULTS

Chapter 4 - INCIDENTAL OR SECONDARY FINDINGS: AN INTEGRATIVE AND PATIENT-INCLUSIVE APPROACH TO THE CURRENT DEBATE

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4.1. Abstract

Incidental or secondary findings (ISFs) in whole exome or whole genome sequencing have been widely debated in recent literature. The American College of Medical Genetics and Genomics' recommendations on diagnostic ISFs have strongly catalysed the discussion, resulting in worldwide reactions and a variety of international guidelines. This article will outline how propositions on levels of terminology, policy, and underlying values are still internationally criticized and adjusted. Unsolved questions regarding ISFs include a suitable terminology, adequate counselling or informed consent procedures, opt-out possibilities, reporting ISFs to (parents of) minors and values regarding professional duty, patient autonomy, and actionability. These questions will be characterized as intrinsically related and reciprocally maintained and hence, symptomatic, single-level reflections will be marked as ineffective. Instead, a level-integrative approach of the debate that explicitly acknowledges this interaction and considers a balance between internationally significant and case-specific solutions, will be advocated. Second, the inclusion of a patient perspective will be strongly encouraged to complement the professional preponderance in the current debate. The examination of lived patient experiences, a qualitative focus on the subjective meaning of ISFs, and a contextualization of meaning processes will be suggested as specific concretizations. This integrative and inclusive approach aims for a more comprehensive understanding of ISFs, a consideration of all relevant stakeholders' perspective and, ultimately, an effective health-care policy.

4.2. Introduction

Incidental findings (IFs) or secondary findings (SFs), being results unrelated to the initial indication for genetic testing, have aroused a vast debate in the literature on whole exome sequencing (WES) or whole genome sequencing (WGS) (1-3). The initial (2013) recommendations on diagnostic IFs by the American College of Medical Genetics and Genomics (ACMG) have initiated the discussion, while the updated ACMG guidelines of 2015 can be perceived as the start of a second and reoriented debate phase (4, 5). As a stimulating precedent, the ACMG guidelines have had an international impact, as (explicitly) confirmed in the many statements that were released shortly after them. When comparing these international documents, a diversity in terminology and policy guidelines on incidental or secondary findings (ISFs) can be identified, which has resulted in currently unsolved points of discussion. "ISFs" is used in this article as a working term ad interim, referring to the entirety of both deliberately pursued and accidentally found results that are unrelated to the indication for diagnostic genetic testing, however irrespective of any further specification

concerning (clinical) validity or utility, policy or values as suggested by existing literature. Rather than taking a final stance in this debate, this article will explicitly indicate the link between the level of semantic choices and the second level of policy recommendations. Finally, commonly cited (bioethical) values will be integrated as a third level. The elaboration of this three-levelled overview of pertinent discussions on ISFs in current literature will, first, reveal how unsolved problems on one particular level affect the overall, international debate and hence how all problems and levels are intrinsically connected. Subsequently, the lack of a genuine patient perspective will be identified as a second obstacle for the debate. Therefore, a level-integrative approach, which explicitly recognizes the levels' interaction, and a patient-inclusive approach will be suggested as necessary steps toward a better understanding of and effective debate on ISFs.

Although the evolution of WES/WGS dissolves the border between diagnostics and both research and screening, this reflection is focused on a diagnostic context, where symptomatic patients enter the health-care system with a specific question (6). This diagnostic situation is considered to be substantially different from a research, screening or direct-to-consumer context with asymptomatic patients/ participants, where the distinction between primary results and ISFs might be even more complex.

4.3. Phase 1: Incidental findings

Referring to a common phenomenon in medicine, ACMG adopted the terminology of IFs in its initial recommendations of 2013 and defined them as "[…] results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility […]" (4). However, labelling findings as incidental in a context of WES/WGS has been terminologically criticized as paradoxical, because discovering numerous variants is intrinsic to these techniques (7, 8). Moreover, the characterization of results as incidental has been considered, also by patients, to suggest a sense of insignificance, which is inappropriate in situations of life-saving findings (9, 10).

ACMG's policy recommendations revealed a more specific understanding of IFs than the definition suggested. A standard analysis and report of (likely) pathogenic variants (class 5 and class 4 variants that, respectively, affect and probably affect function, including the importance of a contextualized interpretation and the absence of a 100% certainty regarding pathogenicity and penetrance) in a minimum list of 56 highly-penetrant and medically actionable genes was recommended in any case of diagnostic WES/WGS, irrespective of the indication for testing and of the patient's age and preference (4, 11-13). This implicated the

obligatory report of IFs concerning both early- and adult-onset conditions to adults and to (parents of) minors. This recommendation has, again, evoked semantic comments, as it is paradoxical to qualify intentionally sought results as incidental (9). Therefore, ACMG's parallel reasoning, in which reporting genomic IFs was compared to reporting unexpected radiological anomalies, has also been doubted (4). While the radiological detection of additional findings cannot be avoided, genomic IFs are oftentimes not inevitable but they are an additional targeted test or they can be covered by use of bioinformatics filters (13, 14). Also the difference between detecting an actual disorder versus a (future) probability has been regarded as discrediting the parallelism (15). However, criticism has exceeded the terminological level and the intentional and mandatory analysis and report of IFs have been fundamentally questioned. First, in an explicit reaction to the ACMG recommendations, the Association of Genetic Nurses and Counsellors (AGNC) has stated that intentionally looking for additional results that exceed the indication for a test or consult, is not a routine action in general medical practice (16). Moreover, the deliberate search for IFs can blur the boundary between diagnostics and screening. This hybridization is, however, not unproblematic, as diagnostics and screening imply different duties, expectations, and values, for both patients/ participants and professionals (17, 18). It can also stimulate a trend of medicalization, in which additional screening is a priori considered as beneficial while it can actually result in an overload of (uncertain) information and a group of "patients-in-waiting" (19, 20). Nonetheless, ACMG seemed to consider this blurring delineation as unproblematic and referred to IFs as "opportunistic screening" (4). The Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) has questioned this "better safe than sorry" attitude, as opportunistic screening might hold additional risks instead of an actual improvement of care (20). Second, obligatory reporting results, also against patients' will, violates the general medical practice and policy (19). Therefore, the Bioethics Commission has upheld the respect for a patient's choice not to be informed about ISFs (20). Despite its recommendation to report serious and actionable IFs, also the European Society of Human Genetics (ESHG) has stressed how, in general, patients should be able, like in every presymptomatic genetic test setting, to apply and change their preference regarding the disclosure of results (8). Also a survey among US-based genetic counsellors about the ACMG guidelines' implementation confirmed the preference for an opt-out possibility of IFs (21). Regarding the mandatory report of results about adult-onset conditions to (parents of) minors in particular, the AGNC and others have stated how this practice is incompatible with general paediatric genetic testing (13, 16, 22).

Ultimately, the policy discussion was grounded in a different prioritizing of values. Promoting the active search for IFs, ACMG referred to the professional duty of avoiding harm, both toward patients and their families (4, 11). Fully respecting this value implicated informing (parents of) minors about IFs concerning adult-onset conditions, as it might be the only

opportunity to avoid serious future morbidity in the child's relatives (4, 23). This way, ACMG's exception on declining presymptomatic tests in minors for adult-onset conditions was justified by a family-wide conception of health benefits (23, 24). In an explicit reflection on the ACMG and ESHG guidelines, also the Canadian College of Medical Geneticists (CCMG) has stated how this practice, in case of unintentional IFs, might be opportune when it can avoid serious medical harm and when explicitly requested by the parents (25). This point of view was shared by laboratory professionals who theoretically did not differentiate between reporting IFs to adults or (parents of) minors and by clinical geneticists and genetic researchers who have considered the return of adult-onset results in minors as possibly opportune (26-28). Also parents considered the possibility of receiving these results as a positive opportunity for additional information about themselves (29). In contrast to the obligatory report of IFs, critics have stressed the professional duty to respect the medical choice of (parents of) patients, including the wish not to be informed, and this in respect of the fundamental value of (future) patient autonomy (13, 19, 22, 30). Therefore, in a reply to the ACMG recommendations, the Public Health Genetics (PHG) Foundation has stated that denying a patient's consent in opportunistic screening is an unethical practice (31). Also a US-based expert forum on the ACMG recommendations stressed the professional duty of respecting patients' right not to be informed (32). ACMG recognized how its recommendations collided with ethical values but explicitly confirmed that, in this case, the duty to avoid harm exceeded the value of autonomy (4).

Possibly, ACMG's position was motivated by the specific US health-care context and by fear of legal consequences for not reporting "all available information". However, it has been argued that the ACMG recommendations even enlarge liability risks, as professionals might be sued, e.g., for delayed disclosure or failure of re-evaluating sequence data, or, on the other hand, for needless or harmful follow-up for IFs (33). Moreover, the frequently divergent claims of other US-based professionals and policy groups threaten the absolute weight of the liability concern (13, 20, 22). Finally, a European versus US geographical background turned out to be of no significant impact on professionals' attitude toward the return of IFs (34, 35).

4.4. Phase 2: Secondary findings

In response to the terminological critique on IFs, alternatives such as "unsolicited", "unanticipated", or "unexpected" findings, or "secondary variants" have been suggested (7-9, 36). The Bioethics Commission has chosen a multiple vocabulary and has discerned anticipatable and unanticipatable IFs, SFs and discovery findings (20). Partly in line with this terminology, ACMG has revised its vocabulary from "incidental" to "secondary" findings, as

this term acknowledges the intentional search for additional pathogenic variants (5, 12, 37). However, none of all the terminological suggestions have remained free of objections, as they might deny a professional's competence to anticipate specific variants, neglect different expectations of different stakeholders, or overlook cases where no primary result has been found (2, 9, 20, 38).

The adjustment of ACMG's vocabulary has coincided with a major change in its recommended policy as a possibility of opting out of SFs has been offered to patients (5). Nonetheless, the idea of, even voluntary, opportunistic screening is incompatible with the intrinsic questioning of SFs by some policy groups. As part of the professional duty of non-maleficence, the Bioethics Commission has advocated "therapeutic parsimony", being a selectivity in chosen tests or interventions, and "diagnostic elegance", being a limitation of potential diagnoses. Therefore, in general, targeted testing is considered as more suitable, as it inhibits the possible downstream of medical, financial, and psychological procedures after identifying ISFs (20). In order to avoid ISFs and their high-cost impact on patients, families, and society, the CCMG, ESHG, and EuroGentest have also recommended, in explicit reflection on previous guidelines such as those of ACMG, an initial targeted testing and a justification of WES/WGS in terms of necessity and proportionality (6, 8, 25).

ACMG's adjusted possibility for opting out of SFs has reinstated the value of patient autonomy. However, on an international level, the absolute versus relative weight of this value and its application to IFs, SFs, or both are unclear. ACMG has made no explicit notion of cases where opt-out is or should be impossible for SFs and also the AGNC has defended autonomy as "the heart of genetic counselling practice" in opportunistic screening (5, 16, 37). The Bioethics Commission has, despite its claim for an opt-out possibility, only granted a relative weight to autonomy: when ISFs are clinically significant, of serious health importance and actionable, a "prudent professional judgment" should be made and the patient's opt-out choice should be respected "to the extent consistent with the clinician's fiduciary duty" (20). Also the ESHG and the PHG Foundation have affirmed how the right not to know IFs does not always exceed the professional duties of beneficence and non-maleficence, e.g., when the information might be actionable and relevant for patients themselves and/or their (future) family (8, 31).

4.5. Medical actionability

In both ACMG's initial and updated recommendations, medical actionability, being the possibility of an improved clinical management by medical treatment or prevention, has been

displayed as a fundamental value (3, 39). In 2016, a semiquantitative metric to score genes regarding their medical actionability has been elaborated, using the criteria of severity and likelihood of disease outcome, efficacy and acceptability of the intervention, and the knowledge-base regarding the previous four criteria (40). No reference is made to the possible disease outcomes for a patient's family or (future) offspring, neither to interventions as patient-performed actions such as lifestyle changes or reproductive choices. Consequently, actionability is conceived as the possibility of strictly medical, professionally performed interventions toward the actual patient. In accordance with this metric, ACMG has updated 5 genes on its initial list, resulting in a minimum list of 59 genes (12, 37). This semiquantitative definition of medical actionability has been widely criticized and, as a first comment, it has been mentioned, e.g., by the Bioethics Commission, how difficult it can be to exactly assess the true medical value and actionability of ISFs at the moment of discovery (20). Variants can have an unknown pathogenicity when discovered in asymptomatic persons and their significance depends on further investigations, of both patients and their family (1, 13, 19). Hofmann (41) even claims how the ACMG list mainly consists of findings of uncertain significance and of results which lack accuracy and actionability. As a second critique, the required professional knowledge to assess a gene's medical actionability and the generalization of a professional criterion into a universal value have been blamed to result in a degree of paternalism that is incongruent with the current, pluralistic, and patient-centred society (14, 39). Finally, it should be noticed how ACMG's use of this semiquantitative metric contradicts its previous argument of a family-wide health interest in case of ISFs concerning adult-onset conditions in minors.

In order to deny the monopoly of a strictly medical and professional actionability, a wide spectrum of alternatives has been suggested. Moret et al. (42) assert a concept of actionability that discerns well-established medical actions, patient-initiated health-related actions, and patient-initiated decisions exceeding health, such as reproductive choices. Stivers and Timmermans consider actionability as an interactional value that is created in the relation between (parents of minor) patients and clinicians. Even if genetic results do not change (parents of minor) patients' (medical) actions, they can be actionable in various meaningful ways, e.g., by facilitating specific services (e.g., educational services for disabled children) or by changing psychological experiences or reproductive choices. Hence actionability is not an objective, medical criterion but is determined by (parents of minor) patients' personal, social, reproductive, etc. context (43). Concepts of actionability that surpass a medical focus acknowledge the personal utility of genetic information and consider warning at-risk relatives and adjusting behaviour or reproductive choices as valuable actions, a perception also shared by the Bioethics Commission (14, 20, 30, 39). This extended actionability approach also recognizes an intrinsic value of genetic knowledge per se, irrespective of any practical use.

Various stakeholders (professionals, patients, research participants, and the general public) have supported this idea and have preferred to return or receive “all results”, regardless of their actionability (36, 39, 44). In line with this enlarged concept of actionability, the PHG Foundation’s list of disclosure criteria for ISFs includes, e.g., the age and general condition of the patient, which suggests a more diverse spectrum of reportable results that exceeds medical actionability (31).

4.6. A level-integrative and patient-inclusive approach

Despite ACMG’s adjustment of its vocabulary, recommended policy, and prioritized value, international disagreement has remained (Figure 1).

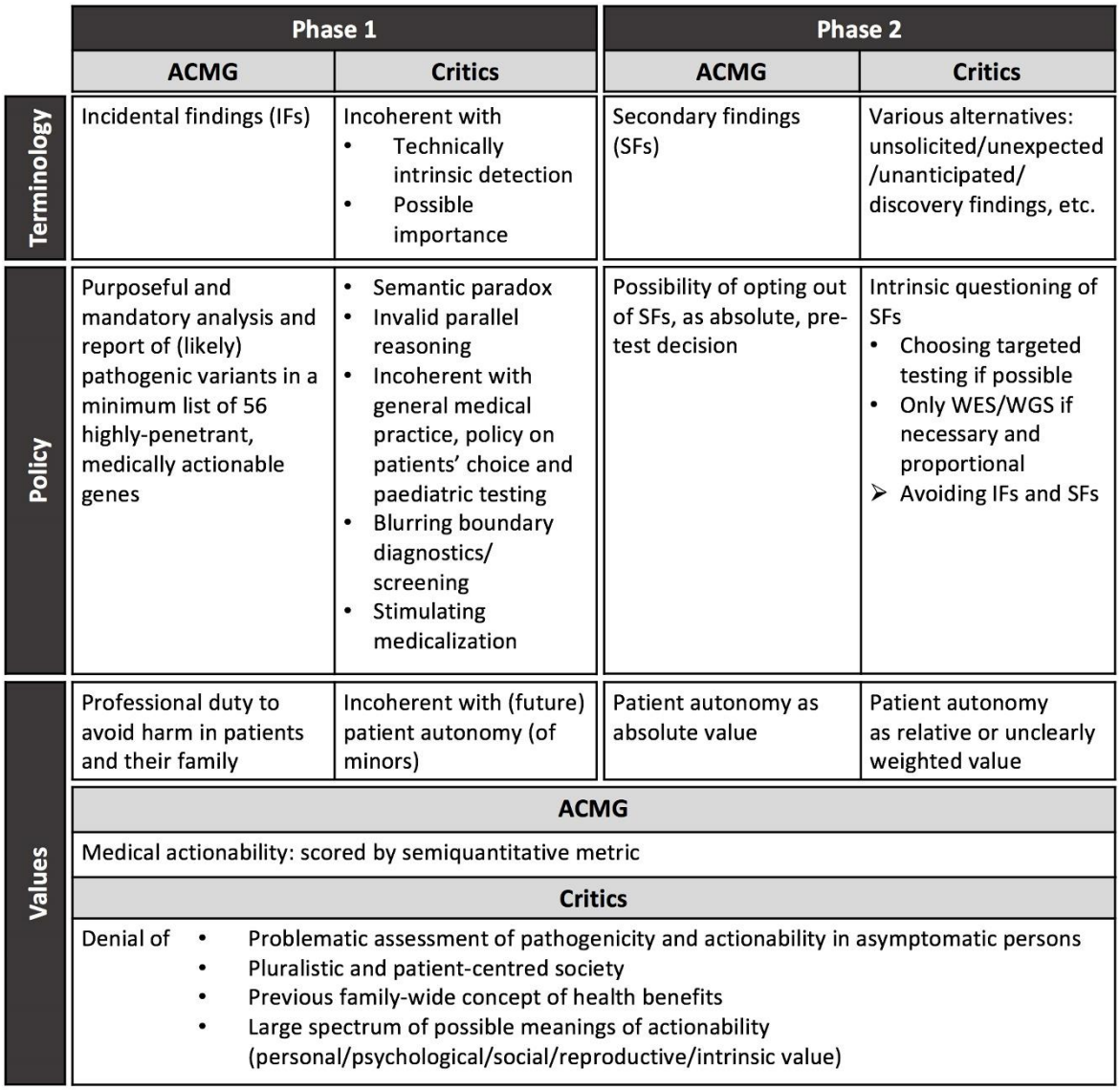

Figure 1 Two-phased, three-levelled debate on ISFs

On terminology level, alternative terms for ISFs are still suggested and used inconsistently, keeping consensus out of reach (7). It also generates a vagueness in policy publications on whether they actually apply to IFs, SFs, or both. On policy level, adequate counselling and informed consent procedures are a general problem regarding ISFs. The evolution toward WES/WGS, providing an enormous amount of information, challenges which information and counselling are required to realize a truly informed consent and a satisfactory understanding of (additional) results (44, 45). Professionals and sometimes (parents of minor) patients themselves have expressed their concern about a limited understanding of WES/WGS, an ignorance that might partially explain people's desire to receive a very broad range of

(additional) results (29, 44, 46). More fundamentally, the feasibility and effectiveness of traditional pre-test procedures in which a large amount of complex information is provided, have been queried (45). To avoid an overload of information and to realize an enhanced understanding, alternative consent procedures have been elaborated, in which binning systems, which (partially) allow (parents of minor) patients to choose which categories of possible results to receive, have been frequently suggested. Berg et al. already elaborated a categorical framework for IFs, where "bin 1 findings", consisting of (likely) pathogenic variants in medically actionable genes, were recommended to report. The return of (likely) pathogenic variants in clinically non-actionable genes depended on a shared decision-making between the (parents of the) patient and the professional, whereas genes and variants of unknown significance should never be reported, as their informative value is unclear (47, 48). Elaborating on such binned systems, tiered/layered procedures of consent have been suggested, where a default package of necessary information is presented to all (parents of minor) patients, while more detailed information is only selectively provided, depending on specific information needs and result preferences (49, 50). Despite the usefulness of these systems, an effective integration in clinical practice is still impeded. First, some categories or bins lack an exact definition, with the concept of actionability as specifically problematic (42). Second, professionals have disagreed if a patient's age can affect the return of specific categories of results, an issue related to the return of ISFs regarding adult-onset conditions in minors (51, 52). Third, despite these binned, tiered, or layered consent procedures, it has been suggested that, in general, too much focus has been put on the informational aspect of counselling and that instead, more attention should be paid to its interactional, collaborative, and ethical nature (45). Besides this general challenge of an adequate counselling process for ISFs, also the policy on opting out requires further clarification. Related to the terminological vagueness, it is, e.g., unclear whether ACMG's and AGNC's opt-out possibility only applies to SFs or also to IFs, a question also linked to the undetermined weight of patient autonomy. A similar vagueness occurs in the Bioethics Commission's recommendation on balancing patients' possible opt-out preference versus professional duties regarding both IFs and SFs. The ESHG and EuroGentest have plead for a clear opt-in and opt-out protocol regarding ISFs, both for adult and minor testing, but again, no specificities have been given (6, 8). The policy of avoiding ISFs and intentionally covering results by bioinformatics filters raises ethical questions because, even though these results are masked for the professional eye, they still exist. It is unclear if this mask actually eliminates the professional duty to avoid harm, an issue also referred to by the Bioethics Commission's claim that the fiduciary duty does not allow professionals to filter additional results exclusively in order to avoid responsibility (17, 20). Also the practice of reporting ISFs (especially those related to adult-onset conditions) in minor testing still raises doubts, on both policy and value levels. An interest has been shown in results that are not (yet) relevant for tested (minor) patients themselves, hence it is debatable

if (minor) patients' results can be used for others' possible benefit or if this is an unacceptable instrumentalization (24). A thorough reflection is needed on values such as (future) autonomy and the right not to know, and whether these values, in the context of current genetics, still have their traditional meaning or if they are in need of a conceptual update.

Regarding the value of actionability, a feasible concept should be elaborated that can effectively guide practice and policy. Berg's semiquantitative metric for medical actionability seems a straightforward procedure to classify ISFs, but a gene's correct categorization can be difficult (14, 37, 53). For example, scoring a gene on the severity of its outcome or scoring an intervention on efficacy is ambiguous when the gene is associated with multiple outcomes or when different interventions are available. It is undecided in these cases whether the most severe or the most likely outcome should be scored or whether very radical interventions should also be considered (53). Moreover, the likelihood of a possible disease outcome and the efficacy and acceptability of an intervention are partly determined by (the parents of) a patient's characteristics and context, an argument also recognized by Berg himself (40). These pitfalls of a rigorous metric show the difficulty to measure actionability by merely medical criteria and the need to find common ground for patients, parents, and professionals on the wide spectrum between a strictly medical interpretation and more subjective and contextualized interpretations.

The aforementioned problems regarding ISFs clearly demonstrate a reciprocal interdependence and hence a strong unity of terminology, policy, and values. The terminological vagueness is reflected in ambiguous guidelines, while the unsettled meaning and weight of ethical values fail to support effective policy recommendations (31). Denying this constant interaction results in limited answers to only partial problems and inhibits an adequate approach of the overall debate. Therefore, as a first recommended approach to the debate, an absolute integration of all levels in every consideration of ISFs is strongly advocated and a withdrawal of symptomatic questions that neglect this interaction is an absolute necessity. This level-integrative approach does not demand the instant and simultaneous solution of all aforementioned problems, nor the pursuit of an international consensus on all levels. However, the debate on ISFs should acknowledge how terminological choices and policy recommendations lack solidity when the underlying levels (of policy and/or values), to which they always (implicitly) refer, are disregarded. This lacking solidity inhibits an effective implementation of level-specific decisions, which can result in a diversified practice, an inequity in access of care and a suboptimal organization of care. On an international level, unsolid and largely heterogeneous answers on terminology, policy, and value problems can undermine the guidance and efficacy of these answers and erode the significance of important principles and values (35). Nonetheless, pertinent ethical, legal, and societal differences exist,

e.g., between the United States and Europe, which devaluates the aim of global guidelines (7, 35). Moreover, the casuistry of a patient's specific context and a professional's particular judgment impede the idea of a strict uniformity (26). A level-integrative approach should consider this balance between the pursuit of internationally significant answers and the necessity of case-by-case solutions on all levels of the ISFs debate.

This level-integrative approach of the debate will still lack important information, as ISFs have been mainly considered by (boards of) professionals. The experiences of (parents of minor) patients who encounter the possibility of ISFs are largely unexplored, which further erodes the debate. Hence, as a second recommended approach, an inclusion of the perspective of actual end-users is advocated, as a necessary complement to the current professional, top-down approach. Numerous publications have stressed the importance of the patient perspective on ISFs but these calls have stayed too vague and have lacked actual realization (4, 13, 15, 20, 37).

Therefore, as a first concretization of the inclusion of a patient perspective, lived experiences of (parents of) a real patient population should be pursued. Current research frequently suffers from a hypothetical bias by interrogating people who have to simulate a different role (e.g., of a patient, parent, or family member) or a different medical situation (e.g., having a diagnostic question or being genetically tested). Hypothetical discussions, however, can be very different from lived experiences, which is demonstrated in the increased selectivity in preferred ISFs by patients with an actual experience of illness and genetic testing (11, 44).

Second, an explicit focus on (possible) ISFs' meaning and significance is suggested. Instead of (quantitatively) measuring (parents of minor) patients' evaluation of professional classifications or recommendations, a qualitative insight in patients' or parents' subjective meaning of ISFs is recommended. This objective is supported by the observation that professionally determined categories or bins for ISFs, e.g., (medically) actionable results, do not necessarily correspond with patients' or parents' perception (44, 48). This discrepancy in terminology and underlying values between important stakeholders holds the risk to make policy instruments ineffective. It is fully acknowledged that more inclusive and subjective perspectives on actionability and other values challenge the counselling process and return of results. Nonetheless, it is doubtful whether this is an acceptable excuse to deny personally useful information to (parents of minor) patients.

Finally, the specific context of a patient's subjective perspective on ISFs should be emphasized. Patient-related factors such as patients' or parents' family history, social support, primary condition, and previous experiences with genetic counselling can all mediate the meaning of

ISFs (20, 39). This suggests that ISFs' significance is not constructed by single-dimension criteria (such as pathogenicity or actionability) but by a complex interaction of multiple, contextualized criteria. Therefore, (parents of minor) patients might also favour more dynamic or staged consent procedures, in which the validity of personal preferences is not limited to a single pre-test moment. Having the possibility to give consent at several times, e.g., prior to testing, prior to receiving (specifically preferred) results, and prior to updates about these results, can allow to weigh values (e.g., actionability, professional duty, personal autonomy, etc.) differently in different situations and to make specifically contextualized decisions. It also allows that information and counselling are (repeatedly) provided and adjusted to evolving scientific knowledge (48, 50). Finally, contextualized and dynamic policy procedures can stimulate or necessitate a diversified terminology to cover the different meanings ascribed to ISFs, which, again, confirms the intrinsic interaction of terminology, policy, and values regarding ISFs (38).

4.7. General conclusion

Despite the international guidelines on ISFs, a complex interaction of various problems still confiscates the debate, which impedes an adequate and effective implementation of the promising techniques of WES/WGS. The diagnostic possibilities of these techniques are captivating but the required knowledge to manage all results and additional information, is challenging. A level-integrative and patient-inclusive approach to the debate on ISFs pursues a more comprehensive understanding of ISFs. It explicitly recognizes, first, the intrinsic interaction between the different levels of the debate and, second, the importance of a lived, subjective, and contextualized patient perspective. Ultimately, the integration and alignment of terminology, policy, and values, and the inclusion of all relevant stakeholders will support the realization of an effective, well-grounded practice regarding ISFs.

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Chapter 5 - CRITERIA FOR REPORTING INCIDENTAL FINDINGS IN CLINICAL EXOME SEQUENCING – A FOCUS GROUP STUDY ON PROFESSIONAL PRACTICES AND PERSPECTIVES IN BELGIAN GENETIC CENTRES

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5.1. Abstract

Background: Incidental and secondary findings (IFs and SFs) are subject to ongoing discussion as potential consequences of clinical exome sequencing (ES). International policy documents vary on the reporting of these findings. Discussion points include the practice of unintentionally identified IFs versus deliberately pursued SFs, patient opt-out possibilities and the spectrum of reportable findings. The heterogeneity of advice permits a non-standardised disclosure but research is lacking on actual reporting practices. Therefore, this study assessed national reporting practices for IFs and SFs in clinical ES and the underlying professional perspectives.

Methods: A qualitative focus group study has been undertaken, including professionals from Belgian centres for medical genetics (CMGs). Data were analysed thematically.

Results: All Belgian CMGs participated in this study. Data analysis resulted in six main themes, including one regarding the reporting criteria used for IFs. All CMGs currently use ES-based panel testing. They have limited experience with IFs in clinical ES and are cautious about the pursuit of SFs. Two main reporting criteria for IFs were referred to by all CMGs: the clinical significance of the IF (including pathogenicity and medical actionability) and patient-related factors (including the patient's preference to know and patient characteristics). The consensus over the importance of these criteria contrasted with their challenging interpretation and application. Points of concern included IFs' pathogenicity in non-symptomatic persons, IFs concerning variants of uncertain significance, the requirement and definition of medical actionability and patient opt-out possibilities. Finally, reporting decisions were guided by the interaction between the clinical significance of the IF and patient characteristics. This interaction questions the possible disclosure of findings with context-dependent and personal utility, such as IFs concerning a carrier status. To evaluate the IF's final relevance, a professional and case-by-case deliberation was considered essential.

Conclusions: The challenging application of reporting criteria for IFs results in diversified practices and policy perspectives within Belgian CMGs. This echoes international concerns and may have consequences for effective policy recommendations.

Keywords

Incidental findings, Secondary findings, Clinical exome sequencing, Disclosure, Professional practice, Focus groups, Qualitative research

5.2. Background

Incidental findings (IFs) and secondary findings (SFs), which are variants in known disease genes unrelated to the diagnostic indication, are subject to ongoing discussion as potential consequences of clinical exome sequencing (ES) (1-3). Since ES simultaneously covers all coding regions of a patient's genome, results unrelated to the diagnostic question can be found unintentionally, as IFs, or deliberately pursued, as SFs (2-5). As ES is increasingly implemented for the diagnosis of monogenic diseases, various policy documents have been published regarding IFs and SFs in the US, Europe and Canada (1-3, 5-8). However, these documents differ on fundamental issues and none of them is accepted as the general standard. Issues regarding (i) a practice of unintentional IFs versus actively pursued SFs, (ii) patient opt-out possibilities and (iii) the spectrum of reportable findings remain unresolved (9-11).

Firstly, the American College of Medical Genetics and Genomics (ACMG) has published highly influential recommendations which advocate the routine analysis of an additional panel of 59 genes and the reporting of all (likely) pathogenic variants when performing clinical ES (2, 3). Pathogenic (class 5) and likely pathogenic (class 4) variants can provide adequate grounds for altering a patient's surveillance or treatment (12). Class 3 variants of uncertain significance (VUS), however, should not be considered as sufficient grounds for clinical decision-making (12). Even though VUS might be reported when possibly relevant to the diagnostic question, their reporting is not advised when identified as IFs (3, 4, 7, 8). According to the ACMG, screening for (likely) pathogenic variants in the diagnostically unrelated gene panel should occur in every case of clinical exome and genome sequencing, as a realisation of the professional duty to avoid harm (2, 3, 10, 13). However, this opportunistic screening has been criticised and the American Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) notes how it might entail additional health risks, overwhelm patients with (ambivalent) information and stimulate a trend of medicalisation (5). Therefore, the Bioethics Commission, and also EuroGentest, the European Society of Human Genetics (ESHG) and the Canadian College of Medical Geneticists (CCMG), are more cautious in their guidelines about reporting SFs and IFs (1, 5, 7, 8). They advocate a strictly necessary and proportional application of ES and, if possible, (exome or genome-based) targeted panel testing, which only analyses a subset of known disease-associated genes and hence minimises the possibility of diagnostically unrelated IFs (1, 4, 7).

Secondly, the ACMG claims a patient's right to opt out of deliberately pursued SFs (13). Taking into account all other international policy documents' advice of targeted testing and their

restraint towards SFs, wide agreement on this opt-out possibility might be assumed (1, 7, 8). International statements are more vague, however, about opting out of unintentional IFs. The Bioethics Commission, ESHG and Public Health Genetics (PHG) Foundation recommend that professionals should make a "prudent professional judgement" (5) concerning their fiduciary duty when a patient wants to opt out of an IF that is relevant, serious, and medically actionable (i.e. enabling surveillance and preventive and/or therapeutic interventions) (1, 3, 5, 14). This way, a patient's right not to know might be overruled by a professional's presumed duty to avoid harm (3). Recently published points to consider for laboratories, however, as well as the Canadian geneticists' position statement, strongly advocate respect for a patient's choice not to know IFs (6, 8).

Thirdly, the specific spectrum of genes or conditions that should be considered as reportable IFs or SFs, as well as the underlying reporting criteria, are strongly debated (15, 16). Lists of conditions and associated genes (including the ACMG gene list) have been challenged by the critique that variants might be classified differently or might be less penetrant and expressive in asymptomatic persons (15). Hence the identification of IFs or SFs as predictive disease risks might be doubted (17). Finally, the possibility of medical actionability has been stressed as an important criterion for reportable IFs and SFs in various recommendations (1-3, 5). Even though a semiquantitative metric has been developed as an attempt to assess medical actionability objectively, this criterion has been criticized (10, 18). On the one hand, the mere availability of a medical intervention does not guarantee its effectiveness, and many interventions for conditions on the ACMG list are not supported in terms of their effectiveness by clinical trials or professional guidelines (14). On the other hand, it has been suggested that the definition of medical actionability is too narrow and should also include reproductive choices or should be complemented by the criterion of personal utility (i.e. a personal interest or benefit that goes beyond improved healthcare outcomes) (15, 19).

Recently, the persistent lack of accord among policy documents has been exemplified in an international comparison of consent forms used for large gene panels, exome or genome sequencing. About half of the studied forms did not indicate their policy on reporting IFs or SFs and many used undefined terms (leaving the reference to IFs and/or SFs and corresponding reporting practices unclear) (20). Moreover, the spectrum of reportable IFs and SFs (if specified) as well as the options to opt in for or opt out of (specific categories of) findings widely varied (20).

The diverse character of recommendations and consent forms and their inclusion of contested terms and criteria permits a non-standardised practice regarding IFs and SFs. However, only a limited amount of research has investigated the actual uptake of policy guidelines regarding

IFs and SFs and has focussed on current reporting practices in a context of clinical ES. A US-based survey identified diverse practices regarding the spectrum of reportable IFs and SFs (which considerably exceeded the ACMG list) and different opt-in and opt-out possibilities (21). Outside the US, two studies, each including laboratories from various countries, have analogously reported a variety in reported IFs (22, 23). This study aims to further assess the actual practice regarding IFs and SFs in clinical ES, as well as to investigate the underlying professional perspectives. This research will also indicate which elements of international policy documents have been incorporated in practice as being most relevant or feasible and which elements demand further consideration or adjustment for efficient and successful policymaking.

5.3. Methods

5.3.1. Recruitment and data collection

To achieve an in-depth understanding of the practice and policy regarding IFs and SFs, a qualitative study was set up in Belgian centres for medical genetics (CMG). Belgium has eight CMGs: three in the Flemish Region, two in the Walloon Region and three in the Brussels Capital Region. Since the aim was not to find out individual or role-specific views but the integrated perspective of each CMG, and to stimulate open conversation and interaction between colleagues, one focus group in every CMG was considered to be most appropriate (24). A purposive sampling approach was used to recruit a multi-disciplinary and representative group of participants in every CMG, including both clinical and clinical laboratory geneticists and possibly other professionals. CMGs were informed about our study and its procedure by a presentation at the Belgian College of Medical Genetics (a federal body for quality of healthcare in medical genetics). Subsequently, a contact (usually the head of department) at each CMG was approached by email or telephone to request participation. If the contact agreed, they suggested a time which suited most of the CMG's professionals.

All focus groups were conducted in a room at the CMG or associated hospital between November 2016 and December 2017, and lasted between 67 and 117 min. All focus groups were moderated by the first author and an observer was present and took field notes in seven out of eight focus groups. Focus groups were moderated in Dutch or English and participants could choose to speak Dutch, French or English.

A semi-structured interview guide, created after a thorough literature review, was evaluated by a multidisciplinary team of an ethicist (HM), geneticist (EDB) and philosopher (ID) and was

used for all focus groups. Open-ended questions and probes to stimulate discussion were used (Table 1). Terminologically, "IF" was used to refer to unintentionally identified, diagnostically unrelated results. "SF" was used to refer to deliberately pursued, diagnostically unrelated findings. The study's specific focus on IFs and SFs in clinical ES for monogenic diseases, excluding preconception, prenatal, screening and research contexts, was emphasised at the outset of every focus group.

How do you describe an IF in a clinical context in your CMG, apart from following guidelines? What terminology do you use?
What differences do you see between IFs in array testing and in clinical ES?
What kind of IFs do you report, firstly from the laboratory to the clinician, and secondly from the clinician to the patient?
What kind of policy regarding IFs would you like to create in the future?
What impact do international guidelines on reporting IFs have on your own practice?
What difficulties do you experience in your practice regarding IFs or SFs? What are the great challenges in the evolution of IFs?
What is your current practice regarding a patient's request to opt out of IFs?
How do you consider the intentional search for SFs?
What is your practice when new information is available about an IF, for example for recontacting patients?

Table 1 Examples of interview questions (chapter 5)

5.3.2. Data analysis

Focus groups were audio-recorded and transcribed verbatim and data are saved until completion of the full research project on a password-protected server. Data were analysed thematically, with an inductive approach and unrestricted by theoretical concepts. The analysis consisted of the consecutive stages of data immersion, code generation, theme identification, theme revision, theme definitions and production of the final report, as described by Braun and Clarke (25). All data were coded by MS, and TM independently coded a substantial subset of the data. Analysis was an iterative and ongoing process during data collection. Text units could be included in more than one code and/or theme and the analysis was supported by use of a software program for qualitative data analysis (NVivo12). During analysis, ideas and reflections were stored as memos. An extensive procedure was developed to ensure the trustworthiness and credibility of the data collection, analysis and report. The procedure combined peer debriefing and a systematic audit trail, and covered both the process and the product of the analysis (26). Following TM's secondary analysis of a data

subset, the transcripts and initial code schemes were reviewed and theme names, definitions and structures were thoroughly discussed by MS and TM. Preliminary thematic structures and draft reports were discussed exhaustively and reviewed by the multidisciplinary group of authors until consensus was reached between all of them. Finally, quotes were selected and, if originally in Dutch or French, translated by MS and TM to illustrate the results. This article adheres to the COREQ guidelines for reporting qualitative research (27).

5.4. Results

All eight Belgian CMGs agreed to participate. Every focus group was composed multi-disciplinarily and involved between 6 and 11 participants, with a total number of 68 participating professionals (Table 2).
Six themes emerged from the data analysis: (i) current and general practice in clinical genetic testing, (ii) the position of genetics in medicine and society, (iii) criteria for reporting IFs, (iv) impact of IFs and SFs, (v) policy guidelines for genetic practice, (vi) guiding values and principles. This article addresses the third theme of the reporting criteria for IFs in a context of clinical ES in adults.

	FG1	**FG2**	**FG3**	**FG4**	**FG5**	**FG6**	**FG7**	**FG8**	**Total**
Participant's profession									
Clinical geneticist	3	3	4	5	3	3	2	2	25
Clinical laboratory geneticist	3	3	4	2	4	2	2	6	26
Genetic counsellor/Psychologist		4	1	2	1	1	2		11
Other (Bio-informatician, Bioethicist, Trainee MD)		1		1			3	1	6
Total	6	11	9	10	8	6	9	9	68

Table 2 Focus group participants (chapter 5)

When considering the reporting of IFs, Belgian CMGs referred to two major criteria: the clinical significance of the IF and patient-related factors.

5.4.1. Clinical significance of the IF

Currently, Belgian CMGs do not analyse the full exome in clinical ES and mainly use exome-based panels, hitherto resulting in a rather limited experience with IFs in clinical ES. However,

whole exome sequencing (WES) was identified as the undeniable future of clinical genetics. Due to the many monogenic conditions, IFs are expected to be frequent when very large panels or even the full exome will be analysed.
Professionals also referred to the possibility of screening additional genes as SFs when sequencing the exome, but a lack of (human, financial, and technical) resources and an unfulfilled need for guidelines (for example regarding reimbursement and the scope of analysis) fail to guarantee the required depth and trustworthiness of additional analyses in clinical WES. This could result in unnecessary interventions or harm and a false sense of security. Therefore, Belgian CMGs do not deliberately pursue SFs and only consider diagnostically unrelated findings in clinical ES when they are unintentionally identified as IFs (Table 3, Quote 1, Quote 2).

According to professionals in Belgian CMGs, reported IFs should be clinically significant, i.e. they should be relevant to a patient's health. CMGs especially referred to pathogenicity and medical actionability as important components of an IF's clinical significance. However, throughout the focus groups, the exact delineation of these criteria and their application in practice has turned out to be challenging.

a. Pathogenicity

A reported IF has to be a clinical risk factor, i.e. a variant predicted to cause disease, and various CMGs apply and advocated a cut-off for pathogenicity in reportable IFs. They suggested only reporting class 5 (pathogenic) and class 4 (likely pathogenic) variants in diagnostically unrelated but known disease genes. Class 3 variants (variants of uncertain significance or VUS), for example in an unrelated breast cancer gene, are not reported, as this might have a significant psychological impact or, as a consequence of unnecessary interventions, medically harmful consequences (Quote 3).

However, several factors complicate the definition of clearly pathogenic IFs. Firstly, verifying IFs' pathogenicity and predictive value in any particular patient is challenging in general, as there is usually no corresponding phenotype (i.e. patients are non-symptomatic for the IF's associated disease). Secondly, professionals described how, in the future, the advice not to report VUS in IFs might not always be realised. When a VUS is identified, it can be difficult to determine whether the affected gene is related to the symptomatic condition or not. CMGs noted that a VUS in a diagnostically relevant gene is sometimes reported, but when the gene's diagnostic relevance is not fully guaranteed, this reporting might undermine the cut-off for pathogenicity in IFs. Thirdly, variant classifications are dynamic and a VUS may be reclassified as a pathogenic variant over time. When this variant turns out to be relevant to the

symptomatic condition, its reclassification may eventually lead to a diagnosis, which patients usually experience as a relief. Therefore, professionals acknowledged the duty to recontact patients regarding the reinterpretation of diagnostic results. In the context of IFs, however, recontacting patients regarding a reclassified VUS, was regarded as logistically impossible. Moreover, professionals suggested that such a delayed report of an IF would only be appropriate if patients explicitly agreed to it, as this finding is not directly related to the indication for testing and does not realise the pursued diagnosis.

Number	Quote	Participant
Quote 1	*"Maybe, at random, we could find something and when we find something that we are sure of, we will tell you. […] But we won't actively look for it."*	FG 8 - P9 Clinical laboratory geneticist
Quote 2	*"There is a filter in accordance with the ACMG recommendations, but it is not used as standard. […] It takes considerable human capacity to analyse those things and currently it is not included in our routine-protocol, to look at those things as standard."*	FG 7 - P7 Clinical laboratory geneticist
Quote 3	*"The reporting of variants where even we don't know whether they mean anything, is the equivalent to reporting non-information which might make a patient despair or ask for an impossible follow-up. […] So I think we have a responsibility as professionals not to go that far."*	FG 2 - P10 Clinical laboratory geneticist
Quote 4	*A: "The example would be, in theory, because now we wouldn't see it, eh, Huntington's disease, if you see that, at whatever age, should you transmit [report] it? So far, the answer is no. […] And any other change for which you have nothing to offer to the patient, we don't report." […]* *B: "But you can have Parkinson's, Alzheimer's … with a point mutation, for example."* *A: "That would be a better example, indeed."*	FG 1 A= P5, Clinical geneticist B= P1, Clinical geneticist
Quote 5	*"[…] and then, during the next pregnancy, they would find out that their child has Duchenne… You don't want to have this [kind of situation], whereas we have seen it during a previous [test], for example in their daughter. So currently, we don't work with an opt-out, to avoid this kind of thing. And I've never met a family who had problems with this [practice]."*	FG 2 - P2 Clinical geneticist

Quote 6	*"[…] so people have to decide between opt-in and opt-out, and I think it is very complex for people to be sufficiently informed about this choice. […] It's hopeless, people can't choose, well, most of them can't. I mean, most people don't have any background knowledge of genetics, so it is extremely difficult."*	FG 4 - P7 Psychologist
Quote 7	*"A possibility to choose… You cannot simply force someone, I mean, you can't just… The aim of informed consent is to make a deliberate choice, so you have to give people the right information, so they can make a choice. I think that is the aim of informed consent."*	FG 6 - P1 Genetic counsellor
Quote 8	A: *"But, perhaps I don't understand, if the patient chooses [an] opt-out, then we don't report. […] If the patient chooses, and it's clear, to opt out, then we don't report."* B: *"But I would anyway! […] I would say, the consequence of not reporting and maybe losing a parent, for example the [patient's] mother very, very young… Those consequences are so important that I would choose to disregard the patient's decision, I would note it down in the file that I choose to disregard, because […] I consider the consequence of not reporting to be worse than the consequences of reporting."*	FG 3 A = P1, Clinical geneticist B = P8, Clinical geneticist
Quote 9	*"So generally, when we have an IF like that, most of the time there is a deliberation between the biologist [clinical laboratory geneticist] who is responsible for the analysis and the clinician [clinical geneticist] who validates the test. […] Sometimes, we even call upon external people, other centres, or people who have the right experience."*	FG 5 - P5 Clinical geneticist

Table 3 Quotes (chapter 5)

b. Medical actionability

Most CMGs exclusively report actionable IFs, which were described as findings for which medical therapy, treatment or preventive screening are available (Quote 4). Several professionals regarded the knowledge of IFs ad infinitum, including non-actionable IFs, as harmful, because this includes information that patients do not understand and cannot handle (practically or psychologically). Professionals also expressed feeling powerless themselves

about non-actionable IFs and feeling “more comfortable with a cancer predisposition than with [a predisposition for] a neuro-degenerative condition”. These professionals considered the limitation of reportable IFs to actionable results as a consequence of their professional duty and responsibility to decide on relevant information. Ultimately, only reporting actionable IFs was presented as a pragmatic way of keeping clinical ES practically feasible, as excluding non-actionable findings reduces the time required for analysis.

Even though they had not actually been in this situation, some professionals remarked that not reporting non-actionable IFs, for example regarding a neuro-degenerative condition, could be an ethically difficult decision, as it would withhold important information from patients and/ or their families. Therefore, one CMG explicitly stated that if they identified serious, non-actionable IFs, these would be reported. Another CMG suggested that non-actionable results might, depending on the specific circumstances, be reported as IFs, but, if a practice for SFs were developed, these deliberately pursued results should only concern medically actionable findings.

The use of a standard list of medically actionable genes was proposed. Many Belgian CMGs use the ACMG list of “highly penetrant and actionable genes” as a (not strictly binding) framework for reportable IFs (2, 3). On the other hand, some CMGs considered such a list as being in conflict with the dynamic reality of treatments and preventions that can become available over time. Hence a variant’s actionability might better be determined at the time of discovery.

Finally, a correlation was suggested between a condition’s actionability and penetrance. Even though risks are subjectively interpreted, “low penetrance” IFs were considered to be too abstract, and classifying them as actionable might create unrealistic expectations regarding the utility of this information. Therefore, as a suggestion for future policy, actionable IFs should be highly penetrant and patients should be counselled in interpreting incomplete penetrance.

5.4.2. Patient-related factors

As a second criterion for reporting IFs, CMGs referred to patient-related factors, being the patient’s preference to know IFs and patient characteristics.

a. Preference to know

ES allows a selection of analysed genes and hence, theoretically, a choice to receive IFs or not. However, not all Belgian CMGs offer this opportunity, and practices on a patient opt-in and opt-out vary widely.

Three CMGs currently offer no opt-out of actionable IFs, although one of them offers an opt-out of non-actionable IFs. Professionals at these CMGs argued firstly that they have the ambition or even the duty to prevent future disease that can be avoided (Quote 5) and secondly that lay people do not truly understand the meaning and possible impact of IFs. In the event of an opt-out, patients would not realise what they are actually declining (Quote 6). As a third argument, two CMGs mentioned their ethics committee's influence on this policy. It did not allow an opt-out of actionable IFs because professionals should report useful information when it is available and, again, because patients would not understand their own decision. Finally, it was observed that patients generally do not dispute the possibility of receiving actionable IFs. One CMG added that, even if an opt-out is not suggested, patients can spontaneously ask for it, but no such cases were mentioned during the focus group.

Despite these arguments, one CMG explicitly discussed its current policy and reported an exception by honouring a patient's request not to look at breast cancer genes during an unrelated clinical ES. Two centres mentioned that it would be good to update their ethics committee on recent developments in clinical ES, possibly to re-evaluate their opt-out policy. Finally, it was recognised that patients might be distressed when discovering future health risks as IFs. Nonetheless, these worries were said to be inevitable, as the risk would probably manifest itself anyway at a later point in life.

Conversely, four CMGs always allow an opt-out of actionable IFs. To justify their policy, these CMGs also referred to the idea that IFs might be complex to comprehend, also in psychological terms. Some patients might not be able to deal with the information, and therefore their preference to opt out of these results should be respected. Moreover, these CMGs stated that patients' general and fundamental right not to know should be honoured (Quote 7). Nevertheless, it was mentioned that only a small minority of patients actually choose to opt out of actionable IFs.

Finally, one CMG, with limited experience with clinical ES, discussed its future policy and the possibility of an opt-out in depth. While some of its professionals strongly defended absolute respect for a patient's choice, one participant claimed that opting out should only be accepted if it has minor implications for the patient's prognosis. When not reporting actionable IFs could

have severe consequences, this professional would overrule a patient's opt-out. Again it was argued that patients do not understand what IFs and an opt-out really mean. Moreover, the possible harm of not reporting an actionable IF would outweigh the harm of being informed against one's will (Quote 8). To reconcile the two perspectives in this CMG, two opposing solutions were suggested for a patient's opt-out: the IF could be reported at a later and more suitable moment, or the IF could be masked in the report from the laboratory to the clinician. That way, situations where the clinician knows but cannot disclose relevant patient information could be avoided.

b. Patient characteristics

Finally, professionals noted that patient characteristics influence whether and how an IF is reported, as patients' (clinical and personal) context interacts with the IF's clinical significance and affects its final relevance. Professionals provided the hypothetical example of the importance of a patient's primary condition for the timing of reporting an IF as well as for the suggested follow-up and counselling, since both results are considered to have an integrated impact on a patient's health and life. A patient's wish for future children or his/her family history of illness might also affect the disclosure of an IF regarding a carrier status or of a non-actionable IF (since it could explain an undiagnosed family condition). These last examples illustrated how personal and family characteristics interact with the definition of actionability and hence might affect an IF's clinical significance and disclosure. Most CMGs did not consider actionability to include lifestyle adjustments or personally useful actions. However, they did discuss actionability in terms of reproductive decision making, which would enable the reporting of IFs concerning a carrier status for a recessive condition. Some professionals do or would not report these findings, because they are not clinically threatening for patients themselves. It was also mentioned that including prenatal possibilities "would make every condition actionable". However, and depending on personal and/or family characteristics and plans, these results can be relevant to relatives and (future) children. Therefore, half of the CMGs would consider the reporting of IFs regarding a carrier status for severe diseases (for example cystic fibrosis or Duchenne muscular dystrophy). Two centres already reported such findings and one does not offer an opt-out of them. Nonetheless, the psychological impact of this disclosure was acknowledged and one CMG testified about a family that was emotionally upset by the disclosure of a cystic fibrosis carrier status.

The interaction between, on the one hand, a patient's characteristics and (clinical, personal, reproductive, family, etc.) context and, on the other hand, the clinical significance (including the actionability) of IFs does not result in a standard outcome, and hence evaluating an IF's final relevance frequently requires a professional, multidisciplinary deliberation (Quote 9). To

facilitate the deliberation process, a national (online) consortium on IFs was suggested, where "difficult cases" could be discussed, as well as a specialist committee to relieve CMGs of the exclusive responsibility regarding disclosure.
Despite the case-by-case deliberation, some professionals would still prefer general guidelines, for example regarding pathogenic variants and actionability, to facilitate the professional decision about disclosure.

5.5. Discussion

An analysis of current practice at Belgian CMGs regarding clinical ES in the context of adult testing revealed a diagnostic focus and a standard procedure of exome-based panel testing, resulting in a low incidence of IFs. Belgian CMGs' collective policy not to deliberately pursue SFs mirrors the avoidance of diagnostically unrelated findings and accords with current laboratory practices and with all international guidelines apart from the ACMG recommendations (1-3, 6-8, 23, 28).

Whether CMGs report an IF is determined by an interaction between the clinical significance of the IF and patient-related factors.

5.5.1. Clinical significance of the IF

Belgian professionals indicated pathogenicity and medical actionability as important components of an IF's clinical significance. These criteria are not surprising in themselves, as they are also stressed by leading American and European recommendations (1-3, 7). Nonetheless, these criteria were extensively discussed because their interpretation and application in practice turns out to be challenging.

The importance of IFs' pathogenicity was unanimously emphasised. However, Belgian CMGs also expressed concerns about IFs' disease predictive value in asymptomatic persons. This idea is echoed internationally, even by the ACMG itself (3, 6, 9, 29, 30). Richards et al. mentioned that variants might be less pathogenic and less penetrant if they are unrelated to the primary test indication and when there is no phenotype or family history of the associated condition (12). The caution with which Belgian professionals approach the pathogenicity of IFs reflects these remarks, as well as the warning that unreliably interpreted and reported results might cause physical and psychological harm (15, 31). The parallel idea expressed by Belgian CMGs regarding a cut-off for pathogenicity in IFs, and the suggestion to only report class 5 and class 4 but not class 3 variants (VUS), accords with international laboratory practices and points to

consider, and with the ACMG recommendations (2-4, 6, 21). Not reporting VUS in IFs from the laboratory to the ordering clinician prevents an over-interpretation of these results' significance for the diagnostic question and needless patient follow-up (6, 23, 32).

Along with pathogenicity, most but not all CMGs assessed an additional threshold for reportable IFs, being their actionability. This criterion, as well as its interpretation as medical actionability, corresponds with an international consensus and might be partly explained by professionals' specific role as medical experts (1, 3, 5, 11, 28-30, 33). Nonetheless, the exclusive reporting of actionable IFs was characterised as a dynamic and ethically difficult policy by some Belgian centres. Some CMGs suggested to identify low penetrance IFs as non-actionable, which refers to a correlation between criteria that has already been indicated by the ACMG and its current list of 59 "highly penetrant and actionable genes" that should be analysed as SFs (2, 3). Conversely, it has also been suggested that variants' low penetrance can be countered by the associated condition's actionability (28, 30).

5.5.2. Patient-related factors

A notable finding of this study is Belgium's diverse practice regarding the opt-out of actionable IFs. The absence of the possibility to opt out was legitimised by the professional aim to avoid harm. However, in-house discussions about this mandatory opt-in policy and professional concerns about the psychological impact of reported IFs illustrated that the superiority of professional duty over a patient's choice is not self-evident. This value conflict was most visible in one CMG's consideration of overruling a patient's choice to opt out when it was considered to have harmful consequences. The denial of a patient's preference, granting this criterion only a relative weight, sounds polemical but is in line with the "prudent professional judgement" which is advocated by bodies including the ESHG and Bioethics Commission (1, 5). It also reflects the idea that the denial of a patient's choice is sometimes inevitable, for example when a patient opts out of clinically relevant or medically actionable IFs (9, 16, 31). The second argument for the obligatory disclosure of actionable IFs, being patients' presumed inability to fully understand their impact, has also been suggested internationally (9, 32). However, postulating a patient's inability to make well-informed decisions might discount the efficacy of counselling procedures (5, 8, 34).

Patients' general acceptance of disclosing actionable IFs supports the consolidation of offering no opt-out. However, an absence of questions might not necessarily equal an omnipresent preference to actually know IFs. When a CMG does not suggest an opt-out, few patients might have the genetic literacy to ask for one spontaneously, since the public understanding of genetics and its possibilities seems to be rather limited (35). Moreover, it takes courage to

dispute the professional authority of an informed consent form or pre-test counselling, or to resist the societal pressure to know as much as possible (33, 36). Finally, a Belgian CMG's claim that an IF, and the corresponding psychological distress, will manifest itself anyway at a later time might not be completely valid, as the incidentally identified variant could have an incomplete penetrance and/or variable expression, an idea related to the uncertain pathogenicity of IFs in asymptomatic persons.

Belgian CMGs that allow an opt-out of actionable IFs emphasise the honouring of patients' wishes and their right not to know. This conflicts with well-known European recommendations but accords with a Canadian position statement and recent points to consider, and it is supported by international professional preferences (6, 8, 30, 37). The Belgian suggestion that results should be masked in the laboratory report for the clinician when patients opt out, has been expressed internationally (31). However, problems might arise when, as a result of changed circumstances or values, patients change their mind and do want to know IFs (16).

Finally, there is a general agreement, both within Belgian CMGs and internationally, that the interaction between an IF's clinical significance and patient characteristics affects the final relevance of an IF (9, 15, 16, 23, 30, 32, 33). This interaction clearly shows in the impact of a patient's personal context on the criterion and definition of IFs' actionability and, more particularly, in the relevance and possible disclosure of IFs regarding a carrier status. Both within Belgian CMGs and internationally, this possible reporting is strongly discussed, as it might enable reproductive and/or (future) family-wide choices and actions (9, 23, 30, 33). Even though reporting a carrier status for recessive conditions is in conflict with Belgian CMGs' general focus on direct, medical actionability, half of them would favour such reporting to adults. This disclosure is supported by international professionals' preferences and recent laboratory points to consider (6, 16, 21, 23). On the other hand, it conflicts with the ACMG recommendations and creates an additional workload for results which are not clinically significant for patients themselves (2, 3, 16, 23). However, this claim of reduced significance is countered by the impact of a reported carrier status on a person's self-concept and specifically by the way it might threaten a person's genetic identity, (future) health perception or wished-for parental role (38, 39), a psychological effect which was also insinuated by two Belgian CMGs. The impact of knowing one's carrier status might even be more substantial in the case of a serious X-linked condition, such as fragile X syndrome, where carrying the premutation might also have clinical consequences for the carrier herself (40). Belgian professionals did not raise this specific example of an IF regarding a carrier status, but nonetheless it goes against their statement that such a finding is non-threatening for patients themselves.

The reporting of IFs regarding a carrier status because of its possible value in the specific (personal or family) context of reproduction, can be considered in the more general debate on personal utility (19). The concept of personal utility might, based on a patient's characteristics and context, categorise findings which allow future (reproductive) choices, psychological or social coping or intrinsically valuable self-knowledge as reportable results, as they enable non-medical but valuable actions (19, 41). Even though CMGs acknowledge the importance of a patient's context and the difficulty of not reporting medically non-actionable IFs, most CMGs are not likely to add these options of personal utility to the actionability-criterion. Moreover, personal utility risks becoming an unspecified umbrella term that justifies the reporting of any kind of results (19, 42). Therefore, Bunnik et al. suggest limiting personal utility to meaningful, technically and clinically valid information which "can reasonably be used for decisions, actions or self-understanding" (42). As a consequence of its problematic definition, Vears et al. even suggest not assessing actionability as a decisive criterion for reporting pathogenically significant IFs (6).

As a second consequence of the interaction between an IF's clinical significance and patient characteristics, the value of professional deliberation is stressed by both Belgian and international professionals (9, 11, 16, 23).
On the other hand, some CMGs' call for guidelines on pathogenicity or actionability is also mirrored in international research, for example, concerning clinical laboratory geneticists who favour a list of conditions and genes that should be considered (9, 11, 15, 23, 29).

The tension between a call for (more) guidelines and a patient-specific, case-by-case deliberation has been identified previously (23). As ES is increasingly implemented in clinical practice, it seems advisable, at least at a local level of CMGs, to create a guiding framework which is clarified to patients before testing and which relieves professionals from the responsibility to individually decide on every case of IFs. To further avoid the chance and injustice of offering different information to different patients, not only within but also between CMGs, an (inter)national consensus on relevant criteria might be pursued as a starting point for reporting practices (20, 22, 23, 43). However, if general guidelines turn out to be unfeasible and the current diversity in national practice, as disclosed by this study, and in international practice and policy documents is maintained, a patient's informed decision on which results to receive, starts with his/her choice of a specific CMG. In that case, it is quintessential for every CMG to disclose its local policy. On the other hand, and in line with the non-standardised outcome of the interaction between the clinical significance of IFs and patient characteristics, a flexibility in guidelines' application has been advocated so they can be accustomed to the particular context (44). Together with the professional expertise in CMGs, this call for a personalised deliberation nuances the need for and effectiveness of a

rigid “one model fits all” policy (23). Therefore, the contextualised application of a guiding framework of reporting criteria for IFs, might result in a personalised, non-standardised outcome.

To our knowledge, this is the first study on reporting practices and criteria regarding IFs which includes nationwide certified CMGs and hence achieves a good coverage of a national, non-commercial practice. The organization of one focus group in every centre revealed the similarities and differences in practice between centres. Moreover, it encouraged an open discussion between colleagues and a clarification of underlying reporting criteria. These results emerged from a Belgian context, with its specific scale and healthcare organisation. Nonetheless, the results of this study might be (partly) transferrable to other (and larger) countries with similar healthcare systems and analogous confrontations with diverse international guidelines, but further research is needed to confirm or deny similarities in practice and policy. As a consequence of Belgian CMGs’ standard practice of diagnostic exome-based panel testing, there is still a limited experience with actual IFs in clinical ES. Consequently, the perspectives expressed by the CMGs might reflect current reporting practices as well as preferable future policies. Future research should identify whether these perspectives are actually effected when the exome is fully analysed in clinical practice and IFs become more frequent.

5.6. Conclusions

Belgian CMGs agree in their reference to common and internationally suggested reporting criteria for IFs. However, these criteria resist a uniform interpretation and hence result in a diversified Belgian practice, which reflects divergent, international policy perspectives. Belgian CMGs consent to the threshold of pathogenicity but concerns about IFs’ predictive value in non-symptomatic persons and VUS in IFs challenge this criterion’s application in practice. Furthermore, (medical) actionability is both an advocated and contested threshold, both internationally and at Belgian CMGs. In their adherence to international perspectives, Belgian CMGs differ most manifestly regarding patient opt-out possibilities for actionable IFs and in the weighing of professional duty versus patient autonomy. Finally, the interaction between the clinical significance of IFs and patient characteristics questions the definition of actionability and the possible reporting of IFs with personal utility such as findings concerning a carrier status. The importance of the patient’s context and the non-standardised outcome of its interaction with IFs’ clinical significance suggest the imminent inclusion of case-by-case reflections in reporting decisions. Accordingly, (international) guidelines for the reporting of

IFs in clinical ES might only be effective when they are sufficiently detailed in terms of the criteria applied as well as responsive to the particularity of each individual case.

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Authors' contributions
MS developed the interview guide, recruited the participants, moderated, transcribed and thematically analysed the focus groups and was a major contributor in writing the manuscript. HM evaluated the interview guide, attended the focus groups as an observer, evaluated thematic structures and fundamentally reviewed draft manuscripts. TM made a secondary analysis of a data subset, including transcripts and initial code schemes, and revised and discussed theme names, definitions and structures with MS until consensus was reached. TM also fundamentally reviewed draft manuscripts. EDB and ID facilitated recruitment and evaluated the interview guide and preliminary thematic structures. EDB and ID exhaustively reviewed draft manuscripts and contributed to the final structure. All authors have read and approved the final manuscript.

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Availability of data and materials
None of the data generated and analysed during this study are publically available for reasons of personal privacy, but they are available from the corresponding author in response to a reasonable request.

Ethics approval and consent to participate
This study is approved by the Commission of Medical Ethics at Ghent University Hospital (reference number B670201628974). Participants signed an informed consent form, and personal information was altered or removed to create an anonymous report.

Consent for publication

All participants signed an informed consent form which included a statement on the anonymised publication of study results.

Competing interests

The authors declare that they have no competing interests.

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Chapter 6 - ETHICAL VALUES SUPPORTING THE DISCLOSURE OF INCIDENTAL AND SECONDARY FINDINGS IN CLINICAL GENOMIC TESTING: A QUALITATIVE STUDY

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6.1. Abstract

Background: Incidental findings (IFs) and secondary findings (SFs), being results that are unrelated to the diagnostic question, are the subject of an important debate in the practice of clinical genomic medicine. Arguments for reporting these results or not doing so typically relate to the principles of autonomy, non-maleficence and beneficence. However, these principles frequently conflict and are insufficient by themselves to come to a conclusion. This study investigates empirically how ethical principles are considered when actually reporting IFs or SFs and how value conflicts are weighed.

Methods: A qualitative focus group study has been undertaken, including a multidisciplinary group of professionals from Belgian centres for medical genetics. The data were analysed thematically.

Results: All eight Belgian centres participated in this study. Ethical values were frequently referred to for disclosure policies on IFs and SFs. Participants invoked respect for patient autonomy to support the disclosure of IFs and opt-out options for IFs and SFs, non-maleficence for the professional delineation of reportable IFs and opt-out options for IFs and SFs and (the particular scope of) beneficence for the mandatory reporting of actionable IFs, the delineation of reportable IFs and a current decline of actively pursued SFs. Professional assumptions about patients' genetic literacy were an important factor in the weighing of values.

Conclusions: In line with the traditional bioethical discourse, the mandatory reporting of actionable IFs might be interpreted as a "technological, soft paternalism". Restricting patients' choices might be acceptable, but then its motives should be valid and its beneficent outcomes highly plausible. Hence, the presuppositions of technological, soft paternalism - patients' inability to make informed decisions, normative rationality, the efficacy of beneficent outcomes and the delineated spectrum of beneficence - should be approached critically. Moreover, distributive justice should be considered an important value in the delineation of the current scope of the ethical debate on IFs and SFs.

This study of guiding values may stimulate the debate on the ethical grounds for a solid policy on IFs and SFs internationally.

Keywords

Patient autonomy, Professional beneficence, Soft paternalism, Distributive justice, Clinical genomic testing, Incidental findings, Secondary findings, Qualitative research

6.2. Background

In clinical exome sequencing (ES), variants in diagnostically unrelated but known disease genes can be unintentionally revealed or actively pursued as, respectively, incidental findings (IFs) and secondary findings (SFs) (1-3). Incidental and secondary findings are the subject of various reporting guidelines and policy documents, for instance in Europe, the US and Canada (1-7). Ethical arguments, especially concerning autonomy, non-maleficence and beneficence, have been frequently cited for reporting these results or not doing so (8, 9). The study presented in this article set out to investigate empirically how professionals consider these and potentially other values in actual practice regarding IFs and SFs in clinical ES.

International healthcare conventions have formalised respect for patient autonomy in the right to receive personal and complete health information (including informed consent before a medical treatment), as well as in the right to decline medical information, treatment and intervention (10-14).

In line with these rights, non-disclosure of clinically relevant information has been ethically rejected and a patient's right to be informed about (specific) IFs has been acknowledged (8, 15). However, whether this right also installs the professional duty to deliberately pursue additional findings as SFs, is contested. The American College of Medical Genetics and Genomics (ACMG) advocates the opportunistic screening of a well-defined list of genes which are clinically significant, highly penetrant (i.e. with a high probability that the pathogenic variant will express the associated condition) and medically actionable (i.e. allowing medical prevention or treatment) (1). According to the ACMG, this pursuit of SFs is the most effective realisation of patients' (family-wide) wellbeing and hence of beneficence, a professional commitment which takes a prominent place in, for example, the Declaration of Geneva (1, 5, 16). Conversely, the European Society of Human Genetics (ESHG), EuroGentest and the Canadian College of Medical Geneticists (CCMG) are more cautious with diagnostically unrelated results; they recommend a minimisation of IFs and they explicitly discourage or seem not to support the active pursuit of SFs (2, 4, 6). Arguments for this cautiousness are the possibility of physical and/or emotional harm (by overwhelming patients with unnecessary or harmful tests, diagnoses or interventions) and hence the professional duty of non-maleficence (3, 8). When IFs are unintentionally identified, these results should only be disclosed if they are highly significant, highly penetrant and medically actionable (17-19).

With respect to patients' right not to know, there is a consensus that explicit patient consent is required for the screening and reporting of SFs (3, 20-22). Since its updated recommendations, the ACMG also agrees with a possible patient opt-out for SFs (23). Respecting patients' choice on disclosure is motivated by the idea that information about

genetic predispositions cannot be imposed because of its possible psychological, family and social impact (24). This indicates that the right not to know is supported not only by the value of patient autonomy but fundamentally grounded in the interest of not being psychologically harmed and hence in the professional duty of non-maleficence (24). Nonetheless, and despite the consensus on an opt-out possibility for SFs, the opt-out of IFs has been debated more intensively. Whereas some professional bodies, such as the CCMG, strongly uphold patients' right not to know, the ESHG and EuroGentest recommend that the final decision on serious and actionable IFs should be made by professionals (2, 4, 6). Consequently, the professional responsibilities to warn, rescue and benefit patients might outweigh the patient's right not to know (3).

The weighing of *prima facie* values such as patient autonomy and professional beneficence is a classic challenge in bioethics (25) and the debate on IFs and SFs turns out to be a prime example of it. Consequently, opposing policies are advocated and many questions are still unanswered. Under which conditions should a patient's wish to opt out of IFs be respected? If this right is not absolute, how (for instance based on which criteria or values) can professionals justify their decision to report these results without patient consent? Should SFs be deliberately pursued as a realisation of the professional duty of care and the patient's right to be informed? And more fundamentally: are autonomy, non-maleficence and beneficence actually guiding principles in professionals' decisions about disclosing IFs and SFs? Or is there a gap between theoretical ethical concerns and practice (26)?
The question whether and how professionals consider these and potentially other values as guiding notions in the reporting of IFs and SFs in a context of diagnostic ES in adults, is the focus of this article.

6.3. Methods

A qualitative study was organised in the eight Belgian centres for medical genetics (CMGs) to achieve an in-depth understanding of professionals' perspective on IFs and SFs. Since the aim of this study was not to determine role-specific or individual views but the integrated perspective of a group of professionals who collaborate in a CMG and might decide on the disclosure of IFs or SFs after inter-professional deliberation, focus groups were chosen over individual interviews (27). Aiming for an active debate and open conversation between colleagues, one focus group in every CMG was pursued (27). A purposive sampling approach was used in every CMG to recruit a multidisciplinary and representative group of professionals who are experienced with clinical ES, including both clinical geneticists and clinical laboratory geneticists and possibly other professionals such as genetic counsellors, bio-informaticians or

nurses (28). Through a presentation at the Belgian College of Medical Genetics (a federal body for the quality of healthcare in medical genetics), representatives of all CMGs were informed about our study and contact information was collected from one or several professionals (usually including the head of department) at every CMG. Subsequently, a contact at every CMG was approached by email or telephone by MS to provide additional information about the focus groups and to request participation. At the contact's request, a preliminary consultation was organised at several CMGs to thoroughly clarify the design and aim of the focus group. If the contact agreed to participate, (s)he or another professional at the CMG contacted eligible colleagues and assembled a representative group of people. To counter last-minute cancellations, contacts were requested to assemble a group of about twelve persons. When participants had been recruited, the contact suggested a time which suited most of the CMG's professionals.

Focus groups were conducted between November 2016 and December 2017 in a room at the CMG or associated hospital and lasted between 67 and 117 minutes. The first author moderated all focus groups in Dutch or English and participants replied in English, French or Dutch. In seven out of eight focus groups, an observer was present and took field notes. Informed consent was obtained from all participants.

A semi-structured interview guide, created after a literature review and including open-ended questions, was used for all focus groups (Table 4). At the beginning of every focus group, the focus on IFs and SFs in clinical ES for monogenic diseases, excluding preconception, prenatal, screening and research contexts, was emphasised.

How do you define IFs in clinical ES?
What kind of IFs do you report, firstly, from the laboratory to the clinician and, secondly, from the clinician to the patient?
What do you think about the intentional search for SFs?
What kind of policy regarding IFs and SFs would you like to develop?
What difficulties do you experience in your practice and (future) policy regarding IFs and SFs?
How is the possibility of IFs addressed during genetic counselling?
What might affect a patient's interest in IFs and SFs?
What is your policy regarding a patient's possibility to opt out of IFs?
How would you define a patient's role in the context of IFs and SFs? How does this role relate to your professional role?
What impact might a reported IF or SF have on patients?
To what extent do you consider a personalised policy concerning IFs and SFs appropriate and feasible?

Table 4 Examples of interview questions (chapter 6)

Focus groups were audio-recorded and transcribed verbatim and data were saved on a password-protected server. The data were analysed thematically (29). The inductive and iterative analysis process was supported by use of the software program NVivo 12 and reflective ideas were stored in memos. To assert the trustworthiness of the data collection, analysis and reporting, an extensive procedure was elaborated, which combined peer debriefing and a systematic audit trail (30). TM conducted a secondary analysis of a substantial subset of the data. Consequently, TM and MS discussed transcripts and initial code schemes, as well as theme names and definitions. Thematic structures and draft reports were reviewed by the multidisciplinary group of all authors until consensus was reached between them all. Finally, illustrative quotes were selected and, if originally in Dutch or French, translated by MS and TM.
This article adheres to the COREQ-guidelines for reporting qualitative research (31).

6.4. Results

All eight Belgian CMGs participated in this study, with a total number of 68 participating professionals (Table 5).

	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8	Total
Function participants									
Clinical geneticists	3	3	4	5	3	3	2	2	25
Clinical laboratory geneticists	3	3	4	2	4	2	2	6	26
Genetic counsellors/Psychologists		4	1	2	1	1	2		11
Others (Bio-informaticians, Bioethicists, MD trainees)		1		1			3	1	6
Total	6	11	9	10	8	6	9	9	68

Table 5 Focus group participants (chapter 6)

Even though participants were not explicitly asked for principles that supported their reporting practices regarding IFs and SFs, professionals frequently referred to ethical values including autonomy, non-maleficence and beneficence, and these concepts emerged from the data as a specific theme. More generally, the identified themes regarded: (i) current and general practice in clinical genetic testing, (ii) the position of genetics in medicine and society, (iii) criteria for reporting IFs, (iv) impact of IFs and SFs, (v) policy guidelines for genetic practice, (vi) guiding values and principles. This article specifically addresses the sixth theme in a context of clinical ES in adults.

6.4.1. Patient autonomy and the right to know

Based on a patient's right to receive relevant information, all participants agreed on patients' right to be informed about some IFs. Therefore, and in the interests of a just policy, all patients should have equal opportunities to receive relevant IFs, independent of the testing techniques used. On the other hand, all Belgian CMGs only reported IFs and did not actively pursue SFs (cf. infra).

Due to all CMGs' current clinical practice of ES-based but filtered panel testing in which a set of known disease-associated genes is analysed, the chance of identifying an IF is not zero but it is rather small and professionals from all CMGs reported limited experience with IFs in clinical ES. As the significance of ever more genes becomes known and used panels contain an increasing number of genes or when testing techniques evolve (and, for instance, include whole exome or whole genome analysis or genome-based panels), it is assumed that the number of IFs will increase.
Several professionals advised that, because of the current use of panels and to avoid unrealistic experiences, patients should be informed that, at this time, not all diagnostically

unrelated health risks will be identifed. However, it was assumed that people's requests for genomic information would increase over time. Consequently, many professionals stressed that, when whole exome or whole genome sequencing becomes basic clinical testing and when it becomes technically feasible to comply with people's growing requests for information, the general population should have a better understanding of genomics and its possible consequences and limits. Unrealistic expectations and genetic determinism should be avoided and people should realise that genetics cannot explain or predict all (health) concerns.

"We have the impression that people go to the geneticist as if they were going to a fortune teller with a crystal ball. [After the consultation] they say "well, this is my future". While we say "I can't tell you anything with a genetic test. I don't know if you have cancer and I don't know if it will come. I can't tell you anything." (P5, FG5)

In line with the need for better informed citizens, the importance of genetic counselling was unanimously emphasised. Counselling should inform patients about the possible outcomes of the test, including IFs, in comprehensive, non-technical terms. Finally, new ways of counselling were suggested, such as collective counselling sessions where general genetic concepts or frequent conditions could be explained.

6.4.2. Patient autonomy and the right not to know

Participants described how ES-based panel testing (as a selection of analysed genes) generally avoids the identification of IFs, which supports the opportunity to respect a patient's wish not to know diagnostically unrelated results. Participants suggested two motives for a patient's preference to opt out of IFs: emotional distress and diagnostic focus. Firstly, the prospect of additional genetic information might engender anxiety and patients might not want to or might not feel psychologically able to deal with this information. One professional explicitly associated a preference not to know with emotional motives, whereas a preference to know was associated with rational motives, for example regarding therapeutic options. Moreover, the inherent degree of uncertainty in IFs and in genetic results in general (because of incomplete penetrance or variable expression, i.e. the variable manner in which a condition is manifested) might engender feelings of doubt instead of knowledge and assurance. Secondly, patients were described as focussed on receiving a diagnosis for their symptomatic condition and hence they considered IFs and SFs less important side notes. This argument was also stated by a professional of a CMG without an opt-out possibility for actionable IFs, but it was in line with some professionals' doubts regarding the centre's current practice.

Besides these two patient motives, some professionals explicitly referred to the fundamental value of patient autonomy and the included right not to know as arguments for

unconditionally respecting a patient's preference. Half of the Belgian CMGs always allowed an opt-out from IFs, including actionable results which were specified as findings for which medical treatment or preventive screening are available. Participants argued that patients cannot be forced to receive unwanted information and that a preference "to stay in denial" should always be respected. The professional duty to avoid psychological harm and emotional distress, potentially caused by IFs, also favoured the possibility of an opt-out.

"When the patient says "No, I don't want to have any other result than what we are looking for", then I think you should not report it. […] Therefore, I think, genetic counselling is very valuable and you have to do everything to respect your patient. I think that's the most important thing. It's not up to us to decide what to report and what not […]." (P7, FG3)

Some professionals suggested that when a patient opts out, IFs might still be reported from the laboratory to the clinician, so clinicians can be attentive for early symptoms during follow-up consultations. It also allows for reporting the IF at a more suitable moment or when the patient asks about it later. Other professionals, however, suggested that declined IFs should be masked in the laboratory report, so situations where the clinician knows but cannot disclose relevant information to the patient are avoided.

Finally, participants discussed the possibility of a selective opt-out from specific (categories of) IFs and professionals at two CMGs (both allowing an opt-out of actionable IFs) would support this practice as soon as IFs can be accurately categorised. However, explaining these categories might become too complex, especially when the number of reportable IFs increases. Professionals at two CMGs without an opt-out possibility already felt that this practice was too complicated. It would increase the professional workload and patients were considered unable to make these stratified choices.

6.4.3. Genetic literacy, patient autonomy and professional beneficence

In all CMGs, a major challenge in clinical ES was discussed, being patients' inability to fully understand the meaning and consequences of IFs. Participants mentioned several reasons for people's limited genetic literacy and inadequate understanding. Firstly, genetic information might be conceptually new, complex, extensive and overwhelming. Secondly, and in contrast to standard medical tests, IFs are usually not expressed in related symptoms and do not reveal an "instant reality". This presymptomatic risk assessment with a delayed relevance and possibly lifelong impact might be difficult to interpret or to use as grounds for decisions. Thirdly, conditions' (incomplete or age-dependent) penetrance might be difficult to understand, especially in unexpressed IFs, and people might not be used to thinking about risks or chances. Finally, genetic tests might be prescribed by non-geneticists. Combined with a lack of time for adequate pre- or post-test counselling, these professionals' limited

experience with genetic medicine might result in an incomplete transfer of information and "uninformed" consent from patients.

Some professionals did not believe that patients' lack of understanding could be resolved within the timeframe of a counselling session and hence they did not believe it was possible for patients to make informed decisions about IFs. Consequently, three Belgian CMGs did not allow an opt-out from actionable IFs. One professional mentioned that opting out can provide temporary psychological relief but eliminates neither the medical risk nor the psychological distress in the long run. Refusing an actionable IF is only a short-term remedy that postpones distress from the time of knowing to the time of expression. Professionals at CMGs without an opt-out possibility feared that patients did not fully understand the potential consequences of opting out, for instance the future benefit that might be declined. Patients might regret it when, later, a medically actionable condition (for example breast cancer) manifested and they might blame professionals for non-disclosure of this risk.
"[…] I think the majority of them [patients], 99% of them, do not know what they are agreeing to or what they are not agreeing to, when they say "I don't want to know or I do want to know."" (P8, FG3)

In addition to the argument concerning patients' genetic literacy, several professionals expressed a feeling of responsibility towards patients. They would experience it as psychologically unbearable and inappropriate to observe but not report a health risk of a possibly preventable condition. Hence for some professionals, this perceived duty of beneficence outweighed the value of patient autonomy and supported the absence of an opt-out possibility for actionable IFs. Professionals of all CMGs debated the interaction between professional beneficence and patient autonomy and in one CMG, this interaction in the case of a potential opt-out was the main point of discussion. Whereas most professionals at this centre advocated a right not to know actionable IFs, one professional upheld the idea of overruling an opt-out choice and nevertheless reporting a medically actionable IF. Arguments for this infringement of a patient's choice were the belief that the consequences of an unreported IF could be more severe than those of denying a patient's preference and, again, the belief that patients do not understand the possible consequences of their own opt-out choice.
"For something like a BRCA1-deletion […], I would not accept an opt-out and I would inform the patient anyway, saying "well, the consequences are so big, so important, [that] I consider it medically more important that you know, than actually to respect your autonomy as a patient." (P8, FG3)

In defence of a mandatory disclosure of actionable IFs, few patients were said to dispute this policy, which suggested patients' trust in the professional practice. It also supported a participant's statement that a mandatory disclosure should not be qualified as a paternalistic

act but as acting in line with patients' interests and with their need for guidance along the diagnostic quest.
Even though adequate understanding for autonomous decision-making was not considered possible by everyone, genetic counselling was generally estimated essential and effective to prepare patients for a potential (mandatory) disclosure of IFs.
"You can compare it to a pregnancy ultrasound. Why do families or mothers want a pregnancy ultrasound? To hear that everything is okay. Very few people think about the possibility of bad news and how to deal with it. And I think, when people enter the [genetic] centre, this is one of our essential tasks. […] So if you incidentally find a [variant in a] Lynch-gene [included in a breast cancer panel], you can say something like "look, this is not the answer, but we have found something else of importance." It is an essential part of our job that, at that time, this [information] is not completely new to patients." (P7, FG2)

Professionals also acknowledged individual variance in the capacity to understand or emotionally bear genetic information. Personalising the policy on IFs (for example by offering some patients more options) was, however, regarded as undesirable because it violates the value of equality and stimulates favouritism and a dual healthcare system. Moreover, offering personalised options entails the difficulty for professionals of estimating a patient's situation and capacities correctly.
It should be noted that at two of three CMGs without an opt-out possibility, professionals did not only rely on ethical arguments but also referred to procedures prescribed by the local ethics committee. Participants mentioned that the ethics committee did not allow an opt-out because it assigned professionals the responsibility of reporting available and useful information and because it considered patients incapable of informed decision-making in the context of clinical ES. Remarkably, some professionals at these CMGs said that if the ethics committee were updated on recent evolutions in clinical ES, a re-evaluation of the opt-out policy might be possible. However, no in-house consensus was reached on this idea.

As a final remark, several professionals stated that, depending on the patient's best interests (including a correct diagnosis), a patient's genetic illiteracy is no reason to dismiss a genetic test *in se*. Even after counselling, numerous patients will not fully realise the meaning and possible consequences of ES (including the possibility of IFs). However, the test would usually be performed anyway, as this was considered to benefit a patient's care.
"I try my best to explain it, but when I notice, at a certain moment, that it [a patient's understanding] stops, but they want another child, then I think, also for the best interest of the patient, let's just start another test. […] Doing nothing, because you think they have not fully understood, while you think it is in their interest to continue, well, then I think, as a clinician: "What would be the best choice of several options?" (P10, FG4)

6.4.4. The scope of ethical values

The last theme applies to the scope of ethical values and their application in practice. This theme was clearly observed in three particular issues concerning the disclosure of diagnostically unrelated findings.

Firstly, despite patients' right to be informed about IFs, this right was limited by professionals' duty of non-maleficence. There was a consensus among professionals at all CMGs to specifically delineate the scope of reportable IFs. Most participants advocated a restriction of reportable IFs to class 5 and class 4 (pathogenic and likely pathogenic) variants in medically actionable genes, but several professionals indicated that this spectrum might change when scientific knowledge increases or societal interests and taboos change. Only one professional mentioned that the professional delineation of reportable IFs could be perceived as "rather paternalistic". Conversely, at more than half of the CMGs, participants stated that their professional expertise should compensate for patients' genetic illiteracy and that it is their professional responsibility to decide which findings are comprehensible for lay people and hence relevant to report. Moreover, reporting "ambiguous" or "nonsensical" data (for instance class 3 variants of uncertain significance (VUS) or medically non-actionable IFs) might result in harmful interventions, (unnecessary) fear or false feelings of certainty, and professionals assigned themselves the duty of avoiding these possible harms.

"Professional bodies have decided that it's about the actionables. Hence only cancer and cardiac conditions have been included [in lists of reportable results]. I think, if you include more, it will become very stratified and one might wonder whether patients still understand what they are signing up for." (P11, FG2)

"Different systems are being used and some [genetic] centres say "let's offer different choices to the patient" and this can go very far. Patients can choose not only whether they want to receive [additional results] or not but also which [additional results] they want to receive. […] I have even seen an [informed consent] form which asked whether you want to receive variants of non-significance or not. So where the idea is something like "in the laboratory, we can't figure it out, so let's leave it up to the patient." (P1, FG2)

In the delineation of reportable IFs, some professionals considered the health of patients' family members as included in the duty of beneficence and hence they supported the disclosure of IFs regarding a carrier status of a recessive condition.

"When patients find out, during a later pregnancy, that their child has Duchenne [muscular dystrophy] although we have seen it in their older daughter… You don't want this to happen. That's why we don't work with an opt-out, to avoid this kind of thing." (P2, FG2)

Secondly, the scope of professional beneficence was sometimes delineated by the spectrum of the "clinical gaze". Some professionals characterised medical responsibilities as not strictly limited to the diagnostic question, which resulted in a more extended perspective of a patient's health. Mainly professionals at two CMGs without an opt-out possibility for actionable IFs advocated this holistic clinical gaze.

"It also creates a responsibility, I think, when a patient consults you for a condition and there is also something else in the family which might be important, that you have to keep this in mind and do something about it. We have had such a discussion, about someone who consulted us for cancer while there was also a history of aneurysms in the family. This was not followed up and the patient died of an aorta aneurysm. Afterwards, it was discussed whether it was the counsellor's responsibility to follow up on this." (P9, FG4)

Other participants, however, defined their fundamental responsibility as more restricted. Patients were characterised as diagnostically focussed and aiming for a specific answer to a particular question. To address this request and to answer patients' questions most efficiently, professionals should adopt this diagnostically focussed clinical gaze. Hence, these professionals supported the use of specific, demand-driven tests that minimise the chance of additional findings.

"I think that we, clinicians, should try to avoid finding IFs as much as possible and so we should use as many filters as possible to avoid them." (P3, FG5)

Finally, and associated with the scope of beneficence, several participants mentioned and showed enthusiasm for a future practice of SFs (described as a practice of opportunistic screening with a presymptomatic risk disclosure). This possibility was mentioned by professionals at both CMGs with and without an opt-out possibility for IFs and it was presented as a practice that could meet patients' increasing demand for genomic information and a practice that could achieve a higher level of care. Some professionals even feared that denying a practice of SFs could someday be labelled a medical error. However, there was a consensus among professionals at all Belgian CMGs not to routinely pursue SFs yet and to consider this practice as currently falling outside the scope of beneficence. Various underlying reasons were mentioned for this limited scope. Firstly, a practice of SFs might be a disproportionate investment of limited budgetary, logistical, human and technical resources. Combined with a lack of specific guidelines, this could result in less valid and potentially harmful results and it would disadvantage a CMG's workflow and lengthen the waiting time for diagnostic results. Secondly, and partly due to lay people's genetic illiteracy, society was not considered ready for a routine practice of SFs. Finally, it was suggested that patients fundamentally do not want to receive additional results (whether IFs or SFs) because of the

intrinsic “bad news” they include. Even though IFs or SFs might be useful, no patient wants to be confronted with additional health risks. Therefore, there was an agreement among professionals on patients’ future right to opt out of SFs. This right was also stressed by professionals of CMGs without an opt-out possibility for actionable IFs.
“You cannot offer a kind of package deal and say “we are going to do this test and you are also obliged to accept these SFs […].” That is something you can’t do, it would be unethical.” (P1, FG7)

The fundamental restraint towards additional “bad news” did not only apply to patients. At two CMGs, participants expressed the professional feeling of emotional distress caused by IFs. Neither patients nor professionals are looking for IFs and a confrontation with these findings is unpleasant to both parties. Hence reporting IFs was characterised as “a dirty job” that still needs to be done; finding the balance between autonomy, beneficence and non-maleficence was experienced as “mental gymnastics” for professionals.
“Most people don’t really want to know [this information] anyway, but I think, if you find it, they should know. But it’s… I try not to get in that situation, if possible […] If I ask for a cardiomyopathy, I don’t want to find BRCA mutations, I don’t want to find a mental retardation mutation! […] as a medical person, as a doctor, I feel that I have to do it, but still, if I were the patient, I wouldn’t be pleased to find out. I would rather know, but I wouldn’t be pleased about it.” (P8, FG3)

6.5. Discussion

Professionals at Belgian CMGs frequently justified their centre’s practice and policy regarding IFs and SFs by ethical principles. As a consequence of the use of ES-based panel testing and a limited experience with IFs in clinical ES, it should be acknowledged that these justifications might not only consider actual practices but also preferable future policies.
In line with international scholarly literature, professionals frequently referred to principles of autonomy, non-maleficence and beneficence (8). The disclosure of IFs was supported by respect for patient autonomy, the professional delineation of reportable IFs was supported by non-maleficence and the spectrum of beneficence, and the decision not to actively pursue SFs was supported by the currently limited scope of beneficence. The possibility of opting out of actionable IFs was the most discussed element during the focus groups and various ethical values regarding this practice were weighed up. Allowing an opt-out was justified by the values of autonomy (respecting a preference not to know) and non-maleficence (not inflicting psychological or medical harm), whereas not allowing an opt-out was mainly justified by the principle of beneficence (preventing future medical harm as a duty of care). The weighing of these values was strongly influenced by professional ideas about patients’ genetic literacy,

their (inadequate) understanding of ES and IFs and their ability to make informed and autonomous decisions. These assumptions affected professionals' final choice regarding an opt-out possibility and resulted in mandatory reporting of actionable IFs at some Belgian CMGs. The mandatorily reporting of IFs, irrespective of patients' preferences, might sound contestable in current, patient-centred ideologies, but it is supported by recommendations by the ESHG and EuroGentest, which advocate a professional final decision regarding the disclosure of serious and actionable IFs (2, 4). Conversely, the policy of half of the Belgian CMGs that allow an opt-out from IFs is supported by Vears et al.'s points to consider for laboratories and by the CCMG position statement which states that "competent adults should be given the option prior to testing to receive (or not receive) incidental findings unrelated to the primary test indication" (6, 7).

If the reporting of IFs occurs against a patient's consent, this disclosure might be conceptualised as medical paternalism, i.e. interference in a patient's autonomy without this patient's consent, but only because the medical professional is genuinely concerned about patients' health and wellbeing and thinks that his/her interference will benefit the patient (32-35). Since the professional's action consists of an epistemic intervention - the disclosure of medical information which is considered useful - the mandatory reporting of actionable IFs can also be labelled as "epistemic paternalism" (36, 37).
In line with traditional bioethical discourse, the mandatory disclosure of actionable IFs at three Belgian CMGs would be considered soft paternalism because patients are assumed to lack the genetic literacy to fully understand the consequences and impact of ES and IFs and hence, in this context, they are unable to make informed, autonomous decisions (25, 38, 39). Soft paternalism is not uncontested but accepted by many as a common medical intervention and is, on occasion, also preferred by patients themselves (25, 40). In addition to the previous conceptualisation, we will refer to the mandatory reporting of actionable IFs as *technological* soft paternalism. In comparison to other medical information that patients might understand, ES-technology and the abundant and complex results it might generate (including IFs) are, also after standard pre-test counselling, considered very complex for the average patient (34, 41). Hence the medical technology used is the specific and context-dependent cause of patients' inadequate understanding and inability to make autonomous decisions, and it is the underlying technological justification of soft paternalism.
In summary, the technological, soft paternalism regarding actionable IFs can be characterised as the professional decision, motivated by patients' best interests, to disclose actionable IFs because patients lack the genetic literacy to understand the technology of ES and its complex results and hence are, in this context, incapable of autonomous decisions.
Despite the technological, soft paternalism's grounds in undeniably complex medical information and its benevolent focus on patients' wellbeing, some remarks can be made regarding its justification and efficacy in the specific context of clinical ES and actionable IFs.

Firstly, as the soft paternalism is grounded in the specific context of ES-technology and its complex results, the mandatory reporting of actionable IFs might be considered a modus of "procedural paternalism": only in the specific context of genetic testing by means of ES-technology and at the specific time of diagnostic testing are patients incompetent and non-autonomous and hence professionals are authorised to decide on the disclosure of results without patients' consent (39), However, it is hard to claim that, even in this specific technological context, every patient lacks the genetic literacy to understand complex ES-results, and hence is incompetent to decide autonomously about the disclosure of these results. It seems that exceptions to technological, soft and procedural paternalism should be allowed but it is unclear how these exceptions are compatible with the principle of justice. These reflections were also expressed by professionals from some Belgian CMGs and in participants' restraint concerning more personalised choices regarding IFs because of their possible violation of the justice principle. Technological, soft paternalism could also be considered a type of "endangerment paternalism", where actions are generally subjected to paternalistic actions because of the risk that at least *some* people are incompetent (39). However, this would imply that some patients are limited in their actions without actual proof of their inadequate understanding, turning the paternalistic intervention into hard paternalism towards autonomous persons (39). Moreover, autonomous decisions about IFs might not require a *full* and technological understanding of ES and instead, autonomy and genetic literacy might be considered a continuum. Rather than an absolute ideal, autonomy can be considered a threshold concept where patients have a *sufficient* understanding and are *sufficiently* competent and autonomous (36, 39). It is also likely that this understanding should not focus on the technology of ES, but rather on comprehensible and practical consequences of test results, an idea which was, along with the suggestion about new ways of counselling, also raised by Belgian professionals (3, 42, 43). The possibility or at least the pursuit of a *sufficiently* informed and autonomous patient does, however, not deny professionals' more profound understanding of ES and genomic results, and this expert epistemic position applies generally in medicine (25). Moreover, the complexity of ES-results is generally acknowledged and literature has shown that the genetic literacy of the general population is rather limited (44, 45). Hence, doubts about patients' ability to make informed decisions about IFs, even after pre-test counselling, are not uniquely Belgian concerns (17, 46). In conclusion, rather than aiming for a fully informed patient decision-making, the issue of IFs might be agreed upon by a dynamic process of shared decision-making, in which both the patient and professional participate actively (33). This idea aligns with the suggestion that counselling and consent should not focus strictly on information provision and patients' individual, rational and autonomous decisions, but should pursue a relational autonomy where patients and professionals reach a decision collaboratively (47). In such a relational decision-making process, respect for autonomy and beneficence might be expressed in such a way that both values can be respected (48).

Secondly, the mandatory reporting of actionable IFs was partly supported by the assumption that an autonomous patient would agree with disclosure. This suggests that a preference to know is the rational preference because it is well-informed. This idea was also expressed by a Belgian professional who considered a desire to know to be a rationally grounded choice, whereas a desire not to know was usually considered emotionally grounded. However, the association between wanting to know and rationality on the one hand, and not wanting to know and emotion on the other hand, could be challenged. Various emotional reasons are possible for wanting to know IFs, for instance a fearful desire to control life as much as possible. Conversely, as also suggested by professionals who support an opt-out and might value non-maleficence (and autonomy) over beneficence, knowledge can be emotionally disturbing and the rational control over one's life can necessitate some degree of ignorance (35).

"Rationality sovereignty" (39), which supports the normative standard of wanting to know, is related to the well-known argument of incoherence, which states that ignorance inherently conflicts with autonomy and that autonomous individuals who want to make informed decisions cannot ignore relevant medical information (14, 36). Likewise, Harris has advocated that patients should be "rational choosers" who base their decisions on "an appropriate level of information" (49). Whether the argument of incoherence is true or not, it does not apply to the mandatory reporting of IFs. If patients need to be competent and autonomous, they need to be informed about the process of testing, the procedure of ES and its possible consequences, including IFs, *before* testing and not *afterwards* about actual IFs. The claim that being adequately informed requires the mandatory reporting of IFs confounds the prerequisites of an autonomous decision (i.e. being adequately informed about the genetic testing procedure and possible results) and its possible consequences (i.e. being informed about identified IFs). The only way to validate this claim is to state that ignorance about actionable IFs can impede future autonomous decisions about one's health and life. However, as stated above, receiving IFs does not absolutely guarantee an enhanced rationality or, as explained below, a better medical and/or psychological outcome.

A last remark should be made on some professionals' claim that few patients dispute the mandatory reporting of actionable IFs. A central clause of medical paternalism concerns the act of going against patients' preferences (33). If most patients seem to value the return of actionable IFs positively, it might be questioned whether the mandatory reporting can actually be classified as a paternalistic intervention. Sandman and Munthe have stated that decisions and interventions are paternalistic whenever they ignore patients' perspectives, even if they do not explicitly go against patients' preferences (33). Even if patients retrospectively approve of professional decisions, their autonomy is partly undermined by being denied some control over the decision-making process (33). Moreover, this retrospective approval might be the

effect of a psychological coping strategy to accept information one cannot unlearn. Nevertheless, from a consequentialist point of view, which also supports paternalism and its beneficent outcomes in general, it might be upheld that the (moral) harm of mandatorily reported IFs is decreased by patients' retrospective approval of the paternalistic and epistemic intervention.

The mandatory reporting of IFs may certainly result in effective prevention or early treatment of disease. However, it might be questioned whether the soft paternalism regarding actionable IFs is absolutely effective. A minimum requirement for paternalism to be justified is that its benefits outweigh its risks (25). This claim echoes the screening criteria of Wilson and Jungner and the American Medical Association (AMA) Principles of Medical Ethics, which state that genetic testing is most opportune when it will meaningfully affect a patient's care (13, 50). Hence it should be demonstrated that mandatorily reporting actionable IFs will benefit a patient's health, a claim which is, however, contested sometimes. Knoppers has warned for the "overpromising" of genetic data and, more generally, the pathogenicity, penetrance and expression of variants in asymptomatic persons have been disputed (51). IFs may vary in reliability and possible use and it should be realised that reporting misinterpreted or uncertain findings might result in unnecessary or harmful follow-ups or interventions (35, 37, 52-55). Moreover, IFs might cause changes in family, social and professional structures, considerable financial costs, problems regarding insurance or, as already mentioned, emotional harm (35, 36). For Belgian professionals who support an opt-out possibility, the values of non-maleficence and patient autonomy might take precedence over professional beneficence because of these possible negative consequences of reported IFs. For professionals who reject an opt-out possibility, these potential consequences are, *per contra*, not considered sufficient reasons to outweigh the professional duty of beneficence. If, however, the advantages of reported IFs were surpassed by (possibly underestimated) negative consequences, then the mandatory reporting of IFs invalidates the benefit that paternalism is supposed to provide and violates the professional duty of non-maleficence (55).

This introduces a last topic: the scope of values and, more specifically, the delineation of a patient's best interest and of a professional's responsibility and beneficence.
Firstly, this topic was reflected in discussions on reportable IFs. Should only results which might benefit a patient's medical interest be disclosed? Or should a medical professional also consider results for a patient's psychological and personal benefit or for the health of his/her family members? Some Belgian professionals referred to a family-wide concept of medical beneficence when arguing for a possible disclosure of IFs regarding a carrier status of a recessive condition, an idea for which international support has increased (7, 56). Bullock's context-sensitive evaluation of patients' best interest further broadens the concept by stating that the disclosure of medical information should be guided by an evaluation of patients' physical health, their short- and long-term psychological wellbeing and respect for and the

facilitation of their (future) autonomy (36). The delineation of a patient's best interest is related to the debate on IFs' actionability and the question of whether these genomic findings should only enable medical interventions or also personally valuable actions, a topic which we have discussed elsewhere (57).

Secondly, questions about the delineation of beneficence were reflected in professionals' divergent ideas on the spectrum of the professional "clinical gaze". Whereas some (especially people working in CMGs without an opt-out possibility) advocated a more holistic clinical gaze that is not strictly bound by the diagnostic question, others defended a professional diagnostic focus, in line with patients' core interest. However, and irrespective of participants' perspective on the clinical gaze or opting out of IFs, no one has currently recommended the deliberate pursuit of SFs. Belgian professionals showed that they were well-acquainted with the ACMG recommendations on SFs and sometimes they (implicitly) referred to these recommendations to explain or justify their CMG's policy on IFs. An example concerned a participant's delineation of the spectrum of reportable IFs ("*Professional bodies have decided that it's about the actionables. Hence, only cancer and cardiac conditions have been included*." P11, FG 2). This echo of recommendations on SFs in the discourse about IFs might be partially caused by a limited experience with IFs in clinical ES but it also illustrates these recommendations' international impact. The intertwinement between the discourse about IFs and the one about SFs can also be discerned in laboratory points to consider, where it is stated that "[i]f a variant on the ACMG list is identified as UF [unsolicited finding] then it should be reported." (7). Despite this echoing of recommendations on SFs, there was a consensus among professionals from Belgian CMGs that the active pursuit of SFs currently exceeds the spectrum of beneficence. Underlying arguments were society's unpreparedness for this practice (an idea associated with genetic illiteracy) and people's fundamental unwillingness to hear bad news (an idea associated with the duty of non-maleficence). However, these problems could be countered by initiatives that increase people's genetic literacy and by an absolute opt-out possibility for SFs. Hence the most fundamental argument for the decline of a practice of SFs might be professionals' statement that this practice is currently an unjust allocation of limited resources. Even though some Belgian professionals were enthusiastic about potentially achieving a "higher level of care" through SFs, this practice was considered currently unfeasible and hence inappropriate. This opinion tallies with the AMA-principle that specific care can be denied when it compromises the provision of more fundamental care and with the ethical acknowledgement of a limited professional duty of beneficence because of limited resources and distributive justice (13, 25). In this sense, Belgian professionals' perspective conflicts with ACMG members' evaluation of screening for SFs as standard medical practice and with the suggestion that if diagnostically unrelated information is that valuable, its discovery should not be left to coincidence but actively pursued (1, 5, 52, 58). Justice, as

argued by this last statement, should not be achieved by withholding the opportunity of SFs from patients but by guaranteeing equal access to these results for all patients (52).
In Belgian CMGs, the current lack of resources and the principle of distributive justice may not only justify the current decision not to actively pursue SFs but also the nationwide use of ES-based panel testing (as both practices limit the amount of analysed genes and hence of required resources). This limitation of possible results (including IFs) is supported by international professionals' questioning of the return and pursuit of IFs and SFs as the most efficient use of limited resources (17, 55, 59, 60). A filtered analysis minimises (but cannot completely avoid) the chance of IFs and - most of the time - it is most efficient in terms of diagnostic clinical relevance, it avoids an information overload and it allows clinicians to maximally realise their clinical task (59). Hence, it is within the boundaries of this panel of available results that concepts of reportable results, opt-out and mandatory disclosure should be considered. It also implies that even the professional duty of geneticists who assign themselves the responsibility of a more holistic clinical gaze is still bound and delineated by the scope of the genetic panel. In other words: for reasons of beneficence, the clinical gaze and the spectrum of professional duty might exceed the diagnostic question but currently, for reasons of distributive justice, this duty does not exceed the scope of the diagnostic panel. Ultimately, this suggests that the value of distributive justice profoundly delineates the scope in which values of autonomy, non-maleficence and beneficence are currently debated. An increase in available resources, decreasing costs of clinical ES-based testing or evolutions in scientific knowledge, societal preferences or people's genetic literacy may (but not necessarily should) affect the impact of distributive justice, the spectrum of reportable results and the weighing of values in an ethical disclosure policy on IFs and SFs.

6.6. Conclusions

Professionals at Belgian CMGs frequently refer to ethical values for disclosure policies on IFs and SFs. Respect for patient autonomy is invoked to support the disclosure of IFs and opt-out options, non-maleficence to support the delineation of reportable IFs and opt-out options and (the scope of) beneficence to support a mandatory reporting of actionable IFs, the delineation of reportable IFs and a current decline of actively pursued SFs. Additionally, the value of distributive justice largely delineates the scope of reportable results and the spectrum in which ethical values are currently debated. Over the coming years, the spectrum of the ethical debate on IFs and SFs might change and initiatives to improve people's genetic literacy might affect the legitimacy of a restriction in patient choices on disclosure. Soft paternalism may be

acceptable, but the validity of its motives and the plausibility of its beneficent outcome should be continuously verified in the context of scientific, economic and societal evolutions.
This study does not address all aspects of IFs and SFs which require ethical reflection. Topics concerning the informing of family members about IFs, the notification of patients when new information on IFs is available and the implications of patients' choices for the use of (electronic) health records or patient portals are not included in the scope of this article but definitely require further research. The results of this study emerge from a Belgian context with its specific healthcare structure. However, the way values are weighed in the context of IFs and SFs might be familiar to or instructive for other countries. Therefore, a more international and collective debate on the ethical grounds for a solid (future) policy on IFs and SFs might be highly valuable.

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Authors' contributions
MS developed the interview guide, recruited participants and moderated the focus groups. She transcribed the focus group recordings and thematically analysed the transcripts. MS was a major contributor in writing the manuscript.
The interview guide was evaluated by HM, who also attended the focus groups as an observer. HM evaluated thematic structures and fundamentally reviewed draft manuscripts.
A secondary analysis of a data subset, including transcripts and initial code schemes, was made by TM. TM and MS discussed and revised theme names, definitions and structures until consensus was reached. TM also fundamentally reviewed draft manuscripts.
EDB and ID facilitated recruitment and they evaluated the interview guide and preliminary thematic structures. Draft manuscripts were exhaustively reviewed by EDB and ID and they both contributed to the final structure of the manuscript.
All authors have read and approved the final manuscript.

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Availability of data and material

None of the data generated and analysed during this study are publically available for reasons of personal privacy, but they are available from the corresponding author in response to a reasonable request.

Ethics approval and consent to participate

This study is approved by the Commission of Medical Ethics at Ghent University Hospital (reference number B670201628974). Participants signed an informed consent form, and personal information was altered or removed to create an anonymous report.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Chapter 7 – AN INTEGRATIVE MEANING OF GENOMIC INCIDENTAL FINDINGS – A QUALITATIVE STUDY AMONG PATIENTS WITH AN INHERITED RETINAL DISEASE

Saelaert M, Mertes H, Moerenhout T, Leroy BP, Van Cauwenbergh C, Devisch I, & De Baere E. An integrative meaning of genomic incidental findings – A qualitative study among patients with an inherited retinal disease. (In preparation)

7.1. Abstract

Genome-based testing may not only answer a patient's diagnostic question but it can also reveal incidental findings (IFs), i.e. predispositions for potential disease that exceed the test indication. Knowledge of patients' interpretation of possible IFs and of motives for (not) wanting to know particular IFs is still limited. This article examines the meaning of IFs from a patient perspective. An interpretative phenomenological analysis was made of 14 interviews with patients with an inherited retinal disease.

Patients assign a complex meaning structure to IFs, including three main components. The first component focusses on the characteristics of an IF and possible consequences of disclosure; the second component applies to the impact of a patient's lived illness experience; the third component addresses a patient's family embedding and its variable relevance in different contexts.

The complex meaning structure of IFs suggests the need for personalised counselling procedures that transcend a strictly clinical and result-centred approach.

7.2. Introduction

Currently, genetic testing by whole-exome sequencing (WES) is increasingly implemented in the clinic as an efficient technique to diagnose Mendelian (monogenic) diseases (1, 2). As WES is able to simultaneously sequence a vast number of genetic regions (3-5), the technique is particularly appropriate for identifying the cause of genetically heterogeneous conditions that may be caused by pathogenic variants in multiple genes (6). Since WES virtually analyses all protein-coding genes, molecular findings may be identified that are beyond the test's diagnostic aim. These diagnostically unrelated and potentially important findings can be unintentionally discovered as incidental findings (IFs) or actively pursued as secondary findings (SFs) (7, 8).

Patients and lay people have shown a strong interest in IFs and SFs and they generally prefer the disclosure of many types of results, including findings associated with an increased cancer risk, early-onset conditions or a carrier status of recessive conditions (3, 9-11). Some studies have indicated a predominant interest in "medically actionable" findings (12-15), meaning results for which a medical treatment or prevention is available that could improve the outcome of the associated condition (16). These medically actionable IFs and SFs are considered an opportunity for disease prevention and future informed medical decision-making (17-19). However, people are not merely interested in the medical significance of genetic results and many also want to receive medically non-actionable IFs and SFs, for instance associated with progressive neurodegenerative conditions or multifactorial conditions (3, 9, 20-22). Many people interpret 'actionability' in a broad sense and refer to

lifestyle changes, the psychological, reproductive and future value of genetic results and the value of knowing in itself (12, 13, 18-20, 22, 23).
Nevertheless, not everyone wants to receive (all) diagnostically unrelated findings (23). Reasons for not wanting to know are the potential costs of additional testing, the complexity of results, a strict focus on diagnostic results or a distrust in the healthcare system (13). The most important reason for not wanting to receive IFs and SFs is the risk of psychological harm and distress and the fear of not being able to emotionally cope with these results (3, 14, 18, 21). This psychological risk has been specifically associated with results without a clear pathologic significance (variants of uncertain significance or VUS) and with medically non-actionable findings (12, 13, 19). Nevertheless, the rationale of emotional harm is mentioned more frequently by professionals than by patients and patients generally suppose that refusing the disclosure of IFs and SFs may be more harmful than receiving these results (11, 19, 21-23).

Despite current research on patient preferences regarding IFs and SFs, many questions remain unanswered. Firstly, research has often focussed on the perspective of cancer patients (3, 12, 15, 19). This is undeniably an important group of stakeholders who represent a large proportion of patients that are genetically tested by WES and potentially confronted with IFs and SFs. Patients with different conditions may, however, have different interests regarding genomic results (18). Hence, the perspectives of patients with other illness experiences should be investigated (23). Secondly, patients have been frequently asked to indicate the categories of IFs and SFs they would like to receive, but it is still unclear how they exactly interpret these categories (3, 10, 23, 24). Most attention has been paid to the category of (medically) actionable results, but also a condition's other characteristics should be explored from a patient perspective. Thirdly, little is known about the underlying motives for patients' preferences regarding IFs and SFs. The opportunity for (future) medical decision-making and lifestyle adjustments, as well as the avoidance of psychological distress are important motives for (not) wanting to know but the possibility of other reasons should be explored. Patients' illness experience and their family history of disease may affect their perspective on IFs and SFs but these suggestions require further investigation (11, 13, 19, 23, 25).
In response to these concerns, this article will profoundly examine the meaning of IFs and SFs from a patient perspective. Particular attention will be paid both to the subjective interpretation of IFs and SFs and to underlying motives for these interpretations and associated preferences (not) to know. Specifically, the meaning of IFs will be investigated in patients with an inherited retinal disease (IRD). This in-depth analysis may contribute to a better care for patients who are diagnostically tested for various genetic conditions.

7.3. Methods

7.3.1. Design

The design and analysis of this qualitative study are based on the method of interpretative phenomenological analysis (IPA) (26). IPA aims to clarify personal meanings of lived experiences or specific objects ('phenomena') in a homogeneous group of people (26). This method is frequently used to understand subjective experiences in healthcare and health psychology and it has also been applied for the interpretation of genetic results (27-29). Moreover, IPA can be used to study people's expectations and interpretations within a broader context of experience (30).

7.3.2. Recruitment and participants

Participants were recruited by purposive sampling. People could be included in the study if they had received a diagnosis of an IRD, were genetically tested, were at least 18 years old and were able to fluently speak Dutch.

IRDs represent a large group of clinically and genetically heterogeneous eye disorders with an estimated collective prevalence of 1 in 2000, affecting about two million people worldwide (31). To date, IRDs have been associated with mutations in over 270 disease genes, making WES-based testing a suitable approach for genetic testing (32). With the approval of Luxturna ™ as the first retinal gene therapy and with the progress of many promising gene-based therapies for IRD, a definite genetic diagnosis in IRD is particularly important (33, 34).

Based on the inclusion criteria, EDB, BL and CVC (a geneticist, ophthalmic geneticist and molecular geneticist involved in patients' clinical care and genetic testing at Ghent University Hospital) selected eligible participants. Selected patients were contacted by BL and EDB and were informed about the study. Those who were potentially interested to participate and agreed to be contacted by the lead researcher, were contacted by telephone by MS; they were given some additional information and were asked for participation. When people agreed to participate, an interview was scheduled. Fourteen patients (ten women and four men), aged between 23 and 51, were interviewed. Twelve participants had undergone a diagnostic WES-based test, of which 11 received positive genetic testing results. One participant received genetic testing results by targeted gene panel testing and one (presymptomatic) participant received a positive result by cascade testing of a familial mutation.

7.3.3. Data collection

MS conducted all in-depth interviews. Interviews took place at the participant's house or in a room at the university or hospital, depending on patients' preferences. All interviews were conducted between January 2017 and February 2018 and lasted between 50 and 150 minutes. When patients are diagnostically tested in Belgian centres for medical genetics, it is not possible nowadays to ask for actively pursued SFs. For this reason, interviews were mainly focussed on IFs. At the start of the interview, IFs were briefly explained. These results were described as "additional genetic and health-related results which are unrelated to IRD". Examples of possible IFs were given and supplementary information was given if required. A practice of SFs was also addressed during the interviews but generally, the focus was more on the diagnostically unrelated character of these findings than on their accidental or active discovery.

A semi-structured interview guide based on a literature study and evaluated by a multidisciplinary team of an ethicist (HM), geneticist (EDB) and philosopher (ID), was used for all interviews. Sociodemographic information (concerning age, work, children, siblings, etc.) was collected throughout the interview. Examples of open-ended interview questions were "How do you experience the condition of IRD and how does it affect your daily life?", "How did you experience the genetic testing process for IRD?", "What are your spontaneous thoughts about the possibility of additional genetic test results that are not related to IRD?", "Which kind of results would you be interested in?", "What, do you think, would be the effect of receiving these results?" and "How would you expect these results to affect your personal life or family relations?". To facilitate and support participants' reflection, sensitising concepts regarding characteristics of IFs-associated conditions, as identified in the literature, were presented. These concepts included the (medical) actionability, penetrance (i.e. the probability that a variant will express the associated condition), estimated age of onset, impact on reproduction and severity, among others. For every concept, a separate card (available in two font sizes) with a brief description was presented. Concepts were defined with a minimal use of jargon and verbally illustrated with examples. These cards were not used when the participant was not able to read them because of low vision. Participants indicated whether they were able and/or willing to use the cards.

7.3.4. Data analysis

Interviews were audio-recorded, transcribed verbatim, made anonymous and saved on a password-protected server until completion of the full research project. If an independent transcriber was involved, the transcripts were checked for accuracy. Software program NVivo12 was used to support data analysis. IPA requires a case-by-case analysis of the transcripts that moves from a descriptive to an interpretative level. Initially, every interview was read multiple times, while descriptive, linguistic and conceptual annotations were made. Secondly, emerging themes were identified inductively. The emerging themes were listed in a

table and connections and higher-order themes were determined. Every transcript was analysed separately in this way, while always allowing for the appearance of new themes and the adaptation of existing themes. Lastly, a table and framework of all superordinate themes and subthemes, thematic connections, definitions, and significant excerpts was composed to construct an overview of all interviews (26). This facilitated an interpretation of the data that exceeded the sum of its parts (35).
As IPA is an interpretative pursuit, an extensive procedure combining peer debriefing and a systematic audit trail was followed to ensure the credibility and trustworthiness of both the process and product of analysis (36). TM independently analysed a subset of the data to validate the analysis of MS. Transcripts, theme definitions and connections were thoroughly discussed by MS and TM. Thematic structures and draft reports were exhaustively reviewed by the multidisciplinary group of authors until consensus was reached between all of them. Finally, quotes were selected, translated and included in the results to support the interpretative results.

7.3.5. Ethics

This study was approved by the Commission of Medical Ethics at the Ghent University Hospital (reference number B670201628974). Written consent was obtained from all participants. The informed consent form was provided digitally when requested. Participants were assured that participation or refusal would have no impact on their treatment and/or relationship with their caregivers and that identifiable results would not be shared with treating physicians or other care givers. Additionally, participants were informed that the interview could always be paused or stopped. Several participants appreciated the interview as an opportunity to tell their story. If participants asked for (professional) psychological support after the interview, they were given the contact information of a genetic counsellor.

7.4. Results

In the inquiry of IFs' meaning from a patient perspective, three superordinate themes were identified:

i. Result-specific qualities
ii. Lived illness experience
iii. Family embedding

These three themes corresponded with the main components of IFs' meaning structure and with underlying motives for (not) wanting to know particular results.
Patients constructed the meaning of IFs throughout the interview and often, their interpretation evolved and became more nuanced. Only one participant persistently expressed the wish to know all possible IFs, including results with an uncertain pathogenic

significance, and only one patient held on to the idea of not wanting to know any IF. Most participants oscillated between wanting to know and not wanting to know and they balanced various conflicting motives. This ambivalence resulted from the simultaneous and interacting impact of all three components of IFs' meaning structure.

"At first sight, you would say "yes". But if you think about it a bit more... I wouldn't want to know what is going to happen. I think it's quite frightening to know that within a few years, you will get cancer or Alzheimer's disease. [...] I think it's an ambiguous thing. On the one hand, you don't want to wait your entire life for something that might happen. On the other hand, it might be useful to know. I don't know." (P3)

Figure 2 illustrates IFs' meaning structure from a patient perspective. In the intersections, examples are given of interactions between different components.

In what follows, each component of IFs' meaning structure is analysed in more detail.

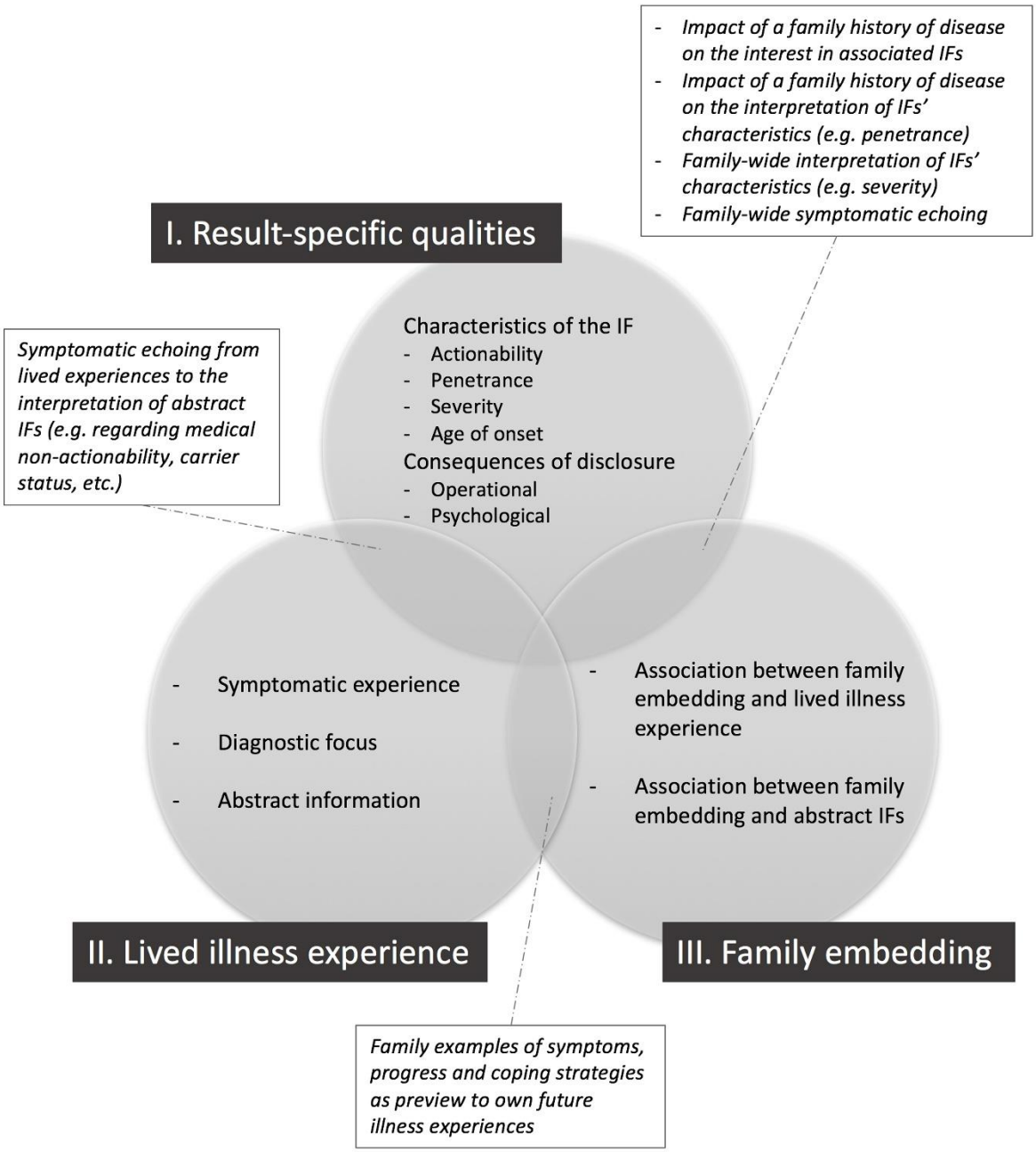

Figure 2 Incidental findings' meaning structure from a patient perspective

7.4.1. Result-specific qualities

The first component of IFs' meaning structure related to potential qualities of a specific genetic test result that may be identified as an IF. During diagnostic testing, none of the participants actually received IFs. Therefore, this meaning component encompassed hypothetical reflections. When considering result-specific qualities of a potential IF,

participants mainly focussed on (i) characteristics of the potential IF and its associated condition and (ii) assumed consequences of disclosure (Figure 2).

a. Characteristics of the IF

Important characteristics of a potential IF and its associated condition were actionability, penetrance, severity and age of onset. Participants interpreted these characteristics in a nuanced way and applied them as motives for (not) wanting to know IFs.

Firstly, an important characteristic of a potential IF was the actionability of the associated condition. One patient mainly stressed possibilities of medical prevention or therapy but usually, actionability was interpreted as a broad concept that exceeded the clinical domain. Therefore, the disclosure of IFs that could empower lifestyle changes or practical actions (such as financial or residential decisions) was also considered valuable. Receiving IFs was considered an opportunity to prepare for future disease, recognise early symptoms, improve one's self-awareness or enjoy life to the fullest.

"Then you know that there are some things to keep in mind. […] Like for Alzheimer's disease…, then I could prepare for that and maybe […] pay attention to or notice first symptoms." (P2)

Several participants characterised actionability as contextualised and dynamic. This interpretation was grounded in the importance of personal living conditions and in expectations of scientific progress.

"Yes, [I would like to be informed about an IF associated with an untreatable condition], because what's not treatable today, might be so in the future." (P2)

Secondly, participants emphasised the importance of a condition's penetrance. Most patients preferred the return of IFs with a high probability to result in the associated condition; disclosed IFs should be "hard mutations" that indicate "real risks". Low-penetrance IFs were presumed to be numerous, overwhelming and potentially resulting in psychological distress or unnecessary actions. Nevertheless, it was difficult to decide on a cut-off threshold for penetrance. Risks were variedly interpreted in terms of percentages ("80% chance") or by comparing them with other disease risks in themselves or others ("your top 10 of risks" or "a higher chance than someone else"). An IF's penetrance was also considered as correlated with other factors such as an associated family history of disease (which was presumed to raise penetrance).

Thirdly, the severity of an IF-associated condition was an ambivalent motive for disclosure. Overall, patients were particularly interested in preconditions for severe diseases and some claimed that these results should always be reported. The main reason for this interest was the idea that these results would definitely stimulate preventive actions. Nevertheless, several participants mentioned that the disclosure of IFs regarding less severe conditions could also be useful, as long as it allowed for (physical or psychological) actions in the near future. One participant explained how for example Alzheimer's disease is especially burdensome for

someone's family members. This suggested an interpretation of severity that did not only include personal impact but also the impact on others.
Finally, patients valued the age of onset of an IF-associated condition in different ways. Two of the youngest participants clearly preferred the disclosure of IFs associated with conditions with an onset during "active life" (regarding work, reproductive decisions, etc.). These conditions were assumed to have the most substantial impact, whereas later-onset conditions were considered as part of '"normal ageing".
"When you're 70 […], I think you're going to have some [physical] problems anyway, for instance a heart disease. So whether you need to know additional risks then, hmm… I think, for me, the limit is about the age of retirement, when life is more relaxed anyway. From that age on, it would matter less to me whether or not I know [about an IF]. They can tell me but I would not worry too much about it. But before you are 65, you are still working, you want children or you have young children… Then I would certainly like to know [about an IF], yeah, for sure." (P1)

A second argument against the disclosure of IFs regarding later-onset conditions involved the warning that this knowledge may trouble people from the time of disclosure and hence have a lifelong psychological impact.
Conversely, two participants between 40 and 50 years old expressed their interest in IFs associated with later-onset conditions. This interest was motivated by these results' potential relevance for family members and by concerns about and previous experiences with illness and death in friends or relatives. The interpretation of a condition's age of onset was summarised in a patient's remark that IFs should be reported in the right context and as soon as they are optimally actionable. Nevertheless, participants also doubted the possibility of accurately predicting a condition's age of onset.

Many participants spontaneously mentioned the interaction between an IF's potential characteristics. An IF-associated condition should, for example, not only be severe but also highly penetrant. Alternatively, the low penetrance of conditions could be countered by severity or highly effective actionability.

b. Consequences of disclosure

Participants were convinced that disclosing an IF has its consequences, either operational (i.e. on actions) or psychological. The specific consequences of a disclosed IF were assumed to largely depend on the particular characteristics of the IF and on someone's character and context.
Operational consequences of disclosure were strongly related to the IF's actionability and participants showed a general willingness to take medical or personal action. Some patients suggested that if an IF allows for preventive actions, especially concerning reproductive decisions, people *should* take action. On the other hand, participants also interpreted

actionability as context-dependent. In the context of IRD, some patients had experienced that an intention to take action cannot always be realised, for instance because of financial, social or family reasons. Consequently, some participants acknowledged that not everyone will take action as a result of a disclosed IF. Additionally, actions may not always realise the expected or desired outcome. This lack of guaranteed success could be a motive for not wanting to know any IF or, conversely, for making no difference between medically actionable and non-actionable results.

"It's all just a matter of definition. […] Some cancers are treatable but what kind of effect do you really realise? 20% of treated patients may live a year longer, so technically, it's treatable. But actually, in terms of quality of life… Ok, 20% of them get an extra year, but 80% of them don't." (P5)

Patients repeatedly mentioned that, in essence, IFs always imply bad news and many participants expected some psychological distress. One patient – who preferred only to receive medically actionable IFs - feared that an IF's psychological impact may be that powerful that the associated condition could actually be expressed. Another participant – who preferred not to receive any IFs - was worried that the disclosure of an IF may cause a constant waiting for the first symptom, even if this might never occur. In line with this idea and despite the desire to receive particular IFs, many participants preferred a partly open and unknown future. Participants considered everyone at risk for some disease, since (health) risks are inherent to life. Being aware of too many risks may be paralysing and may even decrease the actionability of knowledge, since it is practically impossible to act upon every risk. Therefore, life should also be taken as it comes.

"At work, someone died very unexpectedly. But something like that can happen and it can also happen to me: I can get an unexpected disease. However, you have to accept it, you have to move forward." (P11)

On the other hand, patients noticed that refusing IFs only avoids the psychological distress but not the actual, physical risk. Therefore, some participants preferred the disclosure of IFs rather than to remain in ignorance and worry about potentially unreported risks.

"If they told me they would only disclose the identified things [IFs] for which a treatment exists, I would be worried and I would wonder what other things they have found but don't tell." (P6)

Despite concerns about IFs' psychological consequences, most participants considered themselves able to handle these results. Several participants mentioned specific reasons for this assumed ability, usually related to their (scientific, medical, etc.) job or studies. Remarkably, "other people" were not always supposed to be able to cope with IFs, especially not with medically non-actionable IFs. Patients repeatedly emphasised the importance of genetic counselling for a (practically and psychologically) successful coping with IFs.

7.4.2. Lived illness experience

The second component of the meaning structure of IFs (Figure 2) is based on the difference between, on the one hand, lived experiences of symptomatic illness and diagnostic test results and, on the other hand, reflections on presymptomatic conditions and abstract test results. This component contains three subcomponents: symptomatic experience, diagnostic focus and abstract information. The first two subcomponents are related to patients' lived IRD experience, their emphasis on the impact of actual illness (symptomatic experience) and their assessment of the value of diagnostic test results (diagnostic focus). The third subcomponent is related to the presymptomatic character of IFs.
This section will show how the abstract character and interpretation of IFs is affected by symptomatic experiences and a diagnostic focus. Finally, the interaction between the three subcomponents affects patients' valuation of preventive actions.

a. Symptomatic experience

All but one participant experienced IRD-associated symptoms: most patients suffered from night blindness and tunnel vision and most had experienced a visual decline. As professionals were not able to provide an exact prognosis, patients considered the evolution of their IRD unpredictable. Most participants perceived this as distressing or disappointing and some had a feeling of receiving no answer to fundamental questions. Despite the unknown prognosis and based on previous experiences, most participants feared a further deterioration and its potential consequences.
"Especially when I would be living alone and my vision would even be worse, then I would be afraid… How am I supposed to live then? How should I deal with it? I have no answer to the question whether my vision will stabilise or get worse, I just don't know." (P13)

Nevertheless, some participants preferred an unknown prognosis and uncertainty over a definite negative prognosis.
Interviewer: "Suppose there would be a crystal ball about your IRD prognosis, would you want to look into it?"
Participant: "That's a difficult one… I don't know. If the answer would be that I would suffer severe visual impairment only at a later age, then I'd like to know. But if it would be within ten years..." (P4)

The impact of IRD was described as ubiquitous. Participants provided mobility and job-related examples, such the inability to drive a car or the necessity to change or quit one's job. Several participants feared not being considered competent at work or did not feel supported.
"One day, I had to go to my supervisor. (S)he said: "I would rather work with a single-armed person than with you. I don't know what you're capable of and that just doesn't work." If only

someone had helped me a bit and had shown some understanding… However, if that's not possible…" (P9)

The progressive nature of IRD could imply the requirement of giving up more and more things and patients described the psychological and existential impact of this never-ending process. Participants frequently expressed the feeling of having no one who "really understands" their situation.
The use of specific devices to cope with IRD widely varied among patients. Some people used no supportive aids, others used glasses, computer software, a white cane and/or a guide dog. Many participants tried to accept the consequences of their illness and emphasised what was still possible. IRD was part of normal life and dealing with its consequences had turned into a habit. Nevertheless, patients regularly met the limits of coping strategies, since many activities were still challenging or impossible. Patients also perceived the constant need for assistance as confronting, which could result in a rejection of help and devices.
"That girl uses a white cane, but I still have to overcome that obstacle, I just can't do it. […] I think I'm too proud for it… […] My parents say I have to be more open about my [visual] problems. I try to and I asked for assistance at work. But that white cane, that's one step too far…" (P12)

b. <u>Diagnostic focus</u>

When reflecting on the experience of genetic testing, many patients emphasized their specific and delineated interest in diagnostic test results. This diagnostic focus motivated patients' interest in IFs that may explain other symptomatic (non IRD-related) health problems or in IFs that may be relevant to understand their IRD. One participant would, in the end, only be interested in this kind of IFs.
"I have a certain birthmark and it has already been suggested that this may be related with my eye condition. [...] So if they take a broader look [in a genetic test], they may find things that are related in some way. I think that's really a positive thing." (P6)

Patients had generally been appreciative towards the disclosure of diagnostic test results, as these results may be relevant for family members or be a first step towards (future) treatment. Results were also appraised as a proof of professional commitment or scientific success or perceived as a relief *per se*. Some participants mentioned a remarkable effect of disclosed diagnostic test results, namely an increased vigilance towards experienced IRD-related symptoms.
"It might sound silly, but at night, when I watch my clock, I wonder whether I see these numbers as sharp as before. Is the intensity of light still the same?" (P2)

Nevertheless, many patients also minimised the importance of diagnostic genetic test results. These results were merely a confirmation of a clinical diagnosis participants already knew and

the results did not change their illness experience. Contrary to their hopes, most patients realised that medical treatment would not be available on short notice.
"I don't get up every day thinking something like "I hope they're going to find something [a treatment] today". I know they're working on it but they were already working on it fifteen years ago. It's good that they have identified the gene but I realise that scientific research takes a lot of time and money, which is not always available." (P6)

Concerning the relation between patients' symptomatic experience and diagnostic focus, it was remarkable that the symptomatic experience and the familiarity with ubiquitous IRD-related symptoms could query the validity of genetic test results or clinical information. For some patients, negative IRD-test results in family members were not entirely reassuring and could not prevent a vigilance towards potential symptoms.
"I have to admit that I'm attentive all the time. For example, when we walk together outside, especially in the dark, I ask them [children] to look up and I ask whether they can see the stars. Because I can't. If they say they can see them, I'm okay." (P13)

In line with many participants' specific interest in diagnostic test results, various patients noted that IFs would be valuable side-effects of a test but not their core interest and not an aim *per se*. Participants' diagnostic focus did not completely erode the potential value of IFs but it tempered patients' interest and made it more selective. Many patients would not be interested in presymptomatic, diagnostically unrelated findings if there was no symptomatic reason for a genetic test or they would not be willing to pay extra for the return of IFs. Correspondingly, very few participants aspired to actively pursue SFs. As an additional argument, patients stated that they were not more at risk for IF- or SF-associated conditions than the general population.

c. *Abstract information*

Contrary to patients' symptomatic IRD experience and diagnostic focus, patients' considered presymptomatic test results more ambivalent: these results could be valuable but were also quite abstract. The participant who was still asymptomatic for IRD illustrated this ambivalence and oscillated between the feeling of being a patient already and the attenuation of the current consequences of the positive test results.
"I am communicating this [reproductive] information [to my partner] as a patient. It's very emotional for me and maybe less objective. […] Now, for the moment, I received this [IRD] diagnosis, but… One day, I will experience those problems, but not yet today. And that's what matters, I mean, it doesn't change anything right now." (P1)

Equally, patients assigned an ambivalent value to IFs and considered these possible results both valuable and abstract.

"My eye condition is really concrete and tangible and I can specifically say "this is my problem, that's the cause, those are the consequences." […] But if they would inform me about a potential risk for breast cancer, I would talk about it with my parents but not with all my cousins, because, there is nothing uh…, it's not concrete and present yet. It's something different than actually having the disease. It's different to have a predisposition with the chance of not getting the disease." (P6)

To overcome the abstract character of presymptomatic IFs, some participants applied a strategy of what we will call "symptomatic echoing": result-specific qualities (i.e. IF's potential characteristics and consequences) echoed elements of patients' IRD experience, and motives for (not) wanting to know IFs were derived from experienced IRD symptoms and consequences. Many patients wanted to receive medically non-actionable IFs and they frequently explained this preference by referring to the medical non-actionability of the IRD-related test result. The disclosure of this diagnostic result was considered valuable for various reasons and this experience supported the desire to receive non-actionable IFs. Likewise, patients motivated their interest in the disclosure of IFs regarding a carrier status by referring to the autosomal recessive transmission of some types of IRDs. Some participants also suggested that their way of managing IFs would be comparable to their IRD-associated coping strategies, both practically and psychologically.

Nevertheless, the difference between diagnostic, IRD-related results and presymptomatic IFs affected participants' valuation of preventive actions. Many participants described how several of their (professional, mobility-related, etc.) decisions were based on assumptions about the evolution of their IRD. Some participants had learned to use a white cane or to read braille, even though they did not need these skills yet. Patients experienced these preventive actions as emotionally confronting but emphasised their value and usefulness for possibly future situations. Contrarily, patients sometimes questioned the value of preventive actions in function of IFs. IFs may never cause actual disease and consequently, people suspected the usefulness of reorienting one's life towards a future that might never happen. Hence, some participants stated that - also medical - actions concerning IFs could wait until first symptoms would occur.

"Without any problems I wouldn't go to the hospital. If I would feel something, for instance in my breasts, I would ask the doctor for further tests. But for the time being, I have no problems, except for my eyes." (P11)

7.4.3. Family embedding

The last component of IFs' meaning structure addresses patients' interrelational context and, more specifically, patients' embedding in their family context. Patients' family embedding was clearly associated with both previous components of IFs' meaning structure. This last result section will describe the association between a patient's family embedding and their lived

illness experience and the association between family embedding and more abstract IFs. This will indicate the variable relevance of a patient's family embedding in different contexts.

a. Association between family embedding and lived illness experience

When participants had a close, usually older, family member who was also affected by an IRD, they may perceive this family member's symptoms and progress as a possible preview of their own illness evolution. Family members with an IRD could partly counter the uncertainty of an unknown prognosis and their coping strategies were frequently appraised as positive and valuable examples.
"I saw it with my grandfather. Even at his age, he was still able to work with a computer and […] thanks to technology, he could live rather independently. […] He couldn't see anything but he still enjoyed many things. […] He was really an example to me." (P4)

A major concern among participants was the recurrence risk of IRD. Participants specifically valued the disclosure of IRD-related genetic test results for (future or existing) children. Even when their children were not at risk for IRD, they may be attentive to possible symptoms and some felt they may be over-concerned or overprotective.
One patient explicitly associated concerns about the recurrence risk of IRD with a perceived guilt in his/her own parents for "having caused" IRD. Several participants had perceived this guilt and regret in their parents but they all believed that these feelings were unjustified, since medical technologies to avoid the inheritance of IRD used to be unknown or unavailable. Ultimately, they saw IRD as the outcome of a "genetic lottery".
"My parents are very sorry to have a child with IRD and they think they are to blame for it, well, that's how they see it. It's not easy, but they can't do anything about it. They just didn't know." (P7)

Most participants had positive experiences with informing family members about their own IRD diagnosis and associated genetic test results. They considered the disclosure of this possibly important information self-evident or even morally required. Remarkably, two participants took a rather normative position towards family members' reaction on IRD-associated information. They did not understand or would not support reproductive decisions that would not account for the recurrence risk of IRD. They pinpointed reproductive possibilities as one of genetics' greatest value and emphasised the opportunity to "break the chain of IRD".

b. Association between family embedding and abstract IFs

As mentioned in the previous section, participants may consider a family member's IRD-associated symptoms as an example of their own future illness experience. Analogously, a family history of disease could be considered relevant for potential IFs. Many participants

indicated a family example of (IRD-unrelated) illness as a strong stimulus for wanting to know associated IFs. A family history of disease would strengthen the reliability of identified IFs and patients would perceive these kinds of results as not completely unexpected. They also assumed that these findings would be vigorously motivating to take action. Remarkably, some participants were also interested in IFs associated with conditions they had perceived in close friends.

"For those diseases that are common in my family, I would really like to know [whether I have a predisposition]. I also think there should be a kind of motivation to really take action, like a family member who has cancer or Alzheimer's disease. Yes, I think there needs to be this kind of incentive first." (P1)

Conversely, participants were less concerned about the relevance of IFs for family members and future generations. One participant explicitly acknowledged the difference between his/her strong desire not to pass IRD on to future children and his/her undecided interest in (the reproductive relevance of) IFs.

"On the one hand, I think it may be good to know for which diseases I have a predisposition. But on the other hand, maybe I prefer not to know all of this and to see whether it ever comes to that. But then again, I think this is a bit contradictory […] I don't want my children to have IRD. But for other diseases, I wouldn't do the same. It's so difficult to choose one side or the other." (P4)

Several participants would prefer to know IFs regarding a carrier status of recessive conditions. This interest was mainly related to a personal desire to have children rather than to the potential family-wide relevance of these results. One participant's perspective differed significantly from most patients' individual (instead of family-wide) interpretation of IFs' relevance. This patient – with a fulfilled wish to have children - repeatedly mentioned that his/her interest in genetic test results, including IFs, was not personally motivated but primarily grounded on these results' family-wide value. (S)he considered IFs regarding a carrier status equally important than IFs with a direct personal impact.

Finally, most participants indicated that they would only inform their partner and first degree relatives about IFs and a potential family risk. Few felt responsible to inform the extended family and they expected this communication to be rather difficult, as IFs have an abstract (because usually presymptomatic) character. Hence, family members could deem these results irrelevant and useless. Furthermore, family members may not want to know these findings. One participant pointed out that disclosing personal IFs would inherently reveal the possibility of a family-wide risk and could bring family members in an uncomfortable position.

"Some people [in your family] may say "no, I really don't want to know". I think these situations get complicated when you say things like "well, I have an increased risk for this and this." (P1)

7.5. Discussion

This study investigated the meaning of IFs in a diagnostic context from the perspective of adult patients with an IRD. This meaning structure was not only grounded in qualities of the potential IF *per se*, but also in components associated with patients' lived illness experience and family embedding. The different components frequently interacted, which resulted in a complex meaning structure of IFs and in nuanced motives regarding disclosure. This nuanced perspective on IFs and SFs has been reported before and it is an important correction to the assumption of an unspecified patient interest in all genetic information (13, 15, 23, 37, 38). Throughout the interviews, patients' specific interpretation of IFs and associated preferences for disclosure evolved. This evolution, as well as an increasing cautiousness towards IFs and SFs throughout interviews, has already been identified in existing literature (13-15, 21, 39). Our study did not systematically assess disclosure preferences at the start and end of every interview and hence cannot confirm an increased cautiousness or decreasing interest in results. However, this study endorses an increasingly nuanced meaning of IFs' throughout interviews.

The first component of IFs' meaning structure related to result-specific qualities, including an IF's potential characteristics and consequences. With regard to an IF's potential characteristics, patients emphasised the (medical) actionability, penetrance, severity and age of onset of the IF-associated condition. These characteristics have been emphasised by patients before (14, 25) as well as by professionals in policy recommendations (7, 16). However, an accordance between both stakeholders' perspective should be perceived with caution, since they may interpret these characteristics differently.
Firstly, most participants interpreted actionability in a broad sense that largely exceeded medical interventions. The interest in personally useful results has been expressed in other patient-focussed studies but contravenes the disclosure preferences of most professionals (10, 12, 13, 18, 19, 37). Actionability was also considered dynamic and context-dependent and hence not always realisable for everyone (40). Secondly, patients valued IFs' high penetrance as an important criterion for disclosure, which is in line with international guidelines and recommendations (7, 16, 41). Nonetheless, it was considered difficult to decide on a cut-off value for penetrance, a problem which also bothers professionals (42). Thirdly, a condition's impact on family members was sometimes mentioned as an aspect of conditions' severity. This relational interpretation may be a symptomatic echoing of the IRD-associated experience that illness does not only affect the self but also others (23). Lastly, patients expressed a nuanced interpretation of the age of onset of an IF-associated condition. They assumed that the exact prediction of a disease's onset is difficult and they warned for a lifelong psychological impact of a later-onset condition.

Concerning IFs' potential consequences, patients discerned operational (or actionability-related) and psychological consequences. Throughout the interviews, many participants expressed an ambiguous idea on IFs' operational consequences. Participants seemed prompted to act on genetic information and this motivation has been confirmed in the literature (14, 17). In the second component of IFs' meaning structure (lived illness experience), the abstract character of IFs nevertheless attenuated patients' motivation to actually take preventive action, as this action was considered potentially useless (13). Some participants characterised IFs' actionability as a quality that would be mainly valuable when the IF actually results in disease. This way, IFs' presymptomatic character and patients' focus on more urgent medical concerns may result in a lower uptake of (health-related) preventive actions regarding IFs than suggested, an idea that aligns with the moderate operational impact of genetic information in general (38, 43-46). Participants' remark that there is no guaranteed success of actions may additionally weaken IFs' operational consequences. As a hypothesis, this cautiousness towards successful actions may be partially justified by symptomatic echoing and experienced confrontations with the limits of practical and psychological coping strategies for IRD.

Regarding the psychological consequences of disclosed IFs, the possibility of distress has been identified as an important motive for not wanting to know (particular) IFs in this and other studies (14, 18, 21). Several participants did not want to receive too many IFs and preferred a partly open and unknown future (17, 39). This desire may mirror some patients' preference of an uncertain IRD prognosis over the certainty of a negative prognosis. On the other hand, study participants generally trusted their own (but not always others') ability to psychologically cope with IFs (18, 19). This confidence regarding successful coping might be caused by some people's assumption, also in this study, of having a better genetic literacy than "the standard patient" (13, 18, 47). The assumption that the disclosure of IFs will be similar to the neutrally or positively experienced disclosure of diagnostic findings may support participants' confidence in psychological coping (48, 49). A retrospective study has shown that the disclosure of medically actionable SFs did not cause feelings of anxiety or distress, which confirms patients' confidence (43).

The second and third component of IFs' meaning structure do not refer to the potential IF in itself but to a patients' lived experiences and context, of which the importance and impact have already been suggested in the literature (11, 13, 23, 25, 40, 50).

The second component applies to patients' lived illness experience. Participants' symptomatic and diagnostic focus and the strategy of symptomatic echoing suggest a significant impact of lived illness experiences on the interest in and interpretation of potential IFs. Whereas a diagnostic focus may nuance patients' interest in presymptomatic and more abstract IFs, lived illness experiences may affect the interpretation of abstract IFs by a strategy of symptomatic echoing.

On the one hand, existing literature already identified patients' focus on symptomatic conditions and diagnostic test results instead of on potential IFs (13, 17, 23, 51). On the other

hand, several studies suggested that a diagnostic focus may increase patients' wish to receive IFs and SFs, especially if patients had not yet received diagnostic test results (11, 39). The diagnostic odyssey could make patients responsive to any kind of information and they might fear a reduced diagnostic yield by dismissing IFs or SFs (10, 13). Additionally, patients may hope for IFs or SFs that could be associated with their symptomatic condition and hence provide a (partial) diagnosis (19).
With one exception, our study included patients who already received diagnostic results. Still, they expressed an interest in IFs that may be relevant for their IRD-diagnosis. Hence patients' symptomatic and diagnostic focus and the disclosure of diagnostic test results should not be interpreted as elements that absolutely activate or end the interest in IFs. Rather, patients' symptomatic and diagnostic focus contribute to IFs' meaning by modifying or specifying the interest in particular IFs.
Some studies identified similar preferences regarding the disclosure of IFs and SFs among clinical patients and the general population as well as among patients with or without testing experience (12, 25). Further research is required to determine whether these similar preferences may be grounded in different motives or if the impact of lived illness experiences is less pronounced as we currently suspect.

Thirdly, IFs' meaning was affected by patients' family embedding. This family embedding seemed to have a variable relevance in different contexts.
On the one hand, a patient's family embedding could provide valuable examples for future IRD-associated experiences and for potential IFs. This means that a family history of disease could provide a preview of possible illness in both a symptomatic and presymptomatic context. In the context of presymptomatic IFs, a family history of disease could counter IFs' abstract character and stimulate patients' interest in these specific IFs. The importance of a family history of disease for people's interest in IFs has been suggested before (11, 13, 23, 25). This interest may obviously be triggered by a higher personal risk for illness. Moreover, it may be considered a family-wide variant of symptomatic echoing where not personal but family-wide symptomatic experiences reduce the abstract character of IF's potential qualities.
On the other hand, patients' family embedding seemed to be affected differently by diagnostic test results and by potential, more abstract IFs. Whereas most patients were convinced of the family-wide relevance of diagnostic test results, they were generally less aware or concerned about the family-wide relevance of potential IFs. Some patients' were interested in IFs regarding a carrier status of recessive conditions, an interest that has been observed internationally (3, 9-11), but in our study, this interest was mainly motivated by personal reproductive plans and less or not by family-wide benefits. Participants were also less inclined to inform family members about IFs, since these results may be perceived as irrelevant or unwanted. IFs' abstract character may partially explain patients' restricted awareness of IFs' potential family-wide relevance (13). Concerns about bringing bad news or causing psychological distress in family members have been identified before (17, 19, 52, 53) but

conflict with studies that reported stronger motivations to share IFs with relatives (14, 17, 19, 51).

To our knowledge, this is the first IPA-study on IFs' meaning from the perspective of adult patients with an IRD or any other Mendelian disease. Some limitations should be mentioned however. Participants were selected by genetic professionals/treating physicians. They may have excluded persons who they considered unsuitable for participation because of linguistic, psychological or other reasons. Hence a biased sample may have been recruited. Even though all participants had a lived experience of illness and/or genetic testing, IFs' meaning structure did not include actual experiences of disclosed IFs. Some participants explicitly identified this lack of experience as a barrier to an adequate meaning construction. However, the prospective interpretation of IFs' meaning will probably be similar to clinical situations where patients have to decide on disclosure before genetic results are returned. Finally, more women than men participated in this study. No gender differences were observed but the small sample and research design of this study do not allow for a meaningful identification of gender-based differences.

7.6. Conclusion

From a patient perspective, IFs have a complex meaning. This inherently affects effective counselling strategies for WES-based diagnostic testing.
Generally, counselling should not only focus on IF-specific qualities and should transcend a strictly clinical and result-centred approach. Additionally, a patient's lived illness experience and family context should also be considered. Because of the complexity of IFs' meaning, patients must be granted enough time to carefully consider IFs' potential meaning and consequences (14, 22). The context-dependence of IFs' meaning suggests personalised and dynamic counselling procedures (17).
More particularly, the different components of IFs' meaning structure may indicate some specific points of attention. Firstly, patients' nuanced interpretation of IFs' potential characteristics could justify the development of patient-based taxonomies of IFs that complement professionally designed categorisations (23). The indicated interaction between these characteristics also shows that single-dimension taxonomies may be inadequate (23, 25). Secondly, patients' broad interpretation of actionability could be an argument to enable the disclosure of medically non-actionable IFs. Patients should nevertheless be warned about the limits of actionability and the danger of a "therapeutic gap" when effective interventions are unavailable for identified risks (3, 23). Thirdly, the symptomatic and diagnostic focus suggests that patients differentiate a clinical context from a screening opportunity. Counselling procedures should acknowledge this focus but should also help patients to overcome the abstract character of IFs and make them more aware of the potential value, also for family members, of preventive actions for presymptomatic findings. Symptomatic

echoing may a useful strategy to patients but may not always be (medically) correct. Professionals have to assist patients in valid and effective strategies of symptomatic echoing and understanding.
Translating IFs' complex meaning into feasible counselling procedures is a main challenge for the future.

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7.7. References

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PART 4 DISCUSSION

Chapter 8 – DISCUSSION AND REFLECTION

8.1. Main findings

The main objective of this dissertation was to examine the practice and perspectives of genetic professionals and adult patients regarding the disclosure and (ethical) meaning of IFs and SFs in a context of NGS-based clinical genomic testing.

In chapter four, the debate on IFs and SFs was characterised as a multi-levelled discussion. International recommendations and policy documents were examined and important points of discussion were assessed at terminology, policy and value level.
At a semantic level, different terminologies for the concepts of IFs and SFs were discussed, as well as the lack of consensus and its potential consequences. At policy level, recommendations disagreed on the minimisation of IFs (by a filtering of genome-based results), the intentional search for SFs and the blurring boundary between diagnostics and screening. Also the feasibility of traditional counselling and the efficacy of alternative ways of informed consent were under discussion. Finally, respect for patient autonomy, beneficence, non-maleficence and actionability were discussed, as well as these values' relative weight. To this day, the concept of actionability resists a generally accepted definition and interpretations range from semiquantitative, individual and medical (mainly advocated by genetic professionals) to personal, family-wide, reproductive and interactive (mainly supported by lay people). Common ground is still lacking on this wide spectrum between a rigid, medical interpretation of actionability and a contextual, subjective interpretation.
The aforementioned concerns were pointed out as inherently connected and reciprocally sustaining. Without a clear terminology, policy recommendations will be vague or confusing. Without a profound reflection on ethical values, guidelines will lack a solid and effective implementation, which may result in a suboptimal organisation of care. To realise a better understanding of and more effective debate on IFs and SFs, a level-integrative approach and an explicit acknowledgement of the interaction between different levels was advocated. Moreover, a patient-inclusive perspective was encouraged as an addition to the mainly professional approach of IFs and SFs. This complementary perspective should aim to include lived experiences, qualitatively assessed meanings of IFs and SFs and a patient's particular context.

In response to this call for a more comprehensive approach to IFs and SFs, the next three chapters investigated different levels and perspectives within the debate. More specifically, two research questions have been examined:

1. How do genetic professionals in Belgian CMGs report IFs and SFs in NGS-based clinical genomic testing in adults and how do they perceive the (ethical) motives for and consequences of this disclosure?
2. How do genetically tested adult patients perceive the potential disclosure of IFs and SFs and how do they assign meaning to these potential results?

8.1.1. Reporting practices in Belgian CMGs

Chapter five addressed the first research question ("How do genetic professionals in Belgian CMGs report IFs and SFs in NGS-based clinical genomic testing in adults and how do they perceive the (ethical) motives and consequences of this disclosure?") at policy level and discussed actual reporting practices and future policies. This chapter was founded on the results of a focus group study.

Belgian CMGs have limited experience with IFs in clinical ES and currently do not support an active pursuit of SFs. Two major criteria determined professional decisions whether and how to disclose an IF: clinical significance and patient-related factors.

Reported IFs should be pathogenic and actionable but these straightforward criteria challenged a univocal interpretation and application in practice. Concerns about IFs' disease-predictive value for persons without symptoms, the difficulty to determine whether VUS are IFs or related to the symptomatic condition and dynamic variant classifications complicated the application of the pathogenicity-criterion. These challenges resulted in a difficult balance between the disclosure of clinically valuable information and physical and psychological harm that may be caused by reported results.

Most Belgian CMGs only reported medically actionable IFs. This delineation was explained as a professional duty to decide on relevant and useful information and as a pragmatic way of keeping clinical ES practically feasible. Nevertheless, this demarcation could be a difficult decision since it may deny patients potentially important information.

The second reporting criterion, i.e. patient-related factors, largely focussed on patients' preference (not) to know IFs. Belgian CMGs took a substantially different stance on patient opt-out practices. Arguments for CMGs' local opt-out policy were related to the avoidance of future disease, patients' assumed inability to make an informed decision about IFs, the influence of the local ethics committee, the potential harm caused by reported IFs and patients' fundamental right not to know. Deciding on the most suitable opt-out policy was acknowledged as a difficult issue in several CMGs.

Finally, professionals focussed on the interaction between particular patient characteristics and the clinical significance of a specific IFs. This interaction affected the final relevance of an IF and the decision whether and how this IF was reported, especially in the context of results with a reproductive value. The willingness of half of the Belgian CMGs to disclose IFs concerning a carrier status of autosomal recessive conditions questioned the interpretation of the actionability-criterion and the scope of professional responsibilities. Another consequence of the interaction between a specific IF and a particular patient was the need for professional deliberation and the tension between general guidelines and case-by-case procedures.

8.1.2. Underlying values of disclosure policies

Chapter six addressed the first research question ("How do genetic professionals in Belgian CMGs report IFs and SFs in NGS-based clinical genomic testing in adults and how do they perceive the (ethical) motives and consequences of this disclosure?") at the value level. This chapter reflected on the ethical values and principles that professionals in Belgian CMGs invoked for the disclosure of IFs and SFs.

During the focus groups, professionals frequently referred to respect for patient autonomy, professional non-maleficence and beneficence to support local disclosure policies.

Professionals invoked the value of patient autonomy to support the return of IFs. However, they also warned that patients should realise that not all health risks will be identified in a diagnostic test. Patients should better understand the possibilities and limitations of genomics, especially when more IFs or SFs may be reported in the future.

For half of the Belgian CMGs, patient autonomy was not only an argument to report IFs but also a reason to respect patients' wish to opt out of IFs. The value of professional non-maleficence and the avoidance of psychological harm could additionally support patients' opt-out choice. Nevertheless, not all centres allowed patients to opt out of medically actionable IFs. This policy was legitimised by a combination of patients' limited genetic literacy and the professional duty of beneficence. The combination of both arguments and the influence of some CMGs' local ethics committee outweighed the value of patient autonomy in three CMGs.

All Belgian CMGs extensively discussed their local policy regarding a patient opt-out. In the discussion section of chapter six, the absence of an opt-out possibility was conceptualised and critically analysed as a form of technological soft paternalism. Firstly, the general denial of patients' genetic literacy and, more fundamentally, the requirement of an absolute understanding to make informed and autonomous decisions was called into question. Secondly, a normative rationality was challenged, as well as the characterisation of a wish not to know as an emotional choice. Thirdly, the beneficent outcome of disclosed IFs as a solid justification for their mandatory reporting was discussed. Chapter six concluded with a discussion on the scope of ethical values, patient rights and professional duties. A patient's right to be informed about IFs and the spectrum of reportable IFs were limited by professional non-maleficence and by the duty not to report potentially harmful information. However, actionability-concepts that exceed the medical level and that include, for instance, personal or family-wide utility may contest this delineation of reportable results. Finally, the right to know not only IFs but also SFs was denied in all CMGs by the current delineation of professional beneficence and limited resources. Therefore, the value of distributive justice was considered an important factor in the current scope of the debate on IFs and SFs.

8.1.3. IFs' meaning from a patient perspective

Chapter seven changed perspective and addressed the second research question ("How do genetically tested adult patients perceive the potential disclosure of IFs and SFs and how do

they assign meaning to these potential results?"). Based on an IPA-study with 14 participants that had been genetically tested for an IRD, the complex meaning of IFs was described. IFs' meaning structure from a patient perspective consisted of three main components: result-specific qualities, lived illness experience and family embedding.

The result-specific qualities referred to the characteristics of the potential IF and its associated condition, as well as to the assumed consequences of disclosure. Patients particularly considered characteristics of actionability, penetrance, severity and age of onset. These characteristics were interpreted in a nuanced way that frequently exceeded the strictly medical level. Subsequently, patients mentioned possible operational and psychological consequences of disclosed IFs. These consequences were characterised as personal and context-dependent. IFs' operational consequences were associated with these findings' actionability. Patients were generally motivated to act on potentially disclosed IFs but they also mentioned several barriers for preventive actions in response to abstract information. Many patients referred to anxiety and distress as possible psychological consequences of disclosed IFs. For some, this potential distress limited the spectrum of IFs they would like to receive in favour of a partly open future. Nevertheless, most patients considered themselves able to emotionally cope with the disclosure of IFs.

The second component of IFs' meaning structure applied to the impact of patients' lived illness experience and the difference with abstract, presymptomatic information. Most patients exhaustively described the ubiquitous impact of IRD, both practically and psychologically (symptomatic experience). Regarding past experiences with genetic testing, participants emphasised their specific interest in diagnostic test results (diagnostic focus), which tempered and specified their interest in IFs. In contrast with this symptomatic and diagnostic focus, patients assigned an ambivalent statute to presymptomatic IFs as both valuable and abstract information. Patients sometimes countered IFs' abstract statute by use of a strategy of symptomatic echoing in which IFs' potential qualities echoed IRD-associated experiences (regarding, for instance, medical non-actionability).

The third component of IFs' meaning structure concerned patients' family embedding. Patients assigned a variable relevance to this family embedding in a context of symptomatic IRD or in a context of presymptomatic IFs. In a context of symptomatic IRD, a patient's family embedding was deemed relevant in terms of an IRD-associated recurrence risk. This recurrence risk had motivated most participants to inform family members about IRD-associated genetic test results. In a context of presymptomatic IFs, however, patients would be less concerned about diseases' recurrence risk. Patients were generally less concerned about the family-wide relevance of IFs, which affected their motivation to inform relatives about potentially identified IFs. This disclosure was assumed to be challenging and possibly unwanted.

Overall, IFs' complex, context-dependent meaning called for personalised counselling procedures that transcend a strictly clinical and result-centred approach.

8.2. Reflection

Recalling the prologue and the introduction of this dissertation, it may be questioned again whether IFs and SFs may be an opportunity to unleash the creature of Hope from Pandora's box, and if so, how this release is to be realised in an effective, efficient and ethical way. How should identified IFs or SFs be interpreted? Which results can or should be reported? And what may be the meaning and consequences of these results' disclosure?

These questions were partially answered in reference to important criteria, meaning components and values that have been identified and discussed throughout this dissertation, but definite and ready-made answers remain difficult to articulate. The results of the empirical research (as described in chapters five, six and seven) showed how professionals' and patients' perspectives on IFs and SFs are complex and multi-layered. IFs' meaning from a patient perspective results from a complex interaction between various components, including both IF-related qualities and personal, context-dependent elements. Genetic professionals decide on the disclosure of IFs based on criteria of pathogenicity and actionability which are challenging to interpret and to apply in practice. Moreover, IF-related factors interact with patient-related factors and may affect whether an IF is considered relevant and how it is reported. Ethical values of patient autonomy, professional beneficence, non-maleficence and justice may be invoked to support specific policies but these values frequently conflict and their interpretation is challenged in the context of clinical genomic medicine.

Overall, this dissertation revealed nuance and ambiguity in both the professional and patient perspective and experience. Hence, it emphasised the complexity of questions on an effective and ethical disclosure as such and it identified a fundamental uncertainty. When IFs and SFs are an urgent reality that genetic professionals and patients need to cope with in the current clinic, this may evoke a tendency to hide uncertainty and emphasise what is actually understood or what is considered standard knowledge (1).

This general discussion will, however, explicitly acknowledge and thoroughly reflect on the uncertainty that accompanies IFs and SFs. Consequently, uncertainty will be challenged as a necessarily negative or paralysing concept. Should uncertainty be solved before an efficient policy on IFs and SFs can be realised? Or can uncertainty be included as a workable tool in an effective and ethical policy? In this discussion, an explicit analysis of uncertainty in IFs and SFs will indicate possible ways to answer this last question in the affirmative.

8.2.1. A characterisation of uncertainty in IFs and SFs

Complexity and uncertainty are neither unique to IFs and SFs, nor to the domain of genetics and genomics (1-5). A vast amount of literature has been published on medical risk assessment, the communication of probabilities in a healthcare setting and the impact of a patient's particular context on the interpretation of clinical information (6). An exhaustive analysis of genomic or medical uncertainty is beyond the scope of this dissertation but the

taxonomy of uncertainty by Han et al. may support a reflection on the overall results of this dissertation.

In 2011, Han et al. designed a conceptual taxonomy of medical uncertainty. Uncertainty was defined as a "metacognition" and as a conscious awareness of incomplete knowledge that may result in feelings of for instance indeterminacy and doubt (6-8). It was described as a non-monolithic phenomenon that exists in multiple varieties and that can result in a wide spectrum of effects (6). Han et al. wanted to create a framework of uncertainty that was both broad enough to include various types of uncertainty (as experienced in different stakeholders) and detailed enough to clearly distinguish these different types of uncertainty (6).

In the taxonomy of Han et al., medical uncertainty is classified on three dimensions: locus, source and issue (6, 7). The *locus* of uncertainty applies to the particular stakeholder who experiences the uncertainty (7). The *source* of uncertainty is characterised as the cause or fundamental reason for uncertainty (7). This source contains three main components: probability (a phenomenon's fundamental, first-order indeterminacy or the inherent indeterminacy of future outcomes, also called "aleatory uncertainty"), ambiguity (a second-order and epistemic uncertainty caused by unavailable, inadequate or imprecise information) and complexity (uncertainty caused by features of the phenomenon or information itself that complicate understanding, for instance a multiplicity of potential outcomes) (6, 9). Finally, the *issue* of uncertainty is defined as the manifestation, outcome or situation to which the uncertainty applies. This issue can be scientific (including uncertainties about diagnosis, prognosis or treatment), personal (including psychosocial and existential uncertainties) or practical (including uncertainties about the structure of healthcare and about the procedures to access healthcare) (6).
In 2017, Han et al. specifically applied the taxonomy of medical uncertainty to a context of clinical exome sequencing (7). Many components of the source and issue dimensions were refined by adding one or two more levels of additional components (7).

It is not the aim of this discussion to force all of this dissertation's results into the taxonomy of uncertainty. Rather, this taxonomy is an opportunity to better understand the complexity of IFs and SFs and, eventually, to discover possible ways to effectively cope with these results and their inherent uncertainty.
Since Belgian CMGs do not actively pursue SFs and only report IFs when these are accidentally identified by NGS-based clinical genomic testing, this reflection will mainly but not exclusively focus on IFs. To do so, the 2017 taxonomy of medical uncertainties in clinical genome sequencing of Han et al. (7) is applied to a level of detail that is considered necessary and suitable for this discussion (Figure 3).

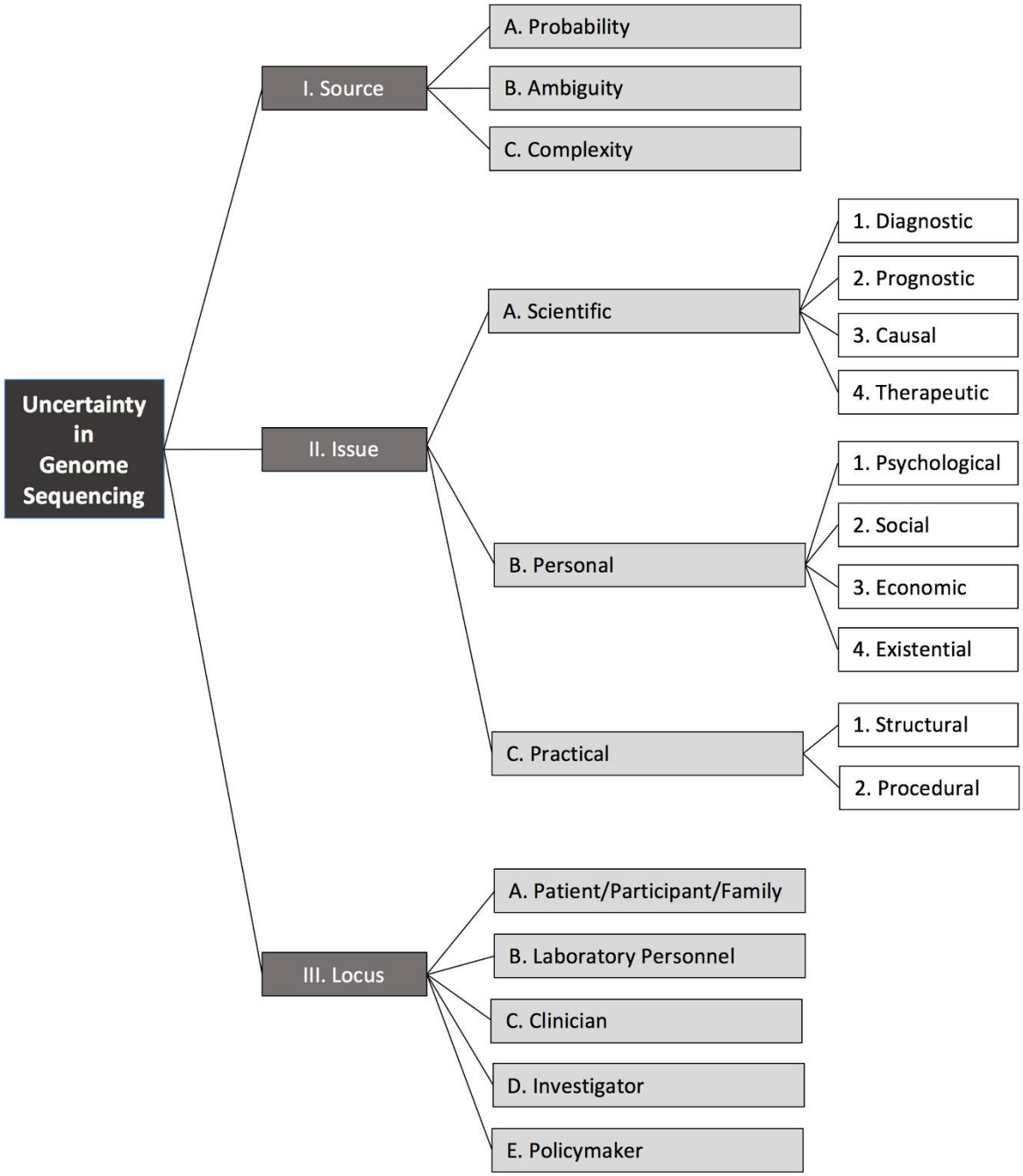

Figure 3 A taxonomy of medical uncertainties in clinical genomic sequencing

In what follows, the taxonomy of Han et al. will be used to more explicitly articulate the uncertainty that has been identified throughout this dissertation. More specifically, uncertainties regarding pathogenicity, the non-standardised relevance of results, actionability and lived experiences will be discussed.

a. Source and issue uncertainty regarding pathogenicity

The study in Belgian CMGs on actual reporting practices for IFs and SFs showed various challenges for a correct interpretation of identified IFs. In this interpretation, genetic professionals were confronted with various causes of uncertainty in IFs (source uncertainty) and uncertain effects of IFs (issue uncertainty).

The reporting criterion of pathogenicity was a first area in which these source and issue uncertainties clearly emerged.
Source uncertainty is intrinsic to IFs as well as to any presymptomatic genetic result, since these findings concern risk assessments (inherently including probability uncertainty) instead of instant diagnoses of actual pathologies.
Additionally, IFs are usually "genotype first" results, which implies that these results have to be interpreted in the absence of the associated phenotype or clinical symptoms, a difficulty which was also mentioned in Belgian CMGs (10, 11). A variant's pathogenicity is usually assessed in cohorts of persons with a personal or family history of the associated disease but less is known about a variant's predictive value for persons without associated symptoms (10, 12-21). IFs' pathogenicity, penetrance and expressivity in unaffected or low-risk persons are still vigorously debated and it is still unclear whether IFs can be classified in the same way as diagnostic results of patients with associated symptoms (10, 20, 22-24). Also IFs' predictive value for populations with a paucity of genomic reference data is still discussed (25). This lack of scientific knowledge about IFs' predictive value enhances IFs' source uncertainty in terms of ambiguity (7).

Very recently, the ACMG and the Clinical Genome Resource have published new recommendations on the interpretation and reporting of constitutional copy-number variants (CNVs)(26). CNVs, including deletions, duplications and triplications, can contribute to the development of diseases such as intellectual disability or autism spectrum disorder but their interpretation is challenging. To support consistent interpretation and reporting practices across different laboratories, a semiquantitative point-based scoring system has been developed, based on the most relevant evidence categories for CNV classification (including, for instance, genomic content, predicted functional effect and evidence from case and control databases). Grounded on the sum of the point values assigned to each evidence category, a CNV is classified as pathogenic, likely pathogenic, of uncertain significance, likely benign or benign, which aligns with previously published sequence variant interpretation guidelines (22). The CNV interpretation recommendations also apply to IFs and SFs and the authors emphasise the importance of classifying CNVs irrespective of the reason for testing. In other words: CNVs with diagnostic relevance and CNVs that were identified as IFs or SFs should be classified in the same way and the same variant should be classified consistently across different patients. A person's phenotype may be taken into account when applying the scoring system but the pathogenic classification should not be solely grounded on someone's

phenotype; instead, variant classification and clinical significance should be considered uncoupled assessments (26).
Nevertheless, the authors warn that even this semiquantitative scoring system may not be able to fully resolve IFs' source uncertainty, since it is not an absolute algorithm that can be applied to all scenarios. It can function as a guide but it does not eliminate the need for sound professional judgement in the evaluation of evidence and in the assessment of a classification. Moreover, changes in technology, scientific evidence and professional experience may require updates of the semiquantitative scoring system (26).

IFs' source uncertainty results in uncertain diagnostic or prognostic consequences, which are specific types of scientific issue uncertainty (7). Because of this scientific uncertainty, genetic professionals repeatedly warned for the interpretation of IFs and SFs as false positives in persons without symptoms (27-30). This cautiousness has been supported by research that identified a difference between the higher amount of identified pathogenic variants in research populations and the lower prevalence of the associated condition in the general population (10). To avoid over-interpretation, laboratories generally do not report VUS IFs to the referring clinician, a practice which aligns with the ACMG recommendations (23, 31-33). Yet, even when an IF has been identified as a (likely) pathogenic variant in a known disease gene, the person's actual diagnosis and prognosis may be uncertain (34).

Conversely, the analysis of additional genes may not be of the same quality as the analysis of primary results in a diagnostic context. Because of this source uncertainty (caused by ambiguity and, more specifically, test limitations), negative results regarding IFs or SFs do not necessarily guarantee an absence of additional pathogenic variants and additional risks (23, 35). This lack of guarantee prompted Christenhusz et al. to perceive an identified IF as un unintentional bonus by virtue of the used test whereas no conclusions should be drawn from the non-identification of IFs (35).

The risk of false positive and false negative results and the general pathogenic uncertainty of IFs and SFs imply that these results' potential benefits and risks are still uncertain (15, 23, 34). Holtzman therefore advised to think of IFs and SFs merely as potential research material (28).

b. Uncertainty because of non-standardised relevance

The focus group study in Belgian CMGs identified that the uncertain interpretation of IFs is not only caused by result-specific qualities but also by the interaction between the specific IF and the particular patient. This interaction results in a non-standardized relevance of IFs.
In the taxonomy of Han et al., this patient-specific and context-dependent interpretation of IFs may be categorised as source uncertainties of ambiguity and complexity that may be caused by a patient's family history of disease, the interaction between a patient's symptomatic condition and the IF or a patient's reproductive plans. It results – on the issue

dimension – in scientific diagnostic or prognostic uncertainty and in personal uncertainty regarding, for instance, the relevance of an IF for a patient's family members or for a patient's desire to have children.
To manage these uncertainties, professionals of Belgian CMGs emphasised the importance of professional deliberation. This call for patient-specific deliberations contrasts with another internationally suggested solution for IFs' interpretative uncertainty, namely more guidelines on the disclosure of IFs and SFs (13, 36-40). Clinical and laboratory geneticists and genetic counsellors have called for more (detailed) guidelines on reportable results and on IFs' pathogenicity, a request also expressed in Belgian CMGs (3, 31, 37, 41).

General guidelines may facilitate a more uniform disclosure practice, both within a clinical institute and across different CMGs. At least at the local level of a particular CMG, it may be recommended to develop a guiding framework on the disclosure of IFs and SFs which is clearly communicated to patients before testing. In terms of efficiency, it relieves professionals from the burden to individually decide on every case of IFs. In terms of justice and patient autonomy, it creates similar opportunities to receive relevant IFs or to decline unwanted information. If different CMGs develop different policy frameworks (which currently is the case in Belgium), it is quintessential for CMGs to be transparent about their disclosure practices since, in that case, patients' rights to know and not to know are already affected by the choice of a specific CMG (39).

Nevertheless, the development of general guidelines – also within a particular genetic centre – will be hindered by the problematic interpretation of important concepts and criteria, such as medical relevance or actionability, and by the dynamic nature of scientific knowledge and variant interpretation (29). Moreover, as a consequence of the aforementioned interaction between genetic test results' relevance and a patient's personal and contextual characteristics, standard guidelines will not be able - both within and across CMGs - to eliminate the need for professional deliberation (39, 42). A context-specific, case-by-case and flexible application of guidelines and professional experience, expertise and judgement may result in non-standardised outcomes and remains indispensable in complex medical situations that resist rigid "one model fits all" policies (3, 13, 31, 37, 39, 43, 44). Such a case-by-case approach, in which guidelines are combined with personal and contextual detail, should not be interpreted as a relativistic approach but as an approach that values the particularities of a situation and the specific needs of an individual (45).

Professional deliberation may also alleviate situations where an identified IF exceeds the treating physician's expertise (20, 29, 46-48). Because of her specific expertise, a physician may not realise or, instead, overestimate the importance of an IF, which may result in suboptimal disclosure practices or improperly counselled patients (29, 47, 49, 50).

c. Issue uncertainty regarding actionability

The concept of (medical) actionability was central to each chapter of this dissertation. Nevertheless, the lack of a straightforward and definite interpretation of this concept was illustrated in the discussions in Belgian CMGs as well as in patient interviews. Since both professionals and patients expressed concerns about this criterion's interpretation, the uncertainty in actionability applies to the *loci* of both stakeholders.
To this day, the interpretation of actionability as a criterion for the disclosure of IFs is mainly or even exclusively decided upon by genetic professionals. From a patient perspective, however, the professional interpretation of actionability may be too broad or too narrow.

On the one hand, the professional interpretation of actionability may be too broad. The theoretical availability of a medical and personal intervention may not equal a patient's ability to realise this action, since actions may be out of reach for a variety of personal, social or financial reasons (51, 52). Hence, even if effective interventions are available, patients may not have access to these potentially beneficent interventions (53). These practically inaccessible actions and interventions are frequently illustrated in the public debate, for instance in the recent cases of "babies Pia and Victor", children with muscle disease SMA1 who needed a medicine with a cost of 1,9 million euro. Several participants in the patient interviews mentioned the context-dependence of actionability, which indicates their acknowledgement of actionability-related uncertainty. On the issue dimension in the taxonomy of Han et al., this uncertainty can be categorised as practical uncertainty (is an intervention or action available in the current healthcare system?) and as personal uncertainty (is an intervention or action available because of personal, economic or social reasons?) (Figure 3)(7).
Another reason why the professional interpretation of actionability may be too broad, is related to the potential impact and consequences of interventions. An IF regarding a pathogenic variant in the *BRCA1*-gene allows a preventive mastectomy to minimise the increased risk for breast cancer. This is, however, a radical intervention and a patient may value its impact as too substantial, especially in combination with the experience of a symptomatic disease, and classify this action as unsuitable (14, 34, 54). Alternative actions such as a regular follow-up with mammograms are available, but what if the patient's clinician promotes a preventive mastectomy as the most efficient risk reduction? And what if clinical interventions do not have the same effect on people who carry a genetic variant but have no symptoms yet (34)? In the taxonomy of Han et al., these questions refer to therapeutic uncertainty: which intervention is most suitable in response to an IF and who (or which *locus*) determines this?

Personal, practical and therapeutic uncertainties concerning the actionability of an IF may not be sufficient reasons for not reporting the result. Professionals may be unable to correctly assess a patient's ability or preference to act and patients should be allowed to make their

own assessment of personally, practically and financially feasible actions. However, uncertainties concerning an IF's actionability should be acknowledged as potential obstacles in the realisation of a finding's actionability. Neither the actionable nature of IFs, nor the mandatory disclosure of results can actually oblige patients to take any kind of action (55, 56). Consequently, the benefit of a reported IF may be undone when the patient is not able to or refuses to take action (11).
People seem to make a distinction between the value of knowing actionable information and truly acting on this information in a presymptomatic context (57-60). A similar limited effect has generally been observed concerning people's lifestyle changes in response to genetic risk information (61). Various participants of the interview study also expressed a dilemma between the motivation to take action regarding potentially identified IFs and the ambivalent value of preventive actions in response to presymptomatic results. Several patients mentioned how results' actionability lacks a guarantee of success, a concern about the context-dependence of actionability that has been identified before and that, more fundamentally, may be influenced by the difficulty to change people's risk perceptions and disease beliefs (61-63). This emphasises the therapeutic uncertainty in actionable IFs and the patient-experienced personal uncertainty regarding possible consequences of disclosed IFs. Research should further examine patients' interpretation of IFs' actionability to avoid an asymmetry between their interpretations and professional expectations.

On the other hand, it has been suggested throughout this dissertation that, from a patient perspective, the professional interpretation of actionability may be too narrow.
From the professional perspective, medical actionability has become a key criterion for disclosure (34, 40, 42). This criterion can be both a necessary condition for disclosure (only medically actionable IFs can be reported) and a sufficient condition for disclosure (medically actionable IFs will be mandatorily reported). In such policies, the values of clinical wellbeing and medical beneficence are assessed as major values in people's life (64, 65).
If, however, IFs' medical actionability is challenged by therapeutic, personal or practical uncertainty, the privileged status of this criterion may be questioned. Moreover, most participants of the patient interview study seemed to dismiss a strict delineation between medically actionable and medically non-actionable IFs and they interpreted actionability in a broad sense, which is in line with international research (44, 63, 66-69). Patients' interest in medically non-actionable IFs may also be motivated by their dynamic and hence non-deterministic and uncertain interpretation of actionability: what is not actionable today, may be so tomorrow. This dynamic interpretation aligns with people's previously identified motivation to receive IFs out of fear to miss out on potentially useful information (70).

The difference between professionals' and patients' interpretation of actionability instigated several researchers to move beyond the professional monopoly on the interpretation of actionability and to increasingly include patient perspectives in reporting criteria for IFs and SFs (49, 71-73).

As mentioned in chapters four and five, considering personal utility as a criterion for disclosure may also raise problems (73). Actionability may become an unspecified umbrella concept and stimulate a trend towards the disclosure of any result (74, 75). Counselling patients about personally useful results may also become very complex and it should be considered whether the costs of interpreting and reporting personally useful results can be outweighed by their potential benefit (76, 77). Patients may overestimate the actionability of personally useful IFs and the ability to control one's health (44, 78).
Because of the interpretative difficulties regarding actionability, it has been suggested to completely discard the criterion of actionability as a threshold for reportable IFs in a context of adult testing (51). Instead, IFs' (likely) pathogenic impact may be a sufficient reason for disclosure (51, 52).

d. Experience-based uncertainty

Besides' patients' experience of uncertainty concerning IFs' actionability, they also seemed to experience a more comprehensive type of uncertainty. This may be explained by a short reference to the prologue and introduction of this dissertation. The myth of Pandora was discussed as an illustration of the genomic paradigm shift that may currently take place in medicine (79, 80). IFs in NGS-based genomic testing could be an ideal opportunity for a gradual transfer from the old to the new paradigm. The indication for testing is still situated in the old, diagnostically focussed paradigm while simultaneously, the genome-wide test creates the opportunity to enter the new and more holistic paradigm. Most patients who were included in the interview study were interested in partially realising the paradigm shift and they wanted to receive (some) diagnostically unrelated information when considered personally valuable.

However, the paradigm shift also needs to be nuanced. NGS-based genomic testing may allow for new and more holistic answers but they are also valued for possible answers to more traditional and diagnostically focussed questions (81). This idea was confirmed by the interviewed patients' nuanced interpretation of and interest in IFs. Patients did not merely ground their interpretation of IFs in result-specific qualities but also in illness- and family related components. Also in the existing literature, is has been suggested that disease-specific elements and personal or medical concerns, hence lived (illness) experiences and context, may affect patients' interest in and interpretation of IFs (29, 61, 63, 65, 68, 69, 82-86). This compound meaning structure of IFs may be considered an empirical elaboration of Christenhusz et al.'s emphasis on a patients' health context and family history for the interpretation of IFs (65).
Because of patients' lived experience of illness and their (family) embedding, they have more and nuanced knowledge about the potential meaning and impact of IFs on their personal life (62, 80, 87, 88). It is exactly this expertise at a personal, psychological and family level that may cause feelings of uncertainty towards the meaning of potential IFs: lived experiences and detailed knowledge about one's personal context generate a greater awareness of elements

that may affect IFs' impact. This was reflected in nuanced and non-deterministic interpretations of possible IFs, for instance regarding these results' psychological, operational and therapeutic effects, and, consequently, in a modest patient interest in these findings. In the categorisation of Han et al., this nuanced interpretation of possible effects can be associated with personal, practical and scientific (therapeutic) uncertainty regarding IFs' effects.
Patients' acknowledgement of uncertainty in IFs, grounded on their expertise in their own experiences and context, is similar to the way genetic professionals are more aware of uncertain scientific interpretations and consequences of IFs precisely because of their scientific expertise. The patient experience of uncertainty in IFs also aligns with lay people's general acceptance of a certain degree of uncertainty in genomic test results and with a bio-medical-psycho-social approach of genetic information (9, 48, 57, 63, 89-93).

Additional reasons besides patients' personal, practical and family expertise may support their nuanced interpretation of potential IFs and their experience of uncertainty.
Firstly, particular elements of lived illness experiences may affect the interpretation of potential IFs, an idea which has been suggested before and which took a central place in the results of the patient interviews (62, 63, 94). Specifically with regard to the concept of uncertainty, it may be questioned whether patients' acknowledgement of uncertainty in IFs could be realised by a strategy of symptomatic echoing. Because of patients' lived experience of illness and genetic testing, they are familiar with some characteristics of genetic test results and information. All interviewed patients but one experienced living with IRD, a blinding disease with an ubiquitous impact and unpredictable prognosis. The receipt of diagnostic genetic test results was experienced positively but it did not fundamentally change or relieve patients' experience, neither did it allow for a more specific prognosis or a treatment on short notice. The experience of the modest or neutral impact of genetic test results may be projected on possible IFs and withhold patients from an over-interpretation (95, 96). Most patients desire the return of specific IFs but the modest impact of diagnostic test results on their illness experience may nuance these results' interpretation and induce an experience-based uncertainty concerning IFs.
This hypothesis of the projection of IRD-experienced uncertainty on possible IFs suggests that symptomatic echoing functions in two opposite ways: it aims to solve the abstract meaning of IFs and it results in a nuanced interpretation of IFs because of experience-based uncertainty regarding genetic test results.

Secondly, a nuanced and uncertain interpretation of IFs may, for some patients, be supported by certain feelings of hope or positive opportunities that are allowed by uncertainty (3, 9). For instance, when there is a 20 to 60 percent chance of disease, patients may emphasise "the better end" of the spectrum (8). This inclination was also perceived in chapter seven where some patients preferred a vague IRD prognosis over a definite negative prognosis. It also aligns with many people's general preference of ignorance over knowledge when it comes to

negative things that may happen and with the idea that uncertainty is the price some people are willing to pay for more autonomy (97, 98).

Finally, several participants of the patient interview study preferred an open, unknown and hence uncertain future and a certain degree of "genetic ignorance" (87). This recognition of and preference for a certain degree of uncertainty in life may be associated with an acknowledgement of fundamental probability uncertainty in Han et al.'s taxonomy of uncertainty (7, 99). It may further support the nuanced interpretation of IFs and temper the interest in IFs and especially in SFs. Health, illness and life cannot be fully predicted, some uncertainty is unavoidable in the human condition and for many people, this is how it should be (9, 54, 60, 100).

8.2.2. Consequences of uncertainty

Throughout this dissertation, many issues and (ethical) problems have been discussed that were related to and affected by the types of uncertainty in IFs and SFs as described above. Two examples concern the concept of binning systems for IFs and SFs and the ethical values that may support specific disclosure policies.

Firstly, in the introduction and in chapter four, the binning system of Berg et al. was mentioned as one of the earliest suggestions for a more standardised disclosure of IFs (101). Almost ten years after Berg et al.'s initial binning framework, its core idea is still frequently suggested as an efficient way to structure genetic counselling sessions and informed consent procedures regarding IFs and SFs (30, 102, 103). Nevertheless, the uncertain pathogenicity and actionability of IFs and SFs, as well as the divergent professional and patient perspectives hinder consistent binning procedures and impede the use of counselling and consent strategies that are based on these procedures (24, 63, 104).

Secondly, as described in chapter six, the uncertain pathogenicity and actionability and the context-dependent relevance of IFs and SFs may affect the ethical arguments for specific disclosure policies. When an IF holds an excessive degree of uncertainty, its value for the realisation of professional non-maleficence and beneficence may be questioned, especially in case of a mandatory disclosure (105, 106). The uncertainty surrounding many IFs prompted Hofmann to reject the validity of arguments concerning a right (not) to know or a duty to know in a context of IFs (107). Hofmann claimed that many IFs are merely data and they do not provide knowledge, hence arguments which refer to the potential value or risks of knowledge do not apply to IFs (107).
Analogously, the benefits that may be realised by an active pursuit of SFs depend on the (uncertain) meaning of diagnostically unrelated test results. As also discussed in Belgian CMGs, elements such as increasing resources, societal evolution and scientific progress may support professionals' responsibility or even duty to actively pursue SFs (108). To this day, however, it

is still unclear whether the required resources for opportunistic screening can be outweighed by its realised benefits and whether a practice of SFs can meet the criteria concerning proportionality and distributive justice (14, 69, 88, 109).

8.2.3. Different perspectives on uncertainty

An application of Han et al.'s taxonomy of genomic uncertainty to the interpretation of IFs by Belgian genetic professionals and patients shows that both stakeholders experience uncertainty in IFs but not always in an identical way (3, 7).

Genetic professionals were concerned about the pathogenic interpretation of IFs and its diagnostic, prognostic, reproductive and therapeutic consequences. Additionally, they experienced uncertainty because of the interaction between a specific IF and the particular patient and the non-standardised outcome of this interaction for an IF's final relevance. Professionals were aware of these uncertainties because of their role-specific, scientific expertise and they may aim to solve these uncertainties by medical and scientific progress, additional guidelines or professional deliberation. These types of professionally experienced uncertainty correspond with the assumption of Han et al. and with prior observations that professionals will generally be more aware of different sources of uncertainty (especially regarding ambiguity and complexity) and scientific (diagnostic and prognostic) issues of uncertainty (3, 7).
Patients, however, expressed IF-associated uncertainties related to a fundamental and inherent unpredictability of health, illness and life and these uncertainties were reflected in non-deterministic interpretations of IFs' potential characteristics and consequences. Patients may be aware of these uncertainties in IFs because of lived experiences of illness and genetic testing and because of their personal context and embedding. These experiences of uncertainty correspond with Han et al.'s assumption that patients will be more aware of fundamental probability uncertainty and more concerned about personal and practical issues of uncertainty (7).
Summarised, whereas genetic professionals were more aware of epistemic causes and scientific consequences of uncertainty, patients mainly focussed on the lived experience of uncertainty and personal and practical consequences of uncertainty (62).

Professionals' and patients' divergent experiences of uncertainty in the interpretation of IFs may be easily explained by their different roles but may nevertheless hinder a mutual understanding of IFs (71). Therefore, this discussion not only aims to identify specific types of uncertainty but also to investigate whether these uncertainties may be integrated as workable tools in an effective and ethical policy on IFs and SFs. As a first step towards an affirmative answer, we advocate a rapprochement of professional and patient-experienced uncertainties.

8.2.4. A rapprochement of uncertainties

Professional and patient-experienced uncertainties do not necessarily turn IFs and SFs into invaluable, threatening or unreportable information, since valuable and workable information does not require an absolute certainty. Medicine inherently takes place in a context of uncertainty and in this realm, both professionals and patients need to make decisions and take action despite a spectrum of unavoidable doubts (8).
To allow for ethical decisions and actions that can be supported by both professionals and patients, it is nevertheless important that this uncertainty is explicitly acknowledged, not only at a theoretical level but also in the practical realm of genetic consults. Genetic professionals and patients should become aware of and try to understand each other's experience of uncertainty, as well as each other's role-specific expertise (6-8). This way, both stakeholders' expertise and uncertainty could become explicitly shared experiences.

a. Professional expertise and modesty

A US-based study of 2010 indicated that a majority of the general population holds strong misunderstandings about basic genetic concepts (110). Consequently, genetic concepts such as whole genome sequencing, IFs or SFs may be difficult to comprehend (44, 85). People's genetic illiteracy and their awareness of what is already known and understood in genomics have been a general concern among professionals (29, 40, 57, 89, 111).
Another part of patients' genetic illiteracy may apply to their rather limited interest in the technical and clinical validity of test results and their unawareness (on the source and issue dimensions) of epistemic and scientific uncertainty in the professional interpretation of genetic test results (4, 18). They also may not realise that they are not aware of this professional uncertainty and hence suffer from "meta-ignorance" (6). This part of patients' illiteracy concerns an ignorance in terms of what is (still) impossible to know and understand in genomic medicine.

Both types of patients' genetic illiteracy may have their consequences. Firstly, people's "meta-ignorance" about what is not yet understood in genomics may result in unrealistic expectations and an optimistic bias towards genomic information in which potential harm is downsized and potential benefit is emphasised (71, 90, 111). Patients' ignorance about genomic uncertainty and their optimistic bias may partly explain their wish to receive a broad range of IFs, including medically non-actionable results or even VUS IFs (29, 46).
Secondly, patients' limited genetic literacy affects the spectrum of results and options they are offered. Various professionals of Belgian CMGs described how patients may not be able to understand and cope with specific types of IFs and how therefore these results are not offered (for instance medically-non-actionable results). One of the most significant consequences of patients' assumed inability to understand the meaning of genomic results regarded the absence of an opt-out possibility of medically actionable IFs. Chapter six

thoroughly discussed this practice in some Belgian CMGs in terms of a technological soft paternalism.

Genetic professionals have an epistemic, scientific and role-specific expertise, including knowledge of what is already understood and what is not yet understood regarding genomics and IFs (7, 65). Based on this role-specific expertise, professionals should try to increase patients' genetic literacy and counter their ignorance about the meaning and potential impact of IFs (99). Moreover, this education should counter patients' meta-ignorance and inform them about what is not (yet) known about genetic test results (6, 7, 65, 112). This implies that professionals should not only invest in traditional patient education but should also allow an "epistemic modesty" in their communication with patients, both during pre- and post-test counselling (4, 65). They should explicitly acknowledge that IFs' meaning and potential consequences may be hard to understand and predict, also for genetic professionals (36, 113).

Professional modesty is an act of transparency that may set realistic patient expectations about the (practical) value of potential results and that may, therefore, result in more informed patient decisions (1, 3, 4, 111, 114). Equally important, professional modesty is an act of respect and honesty towards patients (5). It turns uncertainty into an explicitly shared experience and it may reduce the knowledge gap and disparity between patients and professionals (5). By realising that uncertainty is not only a personal but also a professional experience, patients may feel more aligned with professionals and more supported in their choices. When, for instance, a patient chooses to opt out of IFs, the awareness of professional uncertainty may support this choice as not merely grounded in patient autonomy but also in professional non-maleficence (115). This may relieve patients from the feeling of an exclusive responsibility for the choice made (116). Or, in terms of Fenwick et al., a mutual acknowledgement of uncertainty may indicate that a non-disclosure of IFs should not necessarily be equated to a refusal to rescue or be rescued; since the implications of many IFs are still uncertain, it is still unclear whether their disclosure can be perceived as a professional realisation of a rescue obligation (117).

Counselling, patient education and professional, epistemic modesty will (and should) not turn patients into genomic experts with a scientific and technical knowledge that equals professional competence; compared to patients, genetic professionals will always have an expertise which is inherent to any clinical relationship between professionals and patients, especially in a context of complex information such as genomics (111, 118, 119).
Therefore, the professional expertise on various source and issue uncertainties in IFs may allow genetic professionals to decide on a bottom threshold for reportable IFs. Their expertise on what is both known and still unknown allows them to ensure that reportable IFs meet certain epistemic and scientific criteria - such as clinical validity or relevance - or do not exceed a certain level of uncertainty, for instance regarding ambiguity or complexity uncertainty. If patients desire to receive IFs that do not meet these criteria (for instance VUS IFs or IFs

regarding ancestry or non-paternity), their wish may be declined by professionals' expertise (120, 121). This corresponds with the suggestion that technical and practical factors regarding IFs (for instance IFs' technical or clinical validity) should precede ethical issues (for instance a patient's wish to know) (99). It also accords with professionals' idea that patient preferences may guide disclosure decisions but only as long as these preferences are "reasonable" (24, 71, 122). Nevertheless, the idea of a bottom threshold for reportable IFs based on professionals' specific, clinical expertise conflicts with the perspective of Schaefer and Savulescu. They claimed that if non-clinical interests may support people's right not to know, these interests should also support the right to know and hence allow for the disclosure of IFs because of personal, non-clinical reasons (123). Schaefer and Savulescu defended this idea within a research context, followed by the idea that research participants may also receive information they may misunderstand without further professional counselling if they explicitly agree to this (123). However, such a practice in which patients receive unclear information without any support, is hard-to-defend in a context of clinical care and a rapprochement between professionals and patients.

Finally, some participants of the interview study expressed an appreciation of a fundamental uncertainty and unpredictability of life. Therefore, it may be valuable to pay explicit attention to the most fundamental component of source uncertainty in genomic and medical information, i.e. probability (8). A professional may explain that medical probabilities do not literally represent a person's chance of a single outcome - for instance concerning an IF's penetrance or the success rate of a treatment (8). Probabilities are based on an aggregation of past outcomes whereas the specific characteristics of every individual make future outcomes fundamentally unknown and unpredictable (8). A more explicit acknowledgement of inherent medical uncertainty may help patients to better understand uncertainties which they have personally experienced (124).

b. Patient expertise and contextualised uncertainty

Professional, epistemic modesty regarding IFs mainly applies to the nature and effect of the genetic test result *per se*. Elements concerning a patient's illness and family history may be taken into account as modifying factors for an IF's clinical impact, but professionals may be less able to assess the potential impact of a disclosed IF on patients' lived (illness) experience or family embedding. In terms of IFs' compound meaning structure from a patient perspective, this indicates that genetic professionals may be experts in IFs' first meaning component (result-specific qualities) but not necessarily in IFs' other two meaning components (lived illness experience and family embedding). Hence, in the meaning components of IFs that exceed the clinical nature of the result, in may be patients and not professionals who are the expert (125). As described above, it is exactly this expertise and this awareness of the practical and personal consequences of IFs that may confront patients with uncertainty in IFs.

In analogy with patients' genetic illiteracy, professionals may be illiterate and even meta-ignorant concerning patients' personally experienced and contextualised uncertainty (6). Therefore, professional, epistemic modesty does not only require the acknowledgement of professional uncertainty at a scientific level but also at a level of patients' lived experience and context (65). Just like professionals should share both their expertise and uncertainty during genetic consults, patients should share their expertise at a personal and embedded level, as well as their associated experiences of uncertainty regarding IFs (7). Christenhusz et al. described this attention for a patient's particular experience as "making room for the patient's story" during counselling and consent procedures (65). In a context of uncertain information, personal and embedded values that transcend the clinical level may be especially important (5).

By sharing this personal expertise and uncertainty, professionals should recognise how patients' (illness) context and (family) embedding can affect the interpretation of IFs and, consequently, how different patients can react differently to IFs (18, 36, 49, 54, 87, 104). The inclusion of patients' personal meaning structure, experiences and context intrinsically suggests a tailored, case-by-case counselling approach (14, 37, 39, 91, 111, 114).

Christenhusz et al. did not consider "making room for the patient's story" equivalent to the absolute respect for a patient's choice regarding the disclosure or non-disclosure of IFs (65). In a true rapprochement between patients and genetic professionals, however, equal weight could be given to both stakeholders' expertise and uncertainty. "Making room for the patient's story" without acknowledging that this story may contain strong and sufficient arguments for a patient's preference not to know particular IFs, may not respect the patient as a full member in the rapprochement-process (103). Instead, it could result in a favouring of professional expertise and authority and in a prioritising of the clinical component of IFs' meaning structure over personal and contextualised components (65).

Hence, acknowledging patients as full members in the rapprochement-process implies their right to opt out of IFs, even if these results are supported by criteria of clinical validity, severity, penetrance and actionability or values such as professional beneficence. Whereas scientific expertise may allow professionals to decide on a bottom threshold for reportable results, expertise in lived illness experiences and family embedding may allow patients to decide on an upper threshold of reported results.

Patients' unconditional right to opt out of IFs has been advocated previously (51, 100, 103, 126). This policy is supported by the idea that no one can be obliged to learn genetic information against her will, not even when this information has an immediate clinical utility and may be lifesaving (21, 27, 52, 102, 103). Contrary to Vayena's and Tasioulas' idea, "valuable choices" cannot be equated to choices that realise a better health (127). Instead, true freedom includes choices and actions that are considered (medically) unreasonable (103). This idea corresponds with the suggestion that an informed consent should not only protect patients' bodies but also patients' personal autonomy (128). A patient's best interest can supersede the medical level and personal and contextual elements may sometimes override

the value of medical information (37). Analogously, professionals' fiduciary duties do not only include the duty of medical care but also the duty of loyalty to a patient's interests that may transcend the medical level and the duty to respect a patient's self-determination (53).

In view of the importance of professionals' expertise and their disclosure of scientific and epistemic uncertainty, patient opt-out possibilities should be well-informed. Professionals should explain the meaning and impact of both accepting and declining IFs and patients should realise as good as possible what kind of information they accept or decline. A written informed consent procedure may contribute to this goal but there is a lot of discussion about the most suitable and effective type of informed consent (18). The use of an informed consent form has been questioned more generally since it may originate from a fear of liability or a Western audit culture and since it may create a false feeling of protection both in patients and professionals (14, 36, 48, 129, 130). Instead, the counselling discussion may be more important than the signature of an informed consent form, especially when the readability of the consent document is low (129, 131).
Alternatively, proponents of a written informed consent form have suggested new consent procedures such as broad or binned consent (29). Both types of consent are based on the idea that it is impossible to explain all possible IFs (or SFs) in a specific and detailed way (49, 129). In a broad consent procedure, patients are offered an "all or nothing" choice and they can only choose to generally accept or decline (a predetermined list of) IFs or SFs (30, 129, 132). This procedure is, for instance, suggested by the ACMG which does not recommend the possibility of a partial opt-out (133). In a binned consent procedure, an information overload is avoided by categorising potential IFs or SFs in delineated packages (102, 103). Subsequently, patients may choose which sets of results they want to receive and which sets they want to decline (30, 103). In line with potential implementation problems concerning the binning system of Berg et al. (101), these consent procedures have been criticised because of the difficulties of binning *in se*, the unilateral character of bins, the risk of a professional preponderance in the delineation of bins and the risk of a burden of tick-boxes that can undermine informed decision-making (49, 71, 101, 129).

More generally, patients' focus on lived illness experiences and on diagnostic test results may challenge a successful informed consent procedure concerning IFs or SFs (60, 69, 82, 100). Patients' symptomatic and diagnostic focus during pre-test counselling may cause them to not pay significant attention to IFs and the abstract and uncertain character of presymptomatic IFs may impede patients' appreciation of predictive and preventive medicine (4, 29, 65, 76, 114, 134). The challenging nature of preventive actions regarding asymptomatic IFs has been demonstrated before and indicates that patients with acute or chronic illness concerns may need to be made more aware of preventive possibilities (80, 135). Genetic professionals' expertise will also be indispensable in this context.

This introduces the last part of this discussion, i.e. some points of concern regarding the counselling process for genomic uncertainty in IFs.

8.2.5. Counselling beyond principlism

A rapprochement of uncertainties corresponds with Christenhusz and colleagues' identification of four ethical signposts for the disclosure of genomic IFs (65). They advocated a maximal sharing of clinical geneticists' knowledge, an epistemic modesty about genetic information, a transparent communication of the significance of IFs from a patient perspective and an inclusion of a patient's embedded nature (65). The advocated rapprochement in this discussion nevertheless differs from these ethical signposts by allowing a patient opt-out of IFs and it aimed to more specifically delineate expertise and modesty from both the professional and patient perspective.

The communication of uncertainty may collide with the principle and aim of evidence-based medicine (1, 6, 100, 136). Even though professionals may be aware of medical uncertainty, they may not be used or inclined to explicitly communicate this (1, 5). Hence a rapprochement of uncertainties in IFs may require counselling and consent strategies that go beyond those that are traditionally used. The development of a counselling strategy for IFs exceeds the scope of this dissertation but some main points of concern may be identified.

Patients' response to professional modesty concerning IFs and SFs is still unclear (14). People's appreciation of uncertain medical and genomic information has been associated with their general risk appreciation but also with more contingent factors such as their mood (4, 9, 137). Lay people's ability to correctly interpret uncertain information may also be limited, since this information may be perceived as abstract, complex and confusing (8). Therefore, people may be ambiguous-aversive and use various strategies to avoid uncertainty (3, 8). Founded on a pessimistic appraisal of risks and a fear for the potential outcome of uncertain information, they may *a priori* decline uncertain but potentially valuable information such as IFs (4, 8, 71, 90). Conversely, they may hesitate to accept or they may even deny professional uncertainty and instead hold on to their positive expectations regarding IFs or to an optimistic bias (4, 6, 8, 70, 90). This denial may be supported by traditional expectations towards medical information that should resolve uncertainty and by feelings of frustration when this does not appear to be the case (3, 5, 9, 47, 63, 113). In this last scenario, counselling patients about professional uncertainty concerning IFs and SFs may not strongly affect patients' initial preferences (72).

The possibility of different reactions to uncertainty and professional modesty indicate the importance of a balanced and effective way of communicating IFs' and SFs' scientific ambiguity, complexity and uncertainty (3, 29, 77). Communicating professional uncertainty in a meaningful and understandable way that maintains patients' confidence in professional

expertise may require new communication methods that acknowledge and counter the impact of information's presentation (8, 77, 137). When, for example, the choice concerning IFs is framed as a decision on "possibly life-saving health information", people may be very likely to prefer the return of these result (137). Also particular examples of IF-associated conditions can affect patients' interpretation and choice. Risks associated with cancer, for instance, may be interpreted as very distressing because of the emotional charge that has been associated with cancer (62). Hence the presentation of IFs and SFs, including terminological choices concerning potential outcomes, quantifiable risks and unquantifiable uncertainties requires proper attention and further research (5).

In line with some people's risk adversity, people have expressed concerns about "being left alone" in interpreting IFs and SFs and in coping with these results' clinical, practical and emotional impact (94). Consequently, both in this dissertation and internationally, people have stressed the importance of counselling for a successful coping and for an effective translation of IFs into adequate medical care and lifestyle changes (94, 122, 138, 139). "Making room for the patient's story" and respecting the patient as a full member in the rapprochement-process should not provoke professionals to leave the patient alone in this story or to minimise professional responsibilities under the excuse of patient autonomy.
This call for counselling suggests that professionals may need to transcend the level of scientific information and expertise (43). They may need to take up a more active role in genetic consults and, together with the patient, think about possible (psychosocial, family-wide) consequences of IFs, follow-up consults and suitable coping strategies (2, 43, 113, 125). In other words, they are invited to actively include patients' expertise and uncertainty in their consult and counselling. The importance of a patient's personal context for effective counselling has been emphasised repeatedly and this context should be acknowledged as a legitimate argument (29, 36, 41, 62, 88, 114, 138). Personalised care is a value that cannot be realised from a merely professional perspective; it can only result from an active patient involvement that allows for a real integration of personal and contextual elements.

Therefore, in a rapprochement of uncertainties, IFs should be perceived as dynamic concepts whose meaning is conjointly constructed in oscillation between professionals and patients. Stivers and Timmermans observed how professionals' way of explaining VUS influenced patients' interpretation and how patients' psychosocial experiences subsequently affected their acceptance or denial of the professional explanation (124). Eventually, both parties' interpretation of the VUS was a result of co-construction (124). The authors reported a similar interactional process in genomic consults concerning the meaning of actionability (140). An analogous process of interaction may apply to IFs, where an explicit and mutual acknowledgement of these results' potential uncertainty may enhance shared meaning-making and, subsequently, shared decision-making (1, 3, 141). Similarly, Newson et al. advocated an "ethics of genomic uncertainty" in which professional and patient experiences are constructively incorporated in a reciprocal understanding of uncertainty (2).

Considering IFs as co-constructed information implies caution towards recently developed (online) tools that aim to prospectively assess patients' preference towards IFs without professional assistance or interactional communication (86). Finally, the conjointly constructed meaning of IFs may not only occur at an interactional level between professionals and patients, but may already start at an interactional level and rapprochement between professionals, such as laboratory scientists and clinical geneticists. Closer interactions between these professionals may result in fewer but more clinically relevant results that are reported from the laboratory to the clinic and in a greater trust of clinical geneticists in reported results (142). This, again, emphasises the importance of multidisciplinary professional deliberation and the requirement to integrate a patient's personal story and expertise at different stages of clinical care.

An ethics of uncertainty does not only challenge evidence-based medicine but also principles and values such as autonomous patient choices or professional beneficence (65). Ethical principlism starts from a rational, liberal and rather atomistic perspective (143, 144). It pays less attention to elements of lived experience, context, family embedding, complexity and uncertainty which appeared to be central to this dissertation on IFs and SFs (65).
Therefore, an effective and ethical policy on IFs and SFs may require a reconsideration of principlism. Both professionals and patients may have to reconsider their role of, respectively, scientific information provider and autonomous decision-maker. As well as professionals are invited to transcend the domain of scientific expertise and the value of medical beneficence, patients may have to revise the intention of making autonomous choices that are founded on objective medical knowledge. This reconsideration of traditional roles and expectations was also included in the suggestion of Samuel et al. regarding a more relational approach towards genetic consent (116). In a context of complex and sometimes uncertain genomic information, too much attention may have been paid to the informational aspect of consent (116). Information and autonomy may not be synonyms and both concepts may be inherently connected with emotion and social embedding, especially in a context of genomic information that may have a family-wide relevance (113, 116). This idea of a more relational consent aligns with the idea that people may not be fully rational, independent and autonomous, especially not in a context of complex and uncertain information, illness and care (80). Instead, they may be interdependent, inherently related and dynamically connected with others (116, 118, 145, 146). This way, values of care, such as honesty and trustworthiness, may complement principles of autonomy and beneficence (116, 147). These values can help to ensure that the disclosure of IFs is not merely an act of potential (medical) benefit but a real act of care.

Finally, the merit of a rapprochement between professional and patient uncertainties is in the process itself rather than in a final goal that should be achieved. Some types of uncertainty may be reduced, for instance by scientific progress or a better understanding of a patient's lived experience or context. Inherent characteristics of genomic information, its complex interaction with environmental factors and the dynamics in a patient's context and embedding

nevertheless impede an overall solution of uncertainty and some types of uncertainty cannot be solved by adding ever more complex information (6, 113, 116). Therefore, the rapprochement between professionals and patients does not aim for a definite solution but for an acknowledgement, understanding and active integration of uncertainty in the counselling process for IFs and SFs. As mentioned by Taber et al., uncertainty should not be acknowledged or resolved so patients would make "the right choice" about (not) being informed about IFs or SFs; this uncertainty should rather be acknowledged so patients can decide whether and how the disclosure of these results would be meaningful to them (4).

8.3. Conclusion

In the clinical context of genomic IFs and SFs, a rapprochement of professional and patient experienced uncertainties can be a next step towards an efficient and ethical policy. This rapprochement integrates various perspectives and levels of the current debate on IFs and SFs and it addresses important concerns that have been identified throughout this dissertation.

At policy level, genetic professionals should, firstly, inform patients about the challenging and sometimes uncertain interpretation and application of important reporting criteria for IFs and SFs, such as pathogenicity and actionability. This education and counselling should be grounded on a combination of professional expertise and modesty. In this act of scientific modesty towards patients, professionals should simultaneously recognise the impact of a particular patient's situation and context on the interpretation of reporting criteria. This acknowledgement may take the concept of personalised care and the practice of case-by-case deliberations from a professional to a more patient-inclusive level.
Secondly, IFs' complex, nuanced and context-dependent meaning as perceived from a patient perspective should be acknowledged. Patients' interpretation of IFs transcends the strictly medical and result-centred level and additionally involves elements of personal illness experience and family embedding. In a rapprochement of uncertainties, patients are invited to share their personal and embedded expertise as well as their associated uncertainties regarding IFs.

At value level, a rapprochement of uncertainties may require a reconsideration of values and principles that are frequently invoked to support disclosure policies.
Professional modesty may discredit the disparity between well-informed professionals and illiterate patients and may reduce the knowledge gap between both parties. More generally, an explicitly shared experience of uncertainty questions the definition of autonomy in terms of being (fully) informed.
In turn, the integration of IFs' complex meaning from a patient perspective challenges the delineation of professional beneficence in terms of strictly clinical benefit. If professionals

want to understand and integrate the complex and nuanced perspective of patients, they are urged to transcend the level of scientific expertise and take a perspective that goes beyond clinical benefit.

In a rapprochement of uncertainties, in which both professionals and patients are stimulated to share their expertise and uncertainty and to reconsider traditional values of autonomy and beneficence, the meaning of IFs (and SFs) should be perceived as the result of a dynamic interaction between both stakeholders. This joint construction does not aim for the solution of uncertainty but rather for its explicit acknowledgement as a necessary step towards an ethical policy that respects IFs' and SFs' complexity in both the professional and patient perspective.

8.4. Study limitations and future research

Like any research study, this dissertation has its limitations that simultaneously indicate future research needs.

The first chapter of this dissertation's result section advocated a level-integrative approach of the debate on IFs and SFs. This dissertation's empirical studies mainly focussed on the policy and value levels and did not explicitly address terminological issues. Throughout this dissertation and its underlying studies, the terminology of IFs and SFs was sustained by a clear definition and delineation of these concepts but the difficulties of these terms are acknowledged. Further research should aim for a terminological consensus which is clear and effective for both professionals and patients.

A second limitation of this research project regards the impossibility to analyse the impact of actually disclosed IFs and SFs, both from the professional and patient perspective. In Belgian CMGs, the experience with identified IFs in clinical genomic testing is currently limited because of a standard clinical practice of NGS-based panel testing. Moreover, to this day, SFs are not actively pursued. Hence the qualitative studies in this dissertation partly have an anticipatory and hypothetical character. The need for more research on disclosed IFs and SFs and their impact has been expressed in existing literature (10, 20, 44, 47). Before such research may be optimally conducted in Belgium, major changes in used testing techniques, institutional policies and ethical deliberation may be required.
From a patient perspective, however, the partly anticipatory character of the conducted interviews may accord with the way actual patient choices regarding the return of IFs will have to be made, i.e. before specific results have been identified (30, 97). More generally, genetic centres and healthcare need to develop policy strategies that anticipate situations and problems they have not always experienced yet. The hypothetical character of the conducted interviews was also reduced by including patients who have lived experiences of illness and genetic testing (mostly by use of NGS-based panel testing).

Another limitation of both the focus groups and interviews regarded the fact that, for reasons of feasibility and complexity, not all types of potential IFs or SFs were discussed. The detection of predispositions for multifactorial, including psychological or psychiatric, conditions or pharmacogenetics were not questioned. Neither genetic professionals nor patients did spontaneously mention these types of potential results.

An inherent limitation of the patient interview study regarded the selection of patients with a specific inherited condition. Future research is needed that includes people with other types of hereditary disease. In a multicultural and multi-diverse society, research should also include more people with diverse backgrounds (148).

An important component of IFs' meaning structure from a patient perspective concerned patients' family embedding. Because of the inherent family relevance of genetic test results and patients' ambivalent perspective on this relevance (in diagnostic results versus in potential IFs), the association between IFs, SFs and a patients' family context calls for further research.

Future research should also consider professionals' and patients' responsibility in family communication and its consequences. Patients may inform family members without adequate counselling whereas professionals may harm family members' autonomy and the principle of patient confidentiality when they inform family members (120). In this context, ethical research should consider concepts of personal and family-wide privacy, confidentiality, justice and (genomic) solidarity.

In the general discussion of this dissertation, we advocated a rapprochement of uncertainties regarding IFs and SFs between professionals and patients. Further research should indicate how these uncertainties can be communicated in an understandable and effective way. Also the counselling and consent strategies that are most suitable to support this rapprochement of uncertainties should be identified.

It may be questioned whether one single counselling and consent session can simultaneously inform patients about both diagnostic results and IFs or SFs. A single counselling session may avoid pre-test situations where patients decline or postpone diagnostic testing because of false beliefs about potential IFs and SFs or it may avoid post-test situations where patients miss out on identified IFs or SFs (149). However, it has been questioned whether it is possible and suitable to inform patients about all these types of results in an understandable way within the limits of one pre-test or post-test counselling session (79, 89). Including the issue of IFs and SFs in the diagnostic counselling procedure and informed consent form could make these procedures too long, overwhelming and complicated and may even undermine the positive effects of previous successful counselling (129, 149).

Therefore, staged procedures have been suggested in which information on diagnostic results and IFs or SFs is provided in different counselling sessions and results are returned in different consultations and reports (134, 135, 138, 149). This procedure may avoid an information overload and result in better informed decisions, both regarding diagnostic results and IFs or SFs (89, 149). Staged counselling and consent procedures could align with both professionals' and patients' diagnostic focus and with many patients' more refined perspective on IFs throughout the interview (14, 18, 65, 87, 91, 150-152). This effect of time and reflection can be an important hint for effective counselling and lay people have emphasised the importance of allowing enough time for counselling sessions and decisions on the disclosure of IFs and SFs (54, 91). More research is needed on the feasibility, efficacy and consequences of staged and other counselling procedures in a context of IFs and SFs.

Previous research revealed the potential impact of the counselling person on a patient's specific choice regarding the disclosure of IFs (148). Therefore, more research is needed to identify the most suitable person to take on this counselling role. Clinical geneticists may be well educated to report identified IFs or SFs but it may be unfeasible to accomplish this task all by themselves (43, 48, 88, 153, 154). Therefore, genetic counsellors may successfully take up this role. In Belgium, there is no formal training and no official recognition of this paramedical healthcare profession but countries such as Canada, the US and the UK may provide valuable international examples (13, 48). Research should also consider the potential role of general practitioners in genomic counselling. On the one hand, general practitioners may have a limited genetic expertise (71). This need for genetic "capacity-building" applies to several medical fields, such as oncology, cardiology, gynaecology and primary healthcare (11, 48, 52, 76, 89). In this context, EuroGentest and the ESHG Education Committee have published a minimum set of genetic core competences for all healthcare professionals who work in a primary, secondary and tertiary care context (155). On the other hand, and despite general practitioners' limited genetic expertise, lay people have emphasised the importance of a trusting relationship with the counselling professional (125). General practitioners are still assigned a central role in personal healthcare and they may have a frequent contact with patients and a good knowledge of their medical, personal and family context (48, 65, 88). In view of the complex meaning of IFs from a patient perspective, this more holistic professional perspective may be highly valuable.

The specific perspective and expertise of various clinicians suggests a continuum of stakeholders who each have their own (personal, embedded, scientific) experience, ranging from patients to general practitioners, specialist doctors (for instance cardiologists, gynaecologists, oncologists, ophthalmologists or neurologists), clinical geneticists and clinical laboratory geneticists. The suggested rapprochement of uncertainties may be valuable for all included stakeholders on this continuum.

8.5. References

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Epilogue - LIVED EXPERIENCES OF A RESEARCHER

Qualitative research is not conducted in a vacuum. As demonstrated throughout this manuscript, research participants and the phenomena under consideration are always embedded in a broad context with its material, psychological, social and ethical components. This embedding also applies to the researcher (1). Academics in qualitative research increasingly acknowledge that researchers are an inherent part of the research process (2, 3). In this process, it is essential for researchers to be aware of their personal preconceptions, emotions and experiences throughout the collection and interpretation of data (2). Therefore, I would like to briefly reflect on my own lived experiences throughout the writing of this dissertation.

At the end of 2015, I applied for a research project that would focus on diagnostically unrelated findings in genomics and that would include a qualitative study. I had already been working as a junior researcher for over two years and had conducted over 50 interviews with palliative people with cancer who are living alone. This way, I had experienced both the potential emotional impact of interviews and my appreciation for doing qualitative research.
At the start of the new research project on diagnostically unrelated findings in genomics, I had no clear expectations about the possible emotional impact of this study; I was more concerned about the medical and technical knowledge this study could require. However, when studying the literature and preparing the qualitative studies, I realised this research project could become more personal than I had expected.

Firstly, when analysing the 2013 recommendations of the ACMG (4), I noticed how these recommendations advised to routinely screen for pathogenic variants in genes associated with a condition I personally have. Of course, I had thought about my own genetic condition when I applied for this research project but I honestly did not reflect on it for too long. I had known this diagnosis for almost twenty years, the condition's symptoms had largely become a habit and I do not feel seriously hindered in my daily life.
Secondly, the decision was made to interview people with an IRD. One of the main symptoms I personally experience concern visual problems and for the second time, I realised the possible - yet partial - connection between the research project and myself. I realised that the research project would not only require medical and technical knowledge but also attention for its possible personal and emotional impact. Nevertheless, I assumed that the partial connection between the research topic and myself would not hinder me in my research activities, a message which I also communicated to my supervisors.

Probably every qualitative researcher will, at some point, experience the connection between herself and her research project. At the end of this particular research project, I still consider the partial connection between the research topic and myself neither as an obstacle nor as a precondition for conducting this study. Nevertheless, I cannot deny the personal and emotional impact of this biographical connection (5).

Firstly, I often thought about the effect of having a genetic condition for which an opportunistic screening has been advised. Would I like to be informed about a predisposition for this condition in the context of a diagnostically unrelated test? Since I can hardly imagine not having this condition, this question is difficult to answer and seems almost paradoxical to me. I was genetically tested as a young adolescent and this because of symptoms and a family history. There was nothing presymptomatic or incidental about this situation and the reported results. I value the knowledge of the genetic test result but this appreciation is probably affected by the very fact that this condition is and has been symptomatic for a very long time. Because of this strong embodiment, it may be more sensible to me to reflect, in line with the participants of the interview study, on the potential disclosure of IFs or SFs regarding conditions I have not become physically and personally fused with.
Over the past four years, my lived experience of a genetic condition neither seems to have realised a straightforward personal preference regarding the disclosure or decline of IFs and SFs, nor did it cause a consistent evolution in my personal perspective. Instead, I realised how my perspective on specific IFs and SFs is affected by my personal experiences and context and how difficult it is to make abstraction of this embedding. To me, the questions what IFs and SFs may potentially mean to me and whether I would like to be informed about these results, mainly emphasise the importance and inevitable impact of my own embodiment and lived experience. In terms of this dissertation, it seems to confirm the requirement to transcend a purely medical or result-centred level and to allow a more personalised and contextualised approach to IFs and SFs.

Secondly, I have wondered many times about my attitude towards interview participants who suffer from symptoms I - partly - recognise. It should be emphasised that the visual problem I have is not related to IRD, neither in specific symptoms, nor in prognosis. Nevertheless, my vision has progressively declined over time, can only be partly supported by use of visual aids and it prevents me, for instance, from driving a car. The differences between my own symptoms and those of the participants made me decide to not disclose this personal experience during interviews. I did not consider this disclosure necessary for a better rapport and it might be considered irrelevant or even inappropriate by the interview participants. The partial similarities between my own and the participants' visual experience, however, may have had some effects. In patient stories, I recognised testing procedures and names of clinical institutions or professionals. Practical problems and sometimes emotional and family issues could also sound familiar. The most significant impact of the partial connection between participants and me probably applied to the psychological effect of some participants' story. I felt that some stories deeply affected me, especially when people expressed feelings of anxiety, frustration or shame. Some interviews also induced personal thoughts and doubts about my own experience with a genetic condition, personal coping strategies and family embedding. To cope with the emotional impact of some stories, I made reflexive notes after every interview. In these notes, I pre-analytically reflected on methodological concerns, the overall interview and personal issues. This emotional self-awareness and "embodied

reflexivity" helped me to process the interview at a personal level before initiating the actual analysis in a more attentive way (3).

Once again, I realised and experienced how conducting qualitative research does not only require scientific but also emotional effort and how researchers may impact and are affected by their research project. Trying to understand others' lived experience starts with the explicit acknowledgement that research is not conducted in a vacuum, neither for research participants, nor for researchers. The lack of a protective bell jar may be challenging to qualitative research and make it "messy" sometimes (6), but it can also make it rich and thick, in both a professional and personal way.

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SUMMARY

Over the last years, genome wide testing technologies have been increasingly introduced in the clinic. In these genome-based testing procedures, diagnostically unrelated incidental findings (IFs) can be revealed or secondary findings (SFs) can be actively pursued. IFs and SFs can allow for preventive or therapeutic actions but they may also result in anxiety and distress and needless or harmful interventions. Major challenges regarding these results concern the different perspectives of professionals and patients on disclosure, potentially divergent professional practices as a consequence of conflicting recommendations and a limited understanding of patients' interpretation of IFs and SFs.

The main objective of this dissertation is to examine the practice and perspectives of professionals and patients regarding the disclosure and meaning of IFs and SFs in a context of NGS-based clinical genomic testing in adults. More specifically, this dissertation focusses, first, on the practice, policy and (ethical) motives concerning disclosure from the perspective of genetic professionals in Belgian centres for medical genetics (CMGs) and, second, on the meaning of potential IFs and SFs from the perspective of genetically tested patients.

The results section of this dissertation starts with a critical study of the current debate on IFs and SFs from a multi-levelled perspective. Major points of discussion are assessed at terminology, policy and value level.
In the absence of a terminological consensus, policy issues concerning the minimisation of IFs, the active search for SFs and strategies for feasible and effective counselling are still debated. Values of autonomy, beneficence and actionability are frequently invoked as underlying principles but these concepts may conflict and they challenge a univocal interpretation.
A level-integrative approach that explicitly acknowledges the inherent interaction between the terminology, policy and value levels may stimulate a more effective debate on IFs and SFs. Additionally, this approach should pay more attention to the patient perspective, including patients' lived experience and particular context.

The next three results sections use an empirical and qualitative approach to discuss different levels and perspectives within the debate on IFs and SFs.

Firstly, reporting policies concerning IFs and SFs in a diagnostic context are addressed from the perspective of genetic professionals in Belgian CMGs. A focus group study indicated that SFs are not actively pursued in Belgian CMGs but that a specific subgroup of IFs may be reported. The clinical significance of an IF and patient-related factors are major criteria for disclosure. Concerning IFs' clinical significance, professionals generally emphasised that reported IFs should be pathogenic and actionable. However, these criteria challenge an unambiguous interpretation and several professionals expressed the difficulty of finding the

right balance between clinically valuable and potentially harmful information. With regard to the reporting criterion of patient-related factors, a diversified practice on a patient opt-out for medically actionable IFs was revealed in Belgian CMGs. Clinical, practical and ethical arguments support these local opt-out policies. Finally, an interaction between particular patient characteristics and the significance of a specific IF can affect disclosure. This interaction creates the need for professional deliberation, as well as a tension between general guidelines and a case-by-case approach.

The next chapter of the dissertation focusses on the value level of the debate on IFs and SFs. This chapter identifies and discusses the ethical values and principles that are invoked by professionals of Belgian CMGs for the disclosure of IFs and SFs. Respect for patient autonomy, professional non-maleficence and beneficence are frequently called upon to justify the disclosure of results. All values are particularly at stake in the highly discussed policy concerning a patient opt-out of medically actionable IFs. Some Belgian professionals considered the value of patient autonomy as superseded by professional beneficence, which resulted in a mandatory disclosure of medically actionable IFs. In this chapter's discussion, this mandatory disclosure is conceptualised as a technological soft paternalism. Arguments for this technological soft paternalism, including professional assumptions on patients' genetic literacy and a normative rationality, are critically reflected upon. Also the beneficent outcome of a paternalistic disclosure is questioned. The chapter ends with a reflection on the value of distributive justice as an important factor in the delineation of the current scope of the debate on IFs and SFs.

The last chapter of the results section changes perspective and examines the meaning of IFs from a patient perspective. This chapter presents the results of an interview study with 14 adults with an inherited retinal disease (IRD).
Patients assign a complex meaning to IFs that includes a nuanced and non-deterministic interpretation of an IF's possible characteristics and consequences. From a patient perspective, IFs' meaning largely transcends the result-centred and medical level. This is shown in the way lived experiences of an IRD may affect the interpretation of potential IFs. Patients' illness experience may both temper their interest in IFs and influence the interpretation of IFs' possible characteristics and consequences. Finally, patients' family embedding and history of disease can affect their interest in and interpretation of potential IFs. This association conflicts, however, with patients' more limited concern about the family-wide relevance of potential IFs.
The complex and nuanced meaning structure of IFs from a patient perspective should be taken into consideration in the development of effective counselling procedures.

Both the focus groups with genetic professionals and the patient interviews reveal a high level of complexity concerning the meaning and disclosure of IFs and SFs. Meaning structures and reporting decisions result from a compound and nuanced deliberation process on IFs and SFs,

both in professionals and patients. This way, the results of the empirical studies lead to a reflection on the concept of uncertainty in genomic IFs and SFs. Both professionals and patients experience uncertainty in the interpretation of IFs and SFs but the causes and consequences of these perceived uncertainties diverge. Whereas genetic professionals are more concerned about epistemic causes and scientific consequences of uncertainty, patients mainly focus on lived experiences of uncertainty and personal and practical consequences. Rather than considering these uncertainties as obstacles for an efficient policy on IFs and SFs, a rapprochement of uncertainties between professionals and patients is advocated. In this rapprochement, both stakeholders should become aware of and try to understand different types of uncertainty. A rapprochement of uncertainties may eventually result in a conjointly constructed meaning of IFs and SFs that is optimally adjusted to a particular patient's specific context.

Overall, this dissertation contributes to a nuanced interpretation of genomic IFs and SFs in which the voices of professionals and patients, as well as policy and ethical concerns are given a central position.

SAMENVATTING

De afgelopen jaren werden genoombrede technologieën steeds meer geïntroduceerd in de klinische praktijk. In deze genoombrede testprocedures kunnen diagnostisch ongerelateerde toevalsbevindingen (*incidental findings* of IFs) worden vastgesteld en kunnen secundaire bevindingen (*secondary findings* of SFs) actief worden opgespoord. IFs en SFs kunnen preventieve of therapeutische interventies mogelijk maken maar kunnen ook tot angst of onnodige en schadelijke interventies leiden.
Tot op vandaag stellen IFs en SFs ons voor belangrijke uitdagingen. Deze uitdagingen betreffen onder meer de verschillende perspectieven van professionals en patiënten op de rapportering van IFs en SFs, het gebrek aan uniforme aanbevelingen en mogelijks uiteenlopende rapporteringspraktijken en het beperkt inzicht in de interpretatie van IFs en SFs door patiënten.

Dit proefschrift onderzoekt het perspectief van professionals en patiënten op de rapportering en betekenis van IFs en SFs in een klinische context van genoombrede tests bij volwassenen. Dit proefschrift focust meer specifiek op de praktijk, het beleid en de (ethische) motieven voor de rapportering van IFs en SFs vanuit het perspectief van genetische professionals en op de betekenis van mogelijke IFs en SFs vanuit het perspectief van genetisch geteste, volwassen patiënten.

De resultatensectie van dit proefschrift start met een kritische beschouwing van het huidige debat over IFs en SFs. Belangrijke discussiepunten op vlak van terminologie, beleid en ethische waarden worden hierbij onderzocht.
Voorlopig is er geen consensus over de beste terminologie voor IFs en SFs. Op beleidsniveau worden praktijken betreffende het minimaliseren van IFs, het actief opsporen van SFs en de meest geschikte strategieën voor counseling volop bediscussieerd. Waarden betreffende autonomie, weldoen en de opvolgbaarheid van testresultaten (de handelbaarheid of *actionability* van resultaten, d.w.z. de mogelijkheid tot het stellen van preventieve of therapeutische acties) worden vaak aangehaald als onderliggende beleidsargumenten maar deze concepten kennen geen eenduidige interpretatie en komen regelmatig in conflict.
Het expliciet erkennen van de interactie tussen terminologie, beleid en waarden kan een meer effectief debat over IFs en SFs stimuleren. Daarnaast moet verder onderzoek zich richten op een patiëntenperspectief dat aandacht heeft voor de geleefde ervaring en persoonlijke context van de patiënt.

In de volgende drie hoofdstukken worden de verschillende niveaus en perspectieven binnen het debat over IFs en SFs verder onderzocht aan de hand van kwalitatief onderzoek.

Een focusgroepstudie met professionals onderzocht de rapportering van IFs en SFs in Belgische centra voor medische genetica (CMGs). Professionals in Belgische CMGs sporen SFs niet actief op maar rapporteren wel specifieke IFs. De klinische relevantie van het resultaat en patiëntgerelateerde factoren zijn daarbij belangrijke rapporteringscriteria. Wat de klinische relevantie van IFs betreft, benadrukken de meeste professionals dat gerapporteerde IFs pathogeen en opvolgbaar (*actionable*) moeten zijn. Deze criteria zijn echter moeilijk eenduidig toe te passen in de praktijk, wat tot een moeilijk evenwicht kan leiden tussen klinisch waardevolle en potentieel schadelijke informatie. Wat patiëntgerelateerde factoren betreft, vertonen Belgische CMGs een diverse praktijk inzake de mogelijkheid tot een patiënten *opt-out* voor IFs die medisch opvolgbaar zijn. CMGs ondersteunen hun lokaal *opt-out* beleid door middel van klinische, praktische en ethische argumenten. Tenslotte kan de interactie tussen de concrete patiënt en de specifieke IF de rapportering van resultaten beïnvloeden. Deze interactie maakt professioneel overleg noodzakelijk en creëert een spanning tussen algemene richtlijnen en casus-specifieke benaderingen.

In een volgend hoofdstuk worden de ethische waarden en principes onderzocht die professionals in Belgische CMGs inroepen voor de rapportering van IFs en SFs. Respect voor patiëntenautonomie, niet-schaden en weldoen worden vaak aangehaald als argumenten voor het al dan niet rapporteren van IFs en SFs. Vooral de praktijk betreffende een *opt-out* voor IFs die medisch opvolgbaar zijn, zorgt voor conflicten tussen deze waarden. Sommige Belgische professionals stellen dat in deze kwestie patiëntenautonomie wordt overtroffen door professioneel weldoen, wat resulteert in een verplichte rapportering van IFs die medisch opvolgbaar zijn.
In de discussie van dit hoofdstuk wordt de verplichte rapportering van IFs doorgelicht in termen van een technologisch zacht paternalisme. Professionele veronderstellingen over de genetische kennis van patiënten en de idee van een normatieve rationaliteit worden kritisch bediscussieerd als argumenten voor dit technologisch zacht paternalisme. Ook het positief effect van een verplichte rapportering wordt in vraag gesteld. Tenslotte wordt de waarde van verdelende rechtvaardigheid aangeduid als een belangrijke factor voor de huidige reikwijdte van het debat over IFs en SFs.

In het laatste hoofdstuk van de resultatensectie wordt de betekenis van IFs onderzocht vanuit een patiëntenperspectief. Dit hoofdstuk geeft de resultaten weer van een interviewstudie met 14 volwassenen met een erfelijke netvliesaandoening (*inherited retinal disease* of IRD).
Patiënten kennen een complexe betekenis toe aan IFs en hebben een genuanceerde kijk op de mogelijke kenmerken en gevolgen van IFs. Voor patiënten overstijgt de betekenis van IFs vaak het resultaatspecifieke en medische niveau. Dit komt onder andere tot uiting in de manier waarop de ziekte-ervaring van patiënten enerzijds de interesse in IFs kan temperen maar anderzijds ook de interpretatie van deze mogelijke resultaten beïnvloedt. Tenslotte wordt de betekenis die patiënten toekennen aan IFs ook beïnvloed door hun familiale context

en een eventuele ziektegeschiedenis. Opvallend is dat patiënten daarentegen minder begaan lijken met de eventuele relevantie van IFs voor familieleden.
Voor een optimale counseling is het belangrijk de complexe en genuanceerde betekenisstructuur van IFs te erkennen en mee in rekening te brengen.

De focusgroepen met genetische professionals en de interviews met patiënten geven een sterke complexiteit weer binnen de betekenis en rapportering van IFs en SFs. Zowel bij professionals als bij patiënten zijn toegekende betekenissen en beslissingen over rapportering het resultaat van genuanceerde overwegingen. Dit resulteert in de algemene discussie van dit proefschrift in een reflectie op de ervaren onzekerheid betreffende IFs en SFs. Zowel professionals als patiënten ervaren onzekerheid binnen de interpretatie van IFs en SFs maar de oorzaken en gevolgen van deze onzekerheden zijn vaak verschillend. Terwijl genetische professionals meer begaan zijn met wetenschappelijke oorzaken en gevolgen van onzekerheid, zijn patiënten vooral begaan met de beleving van onzekerheid en de persoonlijke en praktische gevolgen ervan.
Eerder dan deze onzekerheden binnen IFs en SFs te beschouwen als obstakels voor een efficiënt beleid, wordt gepleit voor een expliciete erkenning van en toenadering tussen onzekerheden zoals deze worden ervaren door beide partijen. Door een wederzijds begrip van verschillende types onzekerheid kunnen patiënten en professionals interactief betekenis verlenen aan mogelijke IFs en SFs en dit op een manier die optimaal aansluit bij de specifieke context van de patiënt.

Dit proefschrift wil bijdragen aan een genuanceerde interpretatie van IFs en SFs. Zowel de stem van professionals en patiënten als beleidsmatige en ethische overwegingen worden hierbij geïncludeerd.

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Marlies
27 april 2020

We die so the others can be born
We age so the others can be young
The point of life is live
Love - if you can
Then pass it on
(K. Tempest)

CURRICULUM VITAE

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EDUCATION

2016 – 2020	Doctoral Training Programme - Life Sciences and Medicine Ghent University
2008 – 2010	Master in Cultural Studies (Art Studies and Archaeology) Free University of Brussels (VUB) *Cum laude* Dissertation: A critical reflection on some ethical aspects of pictures. The ethical dimension of war photography. Internship: BOZAR (Centre for Fine Arts)
2005 – 2008	Master in Moral Sciences Ghent University *Magna cum laude* Dissertation: The death of Great Art. A critical investigation of Heidegger's aesthetics.
2003-2005	Bachelor in Moral Sciences Ghent University *Summa cum laude*

PROFESSIONAL EXPERIENCE

01/2020 – present	Scientist Sciensano - Cancer centre
01/2016 – present	Scientific researcher – Doctoral candidate Research Group Philosophy of Medicine and Ethics Department of Public Health and Primary Care Ghent University *Incidental findings in genome-wide sequencing in persons with a Mendelian disease: a bioethical study*

01/2013 – 12/2015 Scientific researcher
Mental Health and Wellbeing Research Group
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Psychosocial needs of single living, palliative patients with cancer: the vision of patients and caregivers

04/2011 – 01/2013 Office assistant
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PUBLICATIONS IN INTERNATIONAL PEER REVIEWED JOURNALS

Saelaert, M., Mertes, H., Moerenhout, T., De Baere, E., & Devisch, I. (2020). Ethical values supporting the disclosure of incidental and secondary findings in clinical genomic testing: a qualitative study. *BMC Medical Ethics, 21*.

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PRESENTATIONS AT NATIONAL AND INTERNATIONAL CONFERENCES, SYMPOSIA AND COLLOQUIA

03/2019 Annual Meeting of the Belgian Society for Human Genetics
Liège
Criteria for reporting incidental findings in clinical whole exome sequencing - Professional practice and perspective in Belgian genetic centres
Oral presentation

08/2018 European Conference on Philosophy of Medicine and Health Care
Lisbon
Incidental or secondary findings in genetics: stairways to a life of certainty?
Oral presentation in special seminar "Technological intrusions in human life: from utopia to dystopia"

06/2018 International Conference on Phenomenology of Medicine and Bioethics
Stockholm
Incidental or secondary findings: a patient perspective on additional genetic results
Oral presentation

06/2018 Flemish Strategic Committee - National Alliance of Socialist Health Insurance Funds

Ethical aspects of predictive healthcare and genetics
Invited lecture

04/2018 Faculty Research Day & Student Research Symposium Ghent University
Incidental or secondary findings - A dual bottom-up approach to the terminological debate
Poster presentation

02/2018 Annual Meeting of the Belgian Society for Human Genetics
Ghent
Incidental or secondary findings - A dual bottom-up approach to the terminological debate (poster presentation)
Poster presentation

08/2017 European Conference on Philosophy of Medicine and Health Care
Belgrade
Incidental findings: Inherent part of patients' identity or unwillingly imposed digitalization?
Oral presentation in special seminar "The digital patient"

01/2017 5 years of cardio-genetics (University Hospital Antwerp)
Ethical reflections on genetics
Invited lecture

09/2016 Interuniversity symposium on qualitative research in medical and health sciences
Qualitative interviews: practical issues
Invited workshop

08/2016 European Conference on Philosophy of Medicine and Health Care
Zagreb
Incidental findings: an opportunity for autonomy or a case of hidden heteronomy?
Oral presentation in special seminar "Inequality, responsibility and patient autonomy"

05/2016 Update on genetics for general practitioners (University Hospital Antwerp)
Ethical implications of genetic screening
Invited lecture

04/2016	Undisclosed issues in qualitative research Co-organiser of a 2-day symposium for doctoral students)

ADDITIONAL EDUCATION

04/2018	Interpretative Phenomenological Analysis 2-day session
10/2017	Begeleiden van schrijfopdrachten 1-day session
02/2017 – 06/2017	Qualitative Research – Expert techniques 5-session course
04/2017 – 09/2017	Making sense of Subjectivity 4-session course
09/2016 – 12/2016	Academic English writing skills 10-session course
07/2016	Let's talk science! - Communication skills for the academic world 3-day session

APPENDIX

This appendix provides an overview and summary of frequently referred to recommendations on the disclosure of incidental and secondary findings in diagnostic, constitutional WES/WGS in adults.

American College of Medical Genetics and Genomics, 2013

Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565-74.

In any case of diagnostic, constitutional WES/WGS (both in adults and in minors), laboratories should actively and routinely screen for and report pathogenic and likely pathogenic variants in a list of 56 genes that are associated with severe, highly penetrant and clinically actionable monogenic conditions that may stay asymptomatic for a long time.

- Disclosure of opportunistic screening results (called incidental findings or IFs) should not be limited by the age of the person being tested (since the IFs may have important implications for family members).

A patient opt-out of opportunistic screening is not possible.

- If patients judge the risks of this opportunistic screening to outweigh the benefits of testing, they should decline clinical sequencing.
- Opportunistic screening is in line with other domains in clinical medicine (e.g. radiology).

The clinician should provide appropriate pre- and post-test counselling and medical follow-up.

The gene list is a minimum-list and is considered a starting point that may be modified over time.

Issues on updating the interpretation of IFs, recontacting patients or ordering clinicians, data ownership and access to raw data are explicitly beyond the scope of these recommendations.

Important changes in the ACMG 2015 recommendations

ACMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med. 2015;17:68-9.

A terminological change is made from incidental findings (IFs) to secondary findings (SFs) to indicate deliberately screened for and diagnostically unrelated findings.

It is still recommended to routinely screen for (likely) pathogenic variants in the list of 56 genes.

Nevertheless, a patient opt-out of actively pursued SFs is possible.

- The decision to opt out should be made during the pre-test informed consent procedure.
- A partial opt-out of SFs is not possible; an opt-out always applies to the entire list of genes.
- Patients should be warned about the ramifications of opting out.

The list of genes that should be screened is a dynamic, ever-changing list that may be updated frequently.

Important changes in the ACMG 2017 recommendations

Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-55.

The gene list concerning SFs is updated from 56 to 59 genes.

- Moreover, the inclusion in the list of pharmacogenomics genes will be considered in future updates.

Association of Genetic Nurses and Counsellors (UK and Ireland), 2014

Middleton A, Patch C, Wiggins J, Barnes K, Crawford G, Benjamin C, et al. Position statement on opportunistic genomic screening from the Association of Genetic Nurses and Counsellors (UK and Ireland). Eur J Hum Genet. 2014;22(8):955-6.

An active, opportunistic screening for diagnostically unrelated SFs cannot yet be considered a routine action in general medical practice. However, if opportunistic genomic screening should be implemented in practice, the following recommendations should be considered:

- Patients should always be able to consent to or opt out of opportunistic screening.
- In case of an opt-out, laboratories should not screen diagnostically unrelated genes.

- Opportunistic screening should only apply to serious, life-threatening and actionable conditions and the benefits of screening should outweigh the potential harms.

Berg et al., 2011

Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. Genet Med. 2011;13(6):499-504.

IFs should be binned in different categories with specific return policies:

- Bin 1 contains (likely) pathogenic variants in clinically valid and actionable genes. These results should always be returned to patients.

- Bin 2 contains (likely) pathogenic variants in clinically valid but medically non-actionable genes.
  The disclosure of these results should be discussed by clinicians and patients during the consent procedure.
- Bin 3 contains variants in genes with an unknown clinical validity and VUS IFs in clinically valid genes.
  These results should never be reported to patients.

Due to increasing experience and new scientific knowledge, this framework will be subject to ongoing revision.

- The categorisation of more complex (non-Mendelian) diseases may require more complex frameworks.

Canadian College of Medical Geneticists, 2015

Boycott K, Hartley T, Adam S, Bernier F, Chong K, Fernandez BA, et al. The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. J Med Genet. 2015;52(7):431-7.

A targeted approach, limited to the analysis of diagnostically relevant genes, is recommended.

- Hence, a minimisation of potential IFs is advocated.

Competent adults have a right not to know and should be able to opt out of IFs; this choice should be made prior to testing.

An active pursuit of SFs is explicitly not endorsed.

The possibilities concerning IFs (which types of IFs may be discovered, which types of IFs will not be reported, which types of IFs may be disclosed if the patient so chooses, etc.) should be discussed during a pre-test written informed consent procedure.

European Society of Human Genetics and EuroGentest, 2013 and 2016

van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson SV, et al. Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2013;21(6):580-4.

Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, et al. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. 2016;24(1):2-5.

An initial targeted approach, limited to the analysis of diagnostically relevant genes, and a justification of WES/WGS in terms of necessity and proportionality are recommended.

- Hence, the avoidance of identified IFs (called unsolicited findings) and SFs is advocated.

Generally, patients should be able, like in every presymptomatic genetic test setting, to apply and change their preference regarding the disclosure of results.

- However, the right not to know IFs does not always outweigh professional responsibility and the duties of beneficence and non-maleficence. When severe and medically actionable IFs are identified that may be relevant for patients and/or their (future) family, these results may be disclosed against a patient's preference.

Clinical (genetic) centres should develop protocols on IFs and SFs, the reporting of these findings and opt-in and opt-out possibilities, so the local policy is clear for a patient before the test is initiated.

- Moreover, guidelines should be developed about informed consent, the disclosure of IFs in case of minor testing, recontacting patients in case of new scientific evidence and data storage.

Public Health Genetics Foundation

PHG Foundation, Hall A, Hallowell N, Zimmern R. Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project. 2013. http://www.phgfoundation.org/documents/326_1369298828.pdf. Accessed June 2017.

In a clinical context and founded on professional responsibilities and the obligations of beneficence and non-maleficence, it is the physician who will decide on the disclosure of IFs rather than the individual patient.

- In some situations, respecting a patient's wish not to know may be justifiable.
- However, when IFs reveal a life-threatening condition that is easily treatable, the physician may be required to disclose this information and override patient preferences.

Patients should be informed about the possibility and potential health impact of IFs and an explicit informed consent for the disclosure of IFs should be obtained.

Presidential Commission for the Study of Bioethical Issues, 2013

Presidential Commission for the Study of Bioethical Issues. Anticipate and communicate: ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts. 2013.

http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf. Accessed June 2017.

A diversified terminology is suggested which contains primary findings, anticipatable IFs (known to be associated with the test or procedure), unanticipatable IFs (not known to be associated with the test or procedure), SFs (actively sought findings per expert recommendation) and discovery findings (findings discovered by using a test or procedure designed to detect a broad array of results).

A "therapeutic parsimony" - i.e. a selectivity in chosen tests or interventions – and a "diagnostic elegance" - i.e. a limitation of potential diagnoses - are recommended.

- Hence, a minimisation of potential IFs is advocated.

- An opportunistic screening for diagnostically unrelated SFs may hold additional risks (health risks, emotional overwhelming, medicalisation, etc.) instead of an actual improvement of care and is therefore not supported.
- Nevertheless, and grounded in their fiduciary duty, professionals should not filter additional results exclusively in order to avoid responsibility.

Decisions on the disclosure and consequences of identified IFs should be made in collaboration between the clinician and the patient.

- However, if severe, clinically significant and actionable IFs are identified while a patient chose to opt out of IFs, then a "prudent professional judgment" should be made about disclosure. In these cases, a patient's choice should be respected to the extent consistent with the clinician's fiduciary duty.

Patients should be informed about the IFs and SFs that may arise from the conducted testing and about the disclosure and management of these results, including which results will be returned and which will not.

- Guidelines and best practices should be developed.

Vears et al., 2018

Vears D, Sénécal K, Clarke A, Jackson L, Laberge A, Lovrecic L, et al. Points to consider for laboratories reporting results from diagnostic genomic sequencing. Eur J Hum Genet. 2018;26(1):36.

A targeted approach in the analysis of NGS-based data is recommended.

- Hence, it is supported to prevent the identification of IFs (called unsolicited findings) as much as feasible.

Only clinically relevant IFs should be reported.

- However, actionability should not be considered a decisive criterion for reporting pathogenically significant IFs.
- Also the reporting of (likely) pathogenic IFs with low or incomplete penetrance and of IFs concerning a carrier status of recessive conditions is supported.

The right not to know is not absolute but a patient's preference not to know IFs should generally be respected.

- The opportunity for other family members to potentially benefit from the identification of IFs is no sufficient reason to overrule a patient's preference not to know.

An active search for SFs is explicitly discouraged.

- If a laboratory actively screens for SFs, this should be performed after written informed consent (with an explicit opt-in choice) and as a separate analysis.

Pre-test informed consent procedures should include adequate genetic counselling in which the types of potentially identified IFs are explained.