

Alma Mater Studiorum – Università di Bologna
in partnership with LAST-JD Consortium
Università degli studi di Torino
Universitat Autònoma de Barcelona
Mykolas Romeris University
Tilburg University

DOTTORATO DI RICERCA IN

Erasmus Mundus Joint International Doctoral Degree in Law, Science
and Technology

Ciclo XXX

Settore Concorsuale di afferenza: 12H3
Settore Scientifico disciplinare: IUS20

TITOLO TESI

Ethical, legal and social issues related to the offer of
whole exome and whole genome sequencing

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Esame finale anno 2018

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Year 2018

Abstract

Whole genome and exome sequencing (WGS and WES) raise numerous ethical, legal and social issues (ELSI), such as related to informed consent and usage of sequencing data in research. These concerns may be amplified when genomic sequencing is offered direct-to-consumer (DTC) bypassing the traditional healthcare system. This thesis discusses ELSI related to WES/WGS and DTC genetic testing, provides an overview of current DTC genetic testing market, and analyses the impact of the recently adopted Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices on DTC genetic testing.

To provide insights into how ethical issues are addressed in DTC offer of WES/WGS, content analysis of websites of relevant DTC companies was conducted; the results were compared to relevant recommendations of expert groups. The analysis revealed the following concerns: lack of pre-test counselling, inadequate informed consent documents for genetic testing and/or for research activities on consumers' samples and data, lack of relevant information and/or presence of potentially misleading descriptions in some of the companies studied. Consequently, consumers might not be aware of all the implications of undergoing WGS/WES, and their informed consent may be compromised.

Another study presented in this thesis evaluated readability of informed consent forms for clinical WGS and WES using the SMOG and the Flesch-Kincaid formulas. All 36 forms studied failed to meet the average recommended reading grade level for informed consent forms, indicating that the content of the forms may not be comprehensible to many patients.

In order to respect patients/consumers, the compliance with ethical standards when offering genetic testing should be strived for, also in the commercial DTC offer of WES and WGS. The findings presented herein indicate specific areas in which practices should be improved and provide reference and guidance for well-informed and potentially policy-relevant discussions between various stakeholders.

Acknowledgments

I would like to thank Dr Heidi C. Howard for her support, guidance, openness to my ideas, attention to details and critical comments, understanding, and advice, which made this work possible.

I thank my supervisors, Prof. Graziadei and Prof. Hoppe for all the support and advice during my PhD Programme.

I also thank all the co-authors for their contributions and very fruitful cooperation, critical inputs and ideas.

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List of abbreviations

AAP – American Academy of Pediatrics

ACMG – American College of Medical Genetics

DTC – direct-to-consumer

ELSI – ethical, legal and social implications/issues

EU – European Union

FDA – Food and Drug Administration

GT – genetic testing

HCP – healthcare professional

HGP – Human Genome Project

IC – informed consent

IF – incidental findings

IVD Regulation – the Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices

NGS – next generation sequencing

PCSBI - Presidential Commission for the Study of Bioethical Issues

WES – whole exome sequencing

WGS – whole genome sequencing

Introduction

Introduction to the research field of ethical, legal and social implications (ELSI) of genomics

‘Three profoundly destabilizing scientific ideas ricochet through the twentieth century, trisecting it into three unequal parts: the atom, the byte, the gene. Each is foreshadowed by an earlier century, but dazzles into full prominence in the twentieth. Each begins its life as a rather abstract scientific concept, but grows to invade multiple human discourses—thereby transforming culture, society, politics, and language.’

Siddhartha Mukherjee in: ‘The Gene: an Intimate History’ [1]

Genetics – the study of heritability and variation of organisms, next to chemistry and information technology, has profoundly and in multiple ways impacted humanity in the last century. The milestones in development of genetics include the discovery of heritability units called genes in the XIX century, solving the structure of DNA (a molecule which makes up genes) in the 1950s, and finally development of technologies allowing ‘reading’ of DNA sequences (the order of the building blocks of DNA, called nucleotides, in which information about functioning of organisms is encoded) in the 1970s. These developments led to increased understanding of the etiology of many diseases, and consequently to provision of timely diagnosis and treatment to patients affected by genetic conditions. On the other hand, knowledge of mechanisms of heritability and evolution underlay the idea of eugenics, “*science of improving stock*” aiming to “*give to the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable than they otherwise would have had*” [2]. Remarkably, the proponents of eugenics misunderstood the mechanism of heredity; they assumed that physical and mental traits are always passed on to offspring, whilst in reality the heredity mechanisms are far more complicated and are influenced by environmental factors. The eugenic movement reached its zenith in Nazi Germany in the 1940s, when compulsory euthanasia, sterilizations, and mass murder were employed as means of ‘racial hygiene’. After the end of the Second World War, the atrocities committed by Nazis, including their medical

doctors were judged in the Nuremberg trials (1945-1949). During the trials, U.S. doctors, Andrew Ivy and Leo Alexander drafted criteria of legitimate research, as a basis for the response to the defendants' claims that Nazis' practices were not distinct from medical research elsewhere [3]. In the verdict of the trials the points suggested by the doctors were reiterated and developed further into the currently known form of the Nuremberg Code. The first point of the Nuremberg Code outlines the requirement of voluntary informed consent for research, which in the coming decades gained significance not only in the practice of medical research, but also in clinical practice, gradually becoming part of international and national legislation [4,5]. Informed consent, together with the principle of confidentiality of health-related information became guiding principles in the subsequent practice of clinical genetics and genetic research, with aims to protect against the misuses of the science of heredity similar to those which left indelible scar on the history of the twentieth century [6,7].

The relevance of the ethical reflection on the practice of medicine and medical research was also recognized decades later the Nuremberg Trials, in the context of the Human Genome Project (HGP) - an endeavour which aimed to sequence (or in simpler words, to obtain a 'readout' of) all the human DNA – the genome. The Human Genome Project was funded in 1990 by the U.S. Congress with a of 3 billion dollars and a proposed timeframe of 15 years [8]. The efforts of international research groups to read the human genetic code were accompanied by the programme on related ethical, legal and social implications, the ELSI Program, for which between 3 and 5% of the U.S. National Institutes of Health and Department of Energy budgets for the Human Genome Project was allocated [9]. The ELSI Program was initially focused on the themes of: privacy and fairness in the use of genetic information, safe and effective implementation of genetic knowledge in clinical practice, education of professionals and public in genetics. The issues studied were meant to be closely related to the ongoing genetic research and informative to related policy developments [10].

The HGP was successfully concluded in 2003 (two years ahead of a schedule) providing a freely accessible high-quality sequence of the entire human genome. This accomplishment fuelled further research endeavours for years to come, which eventually allowed, for example, to identify 1,800 genes related to diseases, improve diagnosis and treatment of many patients [11]. Furthermore, the HGP brought a 'revolution' to genetics research initiating new approach

in studying DNA - *genomics*, which involves large-scale studies of genome sequences using high-throughput technologies and collecting massive amounts of genetic data [12,13]. This is in contrast to the ‘traditional’ approach in genetics which was to study only one or a few specific genes at a time. As the research in genetics and genomics has been flourishing in the years after the completion of the HGP, an ELSI Program has continued to be funded by the U.S. National Institutes of Health influencing the way genomic research is conducted and the implementation of its results in medicine [14]. Moreover, research programmes with a similar scope were established in other countries, and ‘ELSI research’ started functioning as a term indicating a distinctive area of studies [14,15].

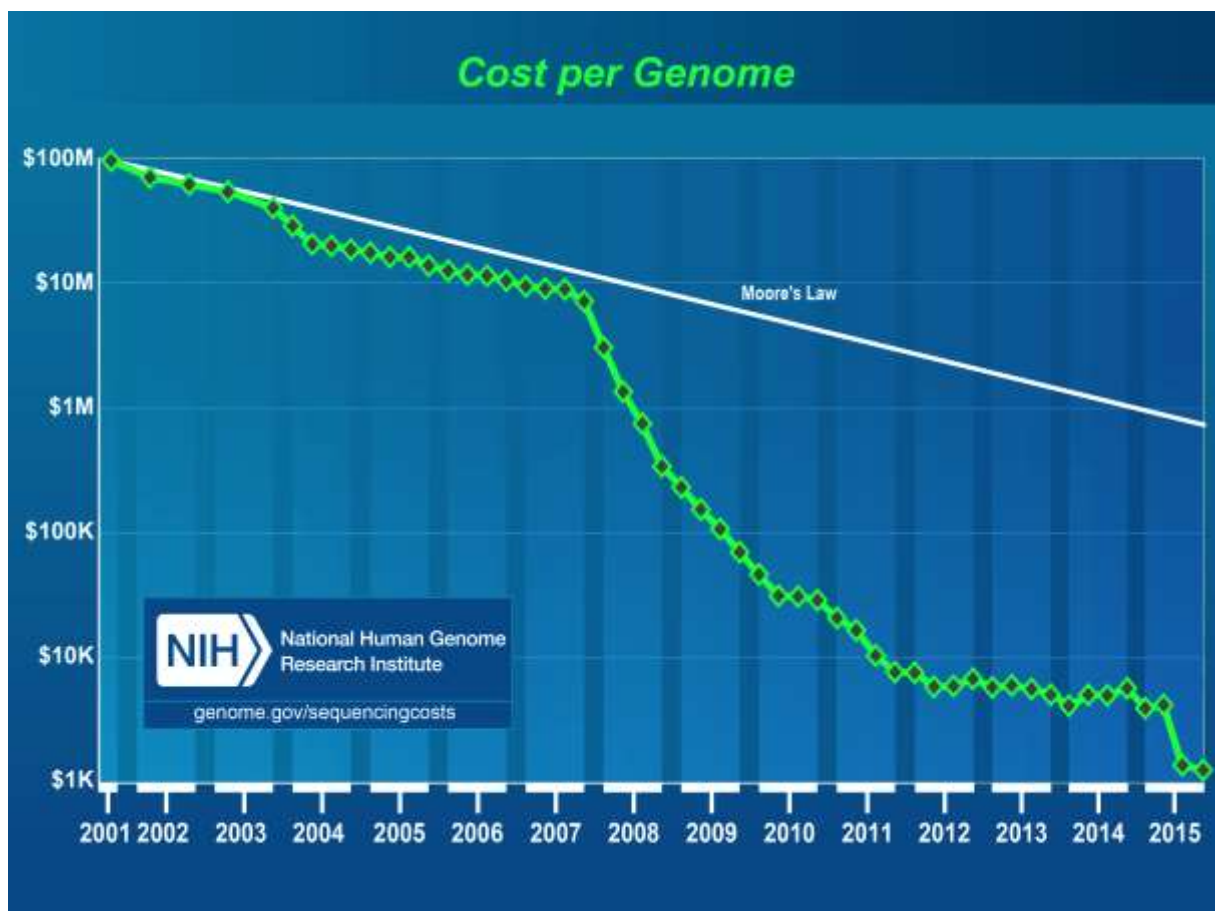
Studies on ethical, legal and social implications of genetics and genomics may be classified as an area of research within bioethics – an interdisciplinary field of study dealing with ethical questions related to biomedical research as well as clinical practice, employing a variety of methods derived from disciplines such as philosophy, social sciences, media studies, legal studies, economics, and others. The research presented in this thesis falls within the area of ELSI of genomics studies as it tackles ethical, legal and social problems raised by new approaches employed in genomic studies, that is, whole exome and whole genome sequencing (WES, WGS).

A novel approach in genetic testing - whole exome and genome sequencing and the related ethical issues

As mentioned earlier, the sequencing of the first human genome took 13 years and cost 2.7 billion of U.S. dollars. In the last decade, the capacities of sequencing technologies significantly advanced allowing for rapid ‘reading’ of many pieces of the genetic code simultaneously, in other words, sequencing DNA in high-throughput and massively parallel manner. Thanks to these next-generation sequencing (NGS) technologies, today it is possible to obtain a whole genome sequence (albeit without a complete interpretation) within a few weeks at a cost under 1000 U.S. dollars, with plans, by some companies, to further reduce this amount to just 100 U.S. dollars [16] (Figure 1). This magnitude of price reduction can be compared to a drop in a cost of an expensive car which could be purchased for around 400 000 USD at the time of the Human Genome Project, and now would cost only 40 cents or less [17].

Consequently, due to the higher availability of next-generation sequencing technologies, the approach of sequencing whole genome or whole exome (the part of genome containing only protein-coding regions) has been increasingly applied in the research and clinical setting. Furthermore, since about 2012 it has been advertised directly-to-consumers.

Figure 1. A graph depicting reductions in DNA sequencing costs in years 2001-2015. "Cost per Genome" - the cost of sequencing a human-sized genome. Trend labelled 'Moore's Law' illustrates hypothetical data based on Moore's Law describing a trend in computer hardware technology, which involves doubling of 'computer power' every two years. The technologies which follow the predictions of Moore's Law are considered to be developing very well. The reduction of price of DNA sequencing technology exceeds these predictions. Source: <https://www.genome.gov/sequencingcostsdata/>.



Whole exome and genome sequencing generate unprecedented amounts of raw sequencing data. Raw exome or genome sequence may be analysed to obtain various types and amounts of results. Importantly, the genome analysis usually aims to provide certain type of information, which is defined priorly to the sequencing. For example, the goals of sequencing may be to

diagnose a neurological disease with unspecific manifestation, estimate predisposition to some diseases, determine presence of genetic variants which could cause a disease in one's offspring. In each of these cases the analysis will focus on relevant, chosen aspects and parts of the genome/exome sequence. However, even if whole genome/exome sequence is analysed using such a targeted approach, there is a possibility of identifying inadvertently unsolicited findings, that is findings unrelated to the original indication for the sequencing. Additionally, a possibility of opportunistic screening can be considered, that is an approach in which a laboratory would analyse a set of genetic variants which are likely to be informative for healthcare of a patient (even if they are unrelated to the initial indication for the sequencing) every time a whole exome/genome is sequenced in clinic. Whatever the policy on the return of sequencing results is followed by a clinical laboratory, the patients should be informed about it and relevant choices should be made in informed consent process for WES/WEG. Given the wide-range of possible findings with various clinical significance, informed consent process seems to be more challenging in the context of genomic sequencing than in the 'traditional' approach to genetic testing focused on one or a few genes. The ethical issues related to unsolicited findings, opportunistic screening, and informed consent are addressed in Chapter 1: 'Current ethical issues related to the implementation of whole-exome and whole-genome sequencing', which provides background for the discussions presented in the subsequent chapters.

Genomic data produced using whole exome and whole genome sequencing may be useful also in research, having potential of bringing benefits at societal level, for example by advancing medical care. At the same time, genomic data are sources of sensitive information about one's health, therefore, their usage requires appropriate safeguards. The issues of informed consent and transparency in the context of secondary uses of genomic data for research (in direct-to-consumer genetic testing companies) are discussed in Chapter 4: 'Ethical issues in consumer genome sequencing: use of consumers' samples and data'.

A novel context of offering genetic testing - direct-to-consumer genetic testing

Whole genome and exome sequencing recently have been offered also outside the traditional healthcare system realm – in the direct-to-consumer (DTC) context. Companies offering direct-

to-consumer genetic testing (DTC GT) target their advertisements at potential consumers of their products – individuals who would undergo the testing. Prior to such DTC companies, advertisements of genetic testing laboratories would be aimed primarily to health care professionals and/or health care institutes. DTC GT is usually purchased through e-commerce, over the Internet, often without any involvement of a medical professional, bypassing the traditional healthcare system. Some of the DTC genetic tests, however, must be ordered by a healthcare professional. After placing an order (usually online), a consumer receives saliva kit, which together with the consumer's saliva sample is sent back to the genetic testing company. The test results are usually delivered online to the consumer. As noted by the Presidential Commission for the Study of Bioethical Issues (2013), by providing health information DTC GT companies “*interact in both the business and medical realms, and could find themselves subject to the ethical principles pertinent to business transactions as well as those of medical care*” [18]. Operating within e-commerce context, at the same time providing health-related information often without involvement of a healthcare-professional, DTC offer of genetic testing has received a lot of criticism since its appearance in 1997. The concerns have been raised mainly from the standpoint of medical ethics and are related to: the adequacy of informed consent, the clinical validity of the testing, advertising practices, impact on the healthcare system, and others.

Chapter 2: ‘Current ethical and legal issues in health-related direct-to-consumer genetic testing’ provides an overview of the current offer of DTC GT and related ethical issues, based on the recent literature and observations of the DTC GT market. Furthermore, as the offer of DTC GT in Europe will likely be affected by the recently adopted Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (the IVD Regulation), the relevant content of the Regulation is discussed in the context of DTC GT.

Empirical study of ethical issues in the offer of whole genome and exome sequencing in direct-to-consumer and clinical context

The two relatively novel approaches, genomic testing and direct-to-consumer offer of genetic testing constitute the core of the objects for which the ethical, legal and social implications are

studied in this thesis. Given the ethical concerns identified in the context of whole genome and whole-exome sequencing (Chapter 1) as well as these raised by direct-to-consumer genetic testing (Chapter 2), a question arises regarding how the ethical issues are addressed in the offer of whole genome and whole exome sequencing directly-to-consumers - an area that had not yet been thoroughly investigated. To address this question the first empirical studies of the offer of whole genome and whole exome sequencing in the direct-to-consumer were conducted and are presented in this thesis (Chapter 3 and 4). These studies focus on the cornerstone principle in medical and research ethics, that is, *informed consent*, both to genetic testing and consent to usage of consumers' biological samples and health-related data for research purposes. The following subquestions served to guide this research:

- A. What is the adequacy of informed consent process for WGS and WES offered directly-to-consumers?
- B. What are practices of companies offering WES/WGS directly-to-consumers regarding consumers' samples and data use, including informed consent?

To answer these questions, a qualitative approach was used incorporating content analysis to examine the relevant content of websites of DTC GT companies offering WGS and/or WES. Content analysis was established as a method in the field of media studies allowing for systematic examination of communicative texts [19]. In the study aiming to answer the first research question deductive approach to content analysis was applied, that is, the analysis was performed using pre-defined categories – essential elements of informed consent suggested in recommendations for informed consent for whole genome sequencing: pre-test counselling, benefits, and risks [20,21] (Chapter 3: 'Content Analysis of Informed Consent for Whole Genome Sequencing Offered by Direct-to-Consumer Genetic Testing Companies'). The categories used in the second study were derived inductively, after initial analysis of the text and they are: purpose and period of samples and data storage, consumer consent, data access and sharing, identifiability and confidentiality of data, and proprietary claims (Chapter 4: 'Ethical issues in consumer genome sequencing: use of consumers' samples and data').

One of the observations encountered in the above outlined studies was that even though some elements of information were presented to consumers, they appeared as potentially difficult to

understand due to usage of complex vocabulary. This observation prompted the third research question regarding the ease of understanding of informed consent documents for whole genome and exome sequencing, namely:

C. How readily understandable are consent forms currently being used for WGS and WES in a clinical setting?

In this study, informed consent forms for clinical WGS and WES (that are used in the healthcare setting to inform medical care) were examined. Informed consent forms for WGS and WES advertised directly-to-consumer, however, stating explicitly that the test is clinical, were also included in this study. To answer the third research question, readability tests were used to determine what reading grade levels were required to comprehend a given text. These readability tests are based on the number of complex words and the length of sentences. The readability study of informed consent forms is described in Chapter 5: ‘Readability of informed consent forms for whole exome and whole genome sequencing’.

Content of the following chapters was published as articles (Chapters 2-5) or as a book chapter (Chapter 1). Details of each publication are outlined in the beginning of each chapter. The contributions of each author to these publications are described in the section “Co-authors’ statements”, in the end of this thesis.

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Chapter 1: Current Ethical Issues Related to the Implementation of Whole-Exome and Whole-Genome Sequencing

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In *Movement Disorder Genetics* 2015; pp. 481-497, Springer International Publishing, DOI:10.1007/978-3-319-17223-1_22

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Abstract

We have briefly discussed herein four of the many aspects that raise concerns in the context of implementation of whole-exome and whole-genome sequencing (mainly) in the clinical realm. Namely, we addressed issues surrounding: (1) the duty to hunt for variants known to have a health impact, (2) such “hunting” or opportunistic screening in children, (3) challenges to the consent process, and (4) the commercialization of genetic testing direct to consumer.

Keywords: whole-exome sequencing (WES), whole-genome sequencing (WGS), genomic variants, genetic testing, opportunistic screening, hereditary diseases, informed consent, direct-to-consumer (DTC) genetic testing, undiagnosed genetic conditions

1.1 Introduction

The Human Genome Project, a global collaborative effort aimed at sequencing the entire human genome, cost over \$2.7 billion and took more than 10 years to complete. The first draft of the human genome was published in 2001 [1]. Since then, rapid advancements in *next-generation* sequencing technologies (NGS, i.e., new high-throughput and massively parallel DNA-sequencing technologies) have led to a drastic decrease in both the price and time needed for genome sequencing. As of 2014, the National Human Genome Research Institute estimates the

average cost of whole-genome sequencing (WGS) at approximately \$4,000–5,000 [2], while the time required for this (without interpretation of variants) has been reduced to several days [3]. For over a decade now, the target price of \$1,000 per genome has been discussed, and recently some companies have announced having reached this goal, or of being very close to it [4]. Moreover, whole-exome sequencing (WES), which analyzes only 1 % of the genome, the protein-coding sections [5], entails lower costs, and for now appears to be preferred in the clinical diagnostic setting [6].

The decreasing cost and time of sequencing have led to the expectation that WES/WGS will become commonplace in medical practice, including diagnostics, as well as in population screening [7, 8]. In the past few years, both WES and WGS have been successfully used to identify causative mutations in some highly selected patients with rare or undiagnosed diseases of genetic origin [7,9–12]. Although the relatively high costs of WES/WGS currently preclude large-scale adoption of genome sequencing in the clinical setting, it has been suggested that rapidly diminishing sequencing costs may soon make the techniques cost-effective in a broader range of clinical cases such as personalized diagnosis and personalized drug therapy. Moreover, some have predicted that sequencing technologies will also be applied in public health programs, such as newborn screening programs [13].

Despite the potential promises of WES/WGS in clinical practice, a number of challenges have been identified with regard to the potential implementation of sequencing technologies in health care. Firstly, even though the analytic validity of WES/WGS has improved dramatically, current sequencing techniques remain imperfect. For example, a recent study reported that, depending on the sequencing platform used, WGS failed to sufficiently cover from 10 to 19 % of inherited disease genes of interest [5,14]. Imperfect analytic validity of WGS is worrisome, since given the large scale of the human genome (>3 billion base pairs), even a very small percentage of erroneous results would translate into a high number of incorrect variants in absolute terms [12].

Secondly, owing to the present limited understanding of the human genome, many variants currently identified through WES/WGS are unclassified; that is to say that they are variants of unknown significance, and their potential effect or impact on an individual's health is yet to be determined [7]. Indeed, debates have been ongoing regarding to what extent such findings

should be reported to patients. Although unknown or unclassified variants may be valuable for research purposes, in the healthcare setting, they might offer little benefit to the individual patient as long as their true meaning has not been correctly understood. Furthermore, a large number of genetic variants, when combined with other genetic variants or environmental factors, may be suspected of playing a role in an individual's predisposition to multifactorial conditions, such as cancer, diabetes, and cardiovascular diseases. However, the predictive value of such results may be low [8]. Although this is not specific to the technique of WGS/WES, given the large amounts of data generated with these approaches, one could predict that there will be more of these variants found with uncertain meaning. Moreover, the use of WES/WGS may reveal variants unrelated to the primary indication for sequencing (i.e., unsolicited or incidental findings) and lead to the question of which findings should be communicated to patients [7], how, and by whom [15]. This issue becomes even more knotty when the individual tested is a child, and findings may be relevant only later in life or may be predominantly informative (at the time of testing) for family members (but not necessarily for the child being tested).

Thirdly, the amount and variety of information obtained through WES/WGS have important implications for information provision and counselling to the patients undergoing the procedure. Due to the complexity of the procedure – including technical aspects of WES/WGS, diagnostic value, likelihood of unsolicited/incidental findings, and implications of the test results for other family members – pretest counselling involving the informed consent procedure could drastically increase the time of the counselling process [16, 17]. Such counselling sessions should, ideally, clearly distinguish among the types of expected results in order to facilitate an informed decision by the patient [18]. Notably, post-test counselling may be equally time-consuming, especially if the patient chooses to receive extensive information on incidental findings [7]. Furthermore, additional counselling and consent sessions may be required in those cases where either the patient's biological sample or data derived through WES/WGS are to be retained for future research purposes.

Evidently, there are several concerns with respect to the implementation of WGS/WES; herein, we outline four important ethical challenges to the implementation of these approaches in clinical care (and the related commercial context). To begin with, the issues related to

unsolicited findings and opportunistic screening in WES/WGS will be discussed: first in more general terms and secondly with respect to a pediatric population. Next, problems with informed consent will be covered. Finally, ethical issues regarding direct-to-consumer genetic testing will be considered.

1.2 Unsolicited Findings and the Duty to Hunt

As alluded to above, the increasing use of high-throughput technologies and approaches in genomics, both in the research and clinical contexts, has increased stakeholders' focus on the topic of unsolicited findings. Unsolicited findings have also been referred to as incidental findings, unsolicited variants, unanticipated results, secondary variants, unexpected or off-target results, unsought results, or unrelated findings [19], as well as non-incidental secondary findings, serendipitous, or iatrogenic findings [20]. The exact meaning of each term as well as their merits has, to some extent, been debated and could, arguably, be even further discussed [19,21,22]. However, for the purpose of this chapter, we will use the term unsolicited finding to mean a result found during research or clinical testing that is beyond the aims of the study or the original reason to conduct clinical testing.

Although unsolicited findings are not specific to genomics, the phenomenon is viewed as needing particular attention given the fact that we can now generate unprecedentedly large quantities of sequencing data in a very short time and therefore have access to a lot of information, whether or not it is related to the initial question posed [23]. Many authors have discussed whether or how unsolicited results should be returned to patients in the clinic [24] or to research participants in a research study [25]. Although there remains a lot of discussion regarding details, there appears to be a consensus taking shape: should a clinician or researcher discover a medically actionable variant with established health impact, this information should be returned to patients/participants [26,27]. For example, the European Society of Human Genetics recommends "If the detection of an unsolicited genetic variant is indicative of serious health problems (either in the person tested or his or her close relatives) that allow for treatment or prevention, in principle, a health-care professional should report such genetic variants" [18]. This being said, the details regarding which variants have utility or impact and the criteria needed to make these decisions are still being debated [23].

Closely related to this topic is the notion of the “duty to hunt” for genomic variants that may have a health impact for patients; that is to say, when performing WES/WGS, do physicians and/or researchers have a duty to actively search the sequence data for variants known to have a health impact but that are not necessarily related to the indication for performing the sequencing in the first place? Although some authors have referred to the findings obtained through this “hunt” as incidental findings [20], others have commented that such intentional “hunting” or searching could not be described as “incidental,” at least not in the “usual sense of the term” and have described the phenomenon as “opportunistic screening” [28,29]. The discussion regarding the return of results, including the duty to hunt, differs somewhat depending on the context, clinical, or research [30]; herein, we focus on the issue of the duty to hunt in the clinical context.

Perhaps, the most well-known stance supporting a duty to hunt in the clinical context comes from the American College of Medical Genetics and Genomics (ACMG) which, in the first half of 2013, published recommendations supporting “that laboratories performing clinical sequencing seek and report mutations of the specified classes or types in the genes listed here. This evaluation and reporting should be performed for all clinical germline (constitutional) exome and genome sequencing, including the “normal” of tumor-normal subtractive analyses in all subjects, irrespective of age but excluding fetal samples” [20]. The ACMG provided a list of 56 genes associated with 24 inherited conditions that should be screened whenever a patient (of any age) is offered sequencing. The list was developed based on what the ACMG called a “consensus-driven assessment of clinical validity and utility” and focuses on conditions with relatively high penetrance and for which an intervention may be possible. Importantly, the list does not include conditions that are already part of newborn screening. The initial recommendations proposed that patients could not refuse the testing of these 56 genes without also forfeiting the access to WES/WGS. However, in the face of criticisms concerning the lack of support for patient autonomy, shared decision-making, and for patients’ right “not to know” [28,31,32], the ACMG changed their stance on this point the following year [33]. The rationale for opportunistic screening is based mainly on the medical benefit for patients and their families, where the identification of a genetic risk could allow for the early adoption of prevention or treatment measures. Furthermore, it is based on the fiduciary duty of clinicians and laboratory personnel to prevent harm. It should be noted, however, that these recommendations are not

meant for sequencing done in the context of preconception, prenatal, or newborn sequencing, nor do they apply to the sequencing of healthy children and adults [20].

A number of concerns have been raised in reaction to these recommendations, including a lack of evidence for establishing the list of genes and the lack of information about frequencies of variants in healthy or not-at-risk populations [28]. Such a lack of information could subsequently lead to erroneous classifications of variants as pathogenic, which could cause needless anxiety and cause patients to seek inappropriate and costly follow-up medical procedures [34]. The fact that important stakeholders, such as members of the public and primary care physicians, were absent from the discussion [32] has also been mentioned as a weakness. Of major concern is also the potentially extremely high costs in terms of time, resources, effort, and money to conduct such screening [32]. Furthermore, there has been criticism regarding the screening of children in this context, especially for adult-onset disorders (see below).

Although other professional associations' and policy groups' guidelines have mentioned opportunistic screening, they have not outright recommended it [29, 35]. Moreover, the European Society of Human Genetics' guidelines on the use of WGS in health care advise that approaches such as targeting and filtering be used to reduce the chances of even encountering unsolicited findings: "When in the clinical setting either targeted sequencing or analysis of genome data is possible, it is preferable to use a targeted approach first in order to avoid unsolicited findings or findings that cannot be interpreted. Filtering should limit the analysis to specific (sets of) genes. Known genetic variants with limited or no clinical utility should be filtered out (if possible neither analyzed nor reported)" [18]. Although only indirectly addressed within the context of the management of incidental findings in the clinical context, the Presidential Commission for the Study of Bioethical Issues recommends that "Medical educators, both in the classroom and clinic, should continue to cultivate 'diagnostic elegance' and 'therapeutic parsimony' amongst practitioners—ordering and conducting only tests and interventions necessary for addressing health concerns related to their patient" [36].

In conclusion, currently, there is no general agreement regarding whether clinicians who use WGS or WES for diagnostic purposes also have a duty to hunt for other variants with health

impacts. There is, however, a large consensus that much more evidence is needed [20, 28, 34] regarding opportunistic screening and its potential impact on the healthcare system and on patients. Even the ACMG recognizes that “there are insufficient data on penetrance and clinical utility to fully support these recommendations, and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected” [20].

1.3 Opportunistic Screening in Children

As previously mentioned, the introduction of WES/WGS in the clinic may revolutionize the potential for finding the (molecular) diagnosis of genetic conditions, including movement disorders. Although this may confer benefits in terms of reducing the diagnostic odyssey, and/or improving patient management [7] as well as revealing potential risks for relatives, it also raises ethical issues in relation to genetic testing in children.

Consider this scenario: 8-year-old Jack is referred to your clinic for investigation of the genetic cause of his progressive ataxia. His parents, who are considering having a second child, are keen to find out the genetic basis of his condition in order to avoid having a second affected child. Given there are several candidate genes, you decide whole-genome sequencing will be most cost-effective. Following testing, you receive the laboratory report which reveals the genetic cause for Jack’s progressive ataxia, as well as a result unrelated to diagnosing the ataxia – that he carries a variant in BRCA1. This variant is expected to be pathogenic and therefore has health implications for Jack, one of his parents, and potentially their extended family members.

As described in the previous section, the use of WES/WGS raises the question as to whether laboratories should limit their reporting of results only to the findings that are relevant to the clinical question at stake or to “hunt” for other variants known to have a health impact. The previously mentioned ACMG guidelines, which recommend the active search of a selected group of genes, including those for conditions with adult onset, have led to a heated debate regarding whether these recommendations should also apply to children. The ACMG states that “masking or tailoring the reporting of such information according to the age of the patient could place an unrealistic burden upon laboratories facing increasing volumes of clinical sequencing. The Working Group also felt that the ethical concerns about providing children with genetic

risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parent of discovering an incidental finding where intervention might be possible. Therefore, the Working Group recommended that recommendations for seeking and reporting incidental findings not be limited by the age of the person being sequenced" [20].

These recommendations appear to be in stark contrast to previous recommendations for predictive testing in children as well as to a set of guidelines which were jointly released by the American Academy of Pediatrics (AAP) and the ACMG in 2013 [37,38]. The AAP/ACMG guidelines recommend that children should generally not receive genetic testing for adult-onset disorders, particularly where no treatment is available [37,38]. It should be noted, however, that the contextual background of testing differs somewhat for each set of guidelines. The AAP/ACMG guidelines are generally situated in a clinical setting where parents may request predictive testing for their child for an adult-onset condition that is already known in the family [37,38]; no particular strategy or tool for testing is mentioned nor do they mention a situation of opportunistic screening. The ACMG guidelines, on the other hand, relate specifically to a situation such as Jack's, described above, where WES/WGS is used as a diagnostic approach [20].

This contextual difference translates to two important distinctions between the WES/WGS diagnostic approach from the standard predictive testing context [39]. First, the nature of the tools or approach used for diagnostic purposes in Jack's case means that the sequence data is already available for the "hunt" rather than a specific test being performed only for the reason of testing an adult-onset condition. Second, the genetic predisposition Jack carries for BRCA1 may not have been identified previously in the family, and reporting of the variant could, therefore, potentially lead to early detection of risk and implementation of screening for both Jack in the future and also for relatives. These are the primary drivers of the ACMG's recommendations for reporting these variants [20].

Although the reporting of results from opportunistic screening might result in health benefits for the children or their family, we must also consider the potential (harmful) impact when one of these variants is identified in a child and disclosed to the family. Standard genetic guidelines

for predictive testing in children often indicate that when there is no medical benefit from performing predictive testing, then it is in the child's best interests to postpone testing until the child is able to make an autonomous decision [37,38,40–42]. That being said, the AAP/ACMG guidelines also leave some room for alternate routes when they state that "...after careful genetic counseling, it may be ethically acceptable to proceed with predictive genetic testing to resolve disabling parental anxiety or to support life-planning decisions that parents sincerely believe to be in the child's best interest" [38]. One of the challenges in the context of genetic testing is that there are many different views regarding exactly what constitutes as being in the child's best interests [43].

One way of determining what is in the child's best interests might be to assess the harms of reporting and not reporting the results from opportunistic screening (or unsolicited findings). Some authors have proposed that the harms of reporting such results in children are limited to the imposition of undesired genetic information on the child and their family [44]. They argue that this is outweighed by the potential harm of removing family members' opportunities to avoid illness through screening [44]. Although genetic guidelines generally recommend against providing predictive testing in young children, few studies have investigated the psychological impact of testing [40–42,45]. There is, therefore, little in the way of evidence to suggest that identification of an unsolicited finding (or results from opportunistic screening) predisposing a child to a genetic condition would cause psychological harm. However, lack of evidence does not equate to evidence of a lack of harm, and therefore, additional empirical studies to investigate this are required.

The ACMG has taken a more family-based approach to what is in the child's best interests. They argue that identification of these pathogenic variants in children benefits the child, first by providing them with important information about their future health risks and, second, through the potential health benefits to their parents should they be detected prior to displaying symptoms of the genetic condition for which a mutation was detected. Therefore, the ACMG believes that the ethical concerns are outweighed by the "potential benefit to the future health of the child and the child's parents" [20]. For this reason, their follow-up recommendations indicated that it could be viewed as unethical if laboratories do not report these unsolicited findings, because they are failing to allow parents to act in their child's best interests and avoid

preventable harm [44,46]. This is in line with literature acknowledging that parents are best placed to consider all the factors that impact on their family and should therefore be allowed to make decisions in a way that takes the family's best interests into account [47]. This being said, whether parents will be sufficiently informed regarding the unsolicited information they might receive in order to make decisions on behalf of their children and their broader family is unclear.

One should consider what else is at stake for the child if we report the results of opportunistic screening (or unsolicited results). A commonly stated argument against predictive testing in children is that, as well as removing their right to privacy (regarding their genetic result), it impinges on their future autonomy, specifically the child's ability to make his/her own decisions about whether they want to know their genetic status when they are older [42]. This concept has been referred to as "the child's right to an open future" and rests on the notion that genetic testing would narrow the child's future options [48,49]. Likewise, when the results of opportunistic screening are reported to the clinician and subsequently to Jack's parents and Jack, we are removing the child's right not to know whether he has a *BRCA1* mutation. From this perspective, preservation of the child's future autonomy would involve either not conducting the screening at all for adult-onset disorders or, in the case of a truly "stumbled upon" incidental finding, to not report it to the clinician. Alternatively, the result could be reported to the clinician and held in trust until the child is able to make an autonomous decision. However, one might also view that by disclosing the results of opportunistic screening to the family, we are in fact broadening the options available to Jack and his family by providing them with opportunities for further screening and preventative care.

Debate continues as to whether laboratories should "hunt for" and report back results for a preset list of genes when WES/WGS is conducted in the clinical setting in children or whether reporting should be restricted to findings relevant to the quest for a diagnosis. Ultimately, it depends on the importance one places on the preservation of the child's right not to know information about their genetic risks compared to the potential health benefits for the family. Given that once information is known, it cannot be "unknown," perhaps the initial premise should be to remain cautious until more evidence is amassed regarding the impact of returning results to children for adult-onset disorders and limit reporting to the original clinical question and, in doing so, promote the child's future autonomy.

1.4 Informed Consent for WES and WGS in Diagnostics

Informed consent in clinical practice functions as a permission given for the performance of a medical procedure by a capacitated patient to whom the information about the procedure has been given, who understands it fully, and voluntarily consents to it. Informed consent has been integrated in most jurisdictions as a legal requirement and supported ethically as ultimate respect for the autonomy of individuals and their right to self-determination [17]. It has been argued that in order to obtain genuine informed consent, the information about the procedure (or in this context the genetic test) presented to a patient should be accurate, relevant, and understandable, and the patient should have the opportunity to freely withdraw consent [17,50]. Yet, obtaining valid and adequate informed consent for some medical procedures poses challenges such as those related to proper communication of the information and its comprehension, which is particularly relevant for informed consent for genetic testing. The fact that clinical genetic testing is usually offered with both pre- and post-test genetic counseling is an indication of how important and potentially complex communication can be in this context. Herein, we offer a list of issues that should be considered when planning for the informed consent procedure for WES/WGS.

Indeed, the implementation of WES and WGS adds further challenges and amplifies those already existing related to the informed consent procedure for “traditional” genetic tests. This is primarily caused by the vast amount of complex information that may be extracted from whole-exome or whole-genome sequence data. This information varies with respect to the clinical significance and predictive value, which may influence the individual’s desire to obtain particular results [51]. Related to this, the potential for unsolicited findings is of particular concern in the informed consent process. Among others, they raise a question about the categories or types of genetic variants (i.e., those with high penetrance or clinical utility or health impact) that should be retrieved from a whole-genome sequence [18,20] and what should be reported to patients. Even if sequencing is targeted and filters are applied to WES/WGS with the aim of obtaining only findings relevant to the medical indication in question, unsolicited findings may nevertheless appear in the process of sequence analysis and interpretation. Although unsolicited findings exceed the initial scope of the test, they may be clinically actionable, which poses questions about the obligation to disclose them [36]. Additionally, the

significance of sequencing data may change with time as our understanding of variants progresses through genomics research. Therefore, the storage of the data should be considered as well as the possibility of reanalyzing and reinterpreting data in the light of new scientific findings and whether the patient agrees to be recontacted for this information (or for any incidental finding). Furthermore, in the case where clinical whole- genome sequencing is coupled with research, this subject, including the issue of data sharing, should be discussed during the informed consent process [52]. Finally, as with other genetic tests, some of the outcomes of WES/WGS for hereditary diseases concern not only the patient but also the relatives or future offspring; thus, this introduces the dilemma of potential obligation to disclose some information to family members [25]. Additional difficulties appear in case of WES/WGS offered for children, whose “right not to know” regarding health prospects should be retained as much as possible [51] in the case of testing for adult-onset conditions. All of the issues outlined above make the process of designing appropriate informed consent procedures in the context of WES/WGS particularly challenging. It is crucial to communicate with the patient regarding these factors and, in particular, to communicate the meaning and implications of the different types of expected findings in an understandable way that would allow truly informed decision-making.

Given these challenges, many societies and experts have attempted to face or overcome the difficulties of informed consent in this new context of WES/ WGS. Ayuso et al. specifically analyzed publications and guidelines concerning or related to informed consent for WGS in the clinical context [53]. The authors found a relatively high level of consistency among the guidelines and proposed a minimum list of information that should be provided to the patient, which are the management of incidental findings, the scope, a description indicating the kind of information to be obtained, the possible benefits and risks, the availability of alternative tests, the voluntary nature of the test, the possibility of refusal, the future use of the data, and the confidentiality of the outcomes. Pretest counseling has been underlined by the authors of the abovementioned publication as well as by other experts in various recommendations as a crucial element of informed consent [53]. Pretest counseling should prevent informed consent from being reduced to the mere signing of a document. It should be ensured through dialogue that the patient truly understands the information provided and is competent to make a choice. Fulfilling

these requirements in the context of WES/WGS will demand time-consuming counseling sessions provided by properly trained professionals [55].

Various authors have also suggested new strategies of informed consent that may minimize information overload by introducing clinically relevant categories of diseases and traits, layers of indispensable and additional information, and informational and decisional phases of consent that require it to be stretched in time [56–59]. Dynamic models of consent, where the use of information technology interfaces places patients at the center of the decision-making process and allows them to be more engaged over the entire time span of use of their sample/information, may also help to ease the challenges of consent for WGS/WES [60]. These different strategies may facilitate the counseling and informed decision-making of the patient regarding the type of test they want to consent to and categories of results that will be returned.

Concluding, informed consent is just one of the elements related to the ethical issues around WES/WGS. Its adequacy may not resolve the other ethical issues related to data handling and return of results; however, efforts should be made to implement the proposed recommendations and new strategies of informed consent for WES/WGS into clinical practice. Thereafter, studies may be conducted toward optimizing informed consent procedures so that it may fulfil its functions more adequately.

1.5 Genetic Testing Beyond the Clinic: Commercialization of Genetic Tests

Although not, strictly speaking, a part of the realm of “clinical” genetics per se, direct-to-consumer (DTC) genetic testing, in many ways, brushes up to the activities of clinical genetics (e.g., some of the types of tests being offered and the inclusion of healthcare professionals in the process). Furthermore, as a relatively new phenomenon, which has sparked a great deal of debate in the last years, we chose to address these activities and their ethical dimensions herein. Unlike the previous sections, however, we do not confine the discussion only to WES/WGS and the companies offering these services DTC, as these are fairly recent, and the ethical issues surrounding companies offering genome-wide testing are very similar to those offering WES/WGS. Furthermore, it is important to note that all three previous topics discussed are relevant concerns, albeit with some variations, for companies offering WES/WGS DTC.

For more than a decade now, several for-profit companies have been commercializing genetic tests through the Internet, often without involving a healthcare professional in their services [61]. Such tests are advertised directly to the public, and consumers may order and receive the tests themselves, or through a healthcare provider [62]. The majority of direct-to-consumer (DTC) genetic testing companies are based in the USA, although the number of companies established in Europe and Asia is also growing [63]. The DTC genetic testing market comprises a very heterogeneous spectrum of companies and products, while its size is still unspecified [64].

Currently, a wide variety of genetic tests is available DTC, including tests for recreational purposes, such as athletic performance and ancestry tests and tests for health-related purposes such as tests for multifactorial or monogenic disorders, test for carrier status, and nutrigenomics and pharmacogenomics tests. While in previous years the most comprehensive testing was offered mostly by companies genotyping hundreds of thousands to millions of SNPs, more recently companies are now also offering whole-genome and whole-exome sequencing directly to the public.

Specifically for conditions under the umbrella of movement disorders, various consumers might be able to find tests DTC, including tests for susceptibility to Parkinson's disease [65], Tourette syndrome [66], and restless legs syndrome [67], as well as carrier tests for ataxia-telangiectasia (ATM) [68] and rare diseases such as myoclonus dystonia (DYT11) and Rett syndrome (MECP2) [68]. In the past, some companies have also offered susceptibility tests for essential tremor, tardive dyskinesia, and progressive supranuclear palsy [69]. Indeed, DTC genetic tests on offer are frequently subject to changes, as the DTC genetic testing market is a particularly dynamic field.

Supporters of DTC genetic testing claim that such tests promote genetic education of consumers, empower them to improve their health by making their own healthcare decisions, and enhance their autonomy [70]. In addition, given that DTC genetic testing may potentially enable consumers to control who has access to their test results, this type of testing is considered, by some, to protect privacy of genetic information toward employers and insurance companies [71].

Nevertheless, DTC genetic testing has also been subject to a lot of criticism over the past years, and concerns have been raised by several authors and professional organizations regarding the potential risks stemming from such tests. One of the main concerns regarding this type of testing has to do with the uncertain clinical validity and utility of many of the tests offered DTC. When it comes to susceptibility testing for common complex disorders, such as Parkinson's disease, where the development of the disorder is usually the result of several genetic mutations acting in combination with other nongenetic factors [72], the predictive value of individual genetic variants remains low [72], and the commercialization of such tests is often considered to be premature [73]. The clinical utility of such tests is also questionable in many cases, since the test results are often not clinically actionable, and the health advice provided along with them is usually generic [74]. When thinking of rare monogenetic disorders, some concerns also exist about the extent to which the pathogenicity of variants is known, as well as penetrance and expressivity, especially in healthy populations, which have traditionally not been studied for such disorders. Moreover, when using WES/WGS, the problems of reporting (or not) variants of unknown significance remain.

In addition, it has been claimed that without genetic counseling and individualized supervision from a healthcare professional, consumers are more likely to misinterpret the test results and potentially take inappropriate healthcare actions or experience unnecessary anxiety [71]. The importance of medical supervision and pre- and post-test genetic counseling in the context of genetic testing for movement disorders is often underlined, since the test results are, in many cases, inconclusive, and their interpretation requires a high level of expertise in genetics [75,76]. Furthermore, in light of the limited clinical interventions available for disorders like Parkinson's disease, performing the appropriate test for the appropriate person is particularly important, in order to avoid unnecessary distress and redundant visits to healthcare professionals [75]. It is important, therefore, that this type of testing is performed in the context of genetic counseling and that it is based on an informed decision of the patient [75]. Despite the fact that lately, many DTC genetic testing companies tend to involve healthcare professionals in their services, various concerns remain. Including a medical prescription on paper for genetic tests is not a guarantee of an adequate informed consent procedure and pretest counseling. In most cases, any physician seems to be allowed to order genetic tests regardless of whether he/she has adequate training to do so. Finally, some healthcare professionals may be employed or

otherwise collaborating or linked with some companies, raising doubts about their impartiality [62].

Several professional organizations, genetic societies, and bioethics committees have addressed concerns related to DTC genetic testing, stressing in guidelines and recommendations the importance of medical supervision, genetic counseling, and informed consent and ensuring the quality of the tests [72,77,78]. Nevertheless, the effective regulation of this field remains a challenge, since the regulatory landscape both in Europe and the USA is rather fragmented and complex, leaving some important gaps [63]. Furthermore, the idea of a “one size fits all” regulation for all types of tests (e.g., ancestry, health related, etc.) may not be the most coherent approach. Finally, enforcement of national legislation may be problematic, given the global character of this industry which operates mostly through the Internet [79].

Conclusion

We have briefly discussed herein four of the many aspects that raise concerns in the context of implementation of whole-exome and whole-genome sequencing (mainly) in the clinical realm. Namely, we addressed issues surrounding (1) the duty to hunt for variants known to have a health impact, (2) such “hunting” or opportunistic screening in children, (3) challenges to the consent process, and (4) the commercialization of genetic testing direct to consumer. Indeed, none of these are new issues per se, but each issue when brought into the context of WES/WGS has new particularities and appears to be exacerbated by these high-throughput approaches. Furthermore, it is clear that the ethical and procedural frameworks previously created to deal with these aspects for “traditional” clinical genetic testing (i.e., where one or few genetic tests were performed usually sequentially) are, at best being challenged by the use of WES/WGS, and at worse, completely inept to properly manage these areas and concerns.

It is evident that, overall, more evidence is needed in order to pave the route to responsibly manage the implementation of WES/WGS in clinical care. Regarding the return of incidental findings and/or opportunistic screening, it will be important to closely study centers and pilot projects that currently offer these services to patients and to study the impact on patients. Additionally, with respect to programs for opportunistic screening, like that proposed by the ACMG, evidence is needed regarding the penetrance and mutagenicity of the 56 genes in

healthy populations. Evidence is also needed specifically regarding the return of results for children, especially for adult-onset disorders. Are children negatively impacted by such information? Is there a benefit to them knowing? With respect to the ACMG guidelines, there is also a need to discuss and reconcile the discrepancies between traditional guidelines that suggest no testing in children for adult-onset disorders unless action can be taken to reduce the chances of developing the disorder. This discussion should also address the fact that DTC genetic testing companies can, and do, test children for adult-onset disorders. Regarding consent, new models and procedures of consent need to be carefully planned to integrate all the aspects and information needed to obtain proper informed consent in the context of WES/WGS. These then need to be tested on patient populations and the impact on patients measured. Finally, the DTC offer of genetic testing should continue to be monitored, as this group of actors has tended to offer services that go well beyond what we have been used to in the traditional clinical context.

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Chapter 2: Current ethical and legal issues in health-related direct-to-consumer genetic testing

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Published in: *Personalized Medicine* 2017, 14(5), 433-445

DOI: 10.2217/pme-2017-0029

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Abstract

A variety of health-related genetic testing is currently advertised directly to consumers. This article provides a timely overview of direct-to-consumer genetic testing (DTC GT) and salient ethical issues, as well as an analysis of the impact of the recently adopted Regulation on In Vitro Diagnostic Medical Devices (IVD) on DTC GT. DTC GT companies currently employ new testing approaches, report on a wide spectrum of conditions, and target new groups of consumers. Such activities raise ethical issues including the questionable analytic and clinical validity of tests, the adequacy of informed consent, potentially misleading advertising, testing in children, research uses and commercialization of genomic data. The recently adopted IVD Regulation may limit the offers of predisposition DTC GT in the EU market.

Keywords: direct-to-consumer genetic testing, genetic testing, consumer genomics, consumer genetics, informed consent, genetic counselling, IVD regulation

2.1 DTC genetic testing and related services

Direct-to-consumer (DTC) genetic testing (GT) (for the purpose of this article we will be using terms 'genetic' and 'genomic' interchangeably) encompass a wide and heterogeneous range of offers, which have constantly been evolving since the emergence of DTC GT almost two decades ago. Given the dynamic nature of the DTC GT market and how it poses (new) ethical and regulatory challenges, in this article we aim to provide overview of the current offer of health-related DTC GT and the related salient ethical issues. Furthermore, as the offer of DTC GT in Europe may be affected by the recently adopted Regulation (EU) 2017/746 of the

European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (the IVD Regulation), we discuss the relevant content of the Regulation in the context of DTC GT.

This article focuses mainly on health-related testing, excluding testing with other main purposes such as ancestry and paternity. However, it is important to note that ancestry test results may reveal health-related information to consumers given the known associations between genetic ancestry markers and disease, some of which have been reported in mainstream media and received attention of ancestry testing consumers [1]. Furthermore, web-based interpretation services can provide health-related information on the basis of raw data received from ancestry genetic testing.

2.1.1 Direct-to-consumer genetic testing definition

Direct-to-consumer genetic testing is a commercial model of genetic testing provision whereby consumers can undertake a test without necessarily any involvement of a healthcare professional (HCP). A consumer can order a test via the Internet or buy it at a pharmacy, (s)he then receives a saliva or swab kit, which together with the consumer's saliva sample is sent to the genetic testing company. The results are usually delivered online to the consumer. A number of DTC GT companies however, do advertise directly to consumers, but then, require that the test be ordered by a healthcare professional and/or that the results be returned to a HCP. This broader definition of DTC GT including testing advertised directly to consumers, but involving a HCP was recognized in 'A Common Framework of Principles for direct-to-consumer genetic testing services' issued by the UK Human Genetics Commission [2] as well as by researchers [3,4]. Supporting this definition is the fact that one of the crucial characteristics of DTC GT, that is to say, advertising directly to consumers, is retained in the model of DTC GT including a HCP.

2.1.2 Current offer of DTC GT – expanded scope, audience and new technology

The first health-related genetic tests marketed directly to consumers were identified almost two decades ago [5]. In 2002, as part of research aiming at identifying the availability of DTC GT, Gollust et al. identified 14 companies selling health-related DTC GT [6]. A recent study by Phillips (2015) revealed that the market of health-related DTC GT has grown significantly in the last decade reaching over hundred companies [7]. Considering that these studies (including

search terms) were performed in English, the total number of companies offering DTC GT may be assumed to be even larger.

Importantly, not only has the number of companies grown in recent years, but their offer has expanded regarding the scope of the tests, technologies used, and the target audiences of the tests. The types of health-related tests offered by DTC GT companies include lifestyle (dietary and fitness) testing, pharmacogenomic tests (concerning reaction to drugs), carrier testing (revealing persons who carry a mutation that may cause a disease in their offspring), and tests providing diagnostic and disease predisposition information. The range of diseases for which companies provide results also varies greatly, starting from single-gene diseases with known genetic cause(s) (i.e. mendelian or monogenetic diseases, e.g. sickle cell anaemia) to conditions having a complex genetic background and for which development is usually the result of several genetic and non-genetic factors acting in concert (i.e. complex diseases, e.g. cancer, diabetes).

Furthermore, the DTC offer of genetic testing varies regarding the amount of data/results provided. Some companies offer single gene tests (e.g. Graceful Earth) [8], others offer the testing of a group of genes relating to a type of disorder (e.g. cardiology-panels offered by Invitae) [9], while others offer genome wide testing of hundreds of thousands of single nucleotide polymorphisms (SNP) and offer a report on over a hundred conditions and traits (e.g. 23andMe) [10]. In recent years, companies, have also been offering whole exome sequencing and whole genome sequencing [11]. Whole genome sequencing generates readouts of (almost) all the DNA present in cells, whilst whole exome sequencing provides sequence of all protein coding regions of DNA; in both cases the amount of genetic information obtained is unprecedented. Once sequenced, the exome or genome can then be analysed for specific, defined purpose(s) (e.g. using targeted gene approach where only a subset of genes is analysed), for example to identify variants relevant to a specific disease, variants related to responses to drugs, or variants associated to (complex) traits.

Currently DTC GT is advertised not only to the (healthy) ‘worried-well’ (i.e. symptomless adults anxious about their health) and persons with higher education levels and disposable income. The decrease in price as well as the expansion of the types of tests offered resulted in the significant expansion of the consumer groups to which DTC GT is explicitly aimed. Namely this encompasses: couples considering having children (carrier screening, e.g. Counsyl) [12], pregnant women (prenatal testing, e.g. Veritas Genetics) [13], and individuals wanting

preimplantation diagnosis/screening tests, which allow for the selection of embryos that have (or not) specific genetic variants can be selected (e.g. offered by Illumina) [14]. Furthermore, parents of new-borns [15] and children [16] are being encouraged by companies, through online advertisements, to purchase the tests for their offspring.

2.1.3 Interpretation and data sharing services for DTC GT consumers

Some DTC GT companies (e.g. 23andMe) provide consumers not only a report describing results of the testing (i.e. the interpretation of genetic variants with respect to disease), but also non-interpreted raw data in a downloadable format [17]. These raw data can then be uploaded on several online genomic data interpretation services, for example: Promethease [18], LiveWello [19], Genetic Genie [20], Sequencing [21]. Such online services provide consumers with health-related information based on the analysis of the raw DNA data.

Furthermore, there are also online services/platforms aimed at DTC GT consumers, to which they can upload their raw genetic data to make them accessible to others (e.g. general public or groups of researchers), for example openSNP [22], DNA.Land [23], Sequencing [21]. Apple has also announced adding a module to its ResearchKit apps allowing consumers to share their genetic data from 23andMe with researchers [24]. Interestingly, there are also companies (Genos, Invitae, Portable Genomics) which are planning to provide consumers platforms for sharing their genetic data for which the consumers would be paid/compensated [25].

2.2 Ethical issues in DTC GT companies

Having originated from outside the traditional health care system, with a plethora of differences from the established clinical genetics offer of genetic testing, health-related DTC GT raises ethical, legal and social implications. These include a long list of issues: lack or problematic involvement of a HCP, adequacy of pre- and post-test counselling, scientific validity and utility of the testing, misleading advertising, potential burden on a healthcare system, testing in minors, secondary uses and privacy of consumers' data, non-consensual uses of testing, and problems related to regulation of DTC GT [26,27]. Many of these ethical issues were identified and discussed to some extent already in the beginning of existence of DTC GT [28]. In the following years, a number of authors further discussed these issues and empirical studies have been conducted to explore the offer of DTC GT and views of different stakeholders (e.g. consumers and healthcare professionals) [29,30]. Furthermore, various expert societies and

advisory bodies such as the UK Human Genetics Commission [2], European Society of Human Genetics [31], European Academies Science Advisory Council [32], have issued recommendations and position statements addressing DTC GT. Moreover, actions were taken by a regulatory authority, the US Food and Drug Administration (FDA), to ensure quality of the offer of DTC GT [33].

Recent literature, both more theoretical or empirical in nature indicates that ethical issues around DTC GT are still not resolved, they are potentially amplified as the technology is evolving and the scope of the offer is expanding [11,34–36]. The aim of the following section is to provide an overview of the current ethical issues of DTC GT and related services, with a focus on analytical and clinical validity of the testing, adequate pre-test counselling and informed consent, potentially misleading advertising, and research uses and commercialisation of genetic data. In the subsequent section, we discuss these aspects from a legal standpoint, and in particular with respect to the changes that will be introduced by the Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (IVD Regulation).

2.2.1 Analytic and clinical validity of the services

The analytic validity (the accuracy with which a genetic variant is identified), clinical validity (how well a variant is associated with a given phenotype/disease) as well as clinical utility (whether or not any intervention/test can improve the healthcare outcome) of many of the DTC genetic tests have been seriously questioned [4,37]. The scientific evidence for clinical validity of tests offered is very limited (especially for complex traits), therefore the commercialization of many of the predisposition tests has been criticized as being premature [37,38]. Furthermore, the disease risk predictions based on genetic data does not consider the environmental/lifestyle (e.g. diet) and family history factors which can modify the genetic risks of diseases to a great extent [37]. Similar concerns about the quality of the reported results may be raised regarding third-party interpretation services, whose interpretation reports may not be based on reliable scientific evidence and may not be understandable to consumers [39].

It is not only the various authors and societies that have been expressing concerns about the validity of DTC GT. 23andMe had been offering Personal Genome Service providing health reports on 254 diseases and conditions including carrier status, disease predisposition, and pharmacogenomic results [33]. In November 2013 the Food and Drug Administration (FDA),

in a warning letter sent to 23andMe, expressed, among others, its lack of ‘assurance that the firm has analytically or clinically validated the PGS [Personal Genome Service] for its intended uses’ and ordered that 23andMe stop marketing its health-related tests until it obtains marketing authorization from the FDA [33]. Consequently, 23andMe limited its offer in the US to ancestry tests, at the same time applying for the FDA marketing authorization for Bloom syndrome carrier status, which was subsequently granted to the company in February 2015 and the test was included in its offer together with other carrier status tests which FDA exempted from its premarket review [40]. Meanwhile, the company has been offering carrier, susceptibility and pharmacogenomic testing for a range of conditions and traits to consumers in countries where the current legal framework does not appear to pose any market barriers, such as Canada, the UK, Denmark, Finland, Ireland, Sweden, and the Netherlands [41]. Moreover, in April 2017 the FDA completed pre-market review and allowed for marketing of another 23andMe genetic test - Personal Genome Service Genetic Health Risk which provides information about predispositions for 10 diseases and conditions [42]. Remarkably, in the related announcement the FDA stated that ‘Results obtained from the tests should not be used for diagnosis or to inform treatment decisions.’, which may indicate that the clinical utility of 23andMe’s tests is still limited [42]. Indeed, some of the variants currently offered by 23andMe are not advised in clinical context by professional recommendations. For example, the testing for APOE variant [10] which is associated with Alzheimer’s disease was described by the American College of Medical Genetics as ‘not clinically recommended due to limited clinical utility and poor predictive value’ together with an indication that in this context ‘DTC genetic testing is not advised’ [43].

Additional problems emerge regarding the interpretation of genetic results. Questions arise as who should be responsible (and liable) for the validity of the results reported as well as who (if anyone) should recontact the patient/consumer if the significance of results changes in the light of new results of genetic research. Is this the responsibility of a physician (if there is one involved in the testing), the DTC GT company, the laboratory which analyses the sample, or database/platform operator used for result interpretation? These issues are regulated to some extent by professional standards (e.g. to be aware of current state of knowledge and/or care in a given profession), and may be addressed, to some extent in the company website descriptions, terms of use and submission agreements (describing the requirements and responsibilities of people adding new data to databases) [44]. This issue does not concern exclusively DTC genetic

testing and interpretation services; however, it may appear more complex in this context given the lack of (adequate) involvement of a HCP in the provision of DTC GT.

One may argue that the limited clinical validity and/or utility of DTC genetic tests are not enough grounds to prohibit their offer outright, provided that these limitations are clearly outlined to consumers. Many companies, indeed, provide this kind of statement e.g. that their services ‘are for research, educational, and informational use only, and are not to be used to diagnose, prevent, or treat any condition or disease or to ascertain the state of health for any individual’ [45]. Doubts arise, however, regarding whether consumers ever read these statements of limitations, given that they are often included in ‘small print’ documents to which consumers agree by ticking ‘I agree’ boxes or by default when using the services [11]. Secondly, even if consumers were well informed about these limitations (indeed, some companies provide explicit well-visible statements about the limitations of testing) [18], questions about potential implications for (public) healthcare systems remain. Should the consumer who obtained results indicating increased probability of a disease contact a HCP within the public healthcare system given that the results are of doubtful validity? Not only may this pose interpretation problems for physicians, it can also result in unnecessary follow-ups and a (financial/resource) burden on a public healthcare system, especially if DTC GT will be gaining in popularity [37]. Notwithstanding, some DTC genetic tests of proven analytical and clinical validity could potentially be useful in clinical care. However, in order for HCP to distinguish valid genetic tests from non-valid tests and to effectively act upon these results if needed, healthcare professionals should be provided with appropriate support [46]. This could come in the form of educational resources like those created in the GENE-EQUIP project [47], or the guidance from the National Institute for Health and Care Excellence (UK) [48]. Adequate legislation setting requirements for solid scientific evidence for analytical and clinical validity of genetic tests entering the market and appropriate labelling of these tests would be desirable in this context. Additionally, placing responsibility on DTC GT companies to provide access to genetic counselling could diminish burden placed on traditional healthcare systems [49].

2.2.2 Informed consent and pre-test counselling

Communicating about genetic information and obtaining valid informed consent for genetic testing is challenged by the complexity of genetic information, and in more recent years, given genomic testing, it is also challenged by the volume of data produced [50]. Therefore, pre-test counselling is recognized as a key element of the informed consent process for genetic testing,

in which relevant information is provided to a person undertaking the test and her/his questions are answered [31]. The lack of involvement of (an adequately qualified) HCP in the provision of genetic testing, as well as often inadequate provision of information about offered testing suggests that DTC GT consumers may not be undergoing this important process as originally described or expected in the traditional health care system [11]. Although a number of DTC genetic tests must be ordered by a HCP, this may not ensure the presence of adequate pre-test counselling given the potential lack of genetics expertise, and potential lack of impartiality if the HCP is hired by a company [3,11]. Furthermore, a study of DTC GT company websites' sections relevant to informed consent (to which consumers agree in order to undertake the test) of companies offering WES/WGS revealed the presence of scarce and potentially misleading information on necessary elements of informed consent (benefits, risks, incidental findings) [11].

Related to informed consent is the issue of non-consensual testing i.e. unlawful testing of a third party using his/her sample without that person's consent, for the purposes of benefiting others or to the detriment of a tested person [27]. The DTC GT context may facilitate this kind of action given the accessibility of testing and the fact that a consumer and not a HCP is responsible for collecting samples for testing (i.e. saliva) and sending it to a company. Although in certain contexts there are laws in place [51] prohibiting this activity and sometimes contractual documents provided by DTC GT company also state the prohibition of non-consensual testing, in practice ensuring that a person whose sample is tested has voluntarily agreed to this procedure poses problems [27]. These issues underline the importance of providing an adequate context for genetic testing provision so that a valid and genuine process of informed consent in which a HCP is involvement is secured.

2.2.3 Advertising

Given the problems with informed consent mentioned above, the potentially misleading advertising of DTC GT, not only via companies' websites but also TV commercials and distribution of emails, seems to be particularly problematic in the context of DTC GT. Additionally, companies in their rhetoric sometimes conflate promotion with "information" or "education" complicating the matter (both for consumers and for regulators) of advertising even more.

Since they appearance on the market, DTC GT companies have been criticised for the potentially misleading claims present on their websites [28]. In 2010 the report of the U.S. Government Accountability Office (2010) revealed that 10 of the 15 DTC GT companies analysed were ‘*engaged in some form of fraudulent, deceptive, or otherwise questionable marketing practices*’ [52]. Furthermore, the analysis of the content of DTC GT websites by Singleton et al. revealed that the information presented on the websites was weighted toward encouraging consumers to purchase the test rather than supporting informed decisions [53]. Borry et al. draw attention to the presence of nonpropositional content of advertisements i.e. appealing pictures and design of DTC GT websites, which may impact consumers perceptions of value of the product and its desirability [54]. In the context of non-invasive prenatal testing advertised directly to consumers, Skirton et al. found that emotive language and misleading information was presented on companies’ websites [55].

2.2.4 DTC GT for ‘reproductive purposes’, newborns and minors

The explicit advertisement of DTC genetic testing to potentially more vulnerable groups such as parents of newborns, minors, and prospective parents amplifies some of the known challenges related to genetic testing outlined in the sections above. In the context of the genetic testing for ‘reproductive’ purposes (i.e. carrier screening, pre-implantation genetic diagnosis/screening, non-invasive prenatal testing) the results can have important implications for the choices of (prospective) parents, for example deciding for an abortion based on genetic test results. In this context, the issues of validity of the testing, provision of information and informed consent as well as advertising are particularly significant.

Moreover, the offer to each of these groups raises specific challenges such as those related to the right not to know of minors and obtaining their assent as well as the more fundamental question of the extent of parental authority in decision making in this new era of genomics [56]. Studies surveying DTC GT companies’ policies regarding testing of minors revealed that companies were performing testing on children’s samples for adult onset diseases, therefore clashing with professional norms, which state, among others, that minors can be tested for adult-onset disorders only if therapeutic or preventative measures are available during childhood for the condition tested [57,58]. A more recent study by Borry et al. indicates similar issues, although in the context of a company explicitly offering testing for newborns [35].

2.2.5 Research uses and commercialisation of consumers' genetic information

Genetic and genomic data are perceived as valuable and their sharing may facilitate diagnosis in patients and the progress of medical research [59]. However, potentially sensitive information about health and ancestry can be retrieved from genetic data; furthermore an entire human genome sequence is unique to each person, therefore in some cases it can be used to (re)identify a person when linked to his/her other personal information [60]. Therefore, using genetic information for research should be accompanied with adequate safeguards to protect privacy, ensure transparency about the uses and sharing practices, and adequate informed consent [61].

Several instances of DTC GT companies performing research have been reported [62,63]. One of the best known and biggest engagement in research by DTC GT consumers has occurred with the company 23andMe, for which over 80% of its 1.2 million customers have consented to participate in research [64]. Consequently, the company may own the largest research databank in the world consisting of genetic information of consented re-contactable subjects. The compliance of these research activities with research ethics requirements, in particular the adequacy of informed consent for participation in research and data privacy, has been questioned [62,63,65]. Similar issues were raised in recent studies of DTC GT websites (one of which investigated companies offering WES/WGS) exploring issues such as secondary uses of samples and data, data confidentiality and privacy. The studies revealed, among others, that some of the companies may perform research on consumers' data and/or samples for which informed consent process seemed not to comply with some of the professional guidelines [36,66].

Interestingly, the company 23andMe not only uses consumers' data for research, but has also sold access to consumers' data affected with Parkinson to a biotech company Genentech for research purposes [65]. Selling access to consumers' data seems to raise similar concerns to those outlined by Sterckx et al. (2014) when discussing patenting activities of 23andMe. In this article, the authors argued, that applying for patents seemed to contrast with company's appeals to promote the public good and, the lack of transparency about it appeared to undermine consumers trust [67]. Furthermore, gaining profit from research performed on consumers' databases, as noticed by Sharon (2016) may seem *'particularly problematic when public money is channeled, indirectly or directly, to their development, as has been the case with 23andMe,*

which recently secured a US\$1.4 million research grant from the NIH to expand its database.'
[68]

Moreover, the problems related to commercialisation of health-related data arise, also in the context of the platforms allowing consumers to share their data and receive compensation for it. On the one hand, paying consumers for access to their data may provide them with an incentive to contribute to research and may appear as a fair and respectful “compensation” for consumers given that the companies and researches (may) benefit financially from using consumers’ data [25]. However, ‘cash-for-DNA’ approach may discourage individuals willing to contribute data for altruistic reasons, while, at the same time being potentially coercive for financially vulnerable individuals, as noticed by Roberts and co-authors (2017) [25]. Furthermore, genetic data commercialisation activities seem to challenge the ideal of open science, data sharing framework based on solidarity and it may as well lead to disparities in research [68].

2.3 DTC GT legislation in Europe

DTC GT in Europe is currently regulated by various laws, both on the national and the European Union (EU) level. Aspects related to patients’ access to GT, the role of healthcare professionals in prescribing the test and/or counselling the patient, as well as the informed consent process are regulated largely by national laws. This is mainly because GT in Europe has been traditionally offered through the public healthcare services and the conditions under which such tests are offered are considered to be part of the clinical practice [69].

The regulation of the clinical practice resides with the Member States rather than the EU, following the principles of subsidiarity and proportionality. These principles mandate that the EU may take legislative action beyond the areas of its exclusive competence, when a given objective may be more efficiently achieved on the EU rather than the national level [70]. As a result, the conditions and restrictions applying to DTC GT may vary across Europe. Currently, there are countries, such as Germany and France, which restrict the GT framework, by adopting strict laws regarding the type of tests that should be available to patients, the channelling of genetic tests through healthcare professionals, mandatory genetic counselling and requirements for informed consent in the context of GT [71]. Although these laws target primarily the provision of genetic tests within the public healthcare system, it has been argued that they also

essentially render illegal the provision of DTC GT [72]. However, there are also many countries in Europe where no specific laws on GT exist. Therefore, when it comes to restrictions related to the involvement of a HCP, genetic counselling and informed consent requirements, DTC GT companies face minimal constraints.

As opposed to aspects related to the context within which genetic tests are provided, several other aspects affecting the governance of GT in Europe are regulated on the EU level. European legislation aims, among others, to promote the harmonization of the internal market and free movement of goods [73], as well as to enhance consumer protection by promoting the fair treatment of consumers and high standards for products that enter the European market [74]. Currently, numerous EU laws are in place, aiming to protect the economic interests and rights of consumers. Such laws cover a wide set of policies, including unfair commercial practices [75], consumer contract law [76], product safety and data protection [74].

Especially with regard to product safety and data protection, recent changes in the regulatory framework are expected to have an impact on the activities of DTC GT companies that are directed to European consumers. The recent adoption of the Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (IVD Regulation) and the General Data Protection Regulation are expected to influence respectively the safety and efficiency standards that DTC genetic tests have to meet when entering the European market and the research activities performed by DTC companies involving genetic information of European consumers. In this section, we will focus on the main changes introduced by the recent adoption of the IVD Regulation and their potential impact on DTC GT.

2.3.1 IVD Directive

Genetic tests with a medical purpose fall within the definition of IVD medical devices and the regulation of their safety and efficiency when entering the European market currently falls under the scope of Directive 98/79 EC on in vitro diagnostic medical devices (IVD Directive) [77]. Based on this Directive, IVD medical devices, unless considered to be ‘low risk’, have to go through a conformity assessment before entering the European market. This means that independent commercial entities called notified bodies, assess whether such devices fulfil the essential requirements of safety and efficiency imposed by the Directive and issue a certificate of conformity (CE mark), allowing devices to circulate in the European market [78].

The impact of the IVD Directive in the effective governance of DTC GT has been questionable [79]. This may be partly because, currently, the vast majority of DTC genetic tests offered by companies are tests for predisposition to common complex disorders. Devices for the purposes of prediction and predisposition are not explicitly covered by the Directive, creating uncertainty regarding whether such tests would actually fall within the scope of the Directive [80].

In addition, under the Directive, most genetic tests are classified as low risk devices requiring only self-assessment by their manufacturer before entering the EU market. This classification has been considered to be particularly lenient in comparison to the respective regulations in the US, Canada and Australia, where most genetic tests are considered to be moderate to high risk devices and are required to go through a pre-market assessment before being placed on the market [80].

Finally, the Directive has caused uncertainty regarding the clinical evidence that must be provided by manufacturers during the pre-market assessment of their devices. In this regard, it has been unclear whether manufacturers are required to provide evidence of clinical validity in order to prove compliance with safety and performance standards, or whether evidence of analytical validity would be sufficient [81]. A clarification on that matter would be of particular importance when it comes to DTC GT. This is because, as mentioned above, most such tests currently available on the market are susceptibility tests to common complex disorders, which often have doubtful clinical validity [37]. Therefore, requiring only evidence of analytical validity during the pre-market assessment of the tests would set the bar of performance rather low.

2.3.2 IVD Regulation

The revision of the IVD regulatory framework has been a long process that has given rise to an animated debate among the EU institutions and different stakeholders. After two public consultations were held, the European Commission issued in September 2012 its proposal for a new Regulation on IVD medical devices. Following the ordinary legislative process, the European Parliament and the Council of the EU published their own versions of the proposal in October 2013 and June 2015 respectively. Finally, after negotiations among these three institutions, a compromise was reached in May 2016. After undergoing legal-linguistic review the final version of the Regulation was adopted by the European Parliament and the Council of the EU in April 2017. The regulation will apply in the member states of the EU and the

European Free Trade Association (EFTA), as well as Turkey, after a 5-year transition period. For the purposes of this section, when we are using the term “Europe” we refer to the countries where relevant EU legislation applies.

When it comes to the governance of DTC GT, the final text of the IVD Regulation contains changes that may cover gaps in the previous regulatory framework and potentially raise standards of safety and efficiency of such tests when entering Europe. In this regard, the changes introduced by the IVD Regulation concern mostly the scope of tests covered, the risk classification system (which determines how much scrutiny an IVD device has to go through during the pre-market assessment), the clinical evidence required, advertising of IVD devices and the availability of genetic counselling for certain types of genetic tests.

Scope of tests covered

In respect to the scope, the final text explicitly recognizes IVD devices providing information on ‘predisposition to a medical condition or a disease’ (Article 2(2)) as being subjected to the Regulation [82]. This amendment eliminates uncertainties regarding whether the majority of DTC GT offered (namely genetic tests for predisposition to common complex disorders) are covered by the Regulation or not. Importantly, the Regulation also clarifies that all IVD medical devices offered through the Internet to a natural or legal person established in the EU must comply with the rules set by the Regulation (Article 6) [82]. This way, it becomes clear that companies also established outside the Union should still comply with the relevant EU rules when offering their products to consumers residing within the EU.

Classification of IVD devices

When it comes to the classification of IVD devices, the Regulation replaces the list-based classification system adopted by the Directive with a new, risk-based classification system. The way IVD devices are classified is particularly important, as it determines how strictly the devices may be assessed before entering the EU market. According to the Directive, the classification of devices was based on predetermined lists. These lists have been criticized as being inconsistent and outdated, and, for many products, as offering inadequate scrutiny [83]. This was particularly the case for the vast majority of genetic tests, which were considered to be low risk devices, requiring, as a result, only a minimum degree of scrutiny before being available to consumers. The risk-based classification system introduced by the Regulation, which will replace the existing list-based system, is largely inspired by the classification system

introduced by the Global Harmonization Task Force [84] and aims to address the inadequacies created by the previous framework. In this regard, according to the Regulation, IVD devices may be divided in four categories based on their intended purpose and potential risks [79]. In this context, the Global Harmonization Task Force has defined risk as ‘combination of the probability of occurrence of harm and the severity of that harm.’[84]. The categories vary from Class A (low risk devices), to Class D (high risk devices). Genetic tests fall under Class C, which means that they are considered to be moderate to high risk devices and they have to go through a pre-market assessment by a notified body before reaching consumers.

Clinical evidence

Furthermore, the IVD Regulation raises the bar for clinical evidence by stating that the assessment of conformity with general safety and performance requirements should be based on ‘scientific validity, analytical and clinical performance data providing sufficient clinical evidence’ (Article 56) [82]. This provision clarifies that evidence of clinical validity (incorporated in the notion of clinical performance) should be provided by the manufacturer, eliminating uncertainties created over the previous regulatory regime regarding whether providing such evidence was mandatory [80]. This amendment may make it more challenging for tests with low clinical validity (for example for many genetic tests detecting predisposition to common complex disorders) to enter the European market.

Advertising

A particularly interesting addition in the IVD Regulation is Article 7 under the title ‘Claims’. In this article, for the first time, European legislation specifically addresses the advertising of IVD medical devices. This article provides that labelling, instructions for use and advertising of such devices must not use misleading content with regard to the device’s purpose, safety or performance. Examples of misleading content for the purposes of this article are ‘creating a false impression regarding treatment or diagnosis, functions or properties which the device does not have’ and ‘suggesting uses for the device other than those stated to form part of the intended purpose for which the conformity assessment was carried out’ (Article 7) [82]. Even though the article does not seem to grant broader protection than that offered by more general laws on consumer protection [85], it grounds these laws in the specific context of IVD medical devices and its symbolic value should not be underestimated. Especially when it comes to DTC GT, the business model of which is largely relying on advertising, having a more specific definition of

what may constitute misleading advertising could potentially contribute in a more efficient regulation of the way such products are promoted to the public.

Informed consent and genetic counselling

During the ordinary legislative process, the European Parliament, in its proposal, had supported that all genetic tests under the Regulation should be classified as prescription-only medical devices and that they must only be advertised to health care professionals and not to consumers. In addition, according to the same proposal, pre- and post-test genetic counselling should be mandatory for predictive, prenatal and diagnostic genetic tests, while informed consent should be written [86]. The above mentioned suggestions gave rise to a heated debate regarding whether regulating such issues at the EU level infringes the principles of proportionality and subsidiarity [87]. Some stakeholders argued that if such provisions were eventually adopted this would result in the Regulation going beyond its purpose (namely to regulate product efficiency and safety) and would ultimately interfere with clinical practice and the way this is organized at the national level [88]. Ultimately these provisions were not included in the final text. Instead, the Regulation acknowledges that the current divergences in national rules on informed consent and genetic counselling do not seem to have a significant adverse impact on the smooth functioning of the internal market. As a result, the Regulation will only provide limited requirements respecting the principles of proportionality and subsidiarity. In this regard, Article 4 of the Regulation prescribes that individuals undergoing genetic tests in the context of healthcare and ‘for the medical purposes of diagnostics, improvement of treatment, predictive or prenatal testing’ should be ‘provided with relevant information on the nature, the significance and the implications of the genetic test’. In addition, in the same context, and specifically for genetic predisposition testing for untreatable conditions and diseases, Member States shall make sure that patients have access to genetic counselling [82]. In this regard, the final text seems to attempt to strike a balance between stressing the importance of informed consent and genetic counselling while respecting the principle of subsidiarity and the right of Member States to regulate clinical practice in their territory as they see fit. This provision, however, will probably have little value for tests offered outside the clinical setting as it is addressed to Member States and in this regard, its impact will likely be limited to the clinical context.

Overall, it may be argued that, when it comes to genetic tests, the IVD Regulation attempts to address weaknesses and uncertainties of the existing regulatory framework, especially

regarding the scope of protection, the risk-classification and requirement for clinical evidence, therefore it is addressing some of the salient ethical issues of DTC GT. In this regard, and specifically with the points discussed above, the Regulation seems to be an improvement compared to the Directive. It is now clear that predisposition tests fall within its scope and the new risk-based classification system and the requirements for clinical evidence may raise the quality bar for genetic tests entering the EU. Furthermore, the Regulation, even though it does not move to harmonize the framework within which genetic tests are offered (and potentially render DTC GT illegal within Europe)- goes beyond the Directive in specifically regulating advertising claims and referring to the need for adequate information and genetic counselling to be available in the context of health-related GT. The Regulation also shows potential for limiting the circulation of DTC GT with low quality in the EU market and deter companies from making exaggerated and unsubstantiated tests. However, it should be kept in mind that the DTC GT industry is global and operating mostly through the Internet. This means that even if such tests fall within the scope of the Regulation, no matter where they come from, the compliance of companies sending their tests to private individuals may be hard to ensure. As a result, the real value of the IVD Regulation for DTC GT will be largely dependent on its enforcement.

2.4 Conclusions

DTC GT and related services raise numerous and complex ethical issues; these are evolving as the DTC GT market is changing and consequently posing (new) challenges to its adequate regulation. The well-known issues of analytic and clinical validity of the testing, inadequate informed consent, and potentially misleading advertising are still relevant and problematic in the context of the current offer DTC GT. Meanwhile, new ethical issues emerged, namely DTC GT targeted to (prospective) parents, “monetization” of genetic data, and quality of third-party interpretation services. In the European context, the recently adopted IVD Regulation addresses some of the ethical concerns related to DTC GT. Specifically, the Regulation raises the bar for clinical evidence required for the tests entering European market, prohibits misleading advertising, and clarifies that companies established outside the European Union should still comply with the relevant EU rules when offering their products to consumers residing within the EU. Other laws in the European context can also be relevant to DTC GT, for example, laws concerning unfair commercial practices and the new General Data Protection Regulation. The

GDPR, which will apply in the EU in May 2018, may require redesigning some of informed consent practices among DTC GT companies, for example to enable easy withdrawal of informed consent [89]. Their relevance to, and impact on DTC GT (e.g. in the context of third-party interpretation services, usage and confidentiality of consumers' genetic data) require further investigation and discussion. To allow well-informed discussion on the ethical and regulatory issues related to DTC GT, empirical studies monitoring the current offers and practices of DTC GT companies and related ethical issues are invaluable.

2.5 Future perspective

The development of the DTC GT market is influenced among others by availability of new technologies, their price and the relevant regulation. Advancements in genomic sequencing technologies and increasing understanding of human genetics has been enabling obtaining more genomic information faster and cheaper. DTC GT companies have been taking advantage of these trends and have been offering a wider range of genetic tests at lower prices. Recently, the US FDA announced its intention to facilitate quicker and least burdensome introduction of some DTC predisposition testing to the market [42]. All of these factors, as well as the general push to make genomics a more mainstream part of medicine, may help support, in the coming years the market expansion of DTC predisposition GT in the US. In the European context, however, the recent IVD Regulation which will apply in 5 years is likely to limit the offer of predisposition DTC GT including the tests offered by the providers based in the US.

Importantly, the business model of the DTC GT companies has been evolving. Selling genetic testing results is no more the only source of profit for the companies. Genomic data have been recognized as useful not only to the individual consumers, but also to researchers; some DTC companies have been taking advantage by selling consumers' data to interested third parties [68]. In this context, a novel genomic data sharing approach seeking to also entitle consumers to profit from sharing their genetic data emerged and may be further developed (e.g. Portable Genomics).

Additionally, the popularity and intake of DTC genetic testing may be dependent to some extent on the way genetics is portrayed in media and perceived by the potential consumers. For example, the story of Angelina Jolie, who underwent a preventive double mastectomy based on genetic risk and a family history of cancer, received extensive media coverage and raised some

awareness about genetic testing. Media coverage, however, may not translate to the correct understanding of genetics [90]. In this context, educating about genetics, its limitations, related ethical issues and responsible communicating about science in media should be recognized as factors which may facilitate informed decisions about undertaking DTC GT and using one's genetic information. The level of genetic literacy in public may influence intake and attitudes of public towards of DTC genetic services.

Executive summary

Direct-to-consumer genetic testing (DTC GT) and related services

- A variety of health-related genetic tests is currently advertised directly to consumers. The tests employ new approaches (whole exome and genome sequencing), may report on a wide range of conditions, and are targeted at new groups such as (prospective) parents (carrier testing, preconceptional and prenatal testing, testing for children).
- Third-party web-based genetic data interpretation and sharing services are available to DTC GT consumers (who have their genomic data downloaded in the required format). Some of the platforms may offer payments for consumers for sharing their data.

Ethical issues in DTC GT companies

- The currently salient ethical issues related to the offer of genetic testing and services include, among others: questionable analytic and clinical validity of the tests, adequacy of informed consent and pre-test counselling, potentially misleading advertising, the offer for children and reproductive purposes, research uses and commercialization of consumers' genomic data.

DTC GT legislation in Europe

- The recently adopted IVD Regulation may render many of the predisposition DTC GT illegal in Europe as it raises the bar for clinical evidence required for the tests entering European market, prohibits misleading advertising, and clarifies that companies established outside the European Union should still comply with the relevant EU rules when offering their products to consumers residing within the EU. The regulation will apply after 5-year transition period.

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Chapter 3: Content analysis of informed consent for whole genome sequencing offered by direct-to-consumer genetic testing companies

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Published in: *Human Mutation* 2016; 37(12):1248-1256, DOI: 10.1002/humu.23122

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Abstract

Whole exome sequencing and whole genome sequencing have become increasingly available in the research and clinical settings and are now also being offered by direct-to-consumer genetic testing companies. This offer can be perceived as amplifying the already identified concerns regarding adequacy of informed consent for both whole exome/genome sequencing and the direct-to-consumer (DTC) genetic testing context. We performed a qualitative content analysis of websites of four companies offering whole exome/genome sequencing DTC regarding the following elements of informed consent: pre-test counselling, benefits and risks, and incidental findings. The analysis revealed concerns including the potential lack of pre-test counselling in three of the companies studied; missing relevant information in the risks and benefits sections; and potentially misleading information for consumers. Regarding incidental findings, only one company, which provides opportunistic screening, provides basic information about their management. In conclusion, some of the information (and related practices) present on the companies' webpages salient to the consent process are not adequate in reference to recommendations for informed consent for whole genome or exome sequencing in the clinical context. Requisite resources should be allocated to ensure that commercial companies are offering high throughput sequencing under responsible conditions, including an adequate consent process.

Key words: whole genome sequencing, whole exome sequencing, direct-to-consumer genetic testing, consumer genomics, informed consent

3.1 Introduction

3.1.1 Whole exome and genome sequencing applications

The relatively recent development of next generation sequencing (NGS) technologies has led to a significant decrease in the cost and time required to perform whole genome sequencing (WGS) and whole exome sequencing (WES) (i.e. the sequencing of only protein coding parts of the genome; for the purpose of this article, in which the high-throughput nature of NGS is most salient, both whole genome and whole exome sequencing may be denoted by ‘WGS’ or ‘whole genome sequencing’). These technologies are more powerful and potentially cost-effective than previous sequencing technologies and have brought a shift in testing approach from the traditional way of testing only one or a few specific genes to obtaining the sequencing information from hundreds or even all the genetic variants in a genome [1].

To date, the use of genomic sequencing approaches has proved to be useful in both the research context and clinical context; for instance, in providing molecular diagnoses for Mendelian disorders [2], for disorders with complex phenotypic presentations such as intellectual disabilities, or neurological diseases [3,4], potentially enabling targeted therapeutic strategies in some cases [5]. WGS can also be used for disease risk predictions [6], preconceptional carrier testing [7] and prenatal testing [8]. In the short to medium-term future, other applications of WGS in health care may materialize, including for newborn screening [9], tissue matching [1] or screening of embryos [10]. Despite these technical possibilities, it is important to note that there are still concerns regarding the accuracy, interpretation of results, cost-effectiveness, as well as ethical issues [11].

Given the relative novelty of NGS in the clinic and the resulting uncertainty related to implementation, the ethical concerns are numerous, and include but are not limited to issues related to the informed consent (IC) process, unsolicited findings management, opportunistic screening, secondary use of data, data management and storage, privacy and confidentiality, duty to re-contact patients (once new information arises), responsibility towards and communication with family members. All these outstanding issues currently, challenge the effective and responsible implementation of genome-based approaches in health management [12] and need to be addressed. Herein we focus on ethical issues of the informed consent process

in the more specific commercial context of direct-to-consumer high throughput sequencing, which overlap with many of the concerns related to the clinical context.

3.1.2 Direct-to-consumer genetic testing (DTC GT) companies

Relatively recently, whole genome sequencing services have also been advertised and offered directly to consumers by some companies. These private, for-profit companies operate outside of the conventional public health care system and advertise genetic tests directly to consumers predominantly via the Internet. However, the companies increasingly are requiring consumers to contact a health care professional (HCP) in order to obtain a test and/or the test results [13]. Such genetic tests which *'are commissioned by the consumer but where a medical practitioner or health professional is involved in the provision of the service'* also fall in the scope of DTC genetic tests according to 'A Common Framework of Principles' on DTC genetic testing issued by the Human Genetics Commission (UK) [14].

The phenomenon of DTC GT, even before WGS was being offered in this context, has received a lot of attention regarding ethical issues, such as the questionable scientific validity and utility of the tests on offer [15], the adequacy of information provision and the informed consent procedure [16], the potential need for medical oversight and genetic counselling [17], the testing of children [18], the research activities conducted by DTC GT companies [16] and the potential burden on the health care system [15]. The adequacy of legislations concerning the activities of DTC GT companies has also been discussed [19]. Considering the vast amount of genomic data obtained in WGS as well as difficulties in being able to properly assess or interpret each variant, one could consider that many, if not all, of the ethical, legal and social implications previously addressed at the DTC GT field are amplified in the context of companies offering WGS directly to consumers. As such, this particular type of DTC GT deserves further attention and study.

3.1.3 Informed consent for WGS

Informed consent is a key component of any responsible research on human subjects or healthcare provision, including the offer of genetic testing (for health purposes), regardless of whether it is provided via a HCP in the conventional health care system or by a private for-profit company. Informed consent constitutes a voluntary permission given by a competent patient to have the test performed after (s)he has been duly informed about the procedure and

purpose of the test, including the results it will generate, as well as the potential risks and benefits. The Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes states that ‘*A genetic test may only be carried out after the person concerned has given free and informed consent to it*’. The document also outlines that the consent should be documented and it may be freely withdrawn at any time [20]. Furthermore, the European Convention on Human Rights and Biomedicine^a, specifies in Article 5 that a person consenting to an intervention in the health field ‘*shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks.*’ [21] Moreover, the importance of informed consent has been recognized in the recently accepted version of the Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices^b:

‘Member States shall ensure that where a genetic test is used on individuals, in the context of healthcare as defined in Article 3(a) of Directive 2011/24/EU and for the medical purpose of diagnostics, improvement of treatments, predictive or prenatal testing, the individual being tested or, where applicable, his or her legally designated representative is provided with relevant information on the nature, the significance and the implications of the genetic test, as appropriate.’ (Article 4a) [22]

In the context of WGS, appropriate provision of information about the testing seems to be a particular challenge considering the complexity of the technology used, the volume of information generated, and the wide-ranging nature of findings. The entire sequence of the genome may provide an unprecedented amount of information of various clinical significance

^a The Convention on Human Rights and Biomedicine is only legally binding for those countries who have signed and ratified it (http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures?p_auth=GV537xJS). While, not all countries have done this (e.g. Germany, UK, Belgium, etc.), the Convention nonetheless, remains a very important moral benchmark and/or ethical framework in Biomedicine for all countries.

^bOn 15 June 2016 the European Parliament and the Council of the European Union have agreed on the draft of the proposal, which will undergo legal-linguistic review and will be adopted by the European Parliament and the Council of the European Union, probably at the end of this year. The rules of the regulation will apply 5 years in the EU member countries after its publication (http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=8863&lang=en).

and predictive value, which may change with time [1]. Furthermore, these results may have profound implications for the (psychological) health (care) and reproductive choices of a patient as well as his or her relatives.

Given these challenges, various authors have proposed models for IC and attempted to determine the necessary elements of an adequate IC process for WGS [23-28]. Ayuso *et al.* (2013) specifically analysed articles from the academic literature and guidelines from ‘societies’ concerning IC for genetic studies and WGS. The authors found a high level of consistency among the documents reviewed and proposed a minimum list of information that should be addressed in IC for WGS: the scope of the test, a description of the test process, the possible benefits and risks, the availability of alternative tests, the voluntary nature of the test, the possibility of refusal, the future use of the samples and the data, the confidentiality of the outcomes and management of incidental findings (IF), and pre-test counseling [27]. Moreover, the authors found that the majority of the documents they studied suggest that IC for whole genome sequencing should be given explicitly [27] (this is understood as being relevant in a context where WGS is only one of the tests being used for diagnosing a disorder, and so an explicit consent should be obtained specifically for the WGS).

Jamal and co-authors (2013) also developed “*core elements*” of content and procedures for informed consent, data sharing, and results management for whole exome sequencing; even though conducted in a research context, the former overlap with core elements of informed consent identified by Ayuso *et al.* for the clinical context [28]. Furthermore, Jamal and co-authors used the core elements to evaluate the practices and policies of 6 U.S. CLIA- certified labs offering clinical exome sequencing, including the presence of the suggested elements in informed consent forms and their readability. The analysis revealed that laboratory policies vary widely, indicating that developing standards for best practices among exome sequencing providers may be beneficial.

Similarly, Henderson *et al.* (2014) [26] have analysed IC forms used in nine NIH-funded studies aiming to develop best practices for clinical applications of WGS. On the basis of the analysis the authors have proposed recommendations, which ‘*can serve as a checklist to help identify gaps and resolve ambiguities in consent forms for sequencing*’, and which are related to the issues outlined by Ayuso *et al.* (2013). For example, Henderson *et al.* suggest describing the meaning of positive, negative and uncertain results, outlining the role of CLIA (Clinical

Laboratory Improvement Amendments) certification, and stating the likelihood of obtaining incidental findings. Furthermore, IC forms for WGS have also been analysed in the context of cancer studies. The examination of these IC forms has revealed the tendency for using samples in other, unspecified types of studies and sharing data with other researchers [29].

Furthermore, IC and the provision of information on company websites have been investigated in the context of DTC GT companies revealing the inadequacies of these practices [16,30,31]. None of the studies, however, specifically addressed IC for WGS in the context of companies advertising or selling WGS directly to consumers. Therefore, herein we present an exploratory qualitative study of the information salient to the IC process, which is provided on websites of companies offering whole genome sequencing in the commercial direct-to-consumer context. In particular, we present information regarding the following elements salient to IC: 1) pre-test counselling, 2) expected benefits and possible risks; and 3) management of incidental findings. The information from company websites is then further contextualized and discussed against the backdrop of guidelines such as those from the Presidential Commission for the Study of Bioethical Issues (PCSB) [32], recommendations for IC for WGS by Ayuso and colleagues [27], and the American College of Medical Genetics (ACMG) recommendations for the reporting of secondary findings [33].

3.2 Methods

This study is an explorative qualitative analysis of the informed consent information for whole genome and/or whole exome sequencing offered by DTC companies. We use a broad concept of DTC, including companies that offer genetic testing without involvement of a HCP, as well as those that aim marketing directly at consumers, while requiring a physician's request to obtain the test. This approach is congruent with the scope of DTC GT given by the Human Genetics Commission, which included situations where *'tests are commissioned by the consumer but where a medical practitioner or health professional is involved in the provision of the service'* [14].

The number and content of DTC genetic and genomic testing companies is often changing; this includes information about informed consent^c. Against this background, and since no other academic article has addressed the specific issue of consent in the distinct context of WGS/WES, we opted for a non-exhaustive explorative qualitative study of a convenient and varied sample of company websites, which were selected between November 2013 and January 2014. Companies were identified through the academic literature (mostly via articles addressing DTC genetics), as well as with a general Internet search in English using the search engine Google and terms including ‘genetic test’, ‘direct to consumer’, ‘whole genome sequencing’ and ‘whole exome sequencing’.

Our qualitative analysis is focused on the websites sections and documents available online that are presented by the companies with which consumers should agree and/or sign in order to undertake the test. Specifically, these are the IC documents, statement of consent, terms of service, terms and conditions, disclaimer and privacy policy (Table 3.1).

For the qualitative content analysis of the relevant documents on the websites, we build on the study of Ayuso et al. (2013) and used the following elements of IC as the major codes: 1) pre-test counselling, 2) expected benefits and possible risks; and 3) management of incidental findings. These were underlined as being particularly important and relevant for IC in the context of WGS [27]. The website documents were accessed in October 2014. The documents were perused for all material relevant to the codes above and were organized under these headings initially by one author (EN); these initial results were reviewed by a second author (HCH) and disagreements were resolved until both agreed on the adequate organization. Final tables including representative quotes were reviewed by three authors.

^c Indeed, some companies’ policies have already changed since our study, and as mentioned in the discussion, it is relevant that future studies return to these companies as well as include novel companies not addressed herein. For example, the version of Illumina’s consent form analysed herein is not available online any more. For a copy of the form please contact the corresponding author.

3.3 Results

3.3.1 The DTC WGS companies identified and the studied website documents

Four companies, Illumina, Gentle, Gene by Gene and Inneova, were identified for this study. At the time of this analysis they offer WES and/or WGS as well as provide different types/scope of data/results and analysis (e.g. carrier status, pharmacogenomics). The basic description and information regarding these four companies are outlined in Table 3.1.

All the companies studied advertise their services directly to consumers on the Internet. However, some websites also contain sections dedicated to physicians, who are required to order the test, except for the company Gene By Gene's offer of research and consumer testing, for which the company does not require a HCP.

All companies' websites analysed provide at least one document and/or a section on the webpage that needs to be agreed to or signed in order to undertake the test (Table 3.1). Three companies have documents on their website with 'consent' in the title; meanwhile, Gene By Gene only has a 'Terms and Conditions' section of the website and specifies that in case of 'Clinical Genetic Testing' the physician has to obtain IC from the consumer; however it does not state whether this includes a physical document that must be signed by the consumer: '*Prior to placing an order, the ordering physician or genetic counselor is responsible for obtaining the informed consent from the patient whose sample is being sent for testing (...)*' (<https://www.genebygene.com/pages/terms>). Such a statement is not included in the section for 'Research and Consumer testing' in 'Terms and Conditions' of Gene by Gene (<https://www.genebygene.com/pages/terms>).

The results of the content analysis regarding the following elements of IC: pre-test counselling, benefits and risks as well as incidental findings are presented below and shown in tables 3.2-3.4.

3.3.2 Pre-test counselling

Only Illumina (seemingly) requires pre-test counselling as a condition for undertaking the test. In the IC form a consumer has to sign the following statements:

‘I have been offered the opportunity to ask questions and discuss with my healthcare provider the benefits and limitations of the test to be performed as indicated on the associated test request form. I have discussed with the medical practitioner ordering this test the reliability of positive or negative test results and the level of certainty that a positive test result for a given disease or condition serves as a predictor of that disease or condition.’
(<http://res.illumina.com/documents/clinical/forms/form-test-req-undiagnosed-disease.pdf>)^d

Another company, Gentle, vaguely suggests some form of pre-test counselling to consumers in its IC section of the webpage: *‘If you still have unanswered questions, be sure to ask us or your physician before you agree to take the DNA test being offered by us.’* (https://www.gentlelabs.com/consent?content_only=true). No information about pre-test counselling was found on the studied websites’ sections of Gene by Gene and Inneova.

3.3.3 Benefits and risks

In the studied sections of the websites, all the companies provide general information about benefits and risks; however specific sections labelled ‘Benefits’ and ‘Risks’ are explicitly distinguished only in the IC documents of Illumina and Gentle. More specific subthemes were identified within the subjects benefits and risks information (Table 3.3, in bold in columns 2 and 3); these were used to classify the benefits and risks and were derived and modified from the classification outlined by Ayuso *et al.*, 2013 [27].

Three companies outline that the results may indicate disease risks and predispositions (Table 3.3). Moreover, Illumina and Gentle state that test results may help to make more informed healthcare choices; Gentle adds that the knowledge from the testing may empower persons to make *‘important life planning decisions’*. Furthermore, Gentle outlines as a benefit, gaining knowledge about one’s carrier status, the possibility of

^d At the time of submitting the article the link to this document was no longer functional. For a copy of the form please contact the corresponding author.

adjusting drug therapy based on the genetic results, and gaining insight into one's ancestry. This company also mentions as a benefit the possibility of participating in research studies conducted by the company.

All the companies provide, at least, a general and/or short description of risks related to undertaking WGS (Table 3.3). The types of risks and concerns mentioned include the following: medical and physical risks, psychological risks, discrimination risks, and implications for family members. Implications for reproductive choices are mentioned only by one company, Inneova: *'I realize the possible far-reaching implications of the information obtained through predictive genetics testing in affecting my life choices as well as those of my relatives, children, and unborn children'* (<http://www.inneova.com/contenu.php?page=terms.php>).

3.3.4 Incidental findings and categorization of genetic information

Only one of the analysed companies, Illumina, directly addresses the issue of incidental findings (IF) in its IC form (Table 3.4). The company refers to the first version of the American College of Medical Genetics' (ACMG) recommendations for reporting of incidental findings (2013) [33] and together with the results of Undiagnosed Disease Test provides an incidental findings report that may contain information on some of 57 variants unrelated to the indication for testing. Meanwhile, in the consent form for Illumina's Predisposition Screen test the possible findings are categorized (into: childhood onset and adult onset; subcategories: medically actionable, not medically actionable, cancer, neurologic conditions) and the consumer has the possibility to opt out of some of them. Although Gentle does not mention IF, the company does emphasize that customers can choose to exclude any condition from the analysis: *'It is important to mention that you can choose to exclude any of the tests from the results before submitting your sample.'*

3.4 Discussion

3.4.1 Informed consent in the context of DTC WGS companies

The content analysis of DTC companies described herein has been conducted using some of the elements of IC for WGS in the clinical setting recommended by Ayuso *et al.* (2013)

[27]. It should be noted that there are significant differences between the offers of WGS in a 'traditional' clinical genetics context versus the commercial DTC setting, even if the latter involves a healthcare professional. As explained in the recent guideline issued by the Presidential Commission for the Study of Bioethical Issues (PCSBI): '*Clinicians owe stringent fiduciary duties to patients, which entail an obligation to act in furtherance of the patient's best interests. Non-clinician DTC providers have less stringent duties, including duties that might be limited or circumscribed by contract. Consumers should be made aware of these distinctions prior to consenting to undergo DTC testing.*' (p.103-104) [32]. Indeed, in the context of DTC companies the contract describing the conditions of the service is usually stated in terms of service to which a consumer has to agree prior to buying the test. However, if the purpose of the test is health-related, signing a contract cannot fully replace the function of IC, which aims, among others, to provide understandable and balanced information about the test [24]. The tests included in this study are advertised as having (to some extent) a health-related purpose or as clinical tests, therefore, the presence of adequate IC in the studied DTC companies appears to be advisable.

3.4.2 Explicit informed consent and pre-test counselling

Explicit informed consent, which is recommended by Ayuso et al. (2013) for clinical WGS, may be defined as one for which '*Those who request consent must provide an explicit statement of the nature and purposes of a proposed course of action, its effects, risks and other features, to those whose consent is sought. Those who are asked to consent must show explicitly that they understand this information and agree to the proposal*' [34]. The process of explicit IC typically involves documents, signatures and formal statements [34]. Therefore, in this study we have focused on the documents or the section of the websites which the consumers have to agree to in order to be tested. However, in order to be genuinely informed consent should not be reduced to signing a document but rather through dialogue with a qualified HCP it should be ensured that the patient truly understands the information provided and is competent to make a choice [35].

Although all four companies provide some form of document addressing consent, only Illumina requires pre-test counselling understood as face-to-face consultation with

a physician. In the other companies studied, most of the tests have to be ordered by the physician meaning that the consumer has to contact one in order to be tested. This, however, does not guarantee that adequate counselling takes place, given the concerns about the expertise in genetics and impartiality of the health care professionals [13]. Indeed, including a third party HCP in the process raises the question of who bears the (fundamental) ethical and legal responsibility for taking adequate consent? Of course, the HCP must adhere to the general medical code of conduct, but depending on her/his specialty, is (s)he aware of the specific guidelines for genetic testing?

Another important result that brings attention to the involvement of healthcare professionals in testing is a lack of involvement of a physician in undertaking the consumer test in Gene By Gene company. Although ‘Terms and Conditions’ state that the services listed in ‘Research and Consumer Testing’ section *‘are not to be used to diagnose, prevent, or treat any condition or disease or to ascertain the state of health for any individual’* (<https://www.genebygene.com/pages/terms>), the description of the test suggests that it may provide health-related information: *‘Sequencing of the exome can help identify variants that may be the genetic cause of a wide range of traits and conditions.’* (<https://www.genebygene.com/pages/research#>). Therefore, the involvement of a genetics professional seems to also be advisable in the case of ‘Research and Consumer Testing’ of Gene By Gene, which could prevent misinterpretation of the results or unnecessary follow-up care.

In addition, although the non-clinician DTC provider may have less stringent duties as stated by the PCSBI [32], the full role of a clinician in the DTC context still remains blurry. It is unknown to what extent physicians in the DTC context follow the same protocol as geneticist follow in the traditional health care system.

Another aspect related to informed consent is the potentially low readership of the consent documents analysed herein. It has already been shown that most of the consumers read very little of the terms of service agreements (e.g. when purchasing software [36] or accessing Wi-Fi). This may suggest that although the documents have the word ‘consent’ in the title and/or are aimed to be read and agreed to, the consumers are not acquainted

with their content. This issue requires further analysis to assess the accessibility and readability of such documents.

3.4.3 Information about benefits and risks

The content analysis of the sections of companies' websites reveals that the information regarding possible risks and benefits is scarce, general and omits some relevant elements such as description of the implications for the reproductive choices, which has been recommended for IC for WGS [27]. Furthermore, some of the outlined information about benefits may be misleading such as regarding the possibility to participate in research studies (Table 3.3), which, in fact, does not necessarily benefit participants *per se* and is associated with various risks. Similarly, knowing the information about the carrier status is mentioned as a benefit in Gentle's IC website section, but the implications for reproductive choices of having this knowledge are not described (Table 3.3). What is more, the information provided in the documents that need to be signed differs from the information placed in other sections of the website, which seem to be more encouraging about the possible results. For example, in the 'Why do a genetic test?' section of the Inneova website they state that:

'The objective of predictive genetics testing from Inneova™ is to determine each person's specific genetic features – and notably vulnerabilities – in order to allow highly-qualified practitioners in anti-aging and preventive medicine identify appropriate measures designed to counter-balance weaknesses and maintain good health, as well as help prevent the development of specific diseases or at least to delay their onset'
(http://www.inneova.com/tout.php?page=prev_why.php&menu=2, under bookmark 'Predictive Genetics').

This may be misleading as consumers may not read the sections 'Terms of Service' or 'Terms and Conditions' [16], but rather take the decisions based on the information available on the main webpages. Finally, the information about the potential risks in the documents of Inneova and Gene By Gene may make an impression that it was designed or written more in a way to protect the company from any liability rather than to explain and inform about potential disadvantages, e.g. *'I agree that ICL (...) assumes no liability*

for any stress, strain, hardship, adverse medical condition, financial loss, or other circumstances that I may suffer as a result of the receipt or reference to any predictive genetics test results and/or interpretations thereof supplied to me by ICL' (<http://www.inneova.com/contenu.php?page=terms.php>).

Some of the findings presented herein are in line with the results of the study of Singleton *et al*, 2012 on informed choice in DTC GT companies, which focuses on the websites of the DTC GT companies containing consumer-focused content excluding terms and conditions and privacy statements, therefore being to some extent complementary to this study. Singleton *et al*. found that the amount of information describing benefits outweighed risks statements and that the websites presented conflicting information stating that the tests can help to prevent diseases, simultaneously giving information that the test cannot be used for diagnosis or treatment [30]. Similarly, Skirton *et. al* found that misleading, conflicting or incomplete information was present on the websites of DTC companies offering non-invasive prenatal testing [37].

3.4.4 Incidental/secondary findings

The last, but not the least element of IC analysed in this study is the management of incidental findings. The term 'incidental findings' refers to '*results that are outside the original purpose for which a test or procedure was conducted*' [32], while secondary findings are results being sought deliberately because of the recommendations of an expert body as it has been defined by the PCSBI in the report on incidental and secondary findings [32]. The issue of incidental and secondary findings appears particularly relevant in the context of WGS generating vast amount of data for analysis [38]. Therefore, this topic has been discussed at great length and various expert societies have addressed it in recommendations. The PCSBI emphasizes the role of IC, and for the particular context of DTC companies suggests that the providers should develop adequate procedures to manage IF and provide consumers with understandable materials explaining these procedures [39]. The American College of Medical Genetics (ACMG) also has issued recommendations for the reporting of secondary findings obtained in WGS (although they use the term incidental findings, this is misleading since what they describe is opportunistic screening and not the strictly 'unsolicited' findings) [33]. This

policy statement of the ACMG suggests that secondary findings concerning 24 indicated conditions (related to 56 gene variants affecting function) should be sought and reported, however the patient may refuse the analysis of some of these genes if they are unrelated to the indication for testing, which should be done during the process of IC [33,40]. In contrast, the recommendations of the European Society of Human Genetics which address incidental findings, do not provide a specific list of reportable conditions but rather suggest narrowing the scope of the sequence analysis and developing guidelines and protocols [41] in order to reduce the chances of encountering IF all together. Finally, some authors propose models of stratification of information derived from WGS, including incidental/secondary findings, which will help the discussion with, and the decision-making by the patient [27,42].

Only one company out of the four studied addresses the issue of incidental/secondary findings and provides a report on IF complying with the recommendations of ACMG [33] (hence conducting opportunistic screening). However, the company does not indicate in the informed consent form for the TruGenome Undiagnosed Disease Test whether the consumer has an opportunity to opt out of the analysis of some of the genes listed by the ACMG. Furthermore, according to the report on the IFs issued by the PCSBI [32] as well as the recent update of the recommendations for reporting secondary findings in genome-scale sequencing [40] the term ‘incidental findings’ used by Illumina is not adequate and in order to comply with the guidelines mentioned it should be replaced by the term ‘secondary findings’. Nevertheless, in the IC for Undiagnosed Disease Test Illumina seems to implement the recommendations included in the primer on IFs for DTC providers, which advise to prepare a plan for the management of incidental and secondary findings and to provide easily accessible information for consumers about this procedure.

The IC form for Illumina’s Predisposition Screen test introduces categories of genetic information which consumer may choose not to receive exercising his/her ‘right not to know’ some of the medical information. The categories of genetic information introduced by Illumina are to some extent in line with those suggested by Ayuso *et al.* (2013) as they arrange the conditions according to the time of onset and medical actionability facilitating the choice of consumers [27].

3.5 Conclusions

Concerning the elements studied herein the consent forms and documents on companies' websites do not appear to fulfil the requirements for genuinely explicit and informed consent for WGS in the clinical setting as suggested by Ayuso et al. (2013). This highlights the present need to develop and implement 'best practices' for the DTC GT context with regard to IC and the provision of information about testing being offered. Moreover, the specific context of the commercial DTC GT companies which involve healthcare professionals could benefit from developing guidelines that specifically address this practice.

This explorative qualitative study has some limitations. Since it considers a small and convenient sample of DTC WGS/WES companies' and a subset of their written policies, it does not provide an exhaustive overview of all companies, their practices and associated ethical issues involved in the consent process. Indeed, we stress that the goal of this article is not meant to be an exhaustive, or generalizable (in a quantitative statistical way) analysis of DTC WGS companies, but rather a qualitative exploration of the activities that exist with respect to consent. Moreover, information provided on other pages of companies' websites not analysed herein may also be relevant to IC process, which requires further investigation. Furthermore, other information such as that related to storage and future use of consumers' samples and data pertain to IC and their presence in the process of IC in DTC companies also needs to be discussed. Finally, it is important to note that the nature of the DTC genetic and genomic testing market is very dynamic and the practices of companies are continuously evolving, thus it is important to monitor and continue to study and reflect on these activities.

In conclusion, we acknowledge that informed consent is just one of the elements related to the ethical issues around WGS. Its adequacy may not resolve the other ethical issues related to the companies that offer WGS, however, as stakeholders in genetics, we should expect and aim to support and provide an adequately informed consent process in order to respect individuals in their health-related decisions.

Acknowledgements

Emilia Niemiec has been supported by Erasmus Mundus Master of Bioethics Fellowship and Erasmus Mundus Joint International Doctoral Programme in Law, Science and Technology Fellowship. Part of this work has been supported by the Swedish Foundation for Humanities and Social Sciences (Riksbankens Jubileumsfond under grant M13-0260:1), the Biobanking and Molecular Resource Infrastructure of Sweden (BBMRI.se), the BBMRI-ERIC, and the CHIP ME COST Action IS1303. Part of this work is also supported by the FWO (Flanders-Québec) project. None of these funding sources have had any involvement in the preparation of this article.

We thank Prof. Michele Graziadei for his insightful comments and Dr Patrick Miqueu for his overall assistance during the work on this project.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Tables (Chapter 3)

Table 3.1 Basic information about the four companies selling WGS included in this study.

The websites were accessed on 23 October 2014. HCP = healthcare professional.

Company name, country and website address	Description of service		Who can order the test ^a	Sections of the websites studied
<p>Illumina, USA (http://www.illumina.com/clinical/illumina_clinical_laboratory.html)</p>	<p>WGS: TruGenome Undiagnosed Disease Test – with analysis and interpretation based on clinical indication;</p>	<p>TruGenome Predisposition Screen – with analysis and interpretation of 1,600 genes that have established associations to a set of conditions or diseases caused by single genes</p> <p>TruGenome Technical Sequence Data – raw data without interpretation</p>	<p>only HCP</p>	<p>Informed Consent (different form for each test, at the time of submitting the article the versions of forms studied were no longer available online; for the copies of the forms please contact the corresponding author)</p>
<p>Gentle, Belgium https://www.gentlelab.com/</p>	<p>WES - with analysis and interpretation of genetic variants related to carrier status, health risks and response to medications (in the time since this analysis was completed, Gentle has stopped selling to “end users”)^b</p>		<p>only HCP</p>	<p>Informed Consent (https://www.gentlelab.com/consent), Terms of Service (https://www.gentlelab.com/terms)</p>
<p>Gene By Gene, USA https://www.genebygene.com/#</p>	<p>Clinical testing</p>	<p>WES - with analysis, search for the variant(s) of potential causative effect for the described phenotype</p>	<p>only HCP</p>	<p>Terms and Conditions (https://www.genebygene.com/pages/terms)</p>
<p>Research and consumer testing</p>	<p>WES and WGS - raw data or with analysis</p>	<p>HCP and non-HCP</p>		

Table 3.1 Continuation

Company name, country and website address	Description of service	Who can order the test ^a	Sections of the websites studied
Inneova, Canada http://www.inneova.com/	WGS – with analysis and interpretation concerning interaction of genes with ageing, nutritional and lifestyle choices and diseases	only HCP	Statement of consent (http://www.inneova.com/contenu.php?page=terms.php), Disclaimer and privacy policy (http://www.inneova.com/contenu.php?page=disclaimer.php)

^aAccording to ‘A common framework of principles for DTC GT services’ issued by the Human Genetics Commission (UK) the type of genetic tests which ‘are commissioned by the consumer but where a medical practitioner or health professional is involved in the provision of the service’ also fall in the scope of DTC genetic tests.

^bAt the time of submitting this article Gentle stated on its company website “In order to focus all our efforts on the clinical diagnostics market, we are no longer-selling the Gentle test to end users. If you are interested in our clinical interpretation services, please contact us.” (<https://store.gentlelabs.com/>)

Table 3.2 Information about the pre-test counselling for WGS offered by the studied companies. The information was accessed on 25 October 2014.

Company name	Pre-test counselling
Illumina	Not provided by the company but required for IC
Gentle	Not provided by the company but recommended in IC
Gene By Gene	No information
Inneova	No information

Table 3.3 Information about the possible benefits and risks of WGS included in the studied sections of the companies' websites. Words in bold in 'Benefits' and 'Risks' columns are identified subthemes. The websites were accessed on 25 October 2014.

Company	Benefits	Risks
Illumina	<p><i>'Your test results may help you and your physician make more informed choices about your healthcare. It is also possible that your test results will not provide any benefit.'</i></p>	<p>Medical and/or physical risks: <i>'Side effects of having blood drawn are uncommon, but may include dizziness, fainting, soreness, bleeding, bruising, and, rarely, infection.'</i> Psychological: <i>'Your test results may reveal information about yourself, or your relatives, that you would rather not know. For example, you may learn information about genetic risks/predispositions to disease, including ones that might not be curable; ancestry; etc.'</i> Implications for family members: <i>'In a trio or parent/child analysis, it may be uncovered that a family member is unrelated to the patient, such as in the case of adoption or non-paternity. It may not be possible to prevent learning such information through this test.'</i> Discrimination risks: <i>'Genetic information could be used as a basis of discrimination. (...) The laws may not protect against genetic discrimination in other circumstances such as when applying for life insurance or long-term disability insurance.'</i></p>

Table 3.3 continuation

Company	Benefits	Risks
Gentle	<p>Knowledge about disease risks and predispositions: 'A person found to have an increased risk of disease might want to choose preventive or therapeutic medical treatments.'</p> <p>Having this knowledge can empower a person and family members to make important life planning decisions, even if a cure is not available at the time of testing. (...) Knowing the genetic predisposition to these conditions allows you to take action, even before symptoms occur.' Information about carrier status: 'DNA-testing can inform a person about his/her carrier status for thousands of genetic conditions.'</p> <p>Many genetic conditions are inherited in a recessive way. Being a carrier will usually not affect the health of the person him/herself, but might affect the health of future children. Screening your carrier status for diseases allows to check whether you might pass on severe conditions to your children.' More tailored drug therapy: 'Another benefit of DNA-testing is that you and your physician can make informed decisions on which medication is best for you.' Possibility to enroll in research studies: 'Having a specific diagnosis could qualify a person to enrol in research studies, which may lead to new treatments.' Insight into ancestry: 'DNA-testing can provide insight into a person's ancestry.'</p> <p>Examination of DNA variations can provide clues about where a person's ancestors might have come from and about relationships between families.'</p>	<p>Psychological: 'The greatest concern pertains to the way a DNA test result might change a person's life. The decision to have DNA testing can be stressful. You may have emotional reactions to learning that you do- or do not— carry a gene change for a certain condition.'</p> <p>Implications for family members: 'Sometimes a test result may not only affect you, but also your family relationships. A person who decides to have DNA testing needs to consider whether to tell other family members. Sometimes the result for one family member can disclose information about the genetic makeup of other relatives, even if they have not been tested.'</p> <p>Discrimination risks: 'In some countries a DNA test result may also affect a person's ability to obtain health, life, disability or long-term care insurance. It could also affect the ability to obtain or keep a job.'</p>

Table 3.3 continuation

Company	Benefits	Risks
<p>Gene By Gene</p>	<p>Knowledge about disease risks and predispositions, information about carrier status, only for 'Clinical Genetic Testing': <i>'The purpose of clinical genetic testing is to evaluate the presence of the predisposition to genetic diseases, to assess the risk for developing a genetic disease, or to determine the carrier status of a known disease-causing mutation.'</i></p>	<p>Psychological, discrimination risks for 'Clinical Genetic Testing' only: <i>' Gene By Gene, LTD. is not responsible for legal, material, social, psychological, or moral consequences related to the results of genetic testing.'</i> Only for 'Research and Consumer Testing': <i>' The customer is aware that some of the information received may be unexpected, and the customer takes responsibility for all possible consequences resulting from test data and sharing this data.'</i></p>
<p>Inneova</p>	<p>Knowledge about disease risks and predispositions: <i>' I understand the basic concept of predictive genetics testing and how it may result in the discovery of genetic predispositions that could indicate an increased or decreased risk of developing certain medical conditions and diseases. I realize the possible far-reaching implications of the information obtained through predictive genetics testing in affecting my life choices as well as those of my relatives, children, and unborn children. (...) ICL is obliged to (...) provide me with predictive genetics test results, as well as an indicative, preliminary personalized report for each test performed based on statistical genetic research into the behaviour and interaction of genes with factors such as aging, nutritional and lifestyle choices, as well as various diseases and how they could affect my health and well being. '</i></p>	<p>Medical, psychological risks, implications for family members, discrimination risks: <i>' I realize the possible far-reaching implications of the information obtained through predictive genetics testing in affecting my life choices as well as those of my relatives, children, and unborn children. (...) I agree that ICL (together with its medical, scientific, and other service partners, subsidiaries and related business entities, legal advisors, agents, or appointees) assumes no liability for any stress, strain, hardship, adverse medical condition, financial loss, or other circumstances that I may suffer as a result of the receipt or reference to any predictive genetics test results and/or interpretations thereof supplied to me by ICL.'</i></p>

Table 3.4 Information regarding the management of incidental findings resulting from WGS included in the studied sections of the companies' websites. The websites were accessed on 25 October 2014.

Company, type of test		Incidental findings	Categorization of the genetic information	Right not to know
Illumina	TruGenome Undiagnosed Disease Test	Provides 'incidental findings' report of variants located in the genes recommended by ACMG	No information	No information
	TruGenome Predisposition Screen	No information	Yes, categories: childhood onset and adult onset; subcategories: medically actionable, not medically actionable, cancer, neurologic conditions	Yes, option for excluding some of the categories from the test results
	TruGenome Technical Sequence Data	Not applicable	Not applicable	Not applicable
Gentle		No information	No information	Yes
Gene By Gene		No information	No information	No information
Inneova		No information	No information	No information

Chapter 4: Ethical issues in consumer genome sequencing: use of consumers' samples and data

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Published in: *Applied & Translational Genomics* 2016; 8:23–30,

DOI:10.1016/j.atg.2016.01.005

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Abstract

High throughput approaches such as whole genome sequencing (WGS) and whole exome sequencing (WES) create an unprecedented amount of data providing powerful resources for clinical care and research. Recently, WGS and WES services have been made available by commercial direct-to-consumer (DTC) companies. The DTC offer of genetic testing (GT) has already brought attention to potentially problematic issues such as the adequacy of consumers' informed consent and transparency of companies' research activities. In this study, we analysed the websites of four DTC GT companies offering WGS and/or WES with regard to their policies governing storage and future use of consumers' data and samples. The results are discussed in relation to recommendations and guiding principles such as the “Statement of the European Society of Human Genetics on DTC GT for health-related purposes” (2010) and the “Framework for responsible sharing of genomic and health-related data” (Global Alliance for Genomics and Health, 2014). The analysis reveals that some companies may store and use consumers' samples or sequencing data for unspecified research and share the data with third parties. Moreover, the companies do not provide sufficient or clear information to consumers about this, which can undermine the validity of the consent process. Furthermore, while all companies state that they provide privacy safeguards for data and mention the limitations of these, information about the possibility of re-identification is lacking. Finally, although the companies that may conduct research do include information regarding proprietary claims and commercialisation of the results, it is not clear whether consumers are aware of the

consequences of these policies. These results indicate that DTC GT companies still need to improve the transparency regarding handling of consumers' samples and data, including having an explicit and clear consent process for research activities.

Keywords: whole-genome sequencing, whole-exome sequencing, direct-to-consumer genetic testing, consumer genomics, human genome research, consent

4.1 Introduction

Direct-to-consumer (DTC) genetic testing (GT) companies operating outside of the traditional healthcare system have attracted numerous critiques of their practices over the last decade [1]. Beyond questioning the clinical validity and utility of the tests, the appropriateness of medical supervision and genetic counselling, some of the concerns centre on the storage and use of consumers' samples and data. These include a number of inter-related issues such as what consumers are told (e.g., during the consent process) about storage and use of samples and data; proprietary claims stemming from secondary uses of sample and data; as well as the coupling of companies' genetic testing offer with research activities. Indeed, an earlier explorative study of DTC GT companies has shown that for some companies the consent to participation in research may not be adequate; it questioned whether the information provided by the companies about their research activities was clear and explicit enough for consumers to understand what they were agreeing to [2]. Furthermore, it highlighted that such ambiguous presentations of information for testing and research activities blur the lines between consumers and research participants, undermine the informed choice of consumers and may potentially undermine public trust in research in general [2,3].

Recent advancements in sequencing technologies have resulted in a significant decrease in the price of whole-exome and whole-genome sequencing (WES, WGS), which has allowed for a greater use of these approaches in both the clinical and research domains causing a shift in testing approach from analysing one or a few genetic variants to the study of an entire exome/genome sequence. WES/WGS generates an unprecedented amount of sensitive health-related genomic data useful in healthcare management and powerful in the research setting [4]. While much of the discussion surrounding the ethical, legal and social implications (ELSI) of these high-throughput approaches has been focused on these settings, much less attention has

been paid to commercial companies offering sequencing services DTC. Given that WES/WGS is likely to become increasingly more available and there is the potential for these services to be coupled with research activities using consumers' data (<http://www.technologyreview.com/news/540711/inside-illumina-plans-to-lure-consumers-with-an-app-store-for-genomes/>), the ELSI of DTC genomics are particularly important to address now. We therefore studied the websites of companies advertising WGS and/or WES DTC to shed light on the information they provide to consumers. More specifically, we analysed webpage documents that consumers should sign and/or agree to when undertaking the test (i.e., depending on the company, sections entitled informed consent, terms and conditions, statement of consent, disclaimer and privacy policy; Table 4.1). We focused on information relevant to storing and using consumers' data and samples. These issues include: i) purpose and period of samples and data storage; ii) consumer consent; iii) data access and sharing; iv) identifiability and confidentiality of data; and v) proprietary claims. Four companies were identified (circa mid-2015) which offer and/or advertise WES and/or WGS DTC: Illumina, Gene by Gene, GeneYouIn, and Inneova. Each stated that they offer WGS and/or WES, although the scope and focus of data analysis and interpretation varied from providing only raw sequencing data to the diagnosis of Mendelian disorders. Moreover, they had different models of provision (e.g., with or without physician referral; Table 4.1). We defined direct-to-consumer genetic/genomic testing as the offer and/or advertisement of testing direct-to-consumers. We considered companies that required a health care professional to order the WGS or WES services also as DTC companies since they were still advertising directly to consumers, and this can have a significant impact on the demand and ultimate use of a product or service. This is congruent with the scope of DTC GT given by the UK Human Genetics Commission, which included situations where “*tests are commissioned by the consumer but where a medical practitioner or health professional is involved in the provision of the service.*” [5].

4.2 Purpose and period of samples and data storage

Three of the four analysed DTC companies (Illumina, Gene By Gene, GeneYouIn) stated on their websites that they may use consumers' data and/or samples for purposes beyond performing the genetic test ordered by the consumer (Table 4.2). Illumina stated that “*leftover specimen and results may be used by Illumina for purposes of quality control, laboratory operations, and laboratory improvement*” (<http://www.illumina.com/content/dam/illumina->

[marketing/documents/clinical/forms/form-test-req-predisposition.pdf](#)). This suggested that the company performs internal quality assurance, for which specific consent is not necessarily required as long as some conditions are met (e.g., actively informing individuals of this use) [6,7]. The period for which the results and specimen would be stored was not specified in the analysed document.

Meanwhile, GeneYouIn indicated that it would store the samples for 90 days and that after this period they would be discarded; the company did not specify the period for data storage. GeneYouIn also stated explicitly that it may use consumers'⁵ data for research, providing a general description of the type of research on its informed consent page:

“You provide your consent for research in which we analyse your genetic data and phenotype information in order to discover or validate associations between certain genetic variations and diseases.” (<https://www.geneyouin.ca/informed-consent>)

Gene By Gene indicated in its terms and conditions that it would store consumer data for 30 days or longer; after this time the data might be permanently deleted, however, the consumer could request storage for a longer period. Regarding the storage of the samples, the company indicated: *“After testing is complete, remaining sample material is stored for 180 days, unless otherwise specified by regulatory agencies.”* However, in the following sentence it stated: *“After 3 months, the sample will be discarded or de-identified and retained for in-house laboratory use”*, making it unclear for what period the samples would be actually stored. Furthermore, Gene By Gene provided a few statements concerning the use of samples and data that appear contradictory: *“Any sample material sent will be used only to perform the specifically ordered testing.”* Meanwhile, a few paragraphs below on the same page, it was written: *“After 3 months, the sample will be discarded or de-identified and retained for in-house laboratory use.”* And: *“The customer specifically understands that they will not receive compensation for any research or commercial products that include or results from your sample, results, or personal record”* (<https://www.genebygene.com/pages/terms>). The last two

⁵ The companies GeneYouIn and Gene By Gene use a word "customer" in the analysed texts. However, as implied in these texts, a customer (meaning a person who buys a test) is simultaneously a consumer (meaning a user of a test). Therefore, we use the word "consumer" throughout this article, also when referring to the quotations on the webpages of GeneYouIn and Gene By Gene.

statements imply that consumers' samples and data may be involved in research beyond quality assurance, which, without further information, appears to contradict the first statement that samples would be used only for the ordered testing. This information is ambiguous and confusing.

The fourth company studied, Inneova, stated that biological samples would be destroyed after performing the test, but did not describe what would happen to the data.

The incomplete information provided by the companies regarding the storage and use of consumers' data and samples is incongruent with the “Statement of the ESHG (European Society of Human Genetics) on direct-to-consumer genetic testing for health-related purposes” [8], which recommends that companies should “*explain what will happen to the sample and the data when the testing process is concluded*”. Furthermore, in case of research activities being performed on the consumers' data or samples, the ESHG (2010) recommends that more detailed information should be provided: “*Informed consent documents for participation in research should disclose the procedures for storing and disposal of samples and genetic information, the time period and conditions for storing them*” [8]. In addition, DTC GT companies should “*have a clearly laid-out plan as to what will happen to the samples and data should the company be sold or go bankrupt*” [8]. None of the web-documents/webpages studied from these four companies provided a description of what will happen in such situations. This echoes results of a study of DTC GT companies conducted by Zawati et al., 2011 [9], in which the authors called for “*clearer institutional frameworks on the issue of closure.*”

Overall, our results show that two companies indicated may perform research on consumer data and/or samples, while two other companies did not make reference to research activities. Furthermore, only one company specified the period of storage for data, while the period of storage for samples was stated clearly by two of four companies. None of the companies made reference to what would happen if the company were sold or went bankrupt.

4.3 Consumer consent

4.3.1 Consent for services

Based on the websites studied, consumers give their consent for the services purchased, including agreeing to the information in the aforementioned documents by ordering the test (<https://www.geneyouin.ca/terms-conditions/>; <https://www.genebygene.com/pages/terms>; <http://www.inneova.info/contenu.php?page=disclaimer.php>) or by signing the form which is sent to the company together with the sample for analysis (<http://www.illumina.com/content/dam/illumina-marketing/documents/clinical/forms/form-test-req-predisposition.pdf>). In the case of the informed consent from GeneYouIn, it was not made explicit how exactly consumers provide consent to the testing (e.g., via signature, a verbal agreement)

“We ask you to provide your informed consent to ensure that, before purchasing GeneYouIn's genetic testing and consulting services, you are not only aware of the benefits, but also understand the limitations and potential risks. Please carefully review the information described below before you purchase any of our services.”
(<https://www.geneyouin.ca/informed-consent/>)

The provision of information and the manner of consenting in the DTC GT context may raise the question of whether consumers have read and fully understood the information to which they agree and thus whether their decision is truly an informed decision. The low readership of sections such as the “terms of service” has already been discussed in the context of online transactions e.g. when purchasing software [10]. However, as noted by the Presidential Commission for the Study of Bioethical Issues (2013), by providing health information DTC GT companies “*interact in both the business and medical realms, and could find themselves subject to the ethical principles pertinent to business transactions as well as those of medical care*” [11]. Therefore, DTC GT companies, depending on the types of tests they sell, can be subject to the e-commerce legal framework, as well as fall within the scope of ethical requirements related to genetic testing in the clinic context and/or in the realm of research participation. One of these requirements is to obtain informed consent for testing and research, which has different functions than the terms of service of a consumer contract [12]. The

informed consent process involves providing consumers certain types of information about testing (e.g. benefits and risks) in an understandable manner. Furthermore, as explained in the Statement of the ESHG the process of informed consent should “*ensure that individuals understand the disclosed information, are legally competent and cognitively capable of acting without external pressure, and give their agreement to all the elements involved.*” [8]. It should also protect against involuntary testing [8,12].

4.3.2 Consent to research

The information about the possibility of performing research on consumers' samples (i.e., for the companies GeneYouIn and Gene by Gene) was not included on the front pages of the companies' websites or the main pages including the description of what the companies offer (Table 4.1). Therefore, it is not clear whether the consumers have been aware of the companies' research activities and if they have been genuinely consenting to them. Furthermore, the provision of information about research activities raises concerns about clarity and understandability of this information for consumers, as mentioned earlier. This type of unclear and non-explicit way of “recruiting” consumers as research participants appears to be in contradiction of the requirement for informed consent. The importance of informed consent for research has been articulated by various guidelines and legal documents, for instance the Statement of the ESHG specifies: “*If samples or data are to be used in any research, this should be clear to consumers, and a separate and unambiguous consent procedure should take place.*” [8]. This recommendation underlines another concern about the adequacy of consent for research activities of the companies, namely the presence of a separate consent procedure. This practice has been acknowledged and supported as it “*enhances autonomy by drawing the customer's attention to the change in the use of their samples and data*” [13]. Neither of the two companies that may conduct research and were examined here offered a separate informed consent form for research. What is even more troubling, they also did not provide a possibility to opt-out of their potential research activities, which has been criticised as a practice undermining the autonomy of consumers [13].

4.3.3 Additional information needed in the consent process

The recommendations for informed consent for research specify that besides information regarding the destination of the consumers' data and samples after performing the test, the consent should include additional elements. For example, the ESHG states:

“Informed consent documents for participation in research should disclose the procedures for storing and disposal of samples and genetic information, the time period and conditions for storing them, inform participants of the identity of any third parties who may be granted access to data or samples, and include also information on the fact that the research may lead to commercialization and patents, on any customers' rights to commercial benefits and on the property of biological samples and data.” [8]

The Global Alliance for Genomics and Health suggests similar types of information to be provided in order to respect the responsible sharing of genomic and health-related data in general, and specifically to support the principle of transparency:

“Provide clear information on the purpose, collection, use and exchange of genomic and health-related data, including, but not limited to: data transfer to third parties; international transfer of data; terms of access; duration of data storage; identifiability of individuals and data and limits to anonymity or confidentiality of data; communication of results to individuals and/or groups; oversight of downstream uses of data; commercial involvement; proprietary claims; and processes of withdrawal from data sharing.” [14]

Similarly, the recommendations on WGS issued by the US Presidential Commission for the Study of Bioethical Issues suggest the presence of particular elements in informed consent, which also apply to commercial WGS:

“Researchers and clinicians should evaluate and adopt robust and workable consent processes that allow research participants, patients, and others to understand who has access to their whole genome sequences and other data generated in the course of research, clinical, or commercial sequencing, and to know how these data might be

used in the future. Consent processes should ascertain participant or patient preferences at the time the samples are obtained.” [15]

In the remainder of this article we discuss some of the elements that have been highlighted in the above documents as being important to communicate to persons undergoing genetic or genomic testing.

4.4 Data access and sharing

All companies stated that they may grant access to consumers' data to a third party that is legally authorized or if it is required by law (e.g., by a court order) (Table 4.3). Illumina, GeneYouIn and Gene By Gene also specified that, with the consumer's consent, they may grant access to the healthcare provider to whom the test results would be released. In addition, GeneYouIn indicated that consumers may withdraw this type of consent and request deletion of their records. Moreover, the company specified that it might share consumers' data with research organizations and that consumers would have an opportunity to opt-out of their data sharing by checking a box in the informed consent.

Inneova, although somewhat indirectly, also mentioned the possibility of sharing data:

“I understand that ICL will not disclose my identity, contact details, or test results to third parties (except to its medical, scientific, and other service partners, subsidiaries and related business entities, legal advisors, agents, or appointees for the purpose of performing genetic testing or interpretation services, as well as any associated administrative transactions, as deemed necessary by ICL in the normal course of business under the terms of this Agreement as well as under its Disclaimer and Privacy Policy).” (<http://www.inneova.com/contenu.php?page=terms.php>)

Although the first clause stated no disclosure, the list of exceptions in brackets was long and vague.

Gene By Gene stated that the samples may be “*retained for in-house laboratory use*” and did not specify any third parties with which sharing would happen other than to state that third-party access will only be given with proper “*authorization in accordance with the Health*

Insurance Portability and Accountability Act”. However, the statement: “*The customer understands that by providing any sample (...) or providing personal information, that the customer acquires no rights in any research or commercial products or services that may be developed by Gene by Gene, LTD. or its collaborating partners.*” (<https://www.genebygene.com/pages/terms>) suggests that consumers' data, in some way, may be indeed, used by “collaborating partners” and hence shared in some way.

Importantly, the companies did not specify the detailed conditions (except mentioning “legal authorization”) under which third parties would gain access to consumer data. Also lacking was information regarding whether the transfer of data would be international and information about oversight of downstream uses of data, both of which are elements suggested in the “Framework for responsible sharing of genomic and health-related data” (called further Global Alliance Framework) in order to respect and support transparency in data sharing [14]. Similarly, the Presidential Commission for the Study of Bioethical Issues recommends:

“Funders of whole genome sequencing research; managers of research, clinical, and commercial databases; and policy makers should maintain or establish clear policies defining acceptable access to and permissible uses of whole genome sequence data. These policies should promote opportunities for models of data sharing by individuals who want to share their whole genome sequence data with clinicians, researchers, or others.” [15]

Although both of these documents highlight the importance of sharing data for maximising research potential, and they encourage making data accessible to researchers, they also stress that sharing should be conducted in a responsible way. Based on our findings, this may not be fully respected by some DTC WGS companies.

4.5 Data security: identifiability and confidentiality

All four companies stated that they provide privacy safeguards for consumers' samples and/or data (Table 4.4). Illumina stated that consumers need the code provided to their healthcare practitioner in order to access their results. Meanwhile, GeneYouIn described generally that it employs “*commercially validated and reasonable computational and organizational safeguards*” (<https://www.geneyouin.ca/terms-conditions/>). Similarly, Gene By Gene stated

that it “*implements administrative, physical and technical safeguards to secure our client's protected health information as defined by HIPAA*” (<https://www.genebygene.com/pages/terms>). Furthermore, Illumina, Gene By Gene and Inneova specified that the samples and/or data would be de-identified. GeneYouIn stated specifically that consumers' genetic and health data would be anonymised. The information provided by the companies seemed, at least to some extent, to fulfil the requirement articulated by the Statement of the ESHG: “*companies offering DTC genetic tests should preserve the customer's privacy, keep their data confidential, inform them about their security procedures (...)*” [8]. They also concur with the recommendations of the PCSBI which states that “*Accessible whole genome sequence data should be stripped of traditional identifiers whenever possible to inhibit recognition or re-identification*” [15]. The Global Alliance Framework, additionally, suggests provision of information about “*limits to anonymity or confidentiality of data*” [14]. GeneYouIn, Illumina and Gene By Gene stated that there are limitations to the privacy safeguards, which may be breached by, for example, the use of malicious software (Table 4.4). Yet information about the possibility of re-identification of anonymised genomic data was missing from the web documents/webpages studied for all four companies. The relevance of this element for informed consent for genome testing was highlighted by Chow-White et al.:

“(...) the consent form should contain language/disclaimer that privacy is not absolutely guaranteed. The unstableness of digital networks and uncertainty of genomic information creates the conditions of privacy without guarantees. The consent form should (...) provide details of data release and sharing, including potential public databases where data could be disseminated and explain the potential of re-identification of anonymized data.” [16]

Moreover, one may argue that using the term “anonymised” is misleading and disingenuous as it has been shown that anonymised genomic data may be re-identified by linking information from different databases [17]. Indeed, the term “pseudonomisation” may be more accurate in the context of genomic data, however it may be too vague for “lay” consumers to fully understand its meaning [18]. To clarify this issue, companies should explain to consumers that although their data will be stripped of personal information (de-identified) there is still a chance of reidentification.

The Statement of the ESHG also suggests that “*possible consequences related to their [results] disclosure to third parties, such as insurance companies and employers, should be discussed*” [8]. Illumina and GeneYouIn stated that there is a risk of discrimination in case of disclosure of the results (Table 4.4). Illumina also mentioned the limitations of legal protections against discrimination: “*The laws may not protect against genetic discrimination in other circumstances such as when applying for life insurance or long-term disability insurance.*” (<http://www.illumina.com/content/dam/illumina-marketing/documents/clinical/forms/form-test-req-predisposition.pdf>). GeneYouIn and Gene By Gene also cited the US Genetic Information Nondiscrimination Act (GINA), which “*prohibits health insurers and employers from discriminating based on genetic information*” (<https://www.genebygene.com/pages/terms>). Furthermore, GeneYouIn mentioned the limitations of current Canadian law: “*While there are different laws in place across the globe that prevent companies from discriminating against people based on race, age, handicaps, and genetic predispositions such laws are not yet fully implemented in Canada.*” (<https://www.geneyouin.ca/informed-consent>). Gene By Gene outlined possible consequences of disclosure, including: “*misuse, mishandling, or misrepresentation*” (<https://www.genebygene.com/pages/terms>).

4.6 Proprietary claims

GeneYouIn and Gene By Gene stated that consumers would not receive any compensation for being involved in research (Table 4.5). Gene By Gene also added that a consumer “*will not receive compensation for (...) commercial products that include or results from [customer's] sample, results, or personal record.*”; and “*customer acquires no rights in any research or commercial products or services that may be developed by Gene by Gene, LTD. or its collaborating partners.*” (<https://www.genebygene.com/pages/terms>). Meanwhile, GeneYouIn explained that it is a custodian of consumers' genetic and health data; however, it did not appear to explicitly outline the implications of this fact. The presence of these elements of information seems to comply with the recommendations of the Global Alliance Framework [14] and the Statement of the ESHG, which suggests inclusion of “*information on the fact that the research may lead to commercialization and patents, on any customers' rights to commercial benefits and on the property of biological samples and data.*” [8]

However, the fact that Gene By Gene consumer's sample could actually *be part* of a commercial product raises particular ethical concerns including whether it is ethically acceptable to sell products that incorporate consumers' samples potentially without providing any benefit-sharing for the consumers [19].

In addition, given the concerns about overall adequacy of the consent process for the companies that may conduct research, we can question whether consumers are well informed about potential commercialisation of research results and their biological material. It has been reported that at least some of the consumers of the DTC GT company 23andMe were not aware of the possibility of commercialising research results, although the company provided a statement about it in its online consent form [20]. Importantly, the information about the potential commercial uses has been shown to be a relevant factor for deciding about whether to participate in research [21]. Therefore, this element of information should be provided to consumers in explicit and clearly understandable form in order to secure their informed choice.

4.7 Conclusions

Our study of particular sections of companies' websites indicates that some DTC WGS/WES companies might have conducted research with consumer data. Moreover, information about these activities, as well as general information about data and sample storage and specific information about data sharing were found to be lacking. For example, we found multiple instances where disclosures did not comply with guidelines of the ESHG concerning the offer of DTC GT [8] or with the recommendations outlined in the “Framework for responsible sharing of genomic and health-related data” [14]. This lack of transparency in the provision of information to consumers could undermine their informed consent. On the bright side, companies were relatively good at providing information about general data security. However, they failed to address the possibility (even if small) of re-identification. Finally, the companies did provide information about proprietary claims and commercialisation.

We recognize that this study is based on a particular set of web documents/webpages sampled at a particular moment in time. As such there is a chance that some of the missing information might have been found elsewhere on the companies' websites. This being said, since the documents we chose are specifically aimed at consumers to read and agree to, we would argue

that the necessary information for data and sample storage, secondary use, and potential data or sample sharing should be included in these documents.

Some of the ethical concerns regarding the research practices of DTC WGS companies discussed herein have been raised previously [3,22]. Furthermore, earlier this year, it was reported that the DTC GT company 23andMe together with the biotechnology company Genentech was to perform WGS on 23andMe consumers' samples, raising concerns about informed consent, data privacy, management of incidental findings and availability of the data to other researchers [23]. Although the ethical and legal study of DTC GT companies has been ongoing for almost a decade, it would appear that some of the ethical concerns about these companies and their research activities have not been resolved, but rather amplified as new sequencing technologies are implemented. Meanwhile, one of the DTC GT companies, 23andMe, has been remarkably successful in recruiting research participants (<http://www.forbes.com/sites/matthewherper/2015/10/14/23andme-prepares-a-comeback-raising-115-million-at-a-1-1-billion-valuation/>), thus gaining a significant share of the general community of biobank research and in doing so, potentially influencing the public perception of research. Noncompliance with ethical standards or recommendations by well-known companies could have significant negative implications for biomedical research in general. Therefore, it is particularly important to examine the behaviour of DTC GT companies and to promote the awareness and adherence to the ethical standards currently accepted and/or aspired to by the research community. In order to achieve this, it would be constructive to have the community of commercial companies weigh in on the development of best practice guidelines for the commercial realm along with relevant stakeholders such as consumers, patients and health care professionals.

Acknowledgements

The authors thank Dr. Misha Angrist for his insightful comments on the manuscript. Emilia Niemiec is supported by an Erasmus Mundus Joint International Doctoral Program in Law, Science and Technology Fellowship. Part of this work has been supported by the Swedish Foundation for Humanities and Social Sciences (Riksbankens Jubileumsfond under grant M13-0260:1), the Biobanking and Molecular Resource Infrastructure of Sweden (BBMRI.se), the

BBMRI-ERIC, and the CHIP ME COST Action IS1303. None of these funding sources have had any involvement in the preparation of this article.

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(accessed 16 September 2015)

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<https://www.geneyouin.ca/terms-conditions/> (accessed 10 August 2015)

Tables (Chapter 4)

Table 4.1 Information about the companies, their WES/WGS services, model of provision of testing, and the website documents studied

Company name & country	Description of service	Model of provision of testing	Sections of the websites studied
<p>Illumina, USA</p>	<p>WGS: TruGenome Undiagnosed Disease Test – <i>“intended to provide information to physicians to aid in the diagnosis of inherited diseases of single-gene etiology (Mendelian diseases)”</i>. TruGenome Predisposition Screen – <i>“analysis and interpretation are performed on 1691 genes that have well-established associations to a set of 1232 conditions (...), and 11 medically actionable genes associated with response to 16 different drugs”</i> TruGenome Technical Sequence Data – <i>“whole-genome sequencing data in two formats: a gVCF and a BAM”</i></p> <p>(http://www.illumina.com/clinical/illumina_clinical_laboratory/trugenome-clinical-sequencing-services.html)</p>	<p>“must be ordered by a licensed physician” (http://www.illumina.com/clinical/illumina_clinical_laboratory/how-to-order.html)</p>	<p>Informed Consent (different form for each test)</p>
<p>GeneYouIn, Canada</p>	<p>WES: VitaSeq™: <i>“With VitaSeq™, assess your risk of cancer, heart disease, autoimmune or neurological diseases.”</i> PregnaSeq™: <i>“With PregnaSeq™, genetic testing can help you optimize your fertility treatment and find out if you and your partner are at risk for passing on preventable diseases.”</i> (https://www.geneyouin.ca/)</p>	<p>do not require HCP for ordering (although 30 minute phone consultation is required before ordering) (https://www.geneyouin.ca/how-it-works/how-to-order/)</p>	<p>Informed Consent, Terms and Conditions</p>

Table 4.1 continuation

Company name & country	Description of service	Model of provision of testing	Sections of the websites studied
Gene By Gene, USA	WES/WGS - raw data or with “alignment and variant calling” (https://www.genebygene.com/pages/research#) or (only for WES) with “ <i>professional RUO</i> [research use only] <i>interpretation</i> ” (https://www.genebygene.com/pages/research?goto=whole-exome-with-interpretation#)	for Clinical Testing service a clinician orders the test (https://www.genebygene.com/pages/genetics#how-to-order); not available for "Research and Consumer" services	Terms and Conditions
Inneova, Canada	WGS – “ <i>screening risk factors and sensitivity to particular molecules which can help a client’s physician recommend specific check-ups as well as optimize the administration of medications and diets</i> ” (http://www.inneova.com/tout.php)	“accept test requests from licensed medical professionals only” (http://www.inneova.com/tout.php)	Statement of consent, Disclaimer and privacy policy

* HCP: health care professional

Table 4.2 Information about consumers' samples and data storage, use and research activities

Company name	Information on storage and use	Period of samples and data storage	Information about research activities
Illumina	Informed consent*: <i>"Pursuant to best practices and clinical laboratory standards, leftover specimen and results may be used by Illumina for purposes of quality control, laboratory operations, and laboratory improvement. All such uses [will be de-identified]**, and in compliance with applicable law."</i> **the phrase found only in the informed consent for TruGenome Predisposition Screen	not available	not available
GeneYouIn	Informed consent*: <i>"You provide your consent for research in which we analyze your genetic data and phenotype information in order to discover or validate associations between certain genetic variations and diseases. These studies will improve the accuracy of our predictions for you and other customers. As the number of our customers grows, our ability to study their combined genetic data and phenotype information further advances scientific and medical research, thus improving health care."</i> Terms and conditions: <i>"Your genetic data will be stored in Your Account, and you appoint GeneYouIn as a custodian of your genetic and health data. By accepting these Terms you agree that your anonymized genetic and health data can be used for research purposes. (...) All biological samples and DNA will be destroyed after 90 days following obtaining the test results, however the information of your genetic code will be stored in Your Account, and you appoint GeneYouIn as a custodian of your genetic and health data. By accepting these Terms you agree that your anonymized genetic and health data can be used for research purposes."</i>	samples - 90 days; data - not available	research may be performed on consumers' data

Table 4.2 continuation

Company name	Information on storage and use	Period of samples and data storage	Information about research activities
Gene By Gene	Terms and conditions*: <i>"Any sample material sent will be used only to perform the specifically ordered testing. After testing is complete, remaining sample material is stored for 180 days, unless otherwise specified by regulatory agencies. After 3 months, the sample will be discarded or de-identified and retained for in-house laboratory use. (...) The customer specifically understands that they will not receive compensation for any research or commercial products that include or results from your sample, results, or personal record".</i>	data - 30 days or longer; samples – unclear: at least 90 or 180 days	contradictory statements: research will not be performed on consumers samples and research may be performed on consumers' samples and data (implicit statement)
Inneova	Disclaimer and privacy policy*: <i>"The DNA is used only for the purpose of predictive genetics testing. Once processed, each DNA sample is discarded following a secure protocol."</i>	samples - discarded after testing; data and results - not available	no research on consumers' DNA samples; no information about research on data

* These denote the specific documents/sections of websites where the quotes can be found.

Table 4.3 Information about consumers' data access and sharing

Company name	Information on data access and sharing
Illumina	<p>Informed consent*: <i>"Illumina keeps test results confidential. Illumina will only release your test results to your healthcare provider, his or her designee, other healthcare providers involved in your medical care, or to another healthcare provider as directed by you (or a person legally authorized to act on your behalf) in writing, or otherwise as required or authorized by applicable law."</i> (http://www.illumina.com/content/dam/illumina-marketing/documents/clinical/forms/form-test-req-predisposition.pdf)</p>
GeneYouIn	<p>Informed consent*: <i>"You authorize GeneYouIn to use and share your anonymized genetic and clinical data with research organizations. If you decide that you do not want us to share your anonymized genetic and clinical data, please initial the check box next to this bullet point. "(...) Please note that GeneYouIn will not disclose your health information without your explicit consent or a legal order. (...) Through our electronic tools, you can grant your physician or other trusted health care provider secure access to your report. If at any time you decide to withdraw your consent, you may request deletion of your records."</i> (https://www.geneyouin.ca/informed-consent) Terms and conditions*: <i>"Access to you biological sample and health data by a court-appointed order will be granted according to the Privacy laws of Canada and Ontario."</i> (https://www.geneyouin.ca/terms-conditions/)</p>
Gene By Gene	<p>Terms and Conditions*: <i>"Test results will be released only to the ordering clinician or genetic counselor. Gene By Gene, LTD will not release results to a third party without proper authorization in accordance with the Health Insurance Portability and Accountability Act (HIPSS) of 1996. (...)The customer understands that by providing any sample, having your sample processed, accessing results, or providing personal information, that the customer acquires no rights in any research or commercial products or services that may be developed by Gene by Gene, LTD. or its collaborating partners."</i> (...) <i>"The customer understands that Gene By Gene, LTD. is not responsible for misuse, mishandling, or misrepresentation of this data by the customer or other third parties who have been given rightful access to the aforementioned data or materials."</i> (https://www.genebygene.com/pages/terms)</p>

Table 4.3 continuation

Company name	Information on data access and sharing
Inneova	<p>Statement of consent*: <i>"I understand that ICL will not disclose my identity, contact details, or test results to third parties (except to its medical, scientific, and other service partners, subsidiaries and related business entities, legal advisors, agents, or appointees for the purpose of performing genetic testing or interpretation services, as well as any associated administrative transactions, as deemed necessary by ICL in the normal course of business under the terms of this Agreement as well as under its Disclaimer and Privacy Policy). I understand that ICL will be absolved of this responsibility to a limited extent as stated in its Disclaimer and Privacy Policy in the case of any legal action, court order, or legislation requiring it to do otherwise."</i> http://www.inneova.com/contenu.php?page=terms.php</p>

* These denote the specific documents/sections of websites where the quotes can be found

Table 4.4 Information on samples' and data identifiability and confidentiality

Company name	Samples' and data identifiability and confidentiality
Illumina	<p>Informed consent*: <i>"You will need to obtain a unique code from your doctor to download your test results. (...) The Internet and wireless services may not be 100% secure. There is always a risk that you may lose the device or the security on the device may be breached and someone else may then gain access to your test results. (...) Discrimination Risks. Genetic information could potentially be used as a basis of discrimination. To address concerns regarding possible health insurance and employment discrimination, many U.S. states and the U.S. government have enacted laws to prohibit genetic discrimination in these circumstances. The laws may not protect against genetic discrimination in other circumstances such as when applying for life insurance or long-term disability insurance."</i> (http://www.illumina.com/content/dam/illumina-marketing/documents/clinical/forms/form-test-req-predisposition.pdf)</p>
GeneYouIn	<p>Informed consent*: <i>"The Genetic Information Nondiscrimination Act (known as GINA) was signed into law in May 2008 in the United States. This legislation offers federal protection against discrimination based on an individual's genetic information in health insurance and employment settings. While there are different laws in place across the globe that prevent companies from discriminating against people based on race, age, handicaps, and genetic predispositions such laws are not yet fully implemented in Canada."</i> (https://www.geneyouin.ca/informed-consent)</p> <p>Terms and Conditions*: <i>"We are not responsible for maintaining security and confidentiality of copies of Your Reports stored outside of GeneYouIn's databases. We are not and cannot be responsible for any personally identifiable information about you that you release on your own, or that you request or authorize us to release. (...) We employ commercially validated and reasonable computational and organizational safeguards against unauthorized disclosure or access to your genetic data or other personally identifiable information about you according to our Privacy & Security Policy. You acknowledge that security safeguards, by their nature, are capable of circumvention and GeneYouIn does not guarantee that your personal identifiable information will not be accessed by unauthorized persons capable of overcoming such safeguards. In particular, our site may be used to access and transfer information, including personally identifiable information about you over the Internet. You acknowledge and agree that GeneYouIn does not operate or control the Internet and that unauthorized users may use malicious software (viruses, worms, trojan horses, and other software) to obtain access to personally identifiable information about you. GeneYouIn will not be liable to you for any damages in connection with unauthorized dissemination of your personal information in accordance with this paragraph."</i> (https://www.geneyouin.ca/terms-conditions/)</p>

Table 4.4 continuation

Company name	Samples' and data identifiability and confidentiality
Gene By Gene	<p>Terms and conditions*: <i>“However, Gene By Gene, LTD implements administrative, physical and technical safeguards to secure our client’s protected health information as defined by HIPAA. (...) Gene By Gene, LTD. will handle all sample specimens in compliance with all applicable laws and regulations. All data received from the customer and data generated will be created, stored, and transferred according to HIPAA guidelines. The customer understands that Gene By Gene, LTD. is not responsible for misuse, mishandling, or misrepresentation of this data by the customer or other third parties who have been given rightful access to the aforementioned data or materials.”</i> (https://www.genebygene.com/pages/terms)</p>
Inneova	<p>Disclaimer and privacy policy*: <i>"ICL uses a specific tracking system to identify your sample as soon as it enters our facilities. Molecular biologists in charge of your sample do not know who the actual sample belongs to, but only see each sample as a number. This tracking number is associated with your name and contact information only within our secure database, which is not accessible by the lab or anyone outside of our company."</i></p>

* These denote the specific documents/sections of websites where the quotes can be found

Table 4.5 Information on the proprietary claims found on the studied pages of the companies' websites

Company name	Proprietary claims
Illumina	not available
GeneYouIn	<p>Informed consent*: <i>“You understand that you will not receive any compensation as a result of having your DNA analyzed, Your Genetic Data, or your Phenotype Information analyzed, or from any other research performed using your Genetic Data or your Phenotype Information.”</i> (https://www.geneyouin.ca/informed-consent) Terms and conditions: <i>“(…) you appoint GeneYouIn as a custodian of your genetic and health data.”</i> (https://www.geneyouin.ca/terms-conditions/)</p>
Gene By Gene	<p>Terms and conditions*: <i>“The customer understands that by providing any sample, having your sample processed, accessing results, or providing personal information, that the customer acquires no rights in any research or commercial products or services that may be developed by Gene by Gene, LTD. or its collaborating partners. The customer specifically understands that they will not receive compensation for any research or commercial products that include or results from your sample, results, or personal record.”</i> (https://www.genebygene.com/pages/terms)</p>
Inneova	not available

* These denote the specific documents/sections of websites where the quotes can be found.

Chapter 5: Readability of informed consent forms for whole exome and whole genome sequencing

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Published in: *Journal of Community Genetics* 2017 (available online, ahead of print)

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Abstract

Whole exome and whole genome sequencing (WES, WGS) can generate an unprecedented amount of complex information, making the informed consent (IC) process challenging. The aim of our study was to assess the readability of English IC forms for clinical whole- exome and genome sequencing using the SMOG and Flesch-Kincaid formulas. We analysed 36 forms, most of which were from US providers. The median readability grade levels were 14.75 (the SMOG formula), and 12.2 (the Flesch-Kincaid formula); these values indicate the years of education after which a person would be able to understand a text studied. All forms studied seem to fail to meet the average recommended readability grade level of 8 (e.g. by Institutional Review Boards of US medical schools) for IC forms, indicating that the content of the forms may not be comprehensible to many patients. The sections aimed at health care professionals in the forms indicate that HCPs should be responsible for explaining IC information to the patients. However, WES and WGS may be increasingly offered by primary care professionals who may not (yet) have sufficient training to be able to communicate effectively with patients about genomics. Therefore, to secure an adequate, truly informed consent process, the task of developing good, legible examples of IC forms along with educating HCPs in genomics should be taken seriously, and adequate resources should be allocated to enable these tasks.

Keywords: informed consent, readability, whole genome sequencing, whole exome sequencing, genetic counselling

5.1 Introduction

5.1.1 The challenge of informed consent

Informed consent (IC) was introduced into research practice as an instrument enabling choice about participation in a study, with the aims to prevent coercion and respect autonomy of research participants, mostly in response to research malpractices that occurred in the last century [1]. The Declaration of Helsinki written in 1964 and amended in subsequent years set the standards for more explicit, documented, and specific (i.e. containing a defined set of elements) informed consent in research [2]. These requirements were gradually implemented both in research and in the clinical context, becoming an integral part of routine research and medical care, as well as a legal requirement in many national legislations [1]. However, the process of adopting the requirements for informed consent in different contexts has not all been smooth sailing. As a consequence of the growing complexity of medical procedures and knowledge about the associated risks and implications, informed consent documents have often become lengthy and difficult to understand [3]. Reaching the standards of explicit, specific, and simultaneously truly informed consent may be often very difficult to achieve - a topic which has been widely debated in academic literature [3]. Many studies have reported low levels of readability and/or understandability of informed consent forms in the USA, which is particularly worrisome given the prevalence of low levels of (health) literacy in the population [4,5]. Furthermore, the importance of providing legible informed consent documents has been supported by medical and research malpractice law cases [6]. Importantly, recognition of the relevance of patients' perspectives and needs, as well as the provision of adequate information by a physician, has given rise to concepts and practices such as shared decision making (i.e. between physician and patient), patient-centered care, and reasonable-patient informed consent standards, which have been implemented in the US and UK healthcare systems [7,8]. While these approaches stress the role of communication processes between a physician and patient, they do not diminish the importance of providing written documents, which should facilitate the discussion, and can be taken home by a patient in order to be considered and reflected upon at the patient's own pace [7]. Therefore, adequate readability and comprehensibility of informed consent forms remain vital elements of the informed consent process.

5.1.2 Informed consent in genetics and genomics

Genetics is a relatively advanced subset of biology, and the task of successfully communicating genetic concepts to a public unfamiliar with the subject can be challenging [9]. Explaining issues related to genomics, including the use of next generation sequencing in order to perform whole exome and whole genome sequencing (WES, WGS), adds to this complexity. These approaches generate an unprecedented amount of information, potentially about thousands of phenotypes, including diseases that may also hold relevance for family members of probands. In addition, the interpretation of these findings may change with time [10]. Whole genome and exome sequencing are being increasingly used in research, clinical and direct-to-consumer settings and their use is predicted to expand [11]. A number of recommendations for informed consent for WGS have been issued to address this challenge. These documents outline and discuss the elements that should be included in the informed consent process and emphasize the crucial role of pre-test counselling [12–15].

A few studies analysed the content of IC forms for WGS and/or WES and discussed the presence (or absence) of a list of core elements [16–19]. Two of these studies also report on readability of IC forms [16,19]. Henderson and co-authors analysed nine informed consent forms for WES and WGS studies funded by the US National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI). Readability was evaluated by the Flesch-Kincaid formula giving a median of 10.8 grade level, which indicates that after 10.8 years of education, an average student would understand most of the text present in the forms [16]. Jamal et al. (2013) analysed six informed consent forms provided by US based laboratories offering clinical exome sequencing. The median readability score (Flesch Reading Ease) among documents was 40 (corresponding to high school to some college grade level) [19–21]. Both of these studies indicate that the readability grade level is above the average recommended grade level of 8 for IC forms as stated by Institutional Review Boards of US medical schools [22]. These results suggest that even if the forms include the required elements of information, they may not be comprehensible to many patients since almost half of Americans read at or below grade level of 8 [22].

Given the particular challenges of communicating information about WGS and WES, their increasing use in health care and the importance of providing the information in a readable

manner, we aimed to provide additional insights into the readability level of a larger sample of informed consent forms for WGS and WES in the clinical context using two readability tests.

5.2 Methods

5.2.1 Search and inclusion criteria for IC forms

The authors searched for informed consent forms using Google search engine (www.google.com) applying 12 combinations of terms from the following groups: (“informed consent”, “consent document”, “consent form”) and (“whole genome sequencing”, “whole exome sequencing”, “next generation sequencing”, “genome wide sequencing”). The search was performed between March and April 2016. Two pairs of authors independently conducted the search using the above search terms combinations. One hundred links retrieved in each search-term-combination were accessed and reviewed. Documents meeting the criteria of consent forms for clinical WGS/WES in English were included in this study. Consent forms developed primarily for research projects and forms that did not have a space for the patient’s signature were excluded. Additional consent forms that were not retrieved in the search, but that were known by the authors from other sources, were also included. The final collection of forms was read and studied for a number of different aspects, including information on return of results, use of samples and data in research, as well as readability. Herein we present only the results of the readability study.

5.2.2 Characteristics of the forms

The following information about the IC forms was extracted from the forms and/or websites of WGS/WES providers: name of provider, country of origin, type of provider (type 1: universities/hospitals/medical centres and their “in-house” and/or owned laboratories; type 2: laboratories/companies not related to a university/hospital/medical centre), for what type of test a form is used (WES/WGS), and who can be tested (child, adult). This information was obtained independently by two authors and discrepancies were resolved in discussion.

5.2.3 Readability

Preparation for analysis

The forms were prepared for the readability analysis by directly converting files from an original portable document format (pdf) to a docx file format or by copying and pasting information from the original document into a Word docx file. Final versions of converted or copied files were verified for accuracy with the original file and any discrepancies were corrected. Additional sections included in the original files with the informed consent forms were excluded for this analysis (e.g. requisition forms, tables for patient information, sample information, address, payment options, clinical information, physician's statements, text explicitly aimed at physicians). Sections of forms addressed to family members submitting a sample for validation of patient's results were included. Headings were also included and each was treated as a complete sentence, even when there was no period in the end. The following phrases and words not constituting the main part of the informed consent form text were removed so that the program would not treat them as full sentences and consequently conflate the resulting readability scores: address and contact information of a provider; indications of fields for signatures, initials, names, addresses and dates of birth; dates of updating/creating forms; pages numbers. Website addresses found anywhere in the text were also removed. Numerals were fully syllabized (i.e., sounded out) in the tests used.

Readability measures

A number of different readability tests have been developed for evaluating reading grade levels. These are based on evaluating parameters, such as word and sentence length, and the number of syllables in words. The reported grade level indicates the number of years of education that a person must have completed to understand the text assessed. In this study, two tests were used to assess the readability: the SMOG formula developed by McLaughlin (1969) and the Flesch-Kincaid formula [23,24]. Basic characteristic of the formulas is shown in Table 5.1. The Flesch-Kincaid formula is the most commonly used for analysis in recent health care literature (years 2005-2008), which is likely to be the result of the embedding of this formula in Microsoft Word software [21]. However, the Flesch-Kincaid formula is expected to predict only about 75% of comprehension (when validated on multiple choice test), meaning that a person who completed the grade level obtained in the test will be able to comprehend 75% of the text [24,25]. Distinctively, the SMOG formula was developed to predict 100% comprehension (validated

using McCall-Crabbs Standard Test Lessons in Reading) [23]. For this reason, the SMOG appears to be a more adequate test to evaluate informed consent forms for which 100% comprehension is expected [21]. Hence, we used the SMOG test as the main evaluative calculation, although we also employed the Flesch-Kincaid formula to obtain results comparable to other studies using this test. Calculation of readability for the two groups of IC forms (type 1 and type 2, Table 5.3) were conducted using SMOG test. The results obtained for these two groups were compared using Mann-Whitney statistical test.

Both tests were performed using the software Readability Studio Professional Edition for Windows, version 2015 (Oleander Software Ltd, Vandalia, Ohio). The calculations were based on the whole text (and not subsamples of the text) and standardized if needed. Additionally, we calculated the word count of informed consent documents as a rough indicator of the time required to read the text.

5.2.4 Information about the informed consent process

In order to have some insight into the informed consent process we also report on the presence of statements mentioning pre-test counselling as well the sections of the forms aimed directly at health care professionals (HCPs).

5.3 Results

5.3.1 Characteristics of forms

We identified 36 informed consent forms for clinical WGS/WES in English: 32 forms were retrieved through the Google search; 4 forms were identified from WES/WGS providers with which the authors were familiar. The majority of forms come from various types of providers in the USA, are used for WES, and are targeted at both adult and children patients. The complete list of form characteristics is outlined in Table 5.2.

5.3.2 Readability results

Figures 1 and 2 illustrate the results of the SMOG and the Flesch-Kincaid formulas. The range of grade level scores for the SMOG formula was 12.7-18.4, with a mean grade level of 14.8 and median of 14.75. For Flesch-Kincaid, the range was 10.3-16.4; mean 12.5 and median of 12.2. The word count ranged between 204 and 3017 words; with a mean of 1679 words and median

of 1489. Figure 3 and Table 5.3 include the values for the SMOG formula and word count obtained in two groups of IC forms: universities/hospitals/medical centres and their “in-house” and/or owned laboratories (type 1) and laboratories/companies not associated with a university/hospital/medical centre (type 2). No significant differences were found between the two groups with respect to word count or readability grade levels.

5.3.3 Information about informed consent process

Thirty-two of the forms mentioned some form of pre-test genetic counselling outlining, for example, that patients should consider, seek and/or obtain pre-test genetic counselling, or that pre-test genetic counselling is recommended/required. Twenty-one forms included text aimed at a HCP stating that a HCP has provided/discussed relevant IC information and/or offered/ensured providing of pre-test counselling.

5.4 Discussion

5.4.1 Very low readability of IC forms

All of the 36 forms studied have a higher reading grade level than that recommended (by US medical school Institutional Review Boards) for IC forms, which is, on average, a grade 8 level [22]. The values obtained in the SMOG calculation are higher than those from the Flesch-Kincaid. This result is expected as the SMOG formula aims to predict 100% comprehension, while the Flesch-Kincaid formula would predict only about 75% comprehension (when validated using multiple choice test) [23,24]. Our results correspond with the relatively high reading grade levels of informed consent forms obtained by Jamal et al. (2013) and Henderson et al. (2014) (which indicated the median grade level of high school to some college in the Flesch Reading Ease formula; and median of 10.8 grade level with the Flesch-Kincaid formula, respectively) [16,19]. The word count of the IC forms we studied ranged from 204 to 3017 words; with a mean of 1679 words and median of 1489, suggesting that a person would need, at least, between 1-15 minute to read the informed consent form content aimed at patients (assuming the pace of reading of 200 words per minute) [26]. However, given the fact that the readability of the texts studied is low, an average patient would probably need much more time to assimilate the content of an IC form. These findings are in line with those of Jamal et al. (2013), which indicate the median word count among the six studied IC forms for WES is 1154 and the range is 724 to 3429 words [19]. Both the results herein and Jamal et al.’s word count

results are lower than the values obtained by Henderson et al. (2014) in a study of 9 IC forms for WES/WGS (mean = 4588 words, range 2917-5757 words) [16,19]. This difference may be related to the fact that Henderson et al. (2014) analysed consent forms used in a research context, and these may have contained additional information such as about the study design (Henderson et al. 2014).

The results indicating low readability of IC forms are not surprising, particularly when comparing them to studies of IC forms in the context of other medical procedures [4]. However, it is interesting that none of the forms in this study, or other previous studies investigating IC for WGS reaches the average recommended readability level of 8th grade [16,19]. This indicates that IC forms may fail to fulfil their intended function of providing understandable information to patients and facilitating communication. The high scores obtained in the SMOG and Flesch-Kincaid formulas indicate that the documents studied use many complex, long words, which are often technical and therefore difficult to understand to an average reader. Indeed, some sections of IC form text were difficult to understand even for the authors; one could imagine that it would be even more complicated for a person not familiar with vocabulary used in genetics, for instance:

'Diagnostic findings not related to phenotype in childhood onset conditions - a single pathogenic or likely pathogenic variant in genes that are known to cause autosomal dominant or X-linked childhood onset conditions, as well as two pathogenic or likely pathogenic variants in genes that are known to cause autosomal recessive childhood onset conditions, even if they are unrelated to the patient's phenotype, will be reported.'
(IC form number 18. The length of this sentence is 64 words; the score in the SMOG formula is 19).

This lack of adequate provision of information in IC forms appears particularly worrisome given that some of the companies offering WES/WGS included in this study also advertise the tests directly-to-consumers. In the direct-to-consumer advertising context, consumers may be provided with encouraging information about the benefits of the testing on the companies' websites, and unless explained in the IC process, they may not be aware of all the limitations and risks of the testing [27]. The need for legible IC forms seems to be even more relevant when WGS and WES is offered to minors; if possible consent or assent should be obtained from

children when testing is offered [28]. Therefore, clear and informative content of IC forms can be very valuable in this context.

Since we hypothesized that the potentially greater presence and involvement of HCPs in designing IC forms might result in increased readability of the forms, we assigned the IC forms to two different groups, assuming that the involvement of HCPs is higher in the first group: group 1 - university/hospital/medical centres and their “in-house” and/or owned laboratories; group 2 - companies/laboratories not associated with a medical center/hospital/university. Readability and word count was compared among these groups (Table 5.3 and Figure 3). No statistically significant differences were found between these two IC forms types with regard to readability scores and word count. These results suggest that involvement of healthcare professionals/genetic counsellors with experience in communication may be similar in these two groups. Indeed, the recent data indicate that an increasing number of genetic counsellors work in diagnostic laboratories [29]. The process of designing informed consent forms, including the involvement and roles of various experts, may be worth investigating further.

5.4.2 Role of a HCP in the informed consent process

The requirement or suggestion to undergo pre-test counselling present in many forms studied, as well as the sections of text stating that a HCP has provided relevant information to the patient (which often should be signed by a HCP) seem to place an obligation on HCPs and genetic counsellors. These statements imply that the physician is responsible for ensuring that the patient is adequately informed and understands the information provided, even if the consent form is not easy to comprehend. Consequently, given the low readability of the forms and the stated obligation of a HCP to explain the relevant information, IC forms in this context may take a role of a “checklist” for a HCP indicating which elements (s)he should explain to a patient, rather than being a sole explanatory material for a patient. Indeed, a study by Bernhardt et al. (2015) showed that during pre-test counselling sessions for genomic sequencing, genetic counsellors and research coordinators modified and adjusted (depending on the context) the information provided to the patients from that presented in the IC forms [30]. Moreover, the study reported that genetic counsellors and research coordinators “*recognized that most patients and participants cannot attend to, let alone understand, all of the information contained in the consent documents.*” [30]. Undoubtedly, the HCP’s role (and often obligation) to communicate and provide information is vital for the IC process, not only

for genomic testing, but in the context of all clinical procedures or tests requiring informed consent. However, considering the predictions that genomics is likely to become part of mainstream practice in medicine, WGS and WES may be increasingly offered by primary care professionals who may not yet have sufficient training or experience to be able to communicate effectively with patients about genomics [31]. In such cases, primary care professionals may be more dependent on IC forms as a communication tool to explain WGS/WES to patients. Consequently, in these circumstances, the explanatory and educational role of informed consent forms should not be underestimated.

The appropriate means of communicating about genomics in IC forms (e.g. usage of understandable vocabulary, length of document etc.) need to be explored, implemented, monitored and revised as needed. To obtain more comprehensive evaluation of the functionality of informed consent forms additional methods such as Suitability Assessment of Materials could be applied [32]. Furthermore, insights from health professionals who have experience in obtaining informed consent for genomic testing could help improve the quality of informed consent forms. For example, the issues indicated by genetic counsellors as most important for patients and most likely to be misunderstood could gain more attention when designing informed consent forms. In addition, reducing the length of other sections of IC forms such as descriptions of technical aspects of sequencing, might potentially increase the readability of the forms [30]. Furthermore, investigating patients' needs and understanding when communicating about genomics could be another important element in the effort to design adequate informed consent information [33].

5.5 Limitations

The limitations of this study include, firstly, that the consent forms were collected at one given point of time, in one language (English) using a specific strategy aimed at finding documents available online. We acknowledge that we may have missed some documents that are currently in use but not publicly available online, and that the studied forms we found may no longer be in use. The study of additional forms in other languages than English could also be of value. Secondly, there are limitations inherent to the readability formulas used. For example, not all the (potentially) difficult words have more than two syllables (for instance “genome”). Furthermore, the readability formulas do not evaluate all the elements influencing readability, for example, graphic design, font type and size, and document layout. Finally, readability and

comprehension are distinctive measures. However, the SMOG and Flesch-Kincaid formulas were validated in tests aiming at evaluating comprehensibility, it has been questioned whether some of them accurately reflect comprehension [21]. Therefore, the readability results only provide an estimation of comprehensibility of informed consent forms. In order to evaluate factual understanding of the documents, a study surveying patients should be conducted.

5.6 Conclusions

Based on the 36 IC forms identified, our results suggest that the IC forms for use in WES/WGS in the clinic may not adequately fulfil their function of explaining relevant information to patients. This function seems to be transferred to some extent to genetic counsellors and/or health care professionals, which may be problematic if a HCP does not have sufficient training in genomics to be able to explain the information to patients. Therefore, moving forward, along with educating HCPs in genomics, it will be essential for good examples of informed consent forms to be developed that will communicate relevant information effectively and facilitate the process of informed consent. Engaging expert groups including clinical geneticists, genetic counsellors, communication professionals, and patients may facilitate this task. In order to ensure responsible implementation of genomic technologies securing an adequate, truly informed consent process should be taken seriously and adequate resources should be allocated to enable fulfilling this task.

Acknowledgements

The authors would like to thank the reviewer for the insightful comments. Emilia Niemiec is supported by an Erasmus Mundus Joint International Doctoral Program in Law, Science and Technology Fellowship. This work has been also supported by the Swedish Foundation for Humanities and Social Sciences (Riksbankens Jubileumsfond under grant M13-0260:1), the Biobanking and Molecular Resource Infrastructure of Sweden (BBMRI.se), the BBMRI-ERIC, the CHIP ME COST Action IS1303, the Ministère de l'Économie, de la Science et de l'Innovation du Québec, PSR-SIIRI-850 (Canada), and the Research Fund Flanders (Belgium). None of these funding sources have had any involvement in the preparation of this article.

Conflict of interest

The authors declare no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the any of the authors.

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Tables (Chapter 5)

Table 5.1 Information regarding the readability formulas used to analyse consent forms

	Flesch – Kincaid formula	SMOG^a formula
Original development and reference	The formula has been designed for evaluating readability of technical texts for US military by Kincaid [24]	McLaughlin [23]
Analysis based on	sentence length and syllable count	Number of complex words (3 or more syllables)
Easier formula for manual calculation (not used in this study)	$G = (12 * (B/W)) + (0.4 * (W/S)) - 16$ <p>G - grade level W – number of words B – number of syllables S – number of sentences</p>	$G = \text{FLOOR}(\sqrt{C}) + 3$ <p>Where: G - grade level C - number of complex words (3+ syllables) FLOOR - round the result of (\sqrt{C}) down to the closest perfect square.</p>
Higher precision formula used by the software in this study	$G = (11.8 * (B/W)) + (0.39 * (W/S)) - 15.59$	$G = 1.0430 * \sqrt{C} + 3.1291$

^aOriginally, McLaughlin recommended using 10 consecutive sentences from the beginning of the text, 10 sentences from the middle and 10 from the end; the formula was meant to facilitate manual calculations. In our study, the calculations were based on the whole text (and not subsamples of the text) and standardized.

Table 5.2 Information about IC forms: the country of origin, provider, type of test, groups to which it is offered.

Characteristics	Number of forms
Total number of forms	36
Country of origin	
USA	29
Germany	2
The Netherlands	2
Australia	1
Canada and Germany	1
Finland	1
Provider	
Type 1: university/hospital/medical centre and their “in-house” and/or own laboratories	18
Type 2: company/laboratory not related to a university/hospital/medical centre	18
Type of test	
WGS	5
WES	24

Table 5.2 continuation

WGS and WES	4
WGS, WES and another genetic test	3
Target group	
Only adults	3
Only children	1
Adults and children	30
Not specified	2

Table 5.3 Grade levels obtained for two categories of IC forms. The Mann-Whitney test was used for comparison of results between these two groups of test providers.

	type 1: universities/hospitals/medical centres and their “in-house” and/or owned laboratories	type 2: laboratories/companies not associated with a university/hospital/medical centre	p-value and Z-score
Grade level SMOG	Range: 12.9 - 17; Median: 14.5	Range: 12.7 – 18.4 Median: 15.4	Z=1.61 p=0.1
Word count	Range: 204 - 3017; median 1405	Range: 544 - 2785; median 1541	Z=0.17 p=0.85

Figures (Chapter 5)

Figure 1 Results of the SMOG calculation for all the forms studied. The indicated ranges include the scores that are equal to or greater than the lowest bound and less than the largest bound for the range.

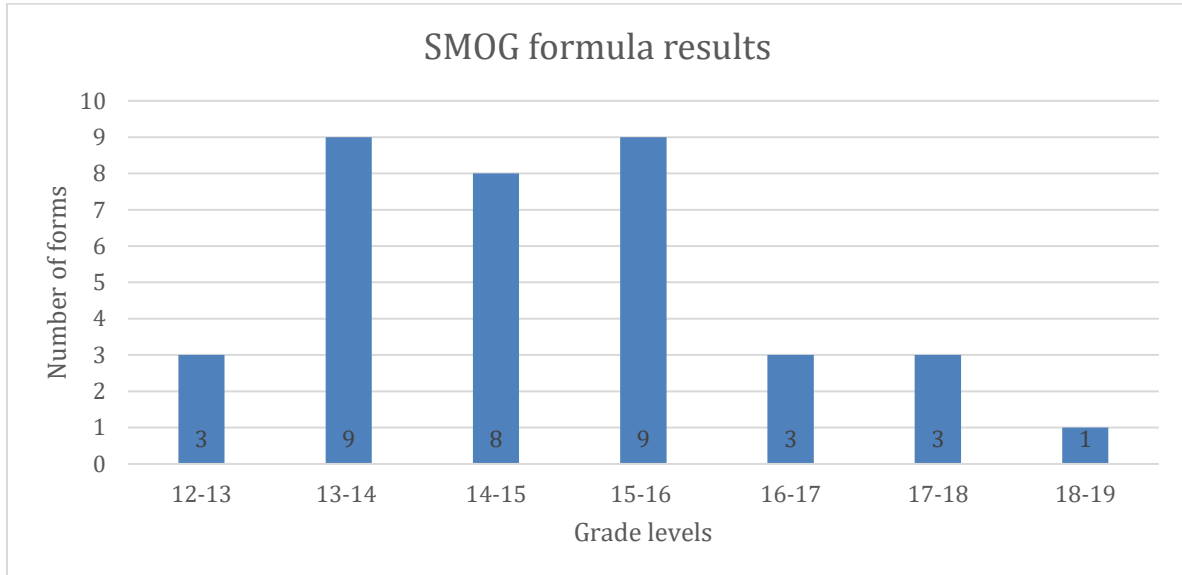


Figure 2 Results of the Flesch-Kincaid calculation for all the forms studied. The indicated ranges include the scores that are equal or greater than the lowest bound and less than the largest bound for the range.

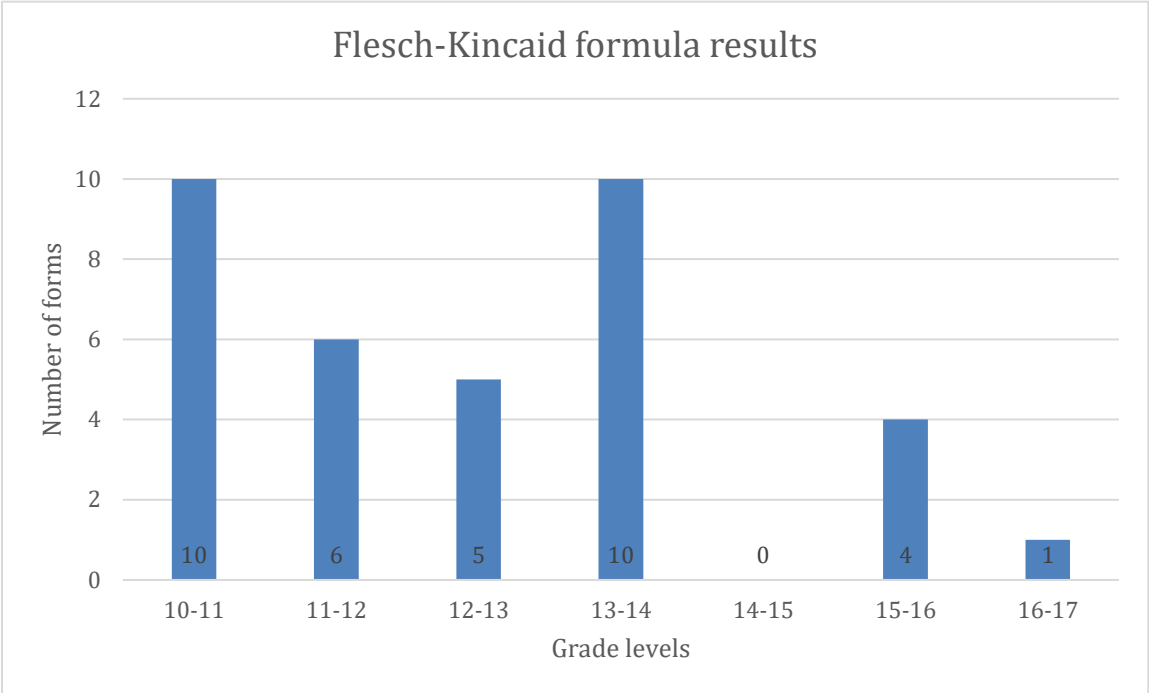
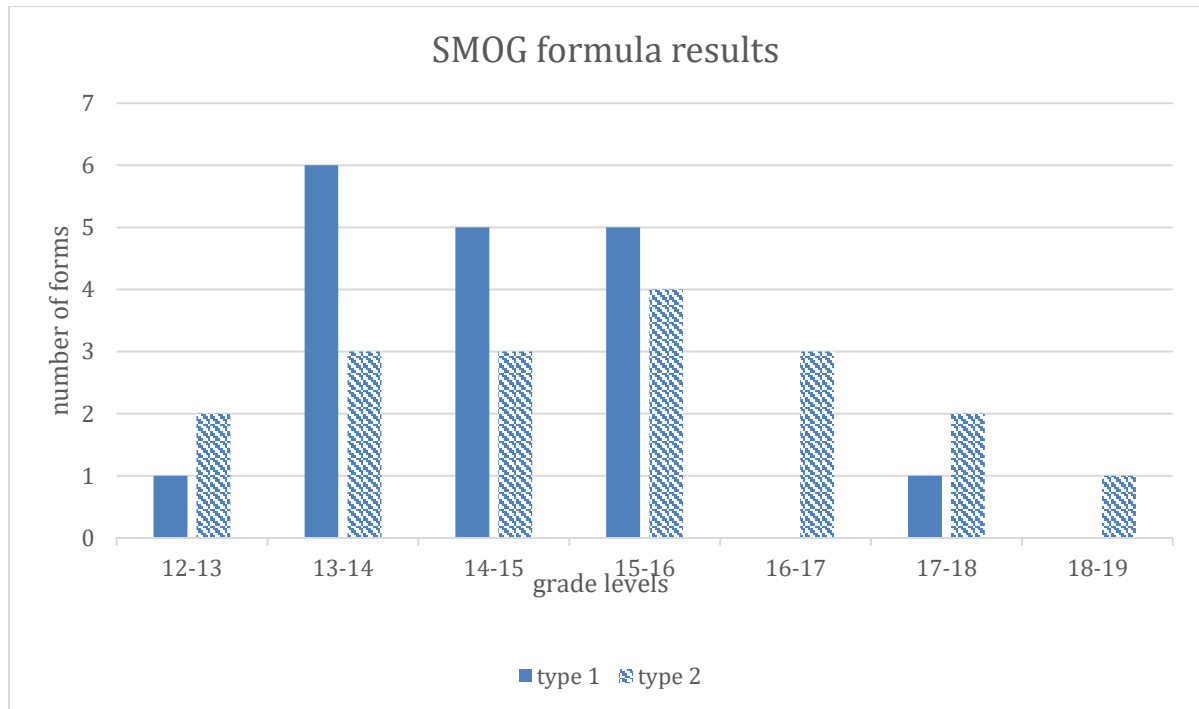


Figure 3 Comparison of readability between groups of IC forms using the SMOG formula. Type 1: universities/hospitals/medical centres and their “in-house” and/or owned laboratories; type 2: laboratories/companies not associated with a university/hospital/medical centre. The indicated ranges include the scores that are equal or greater than the lowest bound and less than the largest bound for the range.



Conclusions and indications for future research

Revealed concerns regarding informed consent for WES and WGS

Involvement of a HCP in the provision of WGS/WES offered directly-to-consumers

The work conducted for this doctoral degree presents the first empirical studies of the offer of whole genome and whole exome sequencing (WGS and WES) in the direct-to-consumer context (Chapter 3 and 4). The analyses provide insights into informed consent process for WGS and WES offered directly-to-consumers revealing a few concerns. Firstly, the lack or limited involvement of a healthcare professional (HCP) in the provision of testing, including potential absence of pre-test counselling. However, all but one tests (for which informed consent was studied) had to be ordered by a physician, this does not guarantee that adequate counselling takes place, given the concerns about the expertise in genetics of general practitioners. Pre-test counselling is a crucial element for an adequate informed consent process for genetic testing, in which individual's questions may be answered and a qualified HCP may ensure that the patient truly understands the information provided and is competent to consent to testing [1]. Recently, Middleton *et al.* argued that DTC GT companies should make adequate genetic counselling available to their consumers to avoid misinterpretation of genetic test results and unnecessary follow-up care [2].

Another issue related to the involvement of a HCP in the context of DTC genetic testing concerns the obligations of a HCP when a consumer contacts her or him with a request to order a genetic test. After undergoing direct-to-consumer genetic testing, a consumer concerned with the results of testing may contact a health-care professional within a public health care system requesting for a follow-up care. Given the doubtful clinical validity of some of direct-to-consumer genetic tests (as discussed in Chapter 2), should a healthcare professional take medical decision on basis of such test results? Indeed, this kind of follow-up care might be futile and be burdensome for the already scarce resources of public healthcare system. On the other hand, a scenario could be considered where a consumer took a genetic testing meeting high standards of clinical and analytical validity and received results indicating need for further medical interventions. Considering these two scenarios, the diversity of genetic tests offered

directly-to-consumers as well as their growing popularity, a help in a form of guidelines from professional societies concerning the issues mentioned above for healthcare professionals would be desirable.

The process of IC in DTC WES/WGS companies

Some of the companies studied did not seem to provide adequate informed consent documents for genetic testing and for research activities on consumers' samples and data. In some instances (company Gene By Gene), an individual could agree to undergoing WGS and/or participating in research activities, just by placing an order and accepting a 'clickwrap' contract by clicking an 'I agree' box (Chapter 3 and 4). Although these practices are common in the e-commerce environment, the fact that the companies offered health-related testing may make them a subject to ethical principles pertinent to medical care [3]. From the standpoint of medical and research ethics, replacing the process of informed consent (which normally consists of dialogue with a HCP as well as a written document) with 'clickwrap' agreement seems to be unacceptable.

One may argue that additional informed consent documents may be provided to the consumer at another stage of provision of the testing, for example, with the saliva kit sent to the consumer; the presence of such documents was not investigated in this thesis. However, arguably the consumers take a decision to purchase the tests on the basis of the information available *before* placing an order and paying for the testing; therefore, the provision of information (studied herein) prior to purchasing the testing is crucial for decision making to undergo the testing. Potential presence of additional documents sent to consumers with saliva kit *after* purchasing the test could be relevant and could result in resigning from undergoing the testing. Such a practice of obscuring information until after purchase, however, could appear as unfair to consumers and precluding from taking informed choice before buying a test. The process of the provision information at different stages of purchasing DTC GT (including the role of a HCP, if one is involved), as well as validity of the agreements require further investigation.

Remarkably, the alleged lack of adequate informed consent for sharing consumer's genetic data became a subject of an ongoing lawsuit against one of the companies studied herein, Gene By Gene, although in the context of its different service (Cole vs. Gene by Gene LTD, <https://www.genomicslawreport.com/index.php/2017/07/18/a-constitutional-challenge-to->

alaskas-genetic-privacy-statute/). The plaintiff alleged that the company had disclosed his data without his consent and asserted injury on the basis of Alaska's Genetic Privacy Act, which requires informed and written consent to sharing and disclosure of one's genetic data. The outcome of this ongoing case may have important implications to consumer genomics industry, in particular to the practices of provision of information by the DTC companies and modes of obtaining informed consent.

Content of the informed consent documents

Not only did the manner of obtaining informed consent in the studied companies appeared to be inadequate, but the content of these documents itself raised concerns. These related mainly to the lack of relevant information and/or presence of potentially misleading descriptions of the testing and secondary uses of consumers samples and health-related data. Consequently, consumers might not be aware of all the implications of undertaking WGS/WES, including the potential benefits and risks, or the usage of their samples and/or health-related data for research purposes. Therefore, consumers' acceptance or the given consent might not be truly informed. Additionally, the lack of transparency in provision of information about the usage of consumers' data for research could undermine trust in research practices in general, including publicly funded research [4] (Chapter 4).

Readability of informed consent forms for whole genome sequencing

One of the observations made when examining companies' websites was that the language used was quite complex, in some instances, to the extent that it could be questioned whether the language could be a barrier to understanding rather than an aid. Building on this finding, the aim of the follow-up study was to investigate the ease of understanding of consent forms for WGS and WES (Chapter 5). The study on readability of informed consent forms for clinical WES and WGS (some of which come from companies advertising directly-to-consumers) showed that none of the forms studied complied with the recommended reading grade level for informed consent forms (that is grade level 8, recommended by Institutional Review Boards of U.S. medical schools). This indicates that the forms probably would not be comprehensible for many, if not most patients. According to the statements present in the studied informed consent forms, the responsibility of explaining the relevant informed consent information to the patients

is placed on a HCP (even if the consent form is not easy to comprehend). This may be problematic if a HCP does not have sufficient training in genomics to be able to explain the information to patients. Therefore, along with developing good examples of informed consent forms facilitating the process of informed consent, the adequate training and education resources for HCPs (such as GEN-EQUIP, <https://www.primarycaregenetics.org>) should be developed, especially given the predictions that WGS/WES will become part of mainstream medical practice [5]. Not only should the achievements of genomics be translated into medical practice, but also its language, as a prerequisite for effective and respectful communication between healthcare professionals and patients [6].

Limitations and the importance of the presented empirical studies

The studies discussed herein have some limitations. The study of DTC GT companies is limited to specific sections of companies' websites; additional informational materials may be provided to consumers by the companies, for example, in the sections of websites not investigated herein, which require further examination. Similarly, the analysis of readability of informed consent is focused solely on informed consent forms in English available online, excluding those in other languages and not available via the Internet. Furthermore, the readability formulas employed provide indication, and not exact measure of comprehensibility of the content of consent forms. Other approaches, such as contacting the healthcare providers and companies to obtain additional information, interviews or surveys of the consumers/patients, healthcare professionals, and companies' representatives, could provide more insights into the current offer of WGS.

Summing up, all the three empirical studies (Chapter 3,4, and 5) reveal concerns regarding informed consent for WGS and WES and the use of consumers' data. The presence of these issues in the context of genomic approaches that generate huge amounts of sensitive data is particularly worrisome. In order to respect patients/consumers, the compliance with ethical standards when offering genetic testing should be strived for, also in the commercial DTC offer of WES and WGS. The studies presented herein indicate specific areas in which practices should be improved, therefore providing reference and guidance for well-informed and potentially policy-relevant discussions between various stakeholders.

Changes in the European legislation regarding genetic testing

Informed consent for genetic testing and pre-test counselling was a subject of heated debate during the preparatory stages of the recently adopted Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices, which will apply in European Union member states after 5 years transition period. In the preparatory phases, different suggestions were made regarding these aspects, from requiring mandatory pre- and post-test genetic counselling for predictive, prenatal and diagnostic genetic tests, as well as written informed consent, to the opinions that such provisions would infringe the principles of proportionality and subsidiarity and could be difficult to implement in daily medical practice [7]. Finally, in its adopted version, the Regulation underlines the importance of informed consent for genetic testing and pre-test counselling, however, it provides limited and rather general requirements in this regard, as discussed in Chapter 2. Furthermore, these provisions are addressed to Member States, therefore their impact will probably be limited to the clinical context, having little value for genetic testing sold directly-to-consumers.

However, importantly, the Regulation sets higher standards for clinical evidence required for genetic tests entering European market. The raised bar for requirements of clinical evidence included in the Regulation may limit the offer of susceptibility genetic testing for complex disorders which have limited clinical validity. Furthermore, the Regulation prohibits misleading advertising, and clarifies that companies established outside the European Union should still comply with the relevant EU rules when offering their products to consumers residing within the EU. Given the ethical concerns related to the offer of DTC genetic testing, not only regarding informed consent, but also questionable clinical validity of some tests and misleading advertising as discussed in Chapter 2, it seems that the recently adopted IVD Regulation may bring some desirable changes to the European DTC GT market. It should be kept in mind, however, that compliance of companies based outside of the European Union sending their tests to private individuals in the EU may be hard to enforce. The real value of the IVD Regulation for DTC GT will, therefore, be largely dependent on its enforcement.

Given that DTC offer of genetic testing involves processing of sensitive health-related data and that DTC GT companies are mostly based on e-commerce business model, other laws in the

European context can also be relevant to DTC GT offers. For example, laws concerning unfair commercial practices and the General Data Protection Regulation, which will apply in the EU in May 2018 setting standards, for example, for informed consent for the use of health-related data [8]. The relevance and impact of other laws, such as national laws, on DTC GT require further investigation and discussion.

Interestingly, while the legislation pertaining to DTC GT in Europe seems to limit the circulation of DTC GT in Europe, on the other side of the Atlantic, the climate for DTC genetics seems to be favourable. In April 2017, the U.S. Food and Drug Administration completed pre-market review and allowed for marketing of 23andMe direct-to-consumer genetic test - Personal Genome Service Genetic Health Risk which provides information about predispositions for 10 diseases and conditions [9]. This decision of the FDA seems to be surprising, as some of the genetic variants approved for the offer are not advised in clinical context by professional recommendations (Chapter 2). The actions of the regulatory authorities and law makers, both in Europe and in the USA, should continuously be subject to scrutiny and discussions. In particular, it may be interesting to investigate the process of evaluating requirements for clinical evidence for the tests allowed for market. Furthermore, decisions and recommendations related to the offer of genetic testing could be investigated from the point of view of conflict of interest, not only in the context of the activities of regulatory bodies, but also advisory committees, and professional societies issuing guidelines in the area of genetics and genomics. The aspect of conflict of interest has already brought some attention in the literature, in the context of some of the practices of the FDA as well as the National Academies of Sciences, Medicine and Engineering [10,11].

Emerging problems and research issues within ELSI of genomics

The market of direct-to-consumer genetic testing is dynamically evolving posing novel ethical challenges, as discussed in Chapter 2. Next to the well-known and still relevant issues of clinical validity of the testing, inadequate informed consent, and potentially misleading advertising, new ethical concerns emerged, such as, “monetization” of genetic data and DTC GT targeted to (prospective) parents. Given these developments, the empirical studies monitoring the current offers and practices of DTC GT companies and related ethical issues are vital. As the

discussion presented in this thesis touches upon broader topics within the ELSI of genomics, in the following paragraph some indications of the current trends in the industry and indications for future research are presented.

Genomic data have been recognized as precious material for research, with the potential to help advance science and improve healthcare; however, they are simultaneously a potential source of sensitive information about one's health and ethnicity, which could be used for discriminatory purposes. Being aware of both benefits of usage of genomic data and risks of their misuses, numerous organizations and stakeholders (for example, Global Alliance for Health and Genomics, American College of Medical Genetics) have been promoting sharing of genetic data in a way that adheres to ethical principles such as respect for individuals and transparency [12–14].

Indeed, growing amounts of health-related, including genomic, data are being collected and shared. National databases storing health-related information have been created, for example, in the UK and in China [15,16]. Numerous mobile applications have been designed to record users' lifestyle and health related data, which may be used by the companies for research purposes [17]. Furthermore, portals encouraging consumers of DTC GT to upload their genetic data for research purposes emerged; some of these services offer compensation to consumers for accessing their data (as discussed in Chapter 2). Genomic and health data has also been recognized as assets by big tech companies (Google, IBM), which have been getting access to population-derived datasets by paying governments [18,19].

All these activities raise numerous concerns and issues to investigate, starting with issues of informed consent and transparency, which still does not seem to be adequately respected, both in the context of collecting data by public entities [15,16], and in the commercial context of DTC genetic testing companies, as discussed in Chapter 4. Furthermore, some authors suggest that the traditional requirement of specific informed consent needs rethinking in the context of novel ways of engaging individuals in research, where digital health data are collected by electronic sensors and shared via Internet of things [20]. Another practice, commercialization of genomic data challenges the ideals of open science and data sharing based on solidarity, in some instances also raising risks of undermining public trust in research. Additionally, the

increasing involvement of commercial entities in biomedical research seems to create disproportion of powers regarding possibilities of performing research on big datasets [17]. Given these concerns, as well as quickly developing activities regarding usage of genomic data, the monitoring of the stakeholders' activities and their implications is essential.

Genetic testing offered in the context of reproductive choices raises specific issues. Legislative frameworks in many countries currently allow the termination of pregnancy on the basis of results of genetic prenatal testing⁶, and more recently, in some places, to select embryos based on their genetic makeup [21,22]. These practices, which have their origins in the 1970s, has been recognized by some authors as recalling the eugenic approach [23]. It has been argued, however, that the current offer of selective abortion is based on accurate science and the value of choice, which would distinguish it from the old eugenic practices [23]. The adherence to these two criteria in the current clinical genetics practices, however, can be questioned. Firstly, the relationships between the phenotypic manifestations of diseases and their genetic background, at least in some instances, again are more complex than it was initially thought. The interpretation of genetic variants poses challenges and often gives only probabilistic indications of their significance; indeed, the cases of misdiagnosis based on genetic information have been reported, including in the context of prenatal testing [24,25]. This criticism related to adherence to scientific rigor in the offer of prenatal testing (and selective abortions) seems to be even more pertinent in the context of recent advancements in prenatal testing and proposals to screen foetuses for more conditions as well as to use whole genome sequencing for prenatal testing, which can be a source of large amount of genetic information about a foetus [26]. Secondly, as shown by studies, ensuring conditions for taking informed choice in the context of the offer of prenatal screening, including provision of adequate information, is challenging [27,28]. The problem of informed consent and informed choice seems to be further problematized in the context of companies advertising prenatal testing directly-to-consumers, some of which were shown to present inadequate information about the testing on their websites

⁶ In some countries abortion is allowed for any reason until certain time (e.g. 12 weeks of pregnancy), after the specified time abortions may be allowed under certain circumstances, including a serious genetic condition of a foetus (e.g. Czech Republic, Norway).

[29]. Finally, the legitimacy and (social) implications of usage of subjective criteria such as ‘normalcy’ and ‘serious disability’ when deciding whether abortion should be offered based on genetic test results are debatable. It is beyond the scope of this section to further explore the foundations of current practices of applying genetic knowledge in the context of reproductive choices and their relation to eugenics. However, given the concerns indicated above, eugenics, values guiding the practice of medical genetics and the limitations of medical knowledge should be a subject of further examination.

Gene editing is a technique which allows to modify DNA of organisms, including humans, involving various approaches, for the purpose, for example, of treating diseases. In 2013 new gene editing tool was developed - CRISPR-Cas9 system, allowing for more precise, faster and cheaper modification of genomes [30]. This technology can be used to introduce changes in the DNA of somatic cells (that is, not inheritable changes) as well as in gametes and embryos in vitro (inheritable modifications). In April 2015, in China, CRISPR-Cas9 gene editing technology was used for the first time in human embryos, for research purposes [31]. This study sparked controversy, prompted debate and extensive media coverage on this issue, as this research on embryo seemed to be a step forward to clinical application (involving implantation of an embryo in uterus and pregnancy) of this gene manipulation technique. The ability to edit genes changes the paradigm in genomics - from diagnosis to treatment or from reading to *modifying* genomes, raising numerous ethical issues, particularly in relation to potential usage of this technology in human embryos in the clinical context. These issues include safety concerns, implications of introducing heritable changes to human genome, moral status of embryos, possibility of using the technology for enhancement purposes, and others. Recognizing potentially profound implications related to the applications of CRISPR-Cas9, the scientists called for moratorium on its usage in embryos in clinic, and called for research into ethical issues of gene editing and public debate, which undoubtedly need to be undertaken to guide responsible implementation of this technology.

Final remarks

The progress of research and technological developments in genomics reached an unprecedented pace in recent decade, opening new possibilities for improved treatment and

prevention of diseases. However, the threat of misusing achievements of genomics still exists, perhaps is even amplified in some respects, as the technology opens new possibilities, for example, to manipulate the human genome, not only in somatic cells but also in germ line cells. History teaches us that science can be embraced as a tool serving ideologies and being detrimental to individuals. In this era of fast scientific progress, it seems to be essential to stay attentive to the ethical dimension of new technologies, learning our lesson from history. Research inquires in the ethical, legal and social implications of genomics, based on good understanding of the science, recognizing its limits and potential risks, and following rigorous methodology should guide the responsible implementation of the technology - in a way that is beneficial and respectful of every person.

References for Conclusions

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Coauthors' statements

Coauthors' statement regarding the book chapter:

**Borry P., Chokoshvili D., Niemiec E., Kalokairinou L., Vears D. F., & Howard H. C. (2015).
Current Ethical Issues Related to the Implementation of Whole-Exome and Whole-Genome
Sequencing. In *Movement Disorder Genetics* (pp. 481-497). Springer International Publishing.**

The content of the chapter was conceptualized by Pascal Borry.

The following authors prepared the sections:

'Introduction' and 'Conclusion' – Pascal Borry and Davit Chokoshvili

'Unsolicited Findings and the Duty to Hunt' – Heidi Howard

'Opportunistic Screening in Children' – Danya Vears

'Informed Consent for WES and WGS in Diagnostics' – Emilia Niemiec

'Genetic Testing Beyond the Clinic: Commercialization of Genetic Tests' – Louiza Kalokairinou

All the authors critically revised the whole chapter and approved the final version.

The authors agree that the book chapter can be included as part of Emilia Niemiec's PhD thesis.

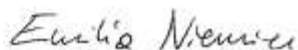
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Heidi Howard



Coauthors' statement regarding the article:

Niemiec E., Kalokairinou L., Howard H. C. (2017) Current ethical and legal issues in health-related direct-to-consumer genetic testing. *Personalized medicine* [Epub ahead of print]

The content of the article was conceptualised by Emilia Niemiec, with substantial contribution of Heidi Howard and Louiza Kalokairinou.

Emilia Niemiec drafted the following sections:

'DTC genetic testing and related services'

'Ethical issues in DTC GT companies',

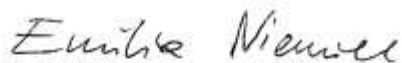
'Conclusions' and 'Future perspective'.

Louiza Kalokairinou prepared the section 'DTC GT legislation in Europe'.

The whole content was critically revised and discussed as needed by all the authors. All the authors approved the final version.

The authors agree that this work can be included as part of Emilia Niemiec's PhD thesis.

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Louiza Kalokairinou



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Coauthors' statement regarding the article:

Niemiec E., Borry P., Pinxten W., & Howard H. C. (2016) Content Analysis of Informed Consent for Whole Genome Sequencing Offered by Direct-to-Consumer Genetic Testing Companies. *Human Mutation*, 37(12), 1248-1256

Emilia Niemiec and Heidi Howard conceptualised and designed the study. Pascal Borry and Wim Pinxten critically revised the proposed methods.

Emilia Niemiec collected and analysed the data. The analysed data were reviewed by Heidi Howard and any discrepancies were resolved in discussion. The data were interpreted by Emilia Niemiec, with contribution of the other authors.

The first draft of the article was prepared by Emilia Niemiec. The other authors critically revised and contributed to the draft article. All the authors approved the final version of the article.

The authors agree that this work can be included as part of Emilia Niemiec's PhD thesis.

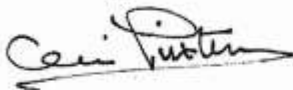
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Coauthors' statements regarding the article:

Niemiec E., Howard H.C. (2016) Ethical issues in consumer genome sequencing: use of consumers' samples and data. *Applied and Translational Genomics*, 8, 23-30

Emilia Niemiec and Heidi Howard conceptualised and designed the study. Emilia Niemiec collected and analysed the data. The analysed data were reviewed by Heidi Howard and discrepancies were resolved. Both authors interpreted the data.

The first draft of the article was provided by Emilia Niemiec, which then was critically revised by Heidi Howard. The final version was approved by both authors.

Heidi Howard agrees that this work can be included as part of Emilia Niemiec's PhD thesis.

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Coauthors' statement regarding the article:

Niemiec E., Vears D.F., Borry P., Howard H.C. (2017) Readability of informed consent forms for whole exome and whole genome sequencing. *Journal of Community Genetics* [Epub ahead of print]

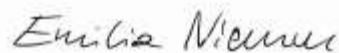
Emilia Niemiec and Heidi Howard conceptualised and designed the study.

The data (informed consent forms) were collected and preliminary analysed by all the authors; the discrepancies in analysis were resolved in discussion. The readability analysis was performed by Emilia Niemiec. The results were interpreted by Emilia Niemiec and Heidi Howard.

The first draft of the article was provided by Emilia Niemiec. All the authors critically revised the draft. The final version of the article was approved by all the authors.

The authors agree that this work can be included as part of Emilia Niemiec's PhD thesis.

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Summary

Whole genome and whole exome sequencing (WGS, WES) are high-throughput approaches, which produce the sequence of (nearly) all the DNA or the protein-coding regions of DNA, respectively, in a given organism. WES and WGS generate unprecedented amounts of data, from which various types of health-related information may be retrieved, such as diagnostic information, results indicating predispositions to diseases, and genetic variants which may cause a disease in one's offspring. Given the amount and the characteristic of genomic information, the offer of whole exome and genome sequencing raises ethical, legal and social issues. These include, among others, questions about which kind of findings should be obtained in genome analysis and returned to patients and how to obtain genuinely informed consent for genomic sequencing. Chapter 1 'Current ethical issues related to the implementation of whole-exome and whole-genome sequencing' provides overview of some of these issues, specifically: problems related to opportunistic screening and unsolicited findings, informed consent and commercial offer of genomic sequencing.

Currently WES and WGS are offered in the context of research, clinical care and direct-to-consumer genetic testing (DTC GT). Direct-to-consumer genetic testing is a commercial model of genetic testing provision where tests are advertised and/or sold directly-to-consumers. Chapter 2 provides a timely overview of direct-to-consumer genetic testing market and salient ethical issues, as well as an analysis of the impact of the recently adopted Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices (IVD) on DTC GT. DTC GT companies currently employ new testing approaches, report on a wide spectrum of conditions, and target new groups of consumers. Such activities raise ethical issues including the questionable analytic and clinical validity of tests, the adequacy of informed consent, potentially misleading advertising, testing in children, research uses and commercialization of genomic data. The recently adopted IVD Regulation may render many of the predisposition DTC GT illegal in Europe as it raises the bar for clinical evidence required for the tests entering European market, prohibits misleading advertising, and clarifies that companies established outside the European Union should still comply with the relevant EU rules when offering their products to consumers residing within the EU.

The direct-to-consumer offer of WES and WGS can be perceived as amplifying the already identified concerns regarding adequacy of informed consent for both whole exome/genome sequencing and the direct-to-consumer genetic testing context. In order to obtain insight into how these issues are approached in DTC GT companies offering WGS, a qualitative content analysis of websites of companies offering whole exome/genome sequencing directly to consumers was conducted. Specifically, information concerning the following elements of informed consent was studied: pre-test counselling, benefits and risks, incidental findings, and storage and use of consumers' samples and data (Chapters 3 and 4). The revealed concerns include, firstly, the lack of engagement of healthcare professionals in offering of the tests, including lack of pre-test counselling. Secondly, some of the companies did not seem to provide adequate informed consent documents for genetic testing and for research activities on consumers' samples and data. From the standpoint of medical and research ethics, replacing the process of informed consent (which normally consists of a dialogue with a healthcare professional and signing IC document) with a 'clickwrap' agreement seems to be unacceptable. Thirdly, the studies revealed that the content of these documents itself raised concerns. These related mainly to the lack of relevant information and/or presence of potentially misleading descriptions of some aspects of the testing as well as the secondary use of consumers samples and health-related data. Consequently, consumers might not be aware of all the implications of undertaking WGS/WES, including the potential benefits and risks, or the usage of their samples and/or health-related data for research purposes. Therefore, consumers' acceptance or the given consent might not be truly informed. Additionally, the lack of transparency in provision of information about the usage of consumers' data for research could undermine trust in research practices in general, including publicly funded research (Chapter 3 and 4).

A presence of required elements of information in informed consent documents does not guarantee that the patients will understand the descriptions of the complex matters related to WGS/WES. To gain insight into how easy to read are IC forms for WGS and WES, the readability of IC forms for clinical WES and WGS was evaluated using the SMOG and Flesch-Kincaid formulas. 36 forms were analysed, most of which were from US providers. The median readability grade levels were 14.75 (the SMOG formula), and 12.2 (the Flesch-Kincaid formula); these values indicate the years of education after which a person would be able to understand a text studied. All forms studied seem to fail to meet the average recommended

readability grade level of 8 (e.g. by US medical schools) for IC forms, indicating that the content of the forms may not be comprehensible to many patients. The sections aimed at health care professionals in the forms indicate that HCPs should be responsible for explaining IC information to the patients. However, WES and WGS may be increasingly offered by primary care professionals who may not (yet) have sufficient training to be able to communicate effectively with patients about genomics. Therefore, to secure an adequate, truly informed consent process, the task of developing good, legible examples of IC forms along with educating HCPs in genomics should be taken seriously, and adequate resources should be allocated to enable these tasks.

The work conducted for this doctoral degree presents the first empirical studies of the offer of whole genome and whole exome sequencing in the direct-to-consumer context (Chapter 3 and 4). All three empirical studies presented herein (Chapter 3,4, and 5) reveal concerns regarding informed consent for WGS and WES and the use of consumers' samples and data. The presence of these issues in the context of genomic approaches that generate huge amounts of sensitive data is particularly worrisome. In order to respect patients/consumers, the compliance with ethical standards when offering genetic testing should be strived for, also in the commercial DTC offer of WES and WGS. To achieve this, it would be constructive to have the community of commercial companies weigh in on the development of best practice guidelines for the commercial realm along with relevant stakeholders such as consumers, patients and health care professionals. The findings presented herein indicate specific areas in which practices should be improved providing reference and guidance for well-informed and potentially policy-relevant discussions between various stakeholders. Furthermore, this research indicates that it is important to continue to monitor the behaviour of DTC GT companies and to promote the awareness and adherence to the ethical standards currently accepted and/or aspired to by the research community.