Up Close and Personal

Ethical Issues in Genomic Testing

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Dichtbij en persoonlijk

Ethische kwesties rond genoomtests

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Chapter 1

Introduction

Achilles was foretold to die young. When he was still a baby, his mother Thetis took him to the river Styx, which separated the world of the living from the realm of Hades. The waters of the Styx were known to bring invulnerability to those who were touched by them. Thetis bathed the infant in the magical Styx. After that, Achilles lived, grew and flourished. As he came of age, Achilles became a fearless warrior and a leader in the Trojan War, during which he acquired a reputation of unassailability. Until, in the midst of battle, a poisonous arrow pierced through Achilles' heel, and killed him... Thetis had held her baby by the heel when she submerged him in the Styx. The waters had left only Achilles' heel vulnerable.

We all have a weak spot. Or rather, we all have multiple weak spots. Our individual weaknesses - and our strengths - are inscribed in every cell of our bodies. Today, we need no longer rely on oracles to learn about these imperfections. Scientists have unravelled the sequence of nucleotides - denoted by the letters A, C, G and T - that make up our DNA and foretell our susceptibilities to diseases. We need not even rely on doctors to learn about our DNA, as commercial companies have started to market genomic testing directly to consumers. Through - commercially offered - genomic testing, we can now identify and quantify our Achilles' heels.

That is, in part. Genes do not determine our fates by themselves: they interact with the environment, in ways we do not yet fully understand. This complexity cripples the attempt to predict our fates solely on the basis of genomic information: the genome has limited predictive value. At the same time, it also leaves room for human agency and opens up a plethora of possibilities, including preventative healthcare, personalised medicine, and reproductive options. Achilles could have devised a leg guard of sorts to shield his weak spot from arrows whizzing past, or he could have stayed out of the raging war altogether. Instead, Achilles opted for a short and glorious life: "If I stay here and fight," he said, "I shall not return alive but my name will live for ever."[1] In a similar vein, genomic risk can be averted through the adoption of healthier lifestyles, kept in check through tailored preventative health monitoring, or simply ignored.

Genomic self-knowledge presents us with choices with respect to the ways in which we perceive ourselves, lead our lives, procreate and take care of ourselves, as well as with respect to what we may or may not wish to know about ourselves. Achilles did not have a choice: when he was still an infant, his weakness was disclosed to him. Achilles might have preferred not to know. We may rather have autonomous choice to precede genomic testing. To avoid unwanted testing, something like informed consent may be required. Further, we may be prone to misinterpretation of genomic risk information, especially in a direct-to-consumer context, in the absence of expert assistance. We may need protection against the harms associated with misunderstood genomic risks. Given the limited predictive value, we must make our choices against a background of considerable uncertainty with regard to the meaning of genomic information.

Recent technological developments in the field of genomics bear both promises and perils, and bring up questions that carry broad ethical ramifications. For we must decide what to do with genomic technologies, with both the information they bring us and the uncertainties they leave us with, and how to implement them in a morally responsible manner - so as to maximise their benefits and minimise their harms. Since commercial companies have struck first and have already proceeded with putting multitudes of tests on the consumer market, the time has come for ethical scrutiny.

This is especially so because at present, the same or related ethical issues are surfacing across the medical arena. Today's patients and consumers are measuring and monitoring their health status, pressing for medical screening and opting for self-testing. Through biomedical research, numerous biomarkers are identified and utilised for the purposes of prediction, prevention and personalised treatments. Imaging technologies are refined and offered commercially. And non-invasive techniques are allowing for more extensive prenatal screening. In all these contexts, health-related information may be increasingly complex, incompletely predictive and difficult to interpret. Ethical concerns related to the provision of not-so-predictive medical information to healthy adults are thus not unique to genomic testing, but characteristic of today's healthcare system generally.

This thesis sets out to give ethical guidance for the provision of not-so-predictive genomic information. It explores what genomic testing is and what it is not, what it can deliver and what it cannot deliver, and it studies the value and the values of genomic testing. In this introduction I will first sketch the state of the field of genomics and its commercial delivery models, to allow for a clear grasp of the research topic at hand, and then turn to an overview of the accompanying ethical issues. Next, I will make a few remarks on the research methodology and present the leading research questions, before concluding with the outline of this thesis.

Genetics and genomics: state of the field

Whereas genetics has traditionally focused on rare disease-causing mutations that follow Mendelian patterns of inheritance, genomics studies the genome in its entirety: all 3 billion pairs of nucleotides that make up our DNA. Genomics has not arisen from clinical medicine, but is foremost a technology-driven, data-driven research enterprise that aims at understanding the functioning of the human genome, and at mapping genomic variation and its effects on health and disease.

Genomics as a field surfaced in the run-up to the Human Genome Project. The Human Genome Project, which started in 1990, was a grand international research collaboration that took 13 years and 3 billion US dollars to sequence the first human genome.[2] It was a humbling experience. There is more to the production of knowledge than sheer quantification, and the hopes and promises of genomics have not materialised easily. It turned out that mice and men possess about the same number of genes, about 20,000, fewer apparently than rice. We share 98% of our DNA with chimpanzees. Genetically speaking, human beings are all the same: genetic variation in humans is estimated to be only about 0,1%. Most of our traits cannot be explained by genetics alone. By now, most genomics researchers have parted with the idea of genetic determinism: they agree that DNA is not a blueprint of life. The genome is not a crystal ball that can reveal our biological futures. Although these metaphors may have

remained in our minds and narratives, they no longer reflect the state of the field of genomics research.

Nonetheless, research groups and commercial companies have taken on the challenge of mapping and making sense of human DNA. Genomics involves big data:[3] while the gathering of vast amounts of genomic data has become quick and easy, the analysis, interpretation and validation of these data are still arduous and costly. Commentators speak of a 'data deluge' in genomics.[4] Although the field is still relatively young and genome interpretation may lag behind, genomics applications have already been finding their way to patients and consumers. Before looking into the ethical implications of the technological happenstance of genomics, it is imperative that we first understand what genomic technologies can and cannot tell us.

Genomic technologies usually map either the whole genome or the exome. The exome is the 'business end' [5] of the genome, the approximately 1% of the DNA that bears codes for building amino acids into proteins. Proteins catalyse, regulate and are otherwise involved in almost all biochemical processes in the body. A change or a 'variation' in a coding region of the DNA may cause changes in resultant amino acids or affect gene expression, which in turn may affect the functioning of proteins. These changes in the 'proteome' (the entire set of expressed proteins) may eventually result in phenotypic (observable) variation.

Human beings tend to differ from one another at about 3 million loci across the genome. These differences can take many forms, ranging from deletions and insertions to copy number variations, and can vary in size. Most genetic variation is accounted for by single nucleotide polymorphisms (SNPs), loci across the genome where single nucleotides (As, Cs, Gs and Ts), tend to differ between individuals. On such a locus, for instance, I might have the CT genotype where you have the CC or TT genotype. SNPs are frequent: they show up in at least 5% of the population. SNPs may or may not themselves have biological effects (they may occur in coding or non-coding regions of the DNA). Regardless of whether they do, they mark or flag stretches of DNA like milestones alongside a road. Through (flagging) such effects, SNPs may be

implicated in disease susceptibility. SNPs can thus indicate the whereabouts of our Achilles' heels.

Many known associations between SNPs and diseases have been discovered through so-called genome-wide association studies (GWAS), which have been conducted worldwide since the mid-2000s. A GWAS compares whole-genomes or exomes of hundreds or thousands of cases (research participants with a disease) and controls (healthy research participants), to see whether SNPs occur more frequently in cases than controls, or vice versa. Over 2000 SNP-disease associations have by now been replicated, which are associated with the pathogenesis of over 300 common human diseases.[6] Usually, the effect sizes of single SNPs on the development of a disease are small: typically, SNPs have odds ratios of about 1,2 (meaning that they occur 1,2 times more in cases than in controls).[7] Beside environmental and other genetic factors, in the pathogenesis of most common diseases, dozens or even hundreds of SNPs may be involved.

A SNP-based genomic test typically takes a few (or a few dozen) validated SNPs together in a risk profile for a particular disease, to estimate an individual's genetic susceptibility to that disease. SNP-based genomic tests generally capture only susceptibilities to multifactorial diseases. Multifactorial or complex diseases are caused by intricate interplays of numerous genetic and non-genetic factors. Exposure to pathogens, toxic substances and radiation, psychosocial factors such as stress or childhood abuse, and lifestyle factors such as smoking, diet and physical exercise, all contribute to the development of multifactorial diseases. In their aetiology (the manner of causation of a disease), multifactorial diseases, such as type 2 diabetes, osteoarthritis, age-related macular degeneration, cardiovascular diseases, auto-immune diseases, psychiatric disorders and many types of cancer, differ from monogenic or Mendelian disorders, in which an alteration in one gene can be necessary and sufficient for crossing the threshold to develop the disease.[8]

The distinction between monogenic and multifactorial diseases is central to this thesis, albeit not unproblematic. Disease aetiology is not dichotomous, but a spectrum. There are diseases, such as familial breast cancer partly caused by a heritable BRCA 1 or 2 mutation, that fit neither of the two extremes, as they are

incompletely penetrant. Diseases caused partly by mutations, like the BRCA mutations, which bring individuals close to the threshold, are usually called major gene disorders.[8] The majority of breast cancers do not implicate the BRCA genes: inherited mutations are responsible for only 5-10% of cases.[9] Somewhere in the middle of the spectrum lies genomic testing for Alzheimer's disease: homozygous carriers of the ApoE-ε4 variant (a SNP), for instance, have a strongly increased risk (estimates range from to 3- to 15-fold) of developing Alzheimer's disease.[10] ApoE variants can be detected through SNP-based genomic testing. It is here, in the middle of the spectrum, where the ethical issues are most complex - and interesting.

Because so many factors (that are incompletely understood) are involved in causing multifactorial diseases, they are hard to predict solely on the basis of genomic information. Therefore, SNP-based tests for multifactorial diseases commonly have little predictive value or clinical validity (the ability of the test to predict the phenotype in question).[11] It is precisely this limited clinical validity that sets genomic testing for multifactorial diseases apart from genetic testing for monogenic diseases, and raises its own ethical issues. For it is not at all clear what predictive tests are telling us when they are not-so-predictive, or what we should do with their results.

Ethical issues of not-so-predictive genomic testing will eventually come to affect us directly, for genomic self-knowledge has now come within reach of average developed-world consumers. Over the past few years, the costs of sequencing have plummeted, such that genomic technologies are developing faster than Moore's law.[12] Today, a whole genome can be sequenced in one day for about 1000 dollars.[13] Much cheaper, quicker and more fragmentary than sequencing are microarray or gene chip technologies, that have been developed for the purposes of GWAS. Microarrays map around a million SNPs in one simple laboratory assay. Array technologies present us with the possibility of acquiring quick and inexpensive - albeit not very predictive - signatures of our personal imperfections. Moreover, they do not require specialised medical procedures, such as blood draws: all that is needed is one simple saliva or cheek swab sample. Consequently, medical professionals need not be involved in the

process, and the healthcare system can be bypassed entirely: array technologies can be brought to consumers directly, by commercial companies.

Genomic testing and direct-to-consumer marketing

Because of their limited clinical validity, the new technological possibilities for genomic testing did not immediately appeal to clinical geneticists. While clinicians remained sceptical of the clinical validity of SNP-based genomic testing, entrepreneurs in the US, Europe and Asia have seized the occasion and started to market such testing directly to consumers. The first players capitalised on the great expectations surrounding the Human Genome Project in the early 2000s, but offered unsound, poor-quality services. These companies offered genetic susceptibility tests for single diseases or clusters of diseases (e.g. 'heart health' or 'bone health') on the basis of one SNP or a handful of SNPs. Samples were sent to laboratories through the mail, and results were reported per e-mail. Often, the tests were performed in uncertified laboratories, and were of hardly any clinical validity. Some companies sold nutrigenetic testing: they based dietary recommendations upon faulty risk profiles or offered spurious nutritional supplements.[14] Other companies did not even perform actual molecular testing. These developments were clearly undesirable. In 2006, the US Federal Trade Commission issued a consumer alert to protect American consumers against the potential harms of 'at-home genetic testing'.[15]

Then, in the spring of 2007, a new generation of commercial genetic testing companies appeared on the market. Three leading companies, 23andme and Navigenics (based in the US) and the Icelandic company deCODEme, set the stage for direct-to-consumer genomic testing. These companies were different. They used state-of-the-art microarray technologies to analyse over a million SNPs in each consumer. Their services were broad, containing test results for dozens or hundreds of diseases and other traits simultaneously. Unlike their predecessors, they did not so much target the 'worried well', but a rather different audience of genetically literate consumers with a fascination for genetics and genomics research, technology and social networking.[16] These companies collaborated with certified clinical laboratories and guaranteed

adequate analytical validity of their testing services. They maintained high standards for information provision and offered in-house professional genetic counselling or social platforms. Company websites were transparent, informative and comprehensive. Whereas original players were subject to the criticism of selling snake oil, that claim did not necessarily apply to this new generation of commercial providers. They did however provoke ambivalent responses: while the 23andme 'retail DNA test' received a lot of media attention and was proclaimed Invention of the Year by Time Magazine in 2008,[17] it continued to be frowned upon by experts and was assessed to be a 'questionable practice' by the US Government Accountability Office.[18] These new tests were given a new name that aptly reflected the marketing strategy of one of the leading companies: in the summer of 2009, the American Journal of Bioethics published a special issue on the topic of 'personal genome testing'.

Over the past few years, the market for genomic testing has undergone further changes. Although companies still advertise directly to consumers, many have abandoned direct-to-consumer sales: they now require physicians to act as intermediaries in the ordering of tests and the interpretation of test results. Two of the leading companies have withered. In the autumn of 2013, the FDA ordered the company 23andme, one of the last of the Mohicans, to halt its direct-to-consumer sales. The FDA expressed concerns about direct-to-consumer access to BRCA 1 testing and testing for a set of relatively predictive pharmacogenomic markers.[19] By that time, the company claimed to have genotyped over 400,000 people across the globe.[20] Other players have appeared on the market. Some companies offer specialised services for paternity or ancestry testing, or testing for 'inborn talents'.[21] The US-based company Counsyl offers preconception carrier screening to couples for over a hundred autosomal recessive disorders. The tests are sold through physicians and obstetricians and reimbursed by many health insurers.[22] Although the centre of action seems to lie in the United States, commercially offered genomic testing has been luring consumers while troubling experts and policy-makers in Europe, Asia, Australia and Africa, as well.[23-26] Online, hundreds of different genomic tests are advertised directly to consumers.[20]

At present, two developments in the field of commercially offered genomic testing are particularly conspicuous: the trend of expanding the scope of genomic tests and the rise of whole-genome or exome sequencing as a financially feasible alternative to microarray technologies. First, many commercial providers offer testing for over dozens or sometimes hundreds of diseases and traits simultaneously. Genomic test packages are gaining clinical validity as they come to include SNPs in genes like BRCA 1 and ApoE, which can be highly predictive - albeit in rare cases. Second, sequencing technologies present us with not just rough sketches but highly detailed technical drawings of our DNA. Whereas SNP-based genomic tests mainly detect common variants conveying minor risks, sequencing technologies may detect rare Mendelian variants conveying high genetic risks (again, not in the majority of tested individuals). Slowly but steadily, the genomic testing industry is starting to mean business. When genomic test packages include predictive tests, they can no longer be simply dismissed for an alleged lack of clinical validity. As predictive genomic testing can have a great impact on consumers, the ethical issues surrounding its commercial provision are becoming progressively pressing.

Genomic testing: ethical and regulatory issues

In response to direct-to-consumer availability of genomic testing, a plethora of ethical, legal and societal issues have been raised in the biomedical and bioethical literatures over the past fifteen years. Experts have called for enhanced oversight and regulation of the genomic testing market.[27-29] National and local media have been paying regular attention to ethical issues and consumer experiences. Across the globe, physicians, epidemiologists, geneticists, medical ethicists, legal scholars, social scientists, anthropologists, historians and philosophers, undertook studies - from empirical, clinical and critical angles - of the phenomenon of commercially offered genomic testing. A quick search for ‘direct-to-consumer genetic testing’ now yields around 300 published articles, and with related search terms like ‘personal genome’, this number reaches over 1600.

Ethics has been an integral part of genomics research from the outset. Five percent of the annual budget of the Human Genome Project was allocated to studies of the ethical, legal and societal implications (ELSI) of genomics research. Also the Netherlands Genomics Initiative (NGI), which started in 2002 on its mission of setting up a 'world-class genomics infrastructure' in the Netherlands, reserved part of its funding for the societal component of genomics research.[30] Within NGI, the Centre for Society and Genomics (CSG) was established to coordinate research projects with the aim of describing, analysing and improving the relationships between society and genomics.[31] This research project was funded as part of the 2008-2013 CSG programme, and was dedicated to address ethical, legal and societal issues surrounding 'testing for multiple genetic variants in multifactorial diseases.'[32]

This section contains an overview of ethical issues associated with genomic testing: clinical validity and utility; issues related to informed consent and counselling; potential harms of testing; privacy concerns; healthcare system implications; and genomic testing of children and minors. It will briefly expound on each of these issues, and will indicate which of them play starring roles in this thesis, and why.

One of the foremost issues has been the lack of clinical validity inherent in testing for most multifactorial (complex) diseases.[11, 33] It has been feared that commercial parties, the main channel through which patients or consumers can access such testing today, fail to provide reliable test results. Companies have repeatedly been found to report inconsistent results between them,[18, 34] as companies' algorithms differ for calculating risk on the basis of SNP data. Moreover, consumers' test results tend to change over time,[35] as companies update their algorithms when new gene-disease associations are discovered.[36] Further, companies do not take environmental or lifestyle factors into account, and thus paint incomplete pictures of overall disease risks. For their lack of predictive value, genomic test results have disdainfully been compared with horoscopes.[29, 37] This raises concerns about the utility of genomic testing, and about its implications: needless to say, health recommendations and medical decisions should preferably not be based upon horoscopes.

In the practice of clinical genetics, patients or clients are typically offered extensive pre-test counselling over the course of multiple face-to-face sessions with trained professionals. Patients receive information about (at minimum) the disease tested for, the pattern of inheritance, their a priori genetic risk, possible test outcomes and follow-up, limitations of the test, psychological impact of testing, consequences for family members and reproduction, consequences with regard to insurance and employment, and the 'right not to know' genetic information.[38] Patients are usually supplied with written materials and requested to take time for considering the pros and cons of the testing offer. In their decision-making processes, patients are assisted by the genetic counsellor or clinical geneticist, but ought not to be pressured. This classic principle of 'non-directiveness' in genetic counselling is meant to respect autonomous decision-making with regard to genetic testing.[39] Guidelines require that the counsellor ensures the client's understanding of all relevant information and asks for informed consent.[38]

The traditional ideals of clinical genetic counselling are far removed from the reality of commercially offered genomic testing. In this online context, pre-test information, counselling and informed consent may be inadequate or lacking altogether.[40, 41] Consumers may be confronted at home, in front of their computers, with awe-inspiring quantitative genomic risk estimates that may not reflect their actual individual disease risks. When genetic counsellors, clinical geneticists or primary care physicians are not present to help interpret and contextualise genomic test results, consumers may misinterpret conveyed risks. Consequently, critics have feared, consumers may be falsely reassured or become unduly worried.[42-45] Besides immediate adverse psychological effects, such as anxiety, these forms of misunderstanding may lead to health-related damage. For instance, those with a low calculated risk of lung or breast cancer or obesity might falsely feel exempt from risk, and might continue to smoke or overeat, forego screening or refrain from adopting healthier lifestyles. Those who have received a high calculated risk of - say - atrial fibrillation or hypothyroidism might seek unnecessary follow-up testing or demand (or even self-administer) pharmaceutical interventions. These are all potential downstream harms of testing, which merit empirical and ethical study.

To a lesser extent than (highly predictive) genetic risk information, genomic risk information can be harmful in other ways, as well. It may be used without consent or misused by employers and insurers, adversaries and competitors, police and the judicial authorities. It may be used to stigmatise or discriminate against genetically at-risk individuals. It should be noted that because of its limited predictive value, most genomic information is hardly useful for the purposes of risk stratification. Thus - if understood correctly - it is not likely to be used by employers or (life) insurers.[46, 47] Nonetheless, and ever since the rise of direct-to-consumer genetic and genomic testing, critics have worried that sensitive and potentially compromising information might not be safe in the hands of commercial companies. Companies might sell samples or data. They might not have adequate data protection measures in place. Further, although some companies claim not to forward data to third parties without customers' explicit consent, it is often unclear what will happen to customers' samples or data when companies merge, are acquired or go bankrupt.[48] Some companies host social platforms and encourage their customers to share data with genetically related strangers.[49] Some companies have opened up their customer databases for scientific research and have collaborated with researchers on academic publications.[50] This too may have privacy implications for consumers: recent studies have shown that it is not impossible to re-identify individual research participants (or consumers) on the basis of aggregate, anonymised published records.[51, 52] DNA, after all, is an identifier in itself.[53]

Although many commentators continue to stress the importance of confidentiality and privacy,[54, 55] it may prove difficult in a digital age to prevent identifiable genomic data from entering and spreading across the public domain. Instead of attempting to halt the release of genomic information, it has been suggested that governments and healthcare systems should focus on the regulation of the uses of genomic information.[56] In Belgium, Austria, Denmark and Sweden, the use of genetic information by insurers has been prohibited since the early 2000s.[57] Many other European countries have established genetics-specific regulations or self-regulations for the insurance industry.[58] In the Netherlands, for instance, life and disability insurers have agreed upon a moratorium in accordance with the law on medical examinations

[Wet op de medische keuringen], not to ask applicants for genetic information below a certain financial threshold.[59] Concerns about privacy and discrimination issues have been especially prevalent in the United States, until the Genetic Information Non-discrimination Act (GINA) was signed into law in 2008. GINA is meant to protect the public against the (mis)use of predictive genetic information by employers and health insurers.[60] Again, concerns regarding discrimination and stigmatisation apply to highly predictive genetic information much more than they do to less predictive genomic information.

Further, healthcare system implications have often been mentioned in discussions of direct-to-consumer genetic testing.[61, 62] It has been feared that the workload for primary care practitioners would increase as patients might turn to their doctors for advice or follow-up testing,[16, 63] thereby also driving up the costs of (collectively funded) healthcare. Moreover, primary care physicians might not be equipped with the expertise necessary for dealing with print-outs from direct-to-consumer genomic testing companies, neither in the US nor in Europe.[64, 65]

One last ethical issue has been genomic testing of children and minors for adult-onset diseases. Broad professional consensus prescribes that predictive genetic testing should be deferred until adulthood, to allow children to grow and attain the capacity for autonomous decision-making.[66] Respect for children's 'right to an open future'[67] entails that they are left to make their own decisions with regard to predictive genetic testing. The 'presumption to defer'[68] is put aside only when there are clear medical benefits to be obtained from testing that cannot be otherwise obtained, for instance through therapeutic or preventive interventions that must commence during childhood in order to be effective.[69] Commercial providers of direct-to-consumer genomic testing have been flying in the face of this professional-ethical principle: some companies advertise family packages of genomic tests or offer special test kits for children.[70] Scholars have expressed conflicting views about whether these traditional ethical principles of clinical genetics should apply to commercially offered genomic testing.[68, 69]

Genomic testing raises a plenitude of ethical issues, many of which pertain not to the whole field, but rather to particular types of testing. We have already seen that clinical validity is an important moral variable. As a general rule, ethical issues become more serious with rising levels of clinical validity, for instance because of the graver psychological impact of predictive test results. Thus, whereas in predictive testing, ethical interventions should focus on the prevention of (psychological) harm, in not-so-predictive testing, ethical interventions should focus the prevention of misinterpretation. Information and communication, it will become clear, are among the major ethical issues in genomic testing of limited clinical validity.

Research approach

Three activities underlie this research project: identification, clarification and justification. In constructing a taxonomy of genomic testing, I have identified ethical issues and morally relevant characteristics of genomic tests (research question 2). In determining what genomic testing is (research question 1) and what the value of genomic testing is (research question 4), I have clarified the relevant concepts. And in assessing whether there is a role for informed consent in genomic testing, I undertook a process of justification (research question 3).

For the identification of ethical issues, I have reviewed and closely monitored a growing body of academic articles on various types of genomic testing. I have looked not only at the scholarly and scientific literature, but also at newspaper articles, company websites, customers stories, blogs, etc. For genomic tests are named, framed and shaped not only by researchers, clinicians and companies, but just as well by end-users, journalists and members of the general public. Further, for the stock-taking of ethical, legal, psychological and societal issues, I have consulted national and international experts, through a series of interviews and an expert meeting.

The primary task of moral philosophers is to clarify.[71] Conceptual clarification is an activity, not a method (it is not a technique, a protocol or a system). It is a non-systematic philosophical activity aimed at exact, descriptive definitions of

terms.[72] Tom Beauchamp, one of the fathers of modern medical ethics, wrote about this activity: "Applied philosophers appear to do what philosophers have always done: they analyse concepts, examine the hidden presuppositions of moral opinions and theories, offer criticism and constructive accounts of the moral phenomena in question, and criticise strategies that are used to justify beliefs, policies, and actions."[73] According to Beauchamp, applied philosophy is not characterised by a single distinct method: for the tackling of moral issues, it seems, many philosophical tools may prove helpful.

In this thesis I try to clarify not only concepts, but also normative positions within the ethical and regulatory debate. In some instances, I take a normative stance myself, and give directions towards policy solutions that are morally acceptable - which is the justificatory business of applied ethics. In my activities of clarification and justification, I employ a way of working [werkwijze]: a commonplace type of dialectics. It starts with an observed incongruity or misconception in written discussions of genomic testing. Often, incongruities lead to hold-ups, stagnancies in the discussions. I try to outline the two extremes (thesis and antithesis) that flank the obstruction, and show their strengths and weaknesses. Then I move to the space in-between, Aristotle's golden mean. For the way forward usually lies in the middle, where minds may meet in moderation. The middle is where practical or political decisions are made, where all parties involved - momentarily - put aside disagreements about underlying ideologies and ethical or political differences, where parties agree on stances or actions to take. When applied ethics aspires to make a practical and realistic contribution, it should therefore seek the middle. My way of working can be recognised most clearly in chapters 3, 6 and 9.

For the justification of normative stances and solutions, I refer to the established principles of medical ethics. From its very outset, the medical profession has been marked by its own values and norms, such as keeping patients from harm and injustice, acting for the benefit of the sick, and confidentiality.[74] In the late 1970s, Beauchamp and Childress have rephrased these values and norms as the famous 'four principles' of biomedical ethics: beneficence, non-maleficence, respect for autonomy and justice,[75] which are taught in almost every medical

school. Although these mid-level principles may have become a bit of a mantra, they are still the flagships of the field of medical ethics, and difficult to sidestep.

The four mid-level principles are underdetermined: they are not always helpful in deciding what (would be the moral thing) to do in real-life situations. They need to be developed further - through a process of revision, elaboration and weighting - in order to be able to inform and guide decision-making or action-taking in concrete circumstances.[76] Mid-level principles or norms must be brought to bear on concrete situations, for instance through what Richardson calls 'specification' of norms: a 'narrowing' and a 'glossing' (adding clauses) of norms, which adds content to them.[77, 78] In the ethics of clinical genetics or genetic screening - from which I have drawn extensively throughout this project - examples of specifications of the four principles can be found, such as non-directive counselling or the screening criterion of a favourable balance of benefits and harms. Mid-level principles are attractive to applied ethicists, because they can be endorsed regardless of one's moral or religious meta-ethical theory and be used as a starting point to solve moral problems.

This research project can be thought of as an exercise in the pragmatic ethics of Hilary Putman, who starts from the observation that moral problems cannot be solved in the way scientific problems can be solved. Nor can they be deduced from binding everlasting principles. They can only derive their force, Putnam claims, "from a shared sense of what is and what is not reasonable."[79] Moral problems can be adjudicated, not solved. Moral judgments are always temporary, provisional and open to revision. In the same vein, my ethical evaluation of genomic testing does not pretend to proclaim the last word on the phenomenon. Erving Goffman wrote, rather impenetrably: "Methodological self-consciousness that is full, immediate, and persistent sets aside all study and analysis except that of the reflexive problem itself, thereby displacing fields of inquiry instead of contributing to them"[80] I take Goffman to mean that with zooming in on foundational questions (e.g. 'On what grounds can I claim that respect for autonomy is important?'), we come not a step closer with what is, according to Putnam, the appropriate application of our moral intelligence:[81] dealing with practical ethical problems.

This thesis is the result of an interdisciplinary research project. In our publications, my co-authors and I have attempted to make relevant and practical contributions to the field of the ethics of genomic testing. Therefore, we have targeted not only an audience of bioethicists (chapters 3, 4, 6, 8, 9), but also one of genomics researchers and geneticists (chapters 2, 5, 7). Applied ethics should reach the audiences for which it is intended, without losing touch of the foundations on which it stands.

Research questions and outline of the thesis

This research project originated with the observation that for the ethical evaluation and regulation of genomic testing, a 'one size fits all' approach is not likely to work. There is no such thing as genomic testing generally: a variety of genomic tests have been put to market, for a variety of diseases and other phenotypic traits, in a variety of ways. And dissimilar tests for dissimilar diseases pose dissimilar ethical issues. This project has set out to identify the most compelling ethical issues in commercially offered genomic testing, and to provide practical ethical guidance for its provision. It is driven by four leading research questions:

1) What is genomic testing?
2) What are the ethical issues?
3) How should informed consent be made possible?
4) What is personal utility?

First, this thesis addresses the question: What is genomic testing? Genomic tests are used, seen and evaluated in so many different ways. While researchers, healthcare professionals and policy-makers may feel inclined to regulate or even ban the direct-to-consumer genomic testing industry, consumers may perceive state intervention to be unduly paternalistic and desire unhindered access to genomic technologies. In the light of these conflicting perspectives, I have tried to define, demarcate and 'frame' genomic testing. Many readers will be familiar with the concept of framing: over the years, it has become part of our folk psychology. Roughly, framing is the selection of "some aspects of a perceived

reality [to] make them more salient in a communicating text."[82] By highlighting some aspects and concealing others, frames tend to steer toward particular perceptions, interpretations and 'problem definitions'[82] of phenomena. Further, they automatically favour - they get their audience in lane for - particular moral evaluations or types of solutions. **Chapter 2** conveys the message that there is more to name-giving and framing than just the picking a term. Deliberately or inadvertently, names and frames can be used to serve policy agendas. **Chapter 3** contains the ethical backbone of my work on naming and framing. It offers a definition of genomic testing and a philosophical discussion of key concepts in the ethical debate: 'testing', 'medical testing' and 'screening'.

Second, in the attempt to define and design policies for genomic testing, it is sometimes overlooked that the variety of genomic tests is matched by a variety of ethical issues. An ethics of genomic testing thus stands in need first of a typology of tests. What types of tests are currently available, and, more generally: what aspects or characteristics of these tests give rise to ethical issues? What are the moral variables that distinguish one genomic test from another? A typology of genomic testing should systematically point out how characteristics of a particular (type of) test, of a disease tested for, and of the context in which the test is offered, lead some ethical issues to apply and other issues not to apply. **Chapter 4** explains the relations between test characteristics and ethical issues, while **chapter 5** focuses on the relations between ethical issues and diseases characteristics. Characteristics of the context are so fine, particularistic, multifaceted and ubiquitous, that it is nearly impossible to capture them in any taxonomy. However, important context-variables, such as direct-to-consumer provision of testing, consumer motivations, or the existence of ethical safeguards, are addressed elsewhere in this thesis (chapters 6-10).

Third, one of the principal problems in genomic testing is the abundance of data that it yields, the clinical significance of which often is often unclear. Consequently, genomic tests of limited clinical validity are easily misinterpreted. Therefore, pre-test information provision, counselling and informed consent are central ethical issues in any morally responsible provision of genomic testing. But is informed consent practically possible for genomic tests

that generate dozens or hundreds of results of varying validity? And what is more: is it desirable? **Chapter 6** discusses whether there is a role for informed consent at all in a direct-to-consumer context. After all, commercial companies may not be bound by the moral and professional obligations of healthcare. Further, it investigates whether traditional models of informed consent are suitable for commercially offered genomic testing. **Chapter 7** presents a proposal for a new model for informed consent, and gives general directions for the design and implementation thereof. **Chapter 8** compares direct-to-consumer genomic testing to other applications of genomic technologies: prenatal screening and new-born screening. In all three contexts, some form of organisation is deemed indispensable to the endeavour of 'making sense' of vast amounts of genomic information. The chapter also attends to the ethical considerations specific to genomic testing in unborn foetuses, children and minors.

Fourth, I investigate the value of genomic testing. Notwithstanding the value proposition of genomic tests (namely, the prediction of disease risks), they often simply lack the required clinical validity and utility. What, then, do consumers seek when they purchase genomic testing? What is the utility of genomic testing? **Chapter 9** is dedicated to the notion of personal utility, which has been proposed repeatedly as an alternative to the traditional criterion of clinical utility. Whereas clinical utility refers to the ability of a genomic test to improve health outcomes, personal utility generally refers to the non-medical value of a genomic test and covers, *inter alia*, psychological and social effects of testing. The notion of personal utility has been used not only to describe wider rationales or motivations for genomic testing, but also - normatively - to advocate direct access to commercially offered genomic testing. Chapter 9 contains a critical discussion of the notion of personal utility.

The values of genomic testing - the moral considerations that are at play when patients or consumers decide whether or not to proceed with testing, or when legislators or policy-makers decide whether or not to restrict testing - are far more plentiful than just their clinical or personal utility. In the general discussion, found in **chapter 10**, I will discuss broader questions with respect to the moral limits of the responsible (commercial) provision of genomic testing.

References

1. Homerus. 800 BCE. The Iliad.

2. Institute National Human Genome Research. 2013. All about the Human Genome Project. http://www.genome.gov/10001772.

3. Hey T., S. Tansley and K. Tolle. 2009. The Fourth Paradigm: Data Intensive Scientific Discovery. Microsoft Corporation.

4. New York Times. 2011. DNA sequencing caught in deluge of data (30 November 2011).

5. Angrist M. 2010. Here Is a Human Being: At the Dawn of Personal Genomics. New York: HarperCollins.

6. Andermann A., I. Blancquaert, S. Beauchamp and V. Déry. 2008. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization 86: 317-319.

7. Andreassen C.N. 2013. The biological basis for differences in normal tissue response to radiation therapy and strategies to establish predictive assays for individual complication risk. In: Pathobiology of Cancer Regimen-Related Toxicities, S.T. Sonis and D.M. Keefe (eds). New York, NY: Springer: 19-34.

8. Becker F., C.G. van El, D. Ibarreta, et al. 2011. Genetic testing and common disorders in a public health framework: how to assess relevance and possibilities. European Journal of Human Genetics 19: S6-S44.

9. Campeau P.M., W.D. Foulkes and M.D. Tischkowitz. 2008. Hereditary breast cancer: new genetic developments, new therapeutic avenues. Human Genetics 124 (1): 31-42.

10. Tanzi R.E. 2013. A brief history of Alzheimer's disease gene discovery. Journal of Alzheimer’s Disease 33: Suppl 1: S5-13.

11. Janssens A.C.J.W. and C.M. van Duijn. 2008. Genome-based prediction of common diseases: advances and prospects. Human Molecular Genetics 17: 166-173.

12. National Human Genome Research Institute. 2013. DNA sequencing costs. https://www.genome.gov/sequencingcosts/.

13. Life Technologies. 2014. Ion Torrent sequencing for all.

14. Government Accountability Office (GAO). 2006. Nutrigenetic testing: Tests purchased from four web sites mislead consumers. GAO.

15. Federal Trade Commission (FTC). 2006. At-home genetic tests: a healthy dose of skepticism may be the best prescription. FTC.

16. McGuire A.L., C.M. Diaz, T. Wang and S.G. Hilsenbeck. 2009. Social networkers' attitudes toward direct-to-consumer personal genome testing. American Journal of Bioethics 9(6-7): 3-10.

17. Hamilton A. 2008. Best inventions of 2008. Time (29 October 2008).

18. Government Accountability Office (GAO). 2010. Direct-to-consumer genetic tests: Misleading test results are further complicated by deceptive marketing and other questionable practices. GAO.

19. Food and Drug Administration (FDA). 2013. Inspections, Compliance, Enforcement, and Criminal Investigations: 23andMe, Inc. (22 November 2013).

20. 23andme: http://www.23andme.com.

21. Map My Gene: http://www.mapmygene.com/inborn.htm.

22. Counsyl: http://www.counsyl.com.

23. Howard H.C. and P. Borry. 2013. Survey of European clinical geneticists on awareness, experiences and attitudes towards direct-to-consumer genetic testing. Genome Medicine 5(5): 45.

24. Brett G.R., S.A. Metcalfe, D.J. Amor and J.L. Halliday. 2012 An exploration of genetic health professionals' experience with direct-to-consumer genetic testing in their clinical practice. European Journal of Human Genetics 20(8): 825-830.

25. Ohata T., A. Tsuchiya, M. Watanabe, T. Sumida and F. Takada. 2009. Physicians' opinion for 'new' genetic testing in Japan. Journal of Human Genetics 54(4): 203-208.

26. Dandara C., J. Greenberg, L. Lambie et al. 2013. Direct-to-consumer genetic testing: to test or not to test, that is the question. South African Medical Journal 103(8): 510-512.

27. Melzer D., S. Hogarth, K. Liddell, T. Ling, S. Sanderson and R. L. Zimmern. 2008. Genetic tests for common diseases: new insights, old concerns. British Medical Journal 336(7644): 590-593.

28. Valles S.A. 2012. Should direct-to-consumer personalized genomic medicine remain unregulated? A rebuttal of the defenses. Perspectives in Biology and Medicine 55(2): 250-265.

29. Patch C., J. Sequeiros and M.C. Cornel. 2009. Genetic horoscopes: is it all in the genes? Points for regulatory control of direct-to-consumer genetic testing. European Journal of Human Genetics 17(7): 857-859.

30. Netherlands Genomics Initiative (NGI). 2005. Genomics 2008-2012: Building and Utilising the Dutch Genomic Infrastructure. NGI.

31. Centre for Society and the Life Sciences (CSG). 2014. Mission and Working Method. http://www.society-lifesciences.nl/en/about-csg/mission-methods.html.

32. Centre for Society and the Life Sciences (CSG). 2014. The repercussions of genetic testing for multifactorial diseases. http://www.society-lifesciences.nl/en/projects/health/project/artikel/the-repercussions-of-genetic-testing-for-multifactorial-diseases.html.

33. Janssens A.C.J.W. and C.M. van Duijn. 2010. An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 1:10.

34. Kalf R.R., R. Mihaescu, S. Kundu, P. de Knijff, R.C. Green and A.C. Janssens. 2013. Variations in predicted risks in personal genome testing for common complex diseases. Genetics in Medicine doi: 10.1038/gim.2013.80 [Epub ahead of print].

35. Shirts B.H. and L.S. Parker. 2008. Changing interpretations, stable genes: responsibilities of patients, professionals, and policy makers in the clinical interpretation of complex genetic information. Genetics in Medicine 10(11): 778-783.

36. Mihaescu R., M. van Hoek, E.J. Sijbrands, et al. 2009. Evaluation of risk prediction updates from commercial genome-wide scans. Genetics in Medicine 11: 588-594.

37. Russo G. 2006. Home health tests are 'genetic horoscopes'. Nature 442(7102): 497.

38. Rantanen E., M. Hietala, U. Kristoffersson et al. 2008. What is ideal genetic counselling? A survey of current international guidelines. European Journal of Human Genetics 16(4): 445-452.

39. Weil J. 2003. Psychosocial genetic counseling in the post-nondirective era: a point of view. Journal of Genetic Counseling 12(3): 199-211.

40. Lachance C.R., L.A. Erby, B.M. Ford, V.C. Allen and K.A. Kaphingst. 2010. Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genetics in Medicine 12: 304-312.

41. Singleton A., L.H. Erby, K.V. Foisie and K.A. Kaphingst. 2012. Informed choice in direct-to-consumer genetic testing (DTCGT) websites: a content analysis of benefits, risks, and limitations. Journal of Genetic Counseling 21: 433-439.

42. Gollust S.E., B.S. Wilfond and S. Hull. 2003. Direct-to-consumer sales of genetic services on the Internet. Genetics in Medicine 5: 332-337.

43. Wasson K., E.D. Cook and K. Helzlsouer. 2006. Direct-to-consumer online genetic testing and the four principles: an analysis of the ethical issues. Ethics and Medicine 22(2): 83-91.

44. Hogarth S., G. Javitt and D. Melzer. 2008. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annual Reviews of Genomics and Human Genetics 9: 161-182.

45. Hudson K., G. Javitt, W. Burke and P. Byers. 2007. ASHG Statement on direct-to-consumer genetic testing in the United States. Obstetrics and Gynecology 110(6): 1392-1395.

46. Joly Y., I. Ngueng Feze and J. Simard. 2013. Genetic discrimination and life insurance: a systematic review of the evidence. BMC Medicine 11(25).

47. Caulfield T., S. Chandrasekharan, Y. Joly and R. Cook-Deegan. 2013. Harm, hype and evidence: ELSI research and policy guidance. Genome Medicine 5(3): 21.

48. Vorhaus D., and L. Moore. 2009. What happens when a personal genomics company goes bankrupt? ScienceBlogs.

49. Koch V.G. 2012. PGTandMe: social networking-based genetic testing and the evolving research model. Health Matrix 22(1): 33-74.

50. Eriksson N., J.M. Macpherson, J.Y. Tung et al. 2010. Web-based, participant-driven studies yield novel genetic associations for common traits. PLoS Genetics 6(6): e1000993.

51. Gymrek M., A.L. McGuire, D. Golan, E. Halperin and Y. Erlich. 2013. Identifying personal genomes by surname inference. Science 339(6117): 321-324.

52. Weil C.J., L.E. Mechanic, T. Green et al. 2013. NCI think tank concerning the identifiability of biospecimens and "omic" data. Genetics in Medicine [Epub ahead of print].

53. Lunshof J.E., R. Chadwick and G.M. Church. 2008. Hippocrates revisited? old ideals and new realities. Genomic Medicine 2(1-2): 1-3.

54. American College of Obstetricians and Gynecologists (ACOG). 2008. Direct-to-consumer marketing of genetic testing. Washington, DC: ACOG.

55. Anderlik M.R. and M.A. Rothstein. 2001. Privacy and confidentiality of genetic information: what rules for the new science? Annual Review of Genomics and Human Genetics 2: 401-433.

56. Lin Z., A.B. Owen and R.B. Altman. 2004. Genomic research and human subject privacy. Science 305(5681): 183.

57. Mossialos E. and A. Dixon. 2001. Genetic testing and insurance: opportunities and challenges for society. Trends in Molecular Medicine 7(7): 323-324.

58. Van Hoyweghen I., K. Horstman and R. Schepers. 2007. Genetic 'risk carriers' and lifestyle 'risk takers'. Which risks deserve our legal protection in insurance? Health Care Analysis 15(3): 179-193.

59. Verbond van Verzekeraars. 2011. Protocol Verzekeringskeuringen.

60. National Human Genome Research Institute. 2012. Genetic Information Nondiscrimination Act (GINA) of 2008. http://www.genome.gov/24519851.

61. Caulfield T. 2009. Direct-to-consumer genetics and health policy: a worst-case scenario? American Journal of Bioethics 9(6-7): 48-50.

62. McGuire A.L. and W. Burke. 2011. Health system implications of direct-to-consumer personal genome testing. Public Health Genomics. 14(1): 53-58.

63. Samuel G.N., C.F. Jordens and I. Kerridge. 2010. Direct-to-consumer personal genome testing: ethical and regulatory issues that arise from wanting to 'know' your DNA. Internal Medicine Journal 40(3): 220-224.

64. Julian-Reynier C., I. Nippert, J.M. Calefato et al. 2008. Genetics in clinical practice: general practitioners' educational priorities in European countries. Genetics in Medicine 10: 107-133.

65. Guttmacher A.E., M.E. Porteous and J.D. McInerney. 2007. Educating health-care professionals about genetics and genomics. Nature Reviews Genetics 8(2): 151-157.

66. European Society of Human Genetics (ESHG). 2009. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. European Journal of Human Genetics 17(6): 720-721.

67. Feinberg J. 1992. Freedom and Fulfilment: Philosophical Essays. Princeton, NJ: Princeton University Press.

68. Mills P. 2010. The sense of proportion: two thoughts about the governance of direct-to-consumer genetic testing for children. Genomics, Society and Policy 6(3): 71-73.

69. Bunnik E.M. 2010. Why not order genomic testing for your children? Genomics, Society and Policy 6(3): 68-70.

70. Howard H.C., D. Avard and P Borry. 2011. Are the kids really all right? Direct-to-consumer genetic testing in children: are company policies clashing with professional norms? European Journal of Human Genetics 19: 1122-1126.

71. Bernard G. 1998. Morality: Its Nature and Justification. Oxford: Oxford University Press.

72. Lemoine M. 2013. Defining disease beyond conceptual analysis: an analysis of conceptual analysis in philosophy of medicine. Theoretical Medicine and Bioethics 34(4): 309-325.

73. Beauchamp T.L. 2003. The nature of applied ethics. In: A Companion to Applied Ethics. R.G. Frey and C.H. Wellman (eds). Malden, MA: Blackwell Publishing.

74. Edelstein L. 1943. The Hippocratic Oath: Text, Translation, and Interpretation. Baltimore: Johns Hopkins Press.

75. Beauchamp T.L. and J.F. Childress. 1979. Principles of Biomedical Ethics. Oxford: Oxford University Press.

76. Bayles M.D. 1987. Moral theory and application. In: Ethical Principles and Practice. J. Howie (ed). Carbondale, IL: Southern Illinois University Press.

77. Beauchamp T.L. 2007. The 'four principles' approach to health care ethics. In: Principles of Health Care Ethics. R.E. Ashcroft, A. Dawson, H. Draper and J.R. McMillan (eds). West Sussex, UK: John Wiley & Sons Ltd.

78. Richardson H.S. 2000. Specifying, balancing, and interpreting bioethical principles. Journal of Medicine and Philosophy 25(3): 285-307.

79. Putnam H. 1983. How Not to Solve Ethical Problems: The Lindley Lectures. Lawrence, KS: University of Kansas.

80. Goffman E. 1974. Frame Analysis: An Essay in the Organization of Experience. Cambridge, MA: Harvard University Press.

81. Putnam H. 2004. Ethics Without Ontology. Cambridge, MA: Harvard University Press.

82. Entman R.M. 1993. Framing: toward clarification of a fractured paradigm. Journal of Communication 43(4): 51-58 (p. 52).

Chapter 2

Naming and framing in genomic testing

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What's in a name? Terminology has the power to shape the ethical and regulatory debate surrounding commercially offered genomic testing. This article discusses the normative effects of naming and framing, and proposes that the medical frame, with its focus on the reduction of harm, should be used in the evaluation and regulation of predictive genomic testing.

The impact of name giving

In recent years, as genomic testing has expanded beyond the realm of traditional clinical genetics and become commercially available, a variety of names have been used to refer to genomic tests. Names are not value-neutral: they emphasise and draw attention to certain characteristics of that to which they refer, and therewith they organise perception and interpretation, a phenomenon known as 'framing'.[1] Names push associated frames to the fore and steer towards either more restrictive or more liberal stances within ethical and regulatory discussions.

Naming and framing in commercially offered genomic testing

Increasing numbers of genomic tests are marketed directly to consumers that estimate individual risks for many complex diseases and other phenotypic traits. Mostly, these tests are targeted to healthy adult individuals as a form of genomic screening and are meant to inform, educate, or entertain. Because the costs of sequencing technologies are rapidly diminishing, genomic testing is likely to become widespread in the near future.

The rise of genomic tests has spurred ethical discussions on their clinical validity and utility, on the psychological impact and social implications for consumers (including discrimination), and on the conditions of a responsible testing offer, such as information provision, informed consent, and genetic counselling. In these discussions genomic tests have been referred to by different names, for instance, 'direct-to-consumer (DTC) genetic testing',[2] 'genetic susceptibility testing',[3] or 'personal genomics services'.[4] which help to frame genomic tests

differently. Names and frames have normative force: by highlighting certain aspects of genomic tests and paying less attention to others, they subconsciously determine the ways in which tests are seen.

Through qualitative conceptual analysis of articles and narratives that have appeared over the years in biomedical and bioethical journals, and also in newspapers, social media, and promotional materials, three prominent frames of genomic testing can be discerned: the technical, medical, and personal frames. The technical frame, which is put forward by names such as 'high-throughput individualized genotyping'[5] and 'large-scale single-nucleotide polymorphism profiling',[6] alludes to the technology-driven origins of the industry and positions genomic testing foremost as a technological possibility. Typically a technological perspective, it focuses on the technical quality and analytical performance of the test. The medical frame is evoked by names such as 'genomic risk profiling'[7] and 'genetic susceptibility testing';[3] it stresses the medical value proposition of genomic testing and focuses on its clinical application. In marketing materials, medical terminologies often stress the potential of genomic test results to help improve health, keep disease at bay, and inform clinical decision making. Finally, the personal frame is put forward by names such as 'personal genome testing'[8] and 'personal genomics services'.[4] The personal frame removes genomic testing from the biomedical domains of research and clinical practice, and places it on a consumer market, for example, as an informational service that will reveal something personal, that may be sought for personal reasons, or may be used for personal purposes.

There are other frames, as well. Names such as 'DTC genetic testing'[2] and 'home DNA testing'[9] refer to further selling points of genomic testing, such as direct access and convenience. Although frames may intertwine and more frames may be in circulation, the distinctions between the technical, medical, and personal frames are especially relevant from an ethical point of view.

Implications of the technical, medical, and personal frames

Each of the three frames is connected with values and normative positions within discussions on ethical or regulatory issues. The technical frame is associated with the values of scientific neutrality and legitimacy.[10] Because it focuses on the technical performance of a genomic test, it has less regard for its value or utility for consumers. The technical frame may lead to a more favourable evaluation of genomic tests by placing the generally very high analytical validity of the technology at the centre of the discussion and directing the attention away from its generally much more limited clinical validity and utility.[11] The technical frame may boost public expectations by emphasizing the promises of genomic technologies while distracting from their lack of utility and from the complexities of their implementation.

The medical frame invokes the values and norms of healthcare and clinical practice. The framing of a genomic test as a medical service may bring along moral responsibilities, because providers may then be held to the quality standards used in healthcare, such as medical professional supervision, psychological support, pre- and post-test genetic

counselling, and informed consent. In criticisms of DTC availability of genomic testing, the medical frame may uncover the clinical limitations of such testing,[11] expose potential harms, and press for regulation and oversight to protect consumers from the risks and implications of testing. The medical frame places the criteria of clinical validity and utility at the forefront in evaluations of new genomic applications,[12] and suggests that a responsible testing offer should meet these criteria.

The personal frame places genomic testing in an altogether different light. Through the personal frame, genomic testing is seen not as a medical technology or a form of medical testing but rather as a way to democratise genomics, as a way to gain self-knowledge, or even as a form of entertainment. The personal frame may suggest that genomic testing should be accessible for consumers outside the healthcare system, because it yields personal information about individuals who are entitled to define its utility for themselves. These definitions of utility are not necessarily health-related, and may include fascination or

recreation.[13] In this context, suggestions have been made to adapt existing evaluative frameworks and replace the criterion of clinical utility with the broader criterion of 'personal utility'.[14] This means that genomic tests may be considered acceptable even when no health benefit is expected.

Using names to serve policy agendas

The effects of framing can be subconscious and continuous in perception and interpretation, but names and frames can also be put to use deliberately. Technical names, for instance, may be used by commercial providers to present genomic tests as scientifically reliable in order to gain consumer trust. Likewise, medical names can be used to suggest clinical usefulness of genomic tests, leading consumers to expectations of medical benefit that may in fact be doubtful. Critics of DTC availability of genomic testing, by contrast, can put forward the medical frame to point out the clinical limitations, risks , and implications of testing and discourage direct access. Proponents of direct access to genomic testing may advance the personal frame to support the position that governments should respect consumer liberty and self-determination and should not hinder access to genomic testing. By presenting genomic testing as a source of entertainment or personal information, however, the personal frame leads audiences to overlook the reality that genomic tests can convey information about disease risks and that they may primarily be conducted for health-related reasons.[13]

Whereas risks and implications of genomic testing are emphasised by the medical frame, they are easily disregarded by the personal frame. Proponents of direct access to genomic testing can thus use personal names to steer the ethical discourse towards a more liberal stance regarding the provision of testing. Vice versa, more conservative or protectionist agendas are best served by medical names, which place genomic testing within well-regulated medical practice and healthcare.

The case of 'personal genome services'

Through the use of names such as 'Personal Genome Service'[15] or 'Personal DNA analysis',[16] commercial providers present their testing services as sources of personal information and evoke the personal frame. The personal frame may work to downplay consumers' expectations of learning clinically relevant medical information. It may draw consumers' attention away from potential harms and implications, such as false reassurance, undue health-related anxiety, and psychological distress.

Although empirical studies so far have found little adverse effects in early adopters of currently available DTC genomic tests of limited clinical validity,[17] it is not clear whether these findings extend to the general public, which may be less genetically literate, or to expanding commercial testing offers that include more predictive tests for diseases such as Alzheimer's disease, Parkinson's disease, or BRCA1 testing. It is well known from the practice of clinical genetics that predictive test results may have both adverse impacts and negative consequences for patients, on psychological, health-related, and societal levels, including insurability and employability, especially for diseases for which preventive options are lacking. Unlike researchers, companies do not always provide adequate pre-test information or require informed consent. Insufficiently prepared consumers who receive predictive test results for diseases such as Alzheimer's disease may experience more harm than good.[18]

To mitigate potential harms, commercial providers of predictive genomic testing should take their cue from the quality standards, safeguards, and levels of specialised support and care that are applied in clinical genetics. Because the medical frame elicits such clinical norms and standards, it forms an appropriate basis for the evaluation and regulation of genomic testing services that contain predictive tests. This does not mean that direct access to genomic testing should be prohibited outright: it might be possible, for instance, to ensure quality and analytical validity, and to implement adequate information provision, informed consent, and counselling, in a DTC context. However, as personal names and frames may obscure health-related and other risks, and fail to convey the need to arrange appropriate safeguards, they should be handled with caution in the

context of predictive genetic testing. A liberal stance may be better suited to genomic testing that is less predictive or non-medical in nature.

Henceforth the medical frame?

Policymaking should not be determined by the overt or subconscious effects of naming and framing, but should focus on the reduction of harm. The potential for harm will rise as commercially offered genomic testing services are increasingly containing predictive tests. Risks and implications of testing should be addressed openly rather than concealed in any morally responsible commercial genomic testing offer. The medical frame, with its attention to potential harms, is regaining its importance as a basis for the evaluation and regulation of genomic testing.

Frames can be used to (mis)lead the public, but their corresponding norms and values may enrich ethical and regulatory discussions. Notably, the medical–ethical principle of protection against harm should ideally be balanced with the values associated with the personal frame: those of liberty of choice and self-determination.

References

1. Goffman E. 1974. Frame Analysis: An Essay in the Organization of Experience. Cambridge, MA: Harvard University Press.

2. Howard H.C. and P. Borry. 2012. To ban or not to ban? Clinical geneticists' views on the regulation of direct-to-consumer genetic testing. EMBO Reports 13: 791-794.

3. Kaphingst K.A., C.M. McBride, C. Wade et al. 2012. Patients' understanding of and responses to multiplex genetic susceptibility test results. Genetics in Medicine 14: 681-687.

4. Gurwitz D. and Y. Bregman-Eschet. 2009. Personal genomics services: whose genomes? European Journal of Human Genetics 17: 883-889.

5. Morgan A., R. Chen and A.J. Butte. 2010. Likelihood ratios for genome medicine. Genome Medicine 2: 30.

6. Hogarth S., G. Javitt and D. Melzer. 2008. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annual Reviews of Genomics and Human Genetics 9: 161-182.

7. Haga S.B., M.M. Carig, J.M. O'Daniel et al. 2011. Genomic risk profiling: attitudes and use in personal and clinical care of primary care physicians who offer risk profiling. Journal of General Internal Medicine 26: 834-840.

8. McGuire A.L., C.M. Diaz, T. Wang and S.G. Hilsenbeck. 2009. Social networkers' attitudes toward direct-to-consumer personal genome testing. American Journal of Bioethics 9, 3-10.

9. Pinker S. 2009. My Genome, My Self. New York Times.

10. Vashlishan Murray A.B., M.J. Carson, C.A. Morris and J. Beckwith. 2010. Illusions of scientific legitimacy: misrepresented science in the direct-to-consumer genetic-testing marketplace. Trends in Genetics 26: 459-461.

11. Teutsch S.M., L.A. Bradley, G.E. Palomaki et al. 2009. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group. Genetics in Medicine 11: 3-14.

12. Frebourg T. 2012. Direct-to-consumer genetic testing services: what are the medical benefits? European Journal of Human Genetics 20: 483.

13. Su Y., H.C. Howard and P. Borry. 2011. Users' motivations to purchase direct-to-consumer genome-wide testing: an exploratory study of personal stories. Journal of Community Genetics 2: 135-146.

14. Foster M.W., J.J. Mulvihill and R.R. Sharp. 2009. Evaluating the utility of personal genomic information. Genetics in Medicine 11: 570-574.

15. 23andme: http://www.23andme.com.

16. Gene Planet: http://www.geneplanet.com.

17. Bloss C.S., N.E. Wineinger, B.F. Darst, N.J. Schork and E.J. Topol. 2013. Impact of direct-to-consumer genomic testing at long term follow-up. Journal of Medical Genetics 50: 393-400.

18. Messner D.A. 2011. Informed choice in direct-to-consumer genetic testing for Alzheimer and other diseases: lessons from two cases. New Genetics and Society 30: 59-72.

Chapter 3

What is genomic testing? Defining, naming and framing genomic testing

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Under review

Abstract

Over the past fifteen years, a wide variety of genomic test have been made available to the public, through biomedical research, in the clinical setting and by way of commercial channels, giving rise to abounding discussions of their ethical, legal and societal implications. This paper sets out to clarify key concepts over which there has been ample disagreement in ethical and regulatory discussions of genomic testing. First, it proposes a 'family resemblances' definition of genomic testing, which includes research, clinical and commercial applications of genomic testing, and encompasses tests that are currently available as well as tests that - given current technological developments - are expected in future. Then, it presents a list of different names that have been used to refer to similar applications, and explains how names help to present genomic tests in a certain light. The paper applies the concept of framing to explain the normative effects of terminology, and discusses the merits and caveats of three dominant frames: the technical, medical and personal frames. Deliberately or inadvertently, the use of names and frames will affect moral judgments about genomic testing, and steer towards normative positions with regard to the ethical and regulatory issues surrounding such testing. Further, the paper discusses the following three conceptual questions:

a) Is a genomic test a test?
b) Is a genomic test a medical test?
c) Is a genomic test a form of genetic screening?

The answers to these questions will affect ethical and regulatory discussions. The conclusion that genomic tests are tests, for instance, entails that their (commercial) provision cannot escape regulatory control. Although the paper argues that genomic testing should not be considered a form of genetic screening, it concludes that it should indeed be thought of as a form of medical testing. This means that the norms and standards that govern medical testing within regular healthcare should apply to genomic testing for disease risks, whether it is offered commercially or through (public) healthcare institutions or professionals. The paper argues that in the light of recent and expected developments in the field of commercially offered genomic testing, including

the advent of whole-genome or exome sequencing and ever-expanding testing offers, the potential for harm will likely rise. Consequently, morally responsible provision of genomic testing will increasingly require traditional medical-ethical safeguards, such as information provision, pre-test counselling and informed consent.

Introduction

Name-giving and framing may influence ethical and policy discussions surrounding commercially offered genomic testing and determine how such testing will be evaluated and regulated. The 'policy outcome'[1] of the genomic testing issue may depend in part on rhetorical effects:

"…if policy makers decide that all predispositional testing is potentially 'dangerous' and should be linked to genetic counselling, then this will give […] the medical profession a monopoly over these tests, limit the role of firms as direct service providers and restrict how much information is available to the public. Alternatively, if most genetic tests are seen as being unexceptional and similar to diagnostics that can be bought over the counter in pharmacies, then the case for medical control and state intervention is much more limited. Under the latter conditions, a larger market for testing and personal genetic information may emerge."[2]

This paper sheds light upon the normative effects of naming and framing of commercially offered genomic testing. First, it introduces the emerging field of genomic testing, the marketing strategies and the technologies used, and the accompanying ethical, legal and societal debate. Then, it uses the concept of framing to explain the connections between terminologies used and normative positions taken, and describes three dominant frames: the technical, the medical and the personal frame. Next, the paper clarifies key concepts over which there has been disagreement in the sometimes messy ethical and regulatory debate, by discussing three conceptual questions: a) is a genomic test a test?; b) is a

genomic test a medical test?; and c) is a genomic test a form of genetic screening? The answers to these questions offered by the technical, medical and personal frames are critically analysed and checked for their consistency. Finally, the paper turns to the policy debate surrounding commercially offered genomic testing, and suggests a way forward, away from naming and framing.

A brief history of the field of genomic testing

Since the completion of the Human Genome Project in 2003, a wide range of genetic and genomic tests have become available to the public in the context of clinical research, through the practice of clinical genetics and on the direct-to-consumer market. Whereas genetics can be defined as the study of a single gene, genomics is the study of the genome in its entirety. For the study of the whole genome or the exome - the 1% of the DNA that carries codes for the production of proteins – two techniques are widely used: sequencing technologies that yield a detailed, base-by-base map of the DNA molecule, and microarray-based technologies, which, at this moment, are cheaper and less time-consuming. Microarray-based technologies map a few hundred thousand or over a million single-nucleotide polymorphisms (SNPs), common one-base variants across the genome. Whereas some of these common variants have no known biological effect in humans, others flag phenotypic differences, such as susceptibilities to complex diseases like cardiovascular diseases, auto-immune diseases, psychiatric disorders and many types of cancer. Single SNPs usually have only slight effects on the risk of developing a disease. Taken together in a risk profile, however, a few dozen SNPs can explain part of an individual's genetic disease susceptibility. Most complex diseases are caused by an interplay of environmental factors and genetic factors. As environmental factors (e.g. lifestyle factors) can be modified, there is a potential for disease prevention in knowing one's genetic susceptibilities. Here lies the promise of empowerment through personalised genomics: genomic testing can generate information that may educate and motivate people to adopt healthier lifestyles, to prevent diseases for which they are at increased genetic risk, and to tailor pharmacological treatments to their individual needs.

In the early 2000s, genomic tests that were marketed directly to consumers estimated consumers' risks of single diseases (e.g. type 2 diabetes) or groups of related diseases (e.g. heart health), and lifestyle recommendations were offered. Some providers sold nutritional supplements on the basis of estimated genetic susceptibilities.[3] Many of the early providers have disappeared from the market, as they were overtaken by a new generation of mostly US-based private companies that in 2007 started offering testing for large numbers of diseases simultaneously, ranging from dozens to hundreds of diseases and other phenotypic traits in one single purchase.[4] These genome-wide tests estimate risks for common diseases of complex aetiology, like type 2 diabetes, osteoporosis, prostate cancer, stroke, schizophrenia and age-related macular degeneration. Increasingly, genomic testing services are also informing consumers about pharmacogenomics traits, about carrier status for recessive disorders, and about monogenic or major gene diseases, such as hereditary breast or colon cancer, which are (largely) caused by a single mutation. Some services include non-medical traits, such as eye colour, earwax type, baldness and muscle performance, as well as ancestry information.

These very broad tests pose a great contrast to traditional clinical genetic testing which targets one gene or a specific set of genes in the context of a specific clinical question. Instead, genomic tests are marketed to healthy consumers to 'take a more active role in managing' their health and 'personalise' their healthcare, to know their genetic risk and 'prepare for the future',[5] without reference to specific clinical questions. The leading companies provide analytically reliable services: they collaborate with certified clinical laboratories and make use of state-of-the-art microarray-based technologies that can quickly genotype up to a million SNPs. Although health benefit is the primary selling point for most genomic testing services,[6] consumers may also be motivated to obtain testing as a source of ancestry information, out of curiosity or as a form of recreation.[7] The gathering of genomic data can be part of a 'quantified self' lifestyle, in which 'patients' or health-consumers manage their own healthcare through self-measurement and self-monitoring.[8]

Many genome-wide tests are not only marketed but also sold directly to consumers: consumers order a test kit online for a few hundred dollars, collect a

saliva or cheek swab sample themselves at home, send the material to a laboratory through the mail, and receive the test results a few weeks later, via e-mail, on a secure personal web page. Some companies offer in-house genetic counselling or 'expert assistance' to help interpret test results. Over the last few years, however, some providers have adapted their delivery models and now require physicians to be involved in the ordering or interpretation of the test.[4] Parallel to the increasing involvement of medical professionals in commercially offered genetic testing is another development: the gradual incorporation of genome-wide technologies in clinical practice for the purposes of diagnosis or treatment stratification. As the costs of sequencing technologies continue to drop, it may soon become efficient to map the genome or the exome in its entirety as a routine procedure.[9] Consequently, healthcare professionals will be confronted progressively with large numbers of genomic test results, many of which are unrelated to the original clinical question. Slowly, clinical genetics and commercial genomic testing appear to be moving in each other's direction. The insights offered in this paper may therefore be of interest to clinical practice and public healthcare, as well.

Defining genomic testing

As a consequence of rapid developments in the field, it is difficult to provide a definition of genomic testing. Genomic testing does not have fixed contours, nor a single solid set of defining features. Some genomic tests may have features in common with other genomic tests, but not necessarily with all genomic tests. The Wittgensteinian concept of 'family resemblances'[10] may be applicable here: genomic tests form a family. Roughly, this family can be circumscribed as broad genome-wide tests, based on SNP-genotyping or sequencing technologies, with the purpose - among others - of risk prediction for multiple diseases and other traits, which are currently (but not necessarily) available through commercial companies, with or without professional medical supervision or counselling, in the absence of a specific medical problem or clinical question. For the scope of this paper, let us settle upon this 'family resemblances' definition of genomic testing.

The ethical, legal and societal debate

In tandem with the emerging field of genomic testing, numerous discussions of its ethical, legal and societal implications have arisen over the last fifteen years. Professional groups have pointed out that commercially offered genomic testing services lack quality assurance and medical-professional expertise.[11] They fear that without adequate information provision and pre-test genetic counselling, genomic testing may have adverse psychological impact and social implications for consumers,[12] including discrimination. They feel that as some (subsets of) genomic testing services may bring more harm than good, depending among other things on the severity of the diseases tested for and the availability of preventive or therapeutic options,[13] these tests should not at all be offered directly to consumers. Commentators have stressed the importance of autonomous decision-making and informed consent,[14] and the inappropriateness of predictive genetic testing in children and minors.[15] Healthcare system implications have also been mentioned, such as the costs of unnecessary follow-up,[16] and the rise of social inequalities as a result of unequal access to testing.[17] One of the central concerns surrounding genomic testing is its predictive value or clinical validity - the accuracy with which a test predicts whether the tested individual will develop a disease.[3] Neither the clinical validity nor the clinical utility – the ability of a test to improve health outcomes – of many genomic tests have yet been established.[18] This has led to severe criticism: experts demand that direct-to-consumer access to genomic testing be either regulated or banned.[19]

Some commentators have questioned the widespread concerns surrounding genomic testing, claiming that the potential for harm is limited.[20] Some have compared genomic testing with astrology,[21] or stated that the main problem with these tests is that they are a waste of money.[22] Often, these claims are based upon the assumption that risk information generated by genomic testing is clinically meaningless and therefore rather harmless.[23] These claims are further connected with the normative position that strict regulation of genomic testing is necessary nor desirable. Many early adopters stress that access to genomic testing should not be hindered: they are enthralled, they indicate that they learn valuable health information, and they claim access to genomic

information as a basic right.[24] Genomic testing gives rise to very different and conflicting responses - from great expectations to calls for a ban – which suggest a great diversity of interpretations and underlying values and principles.

Naming

The diversity in genomic tests and in evaluations of tests is reflected in a diversity of names that have been used in academic and popular media articles to refer to genomic tests over the years (see Textbox 1). Clusters of names can be distinguished that highlight and underscore certain aspects of genomic tests: while some names are neutral descriptions of the technique or the biology (large-scale SNP profiling,[25] polygenics),[26] many bring to the fore medical purposes and applications of testing (genetic susceptibility testing,[27] genomic risk profiling).[28] Other names relate to the direct-to-consumer marketing of tests (DTC genomic testing),[29] the commercial nature of their providers and their online advertising environment (for-profit genetic testing,[1] online whole-genome testing),[30] the do-it-yourself method of taking a DNA sample (do-it-yourself diagnosis,[31] home DNA test kits) [32] or the non-medical purposes of some tests (enhancement testing,[33] lifestyle testing,[34] recreational genomics).[21] Since 2007, Pubmed-listed articles contain more and more names making reference to 'personal' (personal genetic testing).[35]

Predispositional genetic testing [36]
Susceptibility conferring genotype (SCG) testing [37]
For-profit genetic testing [1]
Commercial genetic testing [38]
Lifestyle (genetic) testing [34]
Genetic susceptibility testing [27]
Private access genetic testing [39]
Do-it-yourself diagnosis [31]
Online whole-genome testing [30]
Enhancement testing [33]

Genomic susceptibility testing [40]
Polygenics [26]
Recreational genomics [21]
Home DNA test kits [32]
DNA profiling [41]
Personalized genomic risk assessment [42]
Personal genomic testing [43]
DTC genomic testing [29]
High-throughput individualized genotyping [44]
Full genome testing [45]
Personal genome testing [18]
Direct-to-consumer gene tests [46]
DTC genome scanning services [47]
Testing for low-penetrance genes [48]
DTC personalized genomic testing [49]
Genomic risk profiling [28]
Large-scale or massive-scale SNP profiling [25]
Genomic profiling [50]
Personalized genomics [51]
Multiplex genetic susceptibility testing [52]
DTC genotyping [53]
Personal genetic testing [35]
Polygenic susceptibility testing [54]

Textbox 1: a chronological (but surely not exhaustive) selection of terms used to refer to genomic testing services in the period 2001-2012

As names emphasise certain aspects, name-giving may influence the ways in which that to which is referred, comes to be perceived. This is true especially for 'medical' names and 'personal' names, as they each point at different and potentially opposing purposes or fields of application for the same technology, which are connected with different normative frameworks and ethical

standards. For instance, a choice for a 'medical' name (e.g. polygenic susceptibility testing)[54] rather than a 'personal' name (e.g. personalized genomics)[51] may help elicit associations with healthcare and its values and professional standards. This interpretative, evaluative process can be elucidated with the help of the concept of framing.

The concept of framing

The manner in which a genomic test is evaluated depends in part on the underlying perception of what a genomic test is. Promotional materials from company websites, reports from consumers, statements from professional or governmental organisations and articles published in bioethical or biomedical academic journals showcase a wide spectrum of claims about the nature of genomic tests, ranging from a way for individuals to take their future health into their own hands,[5] 'the first step to a healthy pregnancy',[55] to a test destined to lack predictive power,[56] a form of recreational genomics,[57] or a front-row seat in genomics research.[58] These different perceptions of the nature of a genomic test may be thought of as different frames.

The concept of frames has been developed in the fields of sociology [59] and psychology,[60] and later in media and political studies.[61] Sociologist Erving Goffman used the concept of frames to refer to principles of organisation that allow individuals or communities to understand or to 'locate, perceive, identify, and label' events and experiences.[59] Frames determine the way something is seen, understood and evaluated. They emphasise certain aspects of a topic, and "structure experience or suggest what the controversy is about, the essence of the issue."[62] Different stakeholders may apply different frames with regard to the exact same thing or situation. Further, Goffman explains that it is possible to undergo a shift of frames, such that something is (suddenly) seen as 'something quite else'.[59] A frame shift may be comparable to what Ludwig Wittgenstein refers to as coming to see something under a different aspect, like a Gestalt switch drawing: the famous drawing that can be seen as a duck or as a rabbit (see Figure 1).[10] Frames can be reconstructed by studying the modes of presentation and rhetorical characterisation of a situation or issue.

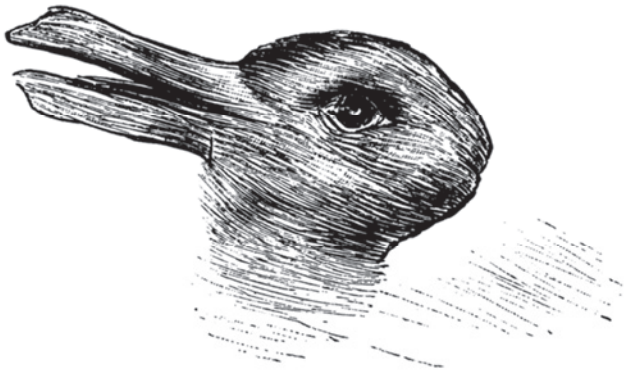

Figure 1: Rabbit-duck, published in the German magazine Fliegende Blätter (1892)

The concept of framing has been taken further by psychologists Tversky and Kahneman, in their empirical psychological studies of the workings of heuristic principles in intuitive judgment and economic decision-making. Frames, understood here as alternative formulations of the same situation, make different aspects of the situation accessible.[63] Tversky and Kahneman have shown that a different framing of the same situation will evoke a different evaluation or decision in many people. Also, different responses may be brought about in the same individual simply by changing the phrasing of the same question.[60] This usually occurs unnoticed: "The basic principle of framing is the passive acceptance of the formulation given."[60]

Although framing effects take place continuously and subconsciously in human experience and heuristics, frames can also be put to use deliberately. Frame analysis in media studies is based on the assumption that the way in which an issue is characterised in news reports can have an influence on how it is understood by audiences. Frames resonate with existing underlying evaluative schemas among their audiences.[64] In the media or in advertising, frames can

be used to steer audiences into processing, interpreting or accepting a piece of information in a certain manner, and to provoke a desired evaluative response.

Frame analysis in genomic testing

The concept of framing has been applied to commercial genomic testing before. In fact, genomic testing may be particularly prone to framing and rhetorical effects, as it is "novel, lacking in precedents and fraught with uncertainties."[1] Thomas F. Gieryn's concept of 'boundary work' has been used in the context of online marketed nutrigenomic tests,[65] which offer personalised dietary advice on the basis of SNP-profiling. Ideological efforts by scientists and policy-makers to discard "irresponsible nutrigenetic companies, who had launched the technology prematurely," it is argued, have led to the emergence of a "new regulatory and marketing category for non-medical or 'lifestyle' genetic tests" and the framing of nutrigenomic tests as 'between medicine and consumer culture.'[65] Through this 'lifestyle' frame, nutrigenomic tests were presented as outside of healthcare and as 'less serious' than clinical genetic tests. As an unintended side-effect, the lifestyle frame legitimised nutrigenomic tests and suggested "they were to be consumed and regulated more lightheartedly or liberally."[65]

Also, the framing of direct-to-consumer predictive genetic testing solely in terms of the management of health risks has been criticised for ignoring or neglecting other, broader aspects and values of such testing.[66] The reasons for consumers to consider these services useful may indeed not align with existing standards for clinical validity and utility, and may involve broader values or goals. Empirical studies have shown that beside the dominant and 'intended script' of medical benefit,[47] curiosity and fascination, recreation, personal interest and 'wanting to be an early adopter of new technologies' are among the main motivators for purchasing a direct-to-consumer genomic test.[7, 47] In one such study, a distinction is proposed between the frame of medical technology and that of information technology. It is argued that the latter may be a more appropriate frame for understanding direct-to-consumer genomic testing.[47]

Technical, medical and personal names and frames

Building upon previous work in frame analysis and existing classifications, we suggest that in the field of genomic testing as defined above, three frames are prominent: the technical, the medical and the personal frame.

Names such as 'massive-scale SNP profiling'[25] and 'high-throughput individualized genotyping'[44] evoke what we call the technical frame. The technical frame refers to the scientific-technological origins of genomic testing. It is associated with the values of scientific neutrality and technical or laboratory quality. The technical frame appears mainly throughout the early stages of inception, research and development, in which names consist in detailed, elaborate and relatively value-neutral descriptions of the technique under development. When moving toward the stages of application, implementation or marketing, name-giving and framing will likely evolve. For communication to a wider audience, names that are shorter, less precise but more user-friendly are needed. In the translation of new genomic technologies to wider audiences, medical and personal names and corresponding frames arise.

The medical and personal frames are more immediately connected to normative issues. The medical frame is brought to the fore by names such as 'genomic susceptibility testing'[40] and 'genomic risk profiling',[28] and focuses on health and disease, risks and susceptibilities. It emphasises medical aspects of genomic testing and refers to clinical goals, norms and values. The medical frame is associated with the medical-ethical principles of beneficence and non-maleficence. The personal frame on the other hand, with names such as 'personal genetic testing'[35] and 'personalized genomics',[51] underlines that genomic information says something about the individual. It also suggests that genomic information belongs to - or should be controlled by - the individual, and that it can be sought for personal reasons and used in personal ways. The personal frame stresses the principle of autonomy, and the values of liberty, access, democratisation and empowerment.[67] Whereas the medical frame positions genomic testing firmly within the sphere of medicine and healthcare, the personal frame tends to place genomic testing outside or alongside the healthcare system.

Besides the technical, medical and personal frames, there are other frames in circulation. Frames related to names like 'DTC genomic testing'[29] and 'private access genetic testing',[39] point at additional value propositions of genomic testing, such as direct-to-consumer access, convenience and privacy. Other frames put forward aspects such as the online marketing environment or the for-profit nature of some of its providers, and may refer to priorities like security or have negative connotations, such as distrust. While various frames are used in the literature, the technical, medical and personal frames appear to be dominant, and have important impact on the ethical debate, as the following case study can help illustrate.

A case study: the Healthy Mommy DNA Insight℠ test

One and the same commercially offered genomic test can be portrayed differently through the technical, the medical or the personal frame. Often subconsciously, frames will steer the evaluation of the genomic test in different directions. To demonstrate the normative effects of framing, we use the example of the Healthy Mommy DNA Insight℠ test offered by the company Pathway Genomics,[68] and describe this test as seen through each of the three frames.

The Healthy Mommy DNA Insight℠ test is marketed in the following manner:

"Genetic Testing as a Catalyst for Behavioral Change:
Clinical studies have shown that individuals who follow a genetically appropriate diet lose weight more easily. With Healthy Mommy DNA Insight℠, patients will have a holistic view of their health and may finally be able to achieve a more desirable weight, manage potential health conditions, as well as have powerful information as to which medications may or may not be right for them."[68]

First, the technical frame may offer a seemingly neutral description of the test. For example, a Pathway Genomics patent for the testing service reads: "Based upon the presence of certain genetic features, genetic markers or polymorphisms, a rules based logic path is executed to arrive at an action plan set of recommendations."[69] Phrases such as 'a rules based logic path' may bestow an impression of scientific legitimacy on the technology. Further, the

technical frame may dryly list the contents of the test: the Healthy Mommy DNA Insight℠ test estimates genetic susceptibility to 37 traits, ranging from traits related to weight and diet (e.g. decreased adiponectin, response to monounsaturated fats), eating behaviour (e.g. eating disinhibition, sweet tooth), metabolic health factors (e.g. decreased HDL cholesterol), exercise response (e.g. insulin sensitivity response to exercise), to nutritional needs (e.g. decreased folate, decreased vitamin B2), health conditions (e.g. type 2 diabetes, venous thrombosis) and medication responses (e.g. aminoglycoside-induced hearing loss, methotrexaat toxicity).[68] Another expression of the technical frame may be the claim on the company website that its in-house laboratory meets CLIA regulations and state licensure requirements.[68] The technical frame will focus on the technical aspects of the test as a way to obtain genomic data, without paying much attention to the ways in which these data will be used.

Second, the name itself (the Healthy Mommy DNA Insight℠) evokes the medical frame, which presents the service as a test for risk factors for medically relevant conditions such as elevated LDL cholesterol, elevated triglycerides and obesity. To enthusiasts thinking from the medical frame, the test may seem a useful way to learn about genetic susceptibilities to behaviours and traits that may be harmful to the health and well-being of pregnant women – this is precisely the company's marketing strategy. To sceptics thinking from the medical frame, on the other hand, it may seem that in order to estimate cholesterol levels, a simple blood test at the doctor's office will suffice, or that obesity can be established more accurately just by looking at someone. Is there any need for an expensive genomic test? And how reliable is this test anyway? The test predicts genetic susceptibilities to type 2 diabetes, osteoarthritis and venous thrombosis, which are serious medical conditions for which genomic testing has notoriously little predictive value. It is not clear whether test results have any clinical validity. Also, it is not clear whether commercial companies are capable of offering quality or confidentiality. Companies will surely not provide medical care and supervision. The pharmacogenomic information from the Healthy Mommy DNA Insight℠ may be the only clinically valid and potentially useful test outcome. Knowing that a woman needs twice the average dosage of Clopidogrel or that she should avoid aminoglycosides, for instance, may facilitate tailored treatment regimens and prevent adverse events. But what are

the odds that this woman will need precisely these treatments? Moreover, if she will, her physician could conduct ad hoc targeted and more reliable clinical tests. Is the Healthy Mommy DNA Insight℠ test really the way to go? Will it not lead to unnecessary worries in pregnant women? And what if pregnant women base health and dietary behaviour upon flawed genomic test results? It may harm them and their babies. Is it even morally acceptable to offer such a test directly to pregnant women? Isn't this company selling snake oil?

Finally, as seen through the personal frame, the Healthy Mommy DNA Insight℠ test has the triple aims, according to the company website, of managing postpartum weight loss, identifying behaviours that need to be managed, and promoting improvement in overall health and wellness.[68] The personal frame presents the test as a source of information of personal utility. The test may be health-related in so far as losing weight and a healthy diet are health-related, but is not primarily perceived as a medical test. The test provides insight into one's genetic constitution and can thus inform lifestyle decisions, such as what to eat and in what way to exercise. Through the personal frame, genomic information is considered information about oneself, about one's looks and fitness. Individual citizens are considered entitled to ownership and control of this information. For if I wish to learn about my DNA, if the technology is available, if I am willing to pay for it, and if I am not hurting anyone else, should I not be free to access my DNA? I might feel better about myself if I learn that I have 'heightened food desire' or 'sweet tooth' or 'decreased satiety' as compared with the general population, or that my HDL cholesterol levels respond less to physical exercise. Or I might improve my dietary patterns if I learn that I am at genetic risk for having decreased vitamin B6 or D. I feel that it may be good to know this information about myself, and that I should be allowed to determine in what ways to use it.

Through framing, the very same test can be seen, among other things, as a) a technique to obtain genomic data; b) a service to learn about disease susceptibilities that can be used to adopt preventive interventions, or; c) a source of genomic information that can be sought for personal reasons. Names and frames will do more than just refer to a test: they will influence the way genomic tests are perceived. Such perceptions are more or less directly connected with

policy outcomes. In short: whereas the personal frame works in favour of a liberal access policy, the medical frame steers towards more stringent regulation on the basis of medical-ethical values (see Table 1).

Frame	Medical	Personal
Leading medical-ethical principles	Beneficence and non-maleficence	Autonomy
Other values	Quality Analytical validity Counselling Informed consent	Access Convenience Liberty of choice Self-determination
Notion of utility	Clinical utility	Personal utility
Evaluation and regulation	Restricted access (physician-mediated)	Direct-to-consumer availability

Table 1: The medical frame and the personal frame

Is there a right frame? Clarifying the basic concepts

The technical, medical and personal frames represent conflicting sets of ethical views with regard to commercially offered genomic testing. In this section, the policy implications of the technical, medical and personal frames are elucidated. At the same time, three basic, central concepts are clarified, over which there has been discord in the literature. To this end, the following three questions are discussed:

1. Is a genomic test a test?
2. Is a genomic test a medical test?
3. Is a genomic test a form of screening?

From the discussion of these central concepts, it will follow which of the three frames constitutes the more tenable basis for the evaluation and regulation of commercially offered genomic testing.

Question 1: Is a genomic test a test?

In the literature on the evaluation of genetic and genomic tests, a distinction has been made between an assay and a test. Whereas an assay has been defined as "a method to analyze or quantify a substance in a sample,"[70] a test has been defined as "an assay to detect: (i) a particular genetic variant (or set of variants); (ii) for a particular disease; (iii) in a particular population; and (iv) for a particular purpose."[70] Applied to commercially offered genomic testing, this definition entails that the assay is the laboratory analysis of either about a million SNPs or all more than three billion base pairs of human DNA. For their assays, the leading commercial providers make use of standard gene chips for genotyping SNPs,[5] which are also used by genomics research communities, the analytical validity of which is generally high. SNPs are used to estimate the risks of multiple diseases in healthy adult individuals. According to this definition, a genomic test is not one single test but a set of tests. On the basis of one assay, multiple tests are conducted - by looking at multiple variants, for multiple diseases, and for multiple purposes. Often, the scope of the test (as a set of tests) is dynamic. Companies tend to expand their testing offers regularly as more and more correlations between SNPs and diseases are discovered.[71] Customers receive regular updates of their test results, which contain progressively more diseases and traits. In these instances, genomic testing can be said to be aimed at as many diseases and other traits as possible. Further, the purpose of genomic testing is generally mixed, ranging from disease prevention to reproductive information, from pharmacogenomic information to information on trivial phenotypic traits. Genomic testing may have medical, educational and/or entertainment value and is often multi-purpose. Although current genomic tests differ from their traditional clinical counterparts in both scope and purpose, they should be thought of as sets of tests, not assays.

The distinction between assays and tests has also been defined as follows: a test is the analysis of "any portion of [a] genome sequence for a specific purpose."[72] This definition singles out the purpose of the test as the demarcation line between a test and an assay: it describes a test as 'an interpretive step' which requires 'purposeful analysis'.[72] Thus conceived, the distinction between an assay and a test echoes a general distinction between data and information. A series of Cs, Gs, Ts and As (the four nucleotides of the DNA molecule) in itself does not constitute information. In order for these data to become meaningful, an interpretive step is required. For the interpretation of data, cut-off points or thresholds are usually needed. By analogy, one could think of measuring body temperature (assay) in order to establish the presence or the absence of fever (test). In order for this measurement to be a test for fever and to generate a test outcome - is there or is there not a fever? - one needs a cut-off point of 37,5 degrees Celsius (99,5 degrees Fahrenheit). According to this definition, if interpretation of data occurs and a test outcome (yes or no) is established, the assay is no longer an assay, but a test.

Current commercial providers of genomic testing do attempt to provide purposeful analysis: they calculate their customers' disease risks (information) on the basis of SNPs (data) assembled into profiles. For the presentation of test results, companies usually make use of average population risks as reference values, which can be thought of as thresholds,[73] and show how customers deviate from these reference values on the basis of measured SNPs. However, as for many complex diseases, genomic tests are not capable of accurately predicting whether someone will or will not develop a disease, testing will not generate a 'yes or no' outcome (e.g. a diagnosis). Most customers will deviate only slightly from average population risks.[56] There are no thresholds to determine whether or not such slightly increased or decreased risks are meaningfully increased or decreased risks, i.e. whether the estimated risks pose health risks (or health advantages) for the tested individual. In order for genomic tests for complex diseases to generate meaningful and actionable information (clinically valid and clinically useful information), further interpretive steps will be required.

Genomic testing is characterised by probabilities, uncertainties and incompleteness. It is a matter of debate whether a genomic test should be considered a test after the first interpretive step (of producing probabilities) or after a second interpretive step (of distinguishing between informative and non-informative probabilities). But although genomic tests are not always highly predictive, they do produce more than just data derived from a laboratory assay. They should be considered (sets of) tests – even though they may not always be useful tests.

Those who think through the technical frame or the personal frame may disagree with our conclusion. They may suggest that genomic testing is foremost about obtaining genomic data, and refrain from making claims regarding the interpretation, meaning and utility of these data. The conception of genomic testing as a source of data may imply that it can continue to evade evaluation and regulation. The Food and Drug Administration (FDA) in the United States, for instance, has no say over services that provide genetic data only:[74] as long as commercial providers do not base medical claims upon genomic data, they may put genomic services to market unrestrictedly. The technical frame may thus be used deliberately by companies or proponents of direct access in the attempt to escape regulatory action.[74] Users of the personal frame may claim that individuals should be able to own and to control their genomic data. Companies have been eager to use this rhetoric: the Core Values section on the website of one of the leading providers states that it "provides a service: linking you to your genetic data."[5] Users of the medical frame on the other hand are much more likely to support our conclusion and perceive commercially offered genomic testing as a form of testing.

Question 2: Is a genomic test a medical test?

The question whether genomic tests are medical tests cannot be viewed apart from the policy issue whether genomic tests should be regulated as medical tests - whether or not their provision should be governed by the norms and standards of healthcare. The medical frame may imply the position that genomic testing should be regulated strictly and protectively. It has been argued, for instance,

that all genetic testing, 'as a formal matter' should be considered medical testing, and should therefore submit to the same regulatory safeguards,[75] "because results might have an impact on future medical care and clinical decision making."[76] Most guidelines and regulations, in Europe as well as in the United States of America, apply explicitly to genetic or genomic testing for medical or health-related purposes.[77-79] Naming and framing genomic testing may thus determine whether or not its provision will be subject to EU or FDA regulatory sway. But which of the frames is right? Is a genomic test a medical test?

Genomic tests often yield various types of information, including, we paraphrase, 'things that are useful to know, things we already know, things we don't really want to know, things that aren't true, things you don't want others to know, and things that are fun to know'.[80] Not all information gathered from the genome is medical information. DNA carries information about genealogy, ethnicity, paternity, and non-medical phenotypic traits such as body height and freckling. Some genomic testing offers include traits such as bitter taste perception, the ability to smell the fragrance of asparagus in urine, or earwax type,[5] which are obviously not included for their medical value. Consumers may pursue such 'trivial' types of direct-to-consumer genomic testing for their recreational value.[7] Genomic testing can thus in part be something like a recreational or an informational service. In their Terms of Service sections, companies align with this conception and stress that they make no medical claims, for example: "our Services are for research, informational, and educational purposes only [and are] not intended to be used by the customer for any diagnostic purpose and are not a substitute for professional medical advice."[5] This way, companies position their activities as informational services rather than as medical tests. They advance the personal frame.

There are rational limits to the tenability of the presentation of genomic tests as non-medical, informational, personal services. Firstly, phenotypic traits do not always fit easily into either category (medical or non-medical/personal), for seemingly trivial traits such as alcohol flush reaction, freckling and restless legs syndrome can be connected with illness or ill health. In its 'traits' section, one of the leading companies includes resistance to Norovirus, blood glucose and LDL

cholesterol levels, and chronic Hepatitis B,[5] which are clearly (also) health-related traits. In general, it may not always be possible to disentangle the personal from the medical.

Secondly, it is simply not realistic to present the purpose of genomic testing as non-medical. Genomic tests consist mainly of risk estimates for diseases such as colorectal cancer, brain aneurysm, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, asthma, etc.[5, 68] Steven Teutsch, chairman of the US Secretary's Advisory Committee on Genetics, Health, and Society, said: "If people want to get their ear wax type, be my guest, but when [companies] are [testing] mutations for breast and ovarian cancer and then claim it is not medical testing, that could be problematic."[81] There is no longer a 'split in the market', a boundary line between 'lifestyle testing' (non-medical) and 'predispositional testing' (medical).[34] Many commercial providers of genomic testing are offering very broad packages that include subgroups of tests: test for non-medical traits, tests for medical traits of limited clinical validity, and tests for medical traits of higher clinical validity.[14] It is simply besides the truth to deny the health-related nature of most testing offers.

And finally, the available empirical evidence suggests that consumers engage in genomic testing mainly for health-related reasons: "health-related issues are at the center of individuals' reasons for wanting DTC genetic testing."[7] The two most commonly mentioned reasons for direct-to-consumer genomic testing are the following: to gain health-related information and to learn about individual genetic risk factors for diseases.[47] In a survey among social networkers, 74% of respondents indicated that they would be interested in direct-to-consumer genomic testing 'to see if a specific disease runs in family or is in DNA.'[82] A commentary to this study reads: "irrespective of how genetic profiles are marketed to consumers, the results will tend to be interpreted as having value as information about health risks."[83] In this context the phenomenon of 'misattributed equivalence' has been described: consumers might mistake direct-to-consumer genomic testing to be equivalent to clinical genetic tests with which they are more familiar.[29] Through such associations, consumers may have overly optimistic expectations of the clinical value of genomic tests and

interpret them, company website disclaimers notwithstanding, in a health-related light.

We have argued that the personal frame is not tenable, for it is not in line with the facts to claim that genomic tests in general are non-medical tests. But neither is it rational to hold that genomic tests are always or exclusively medical tests. Although some tests that are available commercially at the moment, such as specialised ancestry testing [84] or paternity testing,[85] are clearly personal in nature, most tests, especially the broad tests that are sometimes called 'genome scans'[86] or 'personal genome tests'[43] had best be thought of as medical, given the primarily health-related nature of the information coming from such tests and the primarily health-related motivations for which consumers seek such testing.

Question 3: Is a genomic test a form of genetic screening?

Similarities between genomic testing and genetic population screening programmes have led commentators to suggest that the commercial provision of genomic testing should be subjected to the regulatory frameworks for screening programmes.[83] In public health, these regulatory frameworks are well-developed and widely accepted for the technical, economic and ethical evaluation of screening programmes.[87-90] The frameworks consist in expanding sets of criteria for the morally responsible offering of screening tests, ranging from the sensitivity and specificity of the test, quality control, and long-term monitoring to the availability of treatment, economic costs and benefits and ethical issues including stigmatisation, confidentiality, informed consent and reporting requirements.[87]

Traditionally, screening programmes have been set apart from clinical practice, including clinical genetic testing, because "the process is usually initiated by the health care providers contacting people who are well."[91] This definition points out two distinguishing features of screening: firstly, it is the healthcare professional who initiates the screening process, and secondly, the persons undergoing screening are healthy. First, unlike screening programmes, which

may be seen to be imposed on individuals,[92] commercially offered genomic tests are privately sought by individual consumers. Consumers pay fair sums for genomic testing and are rarely confronted spontaneously with testing opportunities. Although public awareness of commercially offered genomic testing has recently been on the rise,[93] the majority of citizens in many countries may not yet be aware of its existence. Direct-to-consumer marketing does not constitute an unsolicited, systematic offer, and in this sense, it is unlike screening. Second, screening is aimed at people who exhibit no health problems with the aim of detecting diseases or risk factors.[94] Genomic testing has this 'starting point'[95] in common with screening: whereas clinical medicine starts with a medical problem or a phenotype, genomic testing, like screening, is directed at consumers who are asymptomatic and otherwise well. Moreover, the aims of genomic testing and population screening are similar: the identification of risk factors in order to avert diseases and to improve health outcomes.[96] Finally, the potential harms and disadvantages of genomic tests are similar to those commonly found in screening programmes, such as false negative and false positive results and, consequently, false reassurances and needless worry.[40, 97]

Even though there are similarities between commercial genomic testing offers and genetic screening, it is not clear whether the regulatory frameworks of population screening should apply to commercial companies. Companies are not bound by the professional norms and standards of healthcare, and consumers may not expect them to be. A commercial offer lacks the 'quality label' of the state-initiated offer, and direct-to-consumer genomic testing is clearly not recommended by healthcare authorities. Consumers will understand that they themselves should evaluate the testing offer and choose whether or not to proceed with testing:

"it was the individual who applies for a test in the case of commercial services. Accordingly, it was not the government, but the individual who should weigh, in the light of personal values, convictions and experiences, the advantages and disadvantages of screening."[98]

Thus, while genomic testing has a few features in common with population screening, these similarities do not justify straight-forward application of the evaluative frameworks for screening programmes. Thinking from the medical, protectionist frame, these regulatory frameworks, with their criteria like a favourable risk-benefit ratio, the availability of treatment options and informed consent, and their attention to ethical issues, seem a desirable model for the commercial provision of genomic testing. In contrast, those thinking from the personal frame may argue that the locus of the initiative has decisive normative force, and claim that the moral responsibilities of information and protection lie primarily with the consumer rather than the commercial provider. Moreover, key criteria from screening frameworks, such as 'the condition sought should be an important public health problem' and 'the test should be acceptable to the population',[87] have been formulated for collective, population-based programmes and are much less relevant in privately sought commercial interactions. Because of its individual rather than collective character, we conclude that although genomic testing does have features in common with screening, it is not a form of population screening. The ethics of population screening programmes is not immediately applicable.

Away with the frames: a balance of liberty and protection against harm

From our discussion it follows that the medical frame is most likely to respond to the questions whether genomic testing is a form of testing and whether it is a form of medical testing, in the ways we have argued to be most rational. We may thus conclude that the medical frame should be favoured as a basis for the evaluation of commercially offered genomic testing. Nonetheless, we should not throw the baby out with the bath water: values and interests associated with the personal frame, such as liberty, access and self-determination, should be weighed carefully against the values and interests associated with the medical frame, such as protection against harm. In tackling ethical and regulatory issues in genomic testing, the basic moral question is not how to frame genomic testing, but how to balance the values of liberty and protection against harm.

It is not clear, at present, whether there are major harms involved in genomic testing. The available evidence is divided. Some of the first empirical studies suggest that genomic tests do not adversely affect participants.[52, 99, 100] Also at long term follow-up, studies have found little psychological risk,[101] and no health risks. Most of these studies however have been conducted with genetically literate research participants, with limited and not highly predictive testing offers, and with pre-test information, informed consent, and professional support. In contrast, a few case reports have been published on the experiences of actual users of direct-to-consumer genomic testing services, suggesting serious psychological impact. A bioinformatics expert, for instance, reported to have felt burdened with the family experience of commercially offered genomic testing and with information overload.[102] Two case studies demonstrate how consumers may misunderstand test results and may be deeply impacted by direct-to-consumer genomic testing for Alzheimer's disease.[103] Finally, a genomic test for Factor V Leiden mutations with insufficient and inadequate information has brought psychological harm to affected families.[104] We expect that such case reports paint a convincing picture of what may happen to an insufficiently informed general public when confronted with actual direct-to-consumer genomic testing, much more so than do carefully designed studies among the genetically savvy.

Two current developments may exacerbate the potential for harm: first, companies are increasingly including highly predictive tests for monogenic diseases in their testing offers, such as tests for BRCA 1 and carrier screening for hereditary disorders such as Tay-Sachs or Cystic Fibrosis,[5, 55] which have traditionally been conducted only within the confines of well-regulated clinical genetic centres. Also, some tests for some complex diseases, such as age-related macular degeneration or Alzheimer's disease, are quite highly predictive and may thus convey considerable health risks. As a result, present-day genomic testing can no longer be said to be devoid of clinical validity and utility. Genomic tests are increasingly displaying similarities to clinical genetic tests, so that the medical frame is becoming more and more applicable. Secondly, as a consequence of rapidly developing whole-genome and exome sequencing technologies, the possibility of purchasing whole genomes or exomes may fall within the reach of average European, American or other developed-world

consumers in the not too far-off future. When that happens, commercially offered genomic testing is expected to become based upon sequencing technologies.[49] These technologies are capable of revealing more predictive and clinically relevant information, including sporadic or rare genetic variants causing monogenic conditions. As a result, the medical, psychological and social implications of genomic testing based upon sequencing technologies may become more serious.

Rather than the question whether a genomic test is medical or personal in nature, the potential for harm may be a more appropriate criterion for decision-making regarding the standards and regulations necessary for a morally responsible provision of genomic testing services. Given their potential for harm, (possibly) highly predictive genetic tests, such as those for hereditary cancer syndromes or diseases such as Parkinson's disease or Alzheimer's disease, should adhere to the same standards as those governing tests currently offered through clinical genetics centres. Tests of much more limited clinical validity for more complex diseases, such as type 2 diabetes or obesity, for which preventive or treatment options are available, will be less harmful and may accordingly be regulated more loosely. Tests for personal traits such as eye colour or bitter taste perception may be rather innocent and not require regulation at all. Importantly, tests for other types of personal, non-medical traits, such as homosexuality or tendency to criminal behaviour, might need to be regulated much more carefully because of social implications and privacy issues. Not all personal testing is harmless. Genomic tests that offer broad packages of risk estimates for dozens or hundreds of different types of diseases and traits, will be associated with different levels of potential harm and will thus require different levels of safeguards. Broad genomic testing thus poses enormous challenges for evaluation and regulation.

Where there is a potential for harm in genomic testing - and we expect that for many users, for broad tests that include predictive tests, there is - providers of genomic testing, whether they are commercial companies or healthcare operators, should take appropriate measures to prevent harm from happening. In order to do so, providers may take their cue from medicine and healthcare in general, and from clinical genetics and genetic screening programmes in

particular. These measures, however, should be proportional, and should strive towards an optimal balance between protection against harm on the one hand, and accessibility and consumer liberty and self-determination on the other hand.

One example of a proportional protective measure may be adequate information provision and informed consent. Although informational obligations of healthcare professionals may be more extensive than those of commercial companies,[14] advocates of both the medical frame (or a protectionist stance) and the personal frame (or a more liberal stance) will be able to support the position that good information is necessary for autonomous and informed decision-making, both in the clinical setting and on an accessible market. While they may differ in their assumptions on what good information consists of and on how it should be conveyed to consumers - whether, for instance, the presence of a healthcare professional is required – they may agree that commercial providers should enable informed decision-making by consumers,[14] to which truthful, relevant and accurate pre-test information is a precondition. Requirements for information provision may vary with the potential for harm: whereas in harmless testing ease of access and convenience may be at the forefront, in potentially harmful testing, pre-test information and informed consent are of paramount importance. When the potential for harm is very high, information may not offer sufficient protection, and direct access may not be warranted at all.

Informed consent is meant to enhance self-determination and free choice, and should be possible even in an online, direct-to-consumer environment. The medical frame as a basis for evaluation and regulation does not foreclose direct-to-consumer availability of commercially offered genomic testing. It does however resound the importance of a morally responsible testing offer.

Conclusions

We have argued that a commercially offered broad genomic test should be considered a set of tests and that an important part of this set concerns medical testing. Also, while genomic testing shares some features with population

screening, there are decisive differences, as well. Genomic testing can be "a source of valued information with many different potential purposes."[96] This diversity is reflected in the names genomic tests have been called in the scholarly and popular literatures, and in the frames through which they have been portrayed. Over the past few years, the ethical debate seems to circle in on two types of names and associated frames in particular: the medical and the personal frames. There are upshots and caveats to both frames: the personal frame will stress self-determination, access, information and wider definitions of utility, whereas the medical frame will advocate protection, care and quality. The medical frame will steer toward conservative and more stringent regulation of genomic testing, whereas the personal frame is associated with resistance to paternalism and with a demand for direct access. The personal frame however runs the risks of distracting from health-related, psychological and social risks and implications of testing, and of failing to build in safeguards to avert potential harms. We have argued that in regulatory decision-making, a balance should eventually be struck between the values of liberty and of protection against harm.

Name-giving and framing – inadvertently – influence perception, evaluation and regulation. The effects of naming and framing should not confound policy-making. Rather, regulatory decision-making should be informed by the level of potential harm involved. As a general rule, we propose that the more predictive the genomic test becomes, the more applicable some of the ethical criteria, norms and standards derived from (public) healthcare will be. Examples of such norms and standards are quality control, availability of preventive or therapeutic options, a favourable balance of risks and benefits, informed consent and pre- and post-test counselling. Insofar as genomic tests inform consumers predictively about health-related risks, disease prevention and health management, or convey other potentially sensitive information (e.g. risk estimates for traits such as homosexuality or criminal behaviour), their provision will require the same kinds of safeguards as do other forms of medical testing. This conclusion need not imply that direct access to commercially offered genomic tests should necessarily be avoided: also in a direct-to-consumer context, proportional protective safeguards can be implemented. With its focus on lifestyle, information and personal definitions of utility, the personal frame

points at valuable meanings of commercially offered genomic testing, but should be handled with care. Let us call a spade a spade, and a medical test a medical test.

References

1. Murphy P. and M. Maynard. 2000. Framing the genetic testing issue: discourse and cultural clashes among policy communities. Science Communication 22: 133-153.

2. Cornel M.C., C.G. van El and P. Borry. 2012. The challenge of implementing genetic tests with clinical utility while avoiding unsound applications. Journal of Community Genetics [Epub ahead of print] (p. 206).

3. Government Accountability Office (GAO). 2010. Direct-to-consumer genetic tests: Misleading test results are further complicated by deceptive marketing and other questionable practices. GAO.

4. Borry P., M.C. Cornel and H.C. Howard. 2010. Where are you going, where have you been: a recent history of the direct-to-consumer genetic testing market. Journal of Community Genetics 1: 101-106.

5. 23andme: http://www.23andme.com.

6. Singleton A., L.H. Erby, K.V. Foisie and K.A. Kaphingst. 2012. Informed choice in direct-to-consumer genetic testing (DTCGT) websites: a content analysis of benefits, risks, and limitations. Journal of Genetic Counseling 21: 433-439.

7. Su Y., H.C. Howard and P. Borry. 2011. Users' motivations to purchase direct-to-consumer genome-wide testing: an exploratory study of personal stories. Journal of Community Genetics 2(3): 135-146.

8. Swan M. 2009. Emerging patient-driven health care models: an examination of health social networks, consumer personalized medicine and quantified self-tracking. International Journal of Environmental Research and Public Health 6: 492-525.

9. Ku C.S., D.N. Cooper, C. Polychronakos, N. Naidoo, M. Wu and R. Soong. 2012. Exome sequencing: dual role as a discovery and diagnostic tool. Annals of Neurology 71: 5-14.

10. Wittgenstein L. 1953. Philosophical Investigations. Oxford: Basil Blackwell Ltd. (part I, paragraph 67).

11. American College of Medical Genetics (ACMG). 2004. ACMG statement on direct-to-consumer genetic testing. Genetics in Medicine 6: 60.

12. Gollust S.E., B.S. Wilfond and S. Hull. 2003. Direct-to-consumer sales of genetic services on the Internet. Genetics in Medicine 5: 332-337.

13. Bunnik E.M., M.H. Schermer and A.C. Janssens. 2012. The role of disease characteristics in the ethical debate on personal genome testing. BMC Medical Genomics 19:4.

14. Bunnik E.M., M.H. Schermer and A.C. Janssens. 2012. Informed consent in direct-to-consumer personal genome testing: the outline of a model between specific and generic consent. Bioethics [Epub ahead of print].

15. Howard H.C., D. Avard and P. Borry. 2011. Are the kids really all right? Direct-to-consumer genetic testing in children: are company policies clashing with professional norms? European Journal of Human Genetics 19: 1122-1126.

16. Caulfield T. and A.L. McGuire. 2012. Direct-to-consumer genetic testing: perceptions, problems and policy responses. Annual Review of Medicine 63: 23-33.

17. McGuire A.L., M.K. Cho, S.E. McGuire and T. Caulfield. 2007. The future of personal genomics. Science 317: 1687.

18. Janssens A.C.J.W. and C.M. van Duijn. 2010. An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 1: 10.

19. Caulfield T., N.M. Ries, P.N. Ray, C. Shuman and B. Wilson. 2010. Direct-to-consumer genetic testing: good, bad or benign? Clinical Genetics 77: 101-105.

20. Knoppers B.M. 2010. Consent to “personal” genomics and privacy. EMBO Reports 11: 416-419.

21. van Ommen G.B. and M.C. Cornel. 2008. Recreational genomics? Dreams and fears on genetic susceptibility screening. European Journal of Human Genetics 16: 403-404.

22. Pearson H. 2008. Genetic testing for everyone. Nature 453: 570-571.

23. Bunnik E.M., M.H.N. Schermer and A.C.J.W. Janssens. 2011. Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. BMC Medical Ethics 12: 11.

24. Angrist M. 2010. Here Is a Human Being: At the Dawn of Personal Genomics. New York: HarperCollins.

25. Imai K., L.J. Kricka and P. Fortina. 2011. Concordance study of 3 direct-to-consumer genetic-testing services. Clinical Chemistry 57(3): 518-521.

26. Melzer D., S. Hogarth, K. Liddell, T. Ling, S. Sanderson and R.L. Zimmern. 2008. Genetic tests for common diseases: new insights, old concerns. British Medical Journal 336(7644): 590-593.

27. Williams-Jones B. 2003. Where there's a web, there's a way: commercial genetic testing and the Internet. Community Genetics 6: 46-57.

28. Haga S.B., M.M. Carrig, J.M. O'Daniel et al. 2011. Genomic risk profiling: attitudes and use in personal and clinical care of primary care physicians who offer risk profiling. Journal of General Internal Medicine 26(8): 834-840.

29. Eng C. and R.R. Sharp. 2010. Bioethical and clinical dilemmas of direct-to-consumer personal genomic testing: the problem of misattributed equivalence. Science Translational Medicine 2(17): 17cm15.

30. Editor. 2008. Genome scans get personal with online consumer services. Annals of Neurology 63: A15-17.

31. Wolinsky H. 2005. Do-it-yourself diagnosis. EMBO Reports 6(9): 805-807.

32. Shetty P. 2008. Home DNA test kits cause controversy. Lancet 371(9626): 1739-1740.

33. Geransar R. and E. Einsiedel. 2008. Evaluating online direct-to-consumer marketing of genetic tests: informed choices or buyers beware? Genetic Testing 12(1): 13-23.

34. Martin P. and R. Frost. 2003. Regulating the commercial development of genetictesting in the UK: problems, possibilities and policy. Critical Social Policy 23: 186-207.

35. Kaufman D.J., J.M. Bollinger, R.L. Dvoskin and J.A. Scott. 2012. Risky business: risk perception and the use of medical services among customers of DTC personal genetic testing. Journal Genetic Counseling 21(3): 413-422.

36. Kinmonth A.L., J. Reinhard, M. Bobrow and S. Pauker. 1998. The new genetics: implications for clinical services in Britain and the United States. British Medical Journal 316: 767-770.

37. Holtzman N.A. 1999. Are genetic tests adequately regulated? Science 286: 409.

38. Levitt D.M. 2001. Let the consumer decide? The regulation of commercial genetic testing. Journal of Medical Ethics 27(6): 398-403.

39. Mykitiuk R. 2004. Caveat emptor: direct-to-consumer supply and advertising of genetic testing. Clinical and Investigative Medicine 27(1): 23-32.

40. Hunter D.J., M.J. Khoury and J.M. Drazen. 2008. Letting the genome out of the bottle--will we get our wish? New England Journal of Medicine 358(2):105-107.

41. Wise J. 2009. Should "body MOTs" and DNA profiling be regulated? British Medical Journal 338: b1646.

42. Bloss C.S., L. Ornowski, E. Silver, M. Cargill, V. Vanier, N.J. Schork and E.J. Topol. 2010. Consumer perceptions of direct-to-consumer personalized genomic risk assessments. Genetics in Medicine 12(9): 556-566.

43. Cherkas L.F., J.M. Harris, E. Levinson, T.D. Spector and B. Prainsack. 2010. A survey of UK public interest in internet-based personal genome testing. PLoS One 5 (10): e13473.

44. Morgan A.A., R. Chen and A.J. Butte. 2010. Likelihood ratios for genome medicine. Genome Medicine 2(5): 30.

45. Howard H.C., B.M. Knoppers and P. Borry. 2010. Blurring lines. The research activities of direct-to-consumer genetic testing companies raise questions about consumers as research subjects. EMBO Reports 11(8): 579-582.

46. Kuehn B.M. 2010. Inconsistent results, inaccurate claims plague direct-to-consumer gene tests. Journal of the American Medical Association 304(12): 1313-1315.

47. McGowan M.L., J.R. Fishman and M.A. Lambrix. 2010. Personal genomics and individual identities: motivations and moral imperatives of early users. New Genetics and Society 29(3): 261-290.

48. Ries N.M., R. Hyde-Lay and T. Caulfield. 2010. Willingness to pay for genetic testing: a study of attitudes in a Canadian population. Public Health Genomics 13(5): 292-300.

49. Bloss C.S., B.F. Darst, E.J. Topol and N.J. Schork. 2011. Direct-to-consumer personalized genomic testing. Human Molecular Genetics 20: R132-141.

50. Moonesinghe R., M.J. Khoury, T. Liu and A.C. Janssens. 2011. Discriminative accuracy of genomic profiling comparing multiplicative and additive risk models. European Journal of Human Genetics 19(2): 180-185.

51. Gollust S.E., E.S. Gordon, C. Zayac et al. 2012. Motivations and perceptions of early adopters of personalized genomics: perspectives from research participants. Public Health Genomics 15(1): 22-30.

52. Kaphingst K.A., C.M. McBride, C. Wade et al. 2012. Patients' understanding of and responses to multiplex genetic susceptibility test results. Genetics in Medicine 14: 681-687.

53. Karczewski K.J., R.P. Tirrell, P. Cordero et al. 2012. Interpretome: a freely available, modular, and secure personal genome interpretation engine. Pacific Symposium on Biocomputing: 339-350.

54. Weaver M. and T.I. Pollin. 2012. Direct-to-consumer genetic testing: what are we talking about? Journal of Genetic Counseling 21(3): 361-366.

55. Counsyl: http://www.counsyl.com.

56. Janssens A.C.J.W. and C.M. van Duijn. 2008. Genome-based prediction of common diseases: advances and prospects. Human Molecular Genetics 17: 166-173.

57. Evans J.P. 2011. That personal touch. Hastings Center Report 41: 5-6.

58. Singer E. 2009. The business of personal genomes. MIT Technology Review.

59. Goffman E. 1974. Frame analysis: An essay in the organization of experience. Cambridge, MA: Harvard University Press.

60. Tversky A. and D. Kahneman. 1981. The framing of decisions and the psychology of choice. Science 211: 453-458 (p. 703).

61. Gamson W.A. and A. Modigliani. 1989. Media discourse and public opinion on nuclear power: a constructionist approach. American Journal of Sociology 95: 1-37.

62. Gamson W.A. and A. Modigliani. 1987. The changing culture of affirmative action. In: Research in Political Sociology. R.G. Braungart and M.M. Braungart (eds), 137-177. Greenwich, CT: JAI Press (p. 143).

63. Kahneman D. 2003. A perspective on judgment and choice: mapping bounded rationality. American Psychologist 58: 697-720.

64. Shoemaker P.J. and S.D. Reese. 1995. Mediating the Message: Theories of Influence on Mass Media Content. Boston, MA: Allyn & Bacon.

65. Saukko P.M., M. Reed, N. Britten and S. Hogarth. 2010. Negotiating the boundary between medicine and consumer culture: online marketing of nutrigenetic tests. Social Science and Medicine 70: 744-753 (pp. 745-748).

66. Boenink M. and S. van der Burg. 2010. Informed decision making about predictive DNA tests: arguments for more public visibility of personal deliberations about the good life. Medicine, Health Care and Philosophy 13: 127-138.

67. MacDonald C. and N. Walton. 2009. Personal genomics: democratization, or empowerment, or 'something'. American Journal of Bioethics 6: 46-48.

68. Pathway Genomics: http://www.pathway.com.

69. Pathway Genomics. 2013. Genetic based health management apparatus and methods. (30 May 2013)

70. Zimmern R.L. and M. Kroese. 2007. The evaluation of genetic tests. Journal of Public Health 29(3): 246-250.

71. Mihaescu R., M. van Hoek, E.J. Sijbrands et al. 2009. Evaluation of risk prediction updates from commercial genome-wide scans. Genetics in Medicine 11: 588-594.

72. PHG Foundation. 2011. Next Steps in the Sequence: The Implications of Whole Genome Sequencing for Health in the UK. Cambridge: PHG Foundation (p. 4).

73. Kalf R.R., R. Mihaescu, S. Kundu, P. de Knijff, R.C. Green and A.C. Janssens. 2013. Variations in predicted risks in personal genome testing for common complex diseases. Genetics in Medicine [Epub ahead of print].

74. Vorhaus D. 2011. DTC genetic testing and the FDA: is there an end in sight to the regulatory uncertainty? In: Genomics Law Report.

75. Hogarth S., G. Javitt and D. Melzer. 2008. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annual Review of Genomics and Human Genetics 9: 161-182.

76. American College of Obstetricians and Gynecologists (ACOG). 2008. Direct-to-consumer marketing of genetic testing. Washington, DC: ACOG (p. 1).

77. Food and Drug Administration (FDA). 2011. Summary from the Molecular & Clinical Genetics Panel Meeting. FDA.

78. Council of Europe. 2008. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. Strasbourg: Council of Europe.

79. European Parliament and Council of the European Union. 1998. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

80. Evans J.P. 2008. Recreational genomics; what's in it for you? Genetics in Medicine 10(10): 709-710.

81. Genomeweb. 2009. SACGHS to continue review of DTC genetic testing recommendations through at least October. (12 June 2009).

82. McGuire A.L., C.M. Diaz, T. Wang and S.G. Hilsenbeck. 2009. Social networkers' attitudes toward direct-to-consumer personal genome testing. American Journal of Bioethics 9(6-7): 3-10.

83. Jordens C.F., I.H. Kerridge and G.N. Samuel. 2009. Direct-to-consumer personal genome testing: the problem is not ignorance - it is market failure. American Journal of Bioethics 9(6-7): 13-15.

84. Family Tree DNA: http://www.familytreedna.com.

85. DNA Bioscience: http://www.dna-bioscience.co.uk.

86. Prainsack B., J. Reardon, R. Hindmarsh, H. Gottweis, U. Naue and J.E. Lunshof. 2008. Personal genomes: misdirected precaution. Nature 456: 34-35.

87. Andermann A., I. Blancquaert, S. Beauchamp and V. Déry. 2008. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization 86: 317-319.

88. Khoury M.J., L.L. McCabe and E.R.B. McCabe. 2003. Population screening in the age of genomic medicine. New England Journal of Medicine 348: 50-58.

89. Teutsch S.M., L.A. Bradley and A.O. Berg. 2009. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group. Genetics in Medicine 11: 3-14.

90. Wilson J.M.G. and G. Jungner. 1968. Principles and Practice of Screening for Disease. Geneva: World Health Organization.

91. Nuffield Council on Bioethics. 1993. Genetic Screening: Ethical Issues. London: Nuffield Council on Bioethics (p. 31).

92. Godard B., L. ten Kate, G. Evers-Kiebooms and S. Ayme. 2003. Population genetic screening programmes: principles, techniques, practices, and policies. European Journal of Human Genetics 11 Suppl 2: S49-87.

93. Finney Rutten L.J., S.E. Gollust, S. Naveed and R.P. Moser. 2012. Increasing public awareness of direct-to-consumer genetic tests: health care access, internet use, and population density correlates. Journal of Cancer Epidemiology 2012: 309109.

94. Gezondheidsraad (Health Council of the Netherlands). 2008. Screening: Between Hope and Hype. Dutch Ministry of Health, Welfare and Sport.

95. Hastings R., G. de Wert, B. Fowler et al. 2012. The changing landscape of genetic testing and its impact on clinical and laboratory services and research in Europe. European Journal of Human Genetics 20: 911-916.

96. Burke W., B. Tarini, N.A. Press and J.P. Evans. 2011. Genetic screening. Epidemiologic Reviews 33(1): 148-164 (p. 160).

97. Kaye J. 2008. The regulation of direct-to-consumer genetic tests. Human Molecular Genetics 17(R2): R180-183.

98. Stemerding D., T. Swierstra and M. Boenink. 2010. Exploring the interaction between technology and morality in the field of genetic susceptibility testing: a scenario study. Futures 42: 1133-1145 (p. 1140).

99. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534.

100. Vayena E., E. Gourna, J. Streuli, E. Hafen and B. Prainsack. 2012. Experiences of early users of direct-to-consumer genomics in Switzerland: an exploratory study. Public Health Genomics 15(6): 352-362.

101. Bloss C.S., N.E. Wineinger, B.F. Darst, N.J. Schork and E.J. Topol. 2013. Impact of direct-to-consumer genomic testing at long term follow-up. Journal of Medical Genetics 50(6): 393-400.

102. Corpas M. 2012. A family experience of personal genomics. Journal of Genetic Counseling 21(3): 386-391.

103. Messner D.A. 2011. Informed choice in direct-to-consumer genetic testing for Alzheimer and other diseases: lessons from two cases. New Genetics and Society 30(1): 59-72.

104. Lebel R.R. 2011. That personal touch. Hastings Center Report 41(3): 6-7.

Chapter 4

Personal genome testing: Test characteristics to clarify the discourse on ethical, legal and societal issues

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Abstract

Background

As genetics technology proceeds, practices of genetic testing have become more heterogeneous: many different types of tests are finding their way to the public in different settings and for a variety of purposes. This diversification is relevant to the discourse on ethical, legal and societal issues (ELSI) surrounding genetic testing, which must evolve to encompass these differences. One important development is the rise of personal genome testing on the basis of genetic profiling: the testing of multiple genetic variants simultaneously for the prediction of common multifactorial diseases. Currently, an increasing number of companies are offering personal genome tests directly to consumers and are spurring ELSI-discussions, which stand in need of clarification. This paper presents a systematic approach to the ELSI-evaluation of personal genome testing for multifactorial diseases along the lines of its test characteristics.

Discussion

This paper addresses four test characteristics of personal genome testing: its being a non-targeted type of testing, its high analytical validity, low clinical validity and problematic clinical utility. These characteristics raise their own specific ELSI, for example: non-targeted genetic profiling poses serious problems for information provision and informed consent. Questions about the quantity and quality of the necessary information, as well as about moral responsibilities with regard to the provision of information are therefore becoming central themes within ELSI-discussions of personal genome testing. Further, the current low level of clinical validity of genetic profiles raises questions concerning societal risks and regulatory requirements, whereas simultaneously it causes traditional ELSI-issues of clinical genetics, such as psychological and health risks, discrimination, and stigmatisation, to lose part of their relevance. Also, classic notions of clinical utility are challenged by the newer notion of 'personal utility.'

Summary

Consideration of test characteristics is essential to any valuable discourse on the ELSI of personal genome testing for multifactorial diseases. Four key characteristics of the test - targeted/non-targeted testing, analytical validity, clinical validity and clinical utility - together determine the applicability and the relevance of ELSI to specific tests. The paper identifies and discusses four areas of interest for the ELSI-debate on personal genome testing: informational problems, risks, regulatory issues, and the notion of personal utility.

Background

In discussions on ethical, legal and societal issues (ELSI) surrounding genetic testing, there is no longer any single satisfying definition of what constitutes 'a genetic test'. Practices of genetic testing are becoming more and more heterogeneous, not only with regard to the setting and purpose of testing, but also with regard to the technical aspects of the tests themselves. Some of these technical differences between genetic tests are ethically significant or have implications for legal or societal issues. Therefore, a clear understanding of the relevant test characteristics of genetic tests is a necessity for any meaningful discussion of the ELSI surrounding genetic testing.

Over the last decades, new technologies for genetic testing have been developed that differ in many respects from those used in traditional clinical genetic testing for monogenic diseases. One important development is the advent of personal genome testing on the basis of genetic profiling for the prediction of common multifactorial diseases. Multifactorial diseases, such as cardiovascular diseases,[1] age-related macular degeneration,[2] type 2 diabetes,[3] clinical depression,[4] and many types of cancer,[5] are caused by intricate interplays of multiple genetic factors and non-genetic factors. Through an analysis of those genetic factors, an individual's genetic susceptibility to multifactorial diseases

can be determined. Personal genome testing companies are currently offering such risk prediction services directly-to-consumer, thereby raising a range of new ELSI.

With this paper, we aim to clarify the relations between the more technical characteristics of a genetic test and the ELSI with which the test is associated. We believe that a thorough understanding of the technical characteristics of personal genome tests themselves forms a necessary basis for all further ELSI-discussions in the field. Our focus on the test characteristics implies that, in this paper, we will not be able to discuss other aspects that are relevant to ELSI-discussions, such as characteristics of the diseases tested for, or the settings in which tests are offered. Although there are moral differences, for example, between the offering of personal genome tests by private companies and the offering of the same tests by public health care systems, or between testing for diseases for which there are treatment options available and testing for diseases for which there are no such options, these differences are not the main subject of this paper. As personal genome tests are currently offered almost exclusively in a direct-to-consumer context, we take that context as the background to our discussion.

First, we will introduce the practice of personal genome testing. In the second section, we will distinguish and briefly discuss the following four key test characteristics of genetic testing: from targeted to non-targeted testing, analytical validity, clinical validity and clinical utility. The third section of the paper discloses and discusses four major areas of implications of these test characteristics for the ELSI-debate.

Discussion

Personal genome testing

Personal genome testing for multifactorial diseases is conducted on the basis of genetic profiling. In a genetic profile, multiple genetic variants are combined that are associated with increased or decreased risks for a particular multifactorial disease. Presently, single nucleotide polymorphisms (SNPs) are

used within genetic profiles.[6] SNPs are variations of a single nucleotide, the smallest building block of DNA. Most common SNPs that are known today convey only minor risks.[7] They are distinguished from mutations that cause monogenic diseases, which are rare but convey large risks.

For almost a decade, companies have been offering genetic profiles based on SNPs directly to consumers via the Internet. Initially, personal genome testing companies marketed single profiles for specific health conditions, or a limited set of profiles for related diseases.[8] Today, companies are offering genome-wide profiling services that yield a multitude of profiles not only for common multifactorial diseases, but also for non-medical traits.[9] In recent years, personal genome testing companies have been at the centre of an ongoing critical debate on their ethical, legal and societal issues (ELSI).[10] Within the ELSI-debate, personal genome testing services have been criticised for their lack of clinical validity,[11-13] for being premature,[14] or a waste of private and public money.[15,16]

Other direct-to-consumer companies are starting to offer genetic profiling on the basis of whole-genome sequencing technology: the analysis of all three billion base pairs.[1] Whether providers make use of genome-wide SNP-analysis or whole-genome or exome sequencing technology, however, the prediction of common multifactorial diseases and other complex traits will continue to be based upon multiple genetic variants, and thereby upon the construction of genetic profiles. In this respect, therefore, the scope of this paper is wide and encompasses all potential forms of personal genome testing based on genetic profiling: current and future, commercial and clinical forms, including sequencing technologies.

Test characteristics

There are four key test characteristics relevant to the ELSI-debate to be discussed: from targeted to non-targeted testing, analytical validity, clinical validity and clinical utility (see Table 2).

Test characteristic	Implications	ELSI
From targeted to non-targeted testing	Quantity and complexity of information	The information problem - Informed consent - Information provision (pre-test and post-test) - Informational updates - Incidental findings
Analytical validity	High analytical validity	Regulatory issues
Clinical validity	Generally poor clinical validity (validity varies per disease tested for)	- Psychological risks, health risks and societal risks - Regulatory issues
Clinical utility	Generally poor clinical utility (utility varies per disease tested for)	- Personal perspectives on utility - Changing information

Table 2. Test characteristics of personal genome testing and their implications for the discourse on ELSI

Test characteristic 1. From targeted testing to non-targeted testing

In targeted testing, the patient or consumer is tested for a single particular disease. Clinical genetic testing is by definition targeted, because clinical geneticists are scrutinizing the genome for risks of a particular monogenic disease, or, in the process of diagnosis, for one particular genetic disease to explain clinical symptoms. There are targeted forms of genetic profiling, where an individual's genetic susceptibility to a particular multifactorial disease is estimated on the basis of a set of genetic variants across the genome.[8] Personal genome testing companies have been marketing multi-targeted testing for a

limited range of diseases.[9] Most present-day personal genome testing companies, however, offer non-targeted forms of genetic profiling: they genotype millions of SNPs and construct profiles that convey personal risks for a large and continuously increasing number of multifactorial diseases and other genetic traits.[2]

Quantity and complexity of information

Non-targeted forms of personal genome testing offer unequalled quantities of information on the basis of one single laboratory assay. There are companies that offer predictive information about dozens of multifactorial diseases and other phenotypic traits simultaneously.[3] These quantities of information may be too large for patients or consumers to process. The sheer amount of information conveyed by personal genome testing poses problems of information overload as well as feasibility issues with regard to informed consent requirements.

It is well-known from clinical genetic testing that genetic information is generally found to be complex. This is even more true in the context of multifactorial diseases, for not only are multiple genetic variants, each with their own effect sizes, involved in the causation of multifactorial diseases, there are also environmental factors at play. Multifactorial disease risks are probabilities: they are relative risks and may diverge only slightly from average population risks. Empirical studies have shown that many people find probabilistic information difficult to interpret.[17] People are inclined to perceive risks that are only slightly increased or decreased nonetheless in a dichotomous manner, as either 'high' risk or 'low' risk.[18] They have little prior knowledge of the genetics of multifactorial diseases,[19] and feel incapable of understanding complex genetic risk information.[20] In personal genome testing, for example, consumers may not always understand that negative test results or lower-than-average risks are no guarantee for remaining healthy. In non-targeted forms of testing, the problems of complex information are exacerbated by the enormous quantity of information.

Incidental findings

An implication of the current shift from targeted to non-targeted testing, is that non-targeted testing affects the ELSI-issue of incidental findings. Incidental findings are test outcomes that are unintended or unexpected, for example: SNP-data which are not yet of predictive ability, but may become so in the future as new SNP-disease associations are being discovered. In non-targeted testing, the potential for this type of incidental test outcomes is much greater than in targeted testing, simply because it yields a much larger data set, the significance of which is not yet fully understood. Consequently, ethical issues that have traditionally been associated with clinical genetic testing, such as problems with the disclosure of incidental or future findings and concurrent psychological risks, may at first glance become more urgent for non-targeted personal genome testing. The issue will be further discussed below (see cluster 1).

Test characteristic 2. Analytical validity

The analytical validity of a genetic test refers to the accuracy with which the laboratory assay measures the genetic variant it is designed to identify. This notion includes the capacity that the test will be positive if the genetic variant is present (analytic sensitivity), and negative if it is absent (analytic specificity).[21] In the ethical evaluation of clinical applications of genetic testing, the analytical validity has traditionally been a primary criterion.[22] It is derived from basic consumer rights: a genetic test, like any other product, ought to 'conform to contract' and be as described on its labelling.

Some of the early genetic profiling companies were selling nutritional supplements based on targeted genetic profiling tests of unproven analytical validity.[23,24] There has been a sharp critical debate,[25,26] and in many countries, regulatory bodies have become more alert on direct-to-consumer genetic testing services.[27,28] Presently, however, partly as a result of more responsible conduct of business, analytical validity is no longer a major topic in the ethical debate on personal genome testing. The new generation of personal

genome testing companies is analytically reliable,[4] such that most current "genomic assays have high sensitivity and specificity for measured genetic variants."[29] The industry strives for transparency and truth-in-advertising, and discloses detailed information on the technologies used for their laboratory assays.[5] Although the policy-making process is still ongoing, many companies have responded with improved analytical validity.

Test characteristic 3. Clinical validity

Whereas analytical validity refers to the quality of the laboratory assay, clinical validity is a criterion of the interpretation of assay results, a criterion of the test.[30] Clinical validity is measured by the predictive ability or discriminative power of the genetic variant: its ability to classify individuals as those who will develop the disease and those who will not.[21] Since the effects of SNPs on disease risks are so small, most current personal genome tests lack that discriminative power. By far the largest proportion of patients or consumers will demonstrate personal risks for multifactorial diseases that approximate the average population risk: these risks will prove to be only slightly lower or slightly higher.[31] A genetic profile that yields individual outcomes between 14% and 21% for major depressive disorder cannot be clinically meaningful when the average population risk is 17%. There will only be few consumers with absolute risks that diverge sufficiently from the average population risk to be clinically significant. Therefore, in contrast to that of clinical genetic testing for monogenic diseases, the clinical validity of genetic profiling for multifactorial diseases for the purposes of individual disease risk prediction, so far, has remained rather limited.

Statistical studies are finding that the addition of relatively significant SNPs to conventional risk models does not always improve their discriminatory power, for example: genetic information has not been capable of improving traditional prediction models for type 2 diabetes based on phenotypic risk factors and family history.[32][6] Genetic profiles are expected to gain some clinical validity in the future as they are refined and expanded to include more SNPs or other genetic variants, especially as they may become based on sequencing

technologies.[33] Further, with the inclusion of environmental factors into risk profiles for multifactorial diseases, their clinical validity may gradually increase even further.

Test characteristic 4. Clinical utility

In recent years, there have been conceptual discussions of the criterion of clinical utility, which has been widely used for the (ethical) evaluation of genetic screening programmes.[34] Roughly, there are three perspectives on utility: the public health perspective, the clinical perspective and, finally, the personal perspective,[35] which will be discussed in the next section. Within the public health perspective, in order to have utility, a genetic test must improve health outcomes in terms of morbidity or mortality on the societal level, be cost-effective, and produce benefits that outweigh the risks.[36] The principle of clinical utility requires test results to provide patients with 'actionable options' for prevention or treatment that are accessible and safe and that have been proven to be effective. From the clinical perspective, genetic information must alter clinical management, influence therapeutic decision-making, or lead to better prediction models.[37] Current personal genome testing for multifactorial diseases is not likely to pass the test in either perspective.

Within a clinical perspective, genetic profiling for, for example, type 2 diabetes may become clinically valid in the future, and thus capable of disclosing informative and reliable risks, but it may not necessarily become clinically useful. For it is not always clear what to do with a slightly increased personal risk of developing type 2 diabetes, or whether, say, a 28% absolute chance is a sufficient reason to take preventative action or to alter clinical management. Within a public health perspective, there are established preventive measures available for type 2 diabetes, such as weight loss, exercise, and smoking cessation. These measures are inexpensive, harmless and, in fact, beneficial to the whole of the population. Since it would be worthwhile to prescribe these measures to both high-risk and low-risk individuals for type 2 diabetes, however, the usefulness of the genetic test is minimal. As long as personal

genome tests continue to be of minimal clinical utility, they will not find their way into the clinic.

A personal perspective on utility

The third and personal perspective on clinical utility takes a broader and more subjective view, for it is defined by patients or consumers themselves. It allows for non-medical, particularly psychological motivations for genetic testing, such as solace,[38] family planning or preparation for the future.[29] In clinical genetics, non-medical motivations are often part of the counselling and decision-making processes, paradigmatically in genetic testing for Huntington's disease, for which there are no preventative or therapy options available. Such testing has 'clinical utility' from a personal point of view: test outcomes may offer either reassurance or certainty, and, subsequently, the psychological benefits of 'knowing' and the ability to make important life decisions, including, importantly, reproductive decisions. In the context of new technologies for genetic profiling, critics have proposed to broaden the concept of 'personal utility' much further, so as to include the value of 'information per se',[35] the desire to be reassured, and something like the fun aspect or the entertainment value of knowing about one's genes.

Changing interpretations

The clinical utility of genetic profiles is affected by a further test characteristic, namely that of changing assay interpretations. As genetics research proceeds, more and more gene-disease associations are discovered. Newly found genetic variants are included in ever more extended genetic profiles. As personal genome testing companies offer updates of their profiles, however, the companies' test outcomes are therewith subject to change over time.[39] On the basis of the same biological sample and the same laboratory assay, companies may present diverging, and even contradictory, test outcomes over time. A consumer reports:

“When I had my genome scanned a year and a half ago, using deCODEme's direct-to-consumer genotyping service, the results suggested my lifetime risk of having a heart attack was slightly higher than usual, at 1.12 times the average.

When I logged on to my profile again today, though, I discovered that my chances of developing the same condition now appear to have shot up: my relative risk is now 1.28, giving me a 62.7 lifetime risk of having a heart attack. [....] What has changed, however, is the data that the company uses to calculate genetic risk. In May, deCODEme added six new genetic variations to its algorithm for assessing its customers' risk of having a heart attack, on the back of new research."[40]

The probability of receiving contradictory results over time is quite high. A modelling study on genetic profiling for type 2 diabetes has shown that the update from one relatively strongly predictive SNP by an additional 17 less predictive SNPs, causes 34% of the study's population to switch risk categories either from above average risk to below average risk or vice versa.[41] Due to changing interpretations, personal genome tests yield fluid test results.[7]

Implications for the ELSI debate

In this section, the implications of the test characteristics of personal genome tests for the discourse on ELSI will be discussed. As shown above, the test characteristic of analytical validity is no longer a topic of major concern in the ELSI-debate since the advent of a new generation of personal genome testing services. Therefore, it will not be discussed any further. The three remaining test characteristics (together) do lead to four clusters of ELSI that are of importance to the current debate on personal genome testing in a direct-to-consumer context: informational problems, risks, regulatory issues and notions of utility.

Cluster 1. Non-targeted testing: The information problem

The most important ELSI-issues in personal genome testing are related to information. Within the ELSI-debate, it has already been argued that priority ought to be given to informational problems; critics have stated, for instance, that both public and professional institutions ought to take up the responsibility to inform the general public, to raise awareness of the risks of direct-to-

consumer genetic testing,[42] and to develop reliable information sources for consumers as well as physicians.[43] The previous section has brought to light a subset of test characteristics that together lead to the problem of information within non-targeted genetic profiling: quantity, complexity, and fluidity of information. The informational problem is associated with the practice of non-targeted genetic profiling itself, whether within or outside the clinic, now or in the future.[8]

Discussions of the difficulties surrounding the provision of genetic information are not new: in clinical genetic testing, patients are routinely offered extensive genetic counselling prior to consenting to undergo genetic testing. During counselling sessions, the patient receives detailed information about the disease, the genetic component thereof, the testing procedure, possible outcomes, therapeutic options, implications for reproductive choices and possibilities, consequences for the family, the communication of possible risks to relatives, social implications, privacy issues, potential adverse effects on employment and insurance, etc.[44] Ideally, a well-considered decision is made by the patient and informed consent is obtained on the basis of accurate and detailed information.

In targeted genetic profiling, it will not necessarily be difficult to meet these widely endorsed high standards for informed consent: in all likelihood, the genetic counsellor will be able to deal with most relevant aspects of genetic testing for any single multifactorial disease within the scope of a few counselling sessions. Non-targeted genetic profiling, however, poses the problem of exceptional quantities of information on dozens to over a hundred different diseases. It will be very arduous, if not impossible, to inform patients or consumers beforehand in detail on all relevant aspects for so many diseases without inducing information overload and therewith foregoing the actual aim of informed consent.[45]

The information problem will be even greater for whole-genome sequencing, which will reveal not only SNPs that are weakly associated with risks of multifactorial diseases, but also highly predictive mutations that cause monogenic diseases. As a consequence, the direct-to-consumer availability of whole-genome sequencing services might imply serious psychological risks as

well as health risks, and thus will have important ELSI-implications of its own. These issues, albeit pressing, are beyond the scope of this paper, which focuses specifically on personal genome testing in the context of multifactorial diseases.

Informed consent

Informed consent is intended to protect individuals against unwanted procedures and to acknowledge the individual's capability to decide for himself or herself whether or not to receive information with regard to their health status or to undergo a physical examination or intervention. Informed consent "allows individuals to exercise their fundamental right to decide whether and how their body, body parts and associated data will be used."[46] The right to respect for autonomous decision-making and the protection against misuse of human bodies are among the pillars of health care ethics [47] which hardly any of us will desire to give up. However, the feasibility of informed consent requirements is seriously threatened by the informational problems associated with personal genome testing.

There are three basic responses to the problem of informed consent: first, it could be argued that, if fully specific informed consent is not possible for non-targeted genetic profiling, these services ought not to be made available, at least not in any non-supervised, direct-to-consumer fashion.[13] Second, if it is acknowledged that full and accurate information is not always possible or even available in the genetics of multifactorial diseases, it could be concluded that the ideal of informed consent has become outdated and (for that domain of genetics) had best be abandoned altogether. Third, if it is accepted that the provision of information will necessarily be incomplete, it could be claimed that the procedure ought to focus on the information that is most necessary and indispensable for consumers to give valid consent and to effectively prepare themselves for personal genome testing. Versions of the third ethical position have already been proposed:[48-50] they are to serve the value of consumer autonomy, for they preserve access to personal genome testing and allow for liberty of choice. At the same time, they recognise that patients have a need for and a right to information - for without adequate information, freedom of choice is meaningless.

We also find the third position more convincing than the other two, and believe that informed consent is both possible and required for direct-to-consumer personal genome testing. Further discussion and research are needed to determine exactly what (selection of) information (and to what level of detail) is most crucial for valid informed consent. For example, patients or consumers may need to be informed beforehand in general terms about changing interpretations as a consequence of ongoing genetics research. Also, they may need to be made aware of ELSI-related differences between diseases or types of diseases. Finally, for instance, patients or consumers may need to be given the opportunity to decide in advance what kinds of genetic information they do and do not wish to receive as part of an informed consent process.

Information provision: pre-test and post-test

In personal genome testing for multifactorial diseases, consumers or patients are confronted with a double uncertainty: genetic risks in themselves are probabilistic, and the clinical validity and utility of these risks are doubtful. Patients or consumers are likely to experience difficulties not only during the process of informed consent, but also afterwards, when they receive and interpret their test outcomes. In recent years, there has been disagreement over the way in which test results ought to be provided in personal genome testing, particularly over the question whether face-to-face discussions with a genetic counsellor are deemed necessary. Some have stated that all genetic testing ought to be accompanied by genetic counselling,[51-54] in order to warrant accurate interpretations of test results.[9] Live discussions with genetic counsellors are required in complex cases, such as incidental findings. Others however have argued that "in the context of possible widespread introduction of genetic screening for common diseases, genetic counselling should be concentrated on those conditions that threaten life or have a serious impact on the ability to live life fully."[55] From the second position it follows that the need for face-to-face counselling does not apply to present-day personal genome testing for multifactorial diseases, for serious psychological impact is not to be expected (see cluster 3). This more liberal position, which we believe is preferable to the more stringent position, would allow providers of personal genome testing

services to suffice with the provision of adequate written information, both pre-test and post-test.

Information updates

Most companies or institutions tend to retain biological samples or genetic data sets from their clients or patients.[56] In the future, as new discoveries will occur within the field of human genetics, new and important disease risk information could potentially be deduced from the original data. It is still a matter for debate whether companies or institutions have a moral or legal duty to gather that information and to re-contact their clients or patients. Roughly, there are three possible stances: firstly, companies or physicians do have such moral duty and ought, for instance, to provide regular updates on the clinical interpretation of purchased genetic data sets. Secondly, consumers or patients may prefer to decide individually whether or not they wish to be contacted in the future, and on what conditions. They could be given the opportunity beforehand to express their wishes with regard to future findings. Thirdly, it is a moral responsibility of patients themselves to become or to remain informed on scientific proceedings or to re-contact their companies or physicians if they wish to obtain updated information. The distribution of moral responsibilities, we believe, may depend largely on contextual variables, discussion of which, however, is beyond the scope of this article. On a general level, we think that there are differences in the extent of moral responsibility between companies on the one hand and physicians or health care institutions on the other hand, since the latter can be said to have a stronger professional duty than the former to provide their patients with medical care and follow-up.

Incidental findings

Above, the increased potential for incidental findings has been mentioned for non-targeted personal genome testing. However, it could contrarily be argued that, in non-targeted testing, no finding is incidental. The aim of non-targeted testing is to convey a lot of information on the basis of one biological sample. Personal genome tests are marketed and presented to the public to include a wide variety of SNP-trait and SNP-disease associations, and companies tend to update risks and include more diseases as soon as new SNP-disease associations

have been validated.[10] If the aim is to look for everything, the notion of an incidental finding loses its original meaning. Keeping the patient or consumer perspective in mind, however, it is important to note that they may not always be prepared for finding everything: they may still be surprised by some of the (for them) incidental findings. It could be argued that they ought to be made aware of a right not to know certain (types of) information, as part of an informed consent process.

Cluster 2. Clinical validity and utility: Psychological risks, health risks and societal risks

Theoretically, there are three types of risks to be expected from personal genome testing, as a result of its limited clinical validity: psychological risks, health risks, and societal risks. First, the complexity of genetic information together with the limited predictive ability of the tests themselves, render personal genome testing susceptible to misunderstanding and misinterpretation. Consumers could feel worried about overestimated disease risks and could suffer from undue anxiety. Critics have worried that a class of 'worried well' might come into being,[57-59] especially since some present-day personal genome testing companies tend to exaggerate the clinical validity of their services.

On the other hand, we believe that adverse psychological effects that are well-known from clinical genetic testing, such as emotional distress, depression or survivor guilt as a result of test outcomes, are not to be expected from genetic profiling to the same extent.[60] As test outcomes for multifactorial diseases lack clinical validity, they are much more likely to lead to epistemic uncertainty than to the major psychological impact known from clinical genetics. Moreover, empirical research has shown that even genetic testing of high clinical validity, such as for hereditary breast or colorectal cancer syndromes, leads to much less psychological harm than traditionally thought.[61] The provision of genetic information of more limited clinical validity, such as in type 2 diabetes, appears not to adversely affect individuals at all.[62,63] Thus, the psychological risks involved in personal genome testing are likely to be overestimated. At the same time, however, we acknowledge that the potential for misinterpretation and

misunderstanding of complex genetic information cannot be stressed too frequently.

Secondly, it is frequently argued that there are health risks implied in personal genome testing for multifactorial diseases.[12,25] False reassurance on the basis of testing of limited clinical validity is thought to lead patients or consumers to adopt unhealthier lifestyles, to omit standard preventative measures, or to forego regular screening, thus causing harm to their health. The following example constitutes a worst-case scenario: there are companies that analyse sets of SNPs for calculating the risk of colorectal cancer.[11] These SNPs are associated with common, non-hereditary forms of colorectal cancer and are very weak risk factors of limited clinical validity. The genetic profile offered does not include highly penetrant mutations involved in the causation of 5-10% of cases of monogenic hereditary colorectal cancer syndromes.[64] Hypothetically, consumers from high-risk families could feel reassured on the basis of a few negative SNPs of limited clinical validity, whereas their genomes have not been analysed for other, higher-risk mutations. In reality, however, we expect that at-risk consumers are likely to present themselves at clinical genetics centres for testing, so these cases will be rare in a direct-to-consumer context. At present, there is no empirical evidence to back up the fear of false reassurance. There are indications that the impact upon lifestyle is minimal in most consumers of personal genome testing.[63] Thus, we believe that fears of health risks may be overstated.

Finally, there are at least two perceived societal risks involved in personal genome testing of low clinical validity: indirect economic risks, and loss of public confidence in genetics research and applications. Firstly, on the basis of personal genome test results, consumers may turn to their physicians for advice, follow-up research or medication. As the clinical validity of test results are uncertain, most of the follow-up will be unnecessary while it does drive up the costs of public health care.[15,65] Empirical studies suggest that consumers are indeed likely to consult their physicians for help with the interpretation of tests results obtained from personal genome testing companies.[16,20] Thus, private spending on direct-to-consumer personal genome testing may ultimately lead to higher collective costs of public health care. Secondly, it has been pointed out

that the commercial availability of personal genome testing before it has attained sufficient levels of clinical validity and utility, may undermine public trust in genetics medicine and research.[13,66] It is argued that present-day genetic profiles are of such limited clinical validity that consumers will be disillusioned with their purchase, which could deprive genetics research of its chances to flourish. Changing interpretations may pose further threats to the public perception of clinical utility of personal genetic information.[67]

Although personal genome testing implies its own potential societal risks, there is at least one such risk that has always been paramount to the ELSI-debate on clinical genetic testing, but that lacks ground in the context of genetic profiling for multifactorial diseases: the risk of discrimination or stigmatisation. Genetic profiles of limited clinical validity will not be of interest to insurance companies or employers due to their limited utility for the purposes of risk stratification.[68] Indeed, genetics professionals today generally consider the risk of genetic discrimination to be very low.[69][12] In spite of widespread concern among ELSI-researchers, we therefore think that the fears of discrimination and stigmatisation are not justified in the context of present-day personal genome testing.[13] We agree, however, that the risks of discrimination and stigmatisation will again be of relevance to the ELSI-debate if personal genome testing gains sufficient clinical validity and becomes capable of reliably discriminating between individuals with high and low risks of developing multifactorial diseases.

Cluster 3. Clinical validity: Regulatory issues

A third main ELSI associated with personal genome testing for multifactorial diseases is the legal and societal issue of regulation. The regulatory issue entails the ethical question whether it is morally justifiable to offer genetic tests of limited clinical validity and utility to the public, and if so, on what conditions. Within the regulatory debate, there are roughly two perspectives: the first emphasises the value of protection and the second that of autonomy and consumer choice. From within the first perspective, there have been calls for enhanced government oversight and regulation,[70-72] whereas the second

perspective prioritises respect for consumer liberty, to be complemented with governmental efforts to provide reliable information and to promote self-regulation of the market.[73,74]

Within the first perspective, there are two separate and sometimes conflated positions: the position that genetic tests of unclear informational significance ought not to be offered direct-to-consumer, and the position that genetic testing in general must not be made available commercially (see Table 2). The first position presupposes that personal genome tests are of inferior clinical validity, and that they cannot be said to yield medical information at all. Personal genome tests are considered to be flawed as medical tests, or even as informational products,[11] and thus, they ought not be put onto the market.[13] Contrarily, the second position presupposes that part of the information offered by direct-to-consumer personal genome testing companies may indeed be or become of clinical significance.[25,75] Analogous to clinical genetic testing, clinically valid direct-to-consumer personal genome testing is not without risk, it is claimed (see also cluster 2). Therefore, personal genome testing ought not to be made available commercially, outside of the clinic. Prior consultation of a physician or a genetic counsellor is or should be mandated in all genetic testing, in order to ensure adequate patient protection.

Within the second perspective, it can be maintained either that the risks of current direct-to-consumer personal genome testing of low clinical validity are not sufficiently serious to justify any infliction upon consumer autonomy and liberty of choice, or that the benefits of testing outweigh the risks (see Table 3). Either way, the second perspective states that patients or consumers ought to be allowed to make their own choices on the health care market, and that the availability of personal genome tests ought not to be restricted through government intervention. This means that even if there are psychological or health risks involved in personal genome testing for multifactorial diseases, competent consumers ought to be allowed, on the basis of adequate information, to make autonomous decisions regarding whether or not to undergo such testing.

Does personal genome testing have clinical validity?			
		Yes (or some)	No (or not sufficiently)
Does personal genome testing require regulation	Yes	Because of potentially adverse health impact, and psychological and societal risks, personal genome testing ought to be made available only under medical supervision	Because of the risks of over-interpretation and subsequent health risks, personal genome testing ought not to be allowed on the market
	No	The risks are only minor, whereas access to (potentially or partly) useful genetic information is important and ought not to be hindered by regulatory restrictions	Personal genome testing is to be considered an informational or recreational product: consumer information is sufficient to regulate the market and to protect consumers from any risks

Table 3. Four positions on clinical validity and regulatory requirements

We endorse the more liberal position within the regulatory debate, because we believe that the right to liberty of choice, where possible, must be respected in consenting adults. As discussed above, given the complexity and the quantity of the information, it will not always be easy for consumers to make rational and well-considered decisions with regard to the purchase of direct-to-consumer personal genome testing. We therefore believe that there are limits to the liberal position: providers may be required to make an extra effort to help their customers overcome the information problem.

Cluster 4. Clinical utility: A personal approach to utility

Some groups of consumers appear to be attracted to personal genome testing for multifactorial diseases: some of the first empirical studies suggest that consumer interest is rather high and growing.[20,76] Thus, it seems that personal genome tests as consumer products have some sort of value. Over the last few years, the concept of clinical utility has been widened in order to account for that value. Notions of personal utility have been explored,[35] and suggested in support of liberal attitudes towards direct-to-consumer personal genome testing.[77]

The notion of personal utility is not unequivocal: it refers to different kinds of values, some more weighty than others. Whereas personal utility can refer to values such as a desire for certainty, an opportunity to prepare for the future, or possibilities for reproductive decision-making (see test characteristic 4), there are also more 'frivolous' interpretations that align with the marketing rhetoric used by present-day personal genome testing companies. Apart from medical information, these companies offer genetic information about ancestry and other non-medical phenotypic traits, such as ear wax type, musculature type, eye colour or alcohol flush reaction. Personal genome testing services have been labelled 'recreational genomics'[16,78] and have been compared with astrology.[78] Not only are personal genetic tests marketed as a form of entertainment or even as a hobby,[79] they are also presented as "a ticket to some sort of insight that amuses, edifies or helps one find one's place in society."[80] On company websites, clients report having found out 'who they really are.'[14] Some companies stimulate consumers to share and compare their genetic make-up and to form online social networks around traits or medical conditions.

Critics have warned against the emphasis on the recreational value of personal genome testing: genetic tests cannot and must not be said to be purely (or even primarily) recreational when in fact they inform on (among other things) risks for serious medical conditions.[81] They have also questioned the capacities of consumers to assess personal utility. Consumers who believe that information obtained from personal genome testing is useful for them might have poor understanding and false expectations of the significance and the utility of that

information.[82] Consumers may stop to perceive personal utility after having been informed thoroughly on the benefits and risks of non-targeted forms of genetic profiling. Studies have found that many people indeed tend to lose interest in genetic testing after having been informed about the limitations thereof.[83-85][15] Thus, the notion of personal utility of such tests could be questioned, as it may be based not so much upon considered valuations of consumers, but rather upon misconceptions that could partly be rebutted through the provision of information. In the absence of any clinical validity, we think that personal approaches to clinical utility, especially in the context of testing for disease risks, are unjustified.

On the other hand, in the presence of sufficient, reasonable or increasing levels of clinical validity, we believe that a personal approach toward utility may indeed be sensible: consumers may wish to decide for themselves whether informative non-targeted genetic profiling is valuable for them, and in what way. The high standards of clinical utility that are used within public health care evaluations need not be identical to the standards applicable to individual consumer valuations of personal utility. For example, consumers may find personal utility in knowing their genetic risk for Alzheimer's disease, despite the absence of preventive options. This issue deserves further elaboration, which is beyond the scope of the present article.

Summary

For a well-informed and meaningful discourse on the ethical, legal and societal issues (ELSI) of present-day personal genome testing for multifactorial diseases, it is important to clarify the relevant test characteristics of personal genome tests. Test characteristics that are most essential to the current ELSI-debate are the following: non-targeted testing, high analytical validity, limited clinical validity, debatable clinical or personal utility, and the quantity, complexity and fluidity of the generated personal genetic risk information.

Non-targeted personal genome testing yields a vast amount of information that is complex and probabilistic, sometimes for a dozen to over a hundred

multifactorial diseases simultaneously. Further, test outcomes may change over time as providers include additional genetic variants in their algorithms. Quantity, complexity, and fluidity of genetic information together pose urgent problems with regard to the provision of information and informed consent. Providers of personal genome testing are facing these informational problems at several moments within the testing process: pre-test informed consent, post-test delivery of test results, and post-test dealing with future (incidental) findings and changing interpretations. There is a pressing need for well thought-out models for valid informed consent and information provision in the context of a lot of complex and fluid information in non-targeted personal genome testing.

Since personal genome testing is increasingly based on highly accurate and reliable genome-wide SNP-scanning technology and performed in high-quality laboratories, the test characteristic analytical validity has moved away from the centre of ELSI-discussions. Current debates are focused rather on the clinical validity and utility of genetic profiles for multifactorial diseases, which vary strongly, but are likely to increase given time. Awareness of the currently limited clinical validity is at the basis of both conservative and liberal stances within the regulatory discourse: it is used either as an argument in favour of stricter regulation, or as an argument against it.

The notion of clinical utility is challenged by personal approaches towards the significance and usefulness of genetic information. It is far from impossible that consumers continue to attribute personal utility to genetic information and pursue the acquisition of their genomic data even after having been informed about the current clinical limitations of genetic profiling for multifactorial diseases. Standards of clinical utility that are used for public health evaluations, however, need not be identical to those used for individual valuations of utility.

As a consequence of their limited clinical validity, present-day personal genome tests for multifactorial diseases have a much lower potential for adverse psychological effects than do clinical genetic tests for monogenic diseases. Neither do they imply as many health risks, or societal risks, such as discrimination, stigmatisation and misuse of genetic information by insurance companies or employers. This holds true only on the condition that the general

public as well as other stake-holding parties are sufficiently informed to understand the limitations to the clinical validity and utility of genetic profiling for multifactorial diseases, and are willing to act accordingly. In the future, as genetic profiles will attain more discriminative ability, both traditional psychological risks and concurrent health and societal risks will again be of concern to the discourse on ELSI.

The applicability and the relevance of ELSI-issues to the discourse on personal genome testing will fluctuate with the analytical and clinical validity of genetic profiles, with their clinical utility and with their being targeted or non-targeted. Thus, consideration of test characteristics is indispensable to any valuable ELSI-debate on personal genome testing for multifactorial diseases.

Notes

1. To the knowledge of the authors, the company Knome (pronounced as 'know me') is the only direct-to-consumer provider of whole-genome sequencing that offers (among other tests) risk profiling for multifactorial diseases. See: http://www.knome.com/ (Accessed June 13th, 2011)

2. See for example Navigenics at http://www.navigenics.com or Pathway Genomics athttp://www.pathway.com (Accessed June 13th, 2011)

3. See http://www.23andme.com (Accessed June 13th, 2011). In 2011, the company 23andme offered risk profiles for 195 diseases and other phenotypic traits. [The number of traits tested for increased monthly and reached 254 in 2013.] The company also provided ancestry and carrier status information. While most other direct-to-consumer personal genome testing companies are offering scans for no more than a few dozen diseases, they are likely to expand their services in the future rather than restrict them.

4. Most US-based companies collaborate with CLIA-certified laboratories, see for examplehttp://www.knome.com (Accessed June 13th, 2011). With the Clinical Laboratory Improvement Amendment (CLIA) of 1988, the US government has set quality standards for all laboratory tests, ensuring their accuracy, reliability, and timeliness.

5. The company 23andme states that it makes use of a chip which demonstrates over 99.9% reproducibility: “This means that if [the laboratory] ran the same DNA a second time on a new chip, more than 99.9% of the data would be the same compared to data from the first run.” https://www.23andme.com/you/faqwin/dataaccuracy/ (Accessed June 13th, 2011).

6. There are other diseases that are more promising for predictive genetic profiling: SNPs have been found to be associated with almost 3-fold risks for age-related macular degeneration (AMD). Genetic profiles for AMD have already been made available online (https://www.23andme.com/health/Age-related-Macular-Degeneration/techreport/, http://www.arcticdx.com/ (Accessed

June 13th, 2011)). Relatively strong predictive abilities such as those in genetic profiling for AMD are far from typical for common multifactorial diseases.

7. The fluidity of test results depends in part on the clinical validity of the existing profile: the higher that validity, the less likely it will change with the advancement of genetics research and the inclusion of additional markers.

8. The extent to which the problem of informed consent is present, however, will depend on various aspects, as it will be easier to effectively provide information, for instance, if the amount of diseases tested for is smaller.

9. As these statements have been written before current personal genome testing companies started to offer genome-wide non-targeted genetic profiling, it is not self-evident that the terms "all genetic testing" in these statements also include present-day commercial services.

10. See for example 23andme at http://www.23andme.com or Navigenics athttp://www.navigenics.com (Accessed June 13th, 2011).

11. See https://www.23andme.com/health/Colorectal-Cancer/ (Accessed June 13th, 2011)

12. Respondents were US cancer genetics professionals involved in highly predictive genetic testing for familial cancer syndromes. Respondents may be assumed to consider the risk of genetic discrimination to be lower in case of genetic profiling in the context of multifactorial diseases.

13. It should be noted that misuse and abuse of genetic risk information by employers or insurance companies cannot be excluded completely, for employers and insurance companies are susceptible to misinterpretation of genetic test results, and to overstatement of their significance.

14. See for example Pathway Genomics at http://www.pathway.com (Accessed June 13th, 2011).

15. These studies have been conducted in the context of genetic testing for highly predictive single-gene makers, such as BRCA1 and BRCA2. Women had been informed, for example, that genetic test results are often inconclusive and

that they are of unclear significance in the absence of a family history of breast cancer.[68,70] As the results provided by most genetic profiling services are much more uncertain, one would expect the effect of disappointment found in these studies to be increased for personal genome testing.

References

1. Lotta L.A. 2010. Genome-wide association studies in atherothrombosis. European Journal of Internal Medicine 21: 74-78.

2. Connell P.P., P.A. Keane, E.C. O'Neill et al. 2009. Risk factors for age-related maculopathy. Journal of Ophthalmology 360764.

3. Moore A.F. and J.C. Florez. 2008. Genetic susceptibility to type 2 diabetes and implications for antidiabetic therapy. Annual Review of Medicine 59: 95-111.

4. Wurtman R.J. 2005. Genes, stress, and depression. Metabolism: Clinical and Experimental 54: 16-19.

5. Pogribny I.P. 2010. Epigenetic events in tumorigenesis: putting the pieces together. Experimental Oncology 32: 132-136.

6. Distefano J.K. and D.M. Taverna. 2011. Technological issues and experimental design of gene association studies. Methods in Molecular Biology 700: 3-16.

7. Stolerman E.S. and J.C. Florez. 2009. Genomics of type 2 diabetes mellitus: implications for the clinician. Nature Reviews Endocrinology 5: 429-436.

8. Gollust S.E., B.S. Wilfond and S.C. Hull. 2003. Direct-to-consumer sales of genetic services on the Internet. Genetics in Medicine, 5: 332-337.

9. Borry P., M.C. Cornel and H.C. Howard. 2010. Where are you going, where have you been: a recent history of the direct-to-consumer genetic testing market. Journal of Community Genetics 1: 101-106.

10. Knoppers B.M., D. Avard and H.C. Howard. 2010. Direct-to-consumer genetic testing: driving choice? Expert Review of Molecular Diagnostics 10: 965-968.

11. Hall W. and C. Gartner. 2009. Direct-to-consumer genome-wide scans: astrologicogenomics or simple scams? American Journal of Bioethics 9: 54-56.

12. Kuehn B.M. 2008. Risks and benefits of direct-to-consumer genetic testing remain unclear. Journal of the American Medical Association 300: 1503-1505.

13. Melzer D., S. Hogarth, K. Liddell, T. Ling, S. Sanderson, R.L. Zimmern. 2008. Genetic tests for common diseases: new insights, old concerns. British Medical Journal 336: 590-593.

14. Offit K. 2008. Genomic profiles for disease risk: predictive or premature? Journal of the American Medical Association 299: 1353-1355.

15. Caulfield T. 2009. Direct-to-consumer genetics and health policy: a worst-case scenario? American Journal of Bioethics 9: 48-50.

16. Hunter D.J., M.J. Khoury and J.M. Drazen. Letting the genome out of the bottle - will we get our wish? New England Journal of Medicine 358: 105-107.

17. Hoffrage U., S. Lindsey, R. Hertwig and G. Gigerenzer. 2000. Communicating statistical information. Science 290: 2261-2262.

18. Cameron L.D., K.A. Sherman, T.M. Marteau and P.M. Brown. 2009. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. Health Psychology 28: 307-316.

19. Smerecnik C.M.R., I. Mesters, N.K. de Vries and H. de Vries. 2008. Educating the general public about multifactorial genetic disease: applying a theory-based framework to understand current public knowledge. Genetics in Medicine 10: 251-258.

20. McGuire A.L., C.M. Diaz, T. Wang and S.G. Hilsenbeck. 2009. Social networkers' attitudes toward direct-to-consumer personal genome testing. American Journal of Bioethics 9: 3-10.

21. Teutsch S.M., L.A. Bradley, G.E. Palomaki et al. 2009. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group. Genetics in Medicine 11: 3-14.

22. Haddow J.E. and G.E. Palomaki. 2003. ACCE: A model process for evaluating data on emerging genetic tests. In: Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease. M.J. Khoury, J. Little and W. Burke (eds). New York, NY: Oxford University Press (pp. 217-233).

23. Janssens A.C.J.W., M. Gwinn, L.A. Bradley et al. 2008. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. American Journal of Human Genetics 82: 593-599.

24. Government Accountability Office (GAO). 2006. Nutrigenic testing: Test purchased from four Web sites mislead consumers. GAO.

25. Bowen D.J., K.M. Battuello and M. Raats. 2005. Marketing genetic tests: empowerment or snake oil? Health Education and Behavior 32: 676-685.

26. Mykitiuk R. 2004. Caveat emptor: direct-to-consumer supply and advertising of genetic testing. Clinical Investigative Medicine 27: 23-32.

27. Editor. 2008. Control of direct-to-consumer genetic testing. Lancet 372: 1360.

28. Wadman M. 2008. Gene-testing firms face legal battle. Nature 453: 1148-1149.

29. Khoury M.J., C.M. McBride, S.D. Schully et al. 2009. The Scientific Foundation for Personal Genomics: recommendations from a National Institutes of Health - Centers for Disease Control and Prevention multidisciplinary workshop. Genetics in Medicine 11: 559-567.

30. Zimmern R.L. and M. Kroese. 2007. The evaluation of genetic tests. Journal of Public Health 29: 246-250.

31. Janssens A.C.J.W. and C.M. van Duijn. 2008. Genome-based prediction of common diseases: advances and prospects. Human Molecular Genetics 17: R166-173.

32. van Hoek M., A. Dehghan, J.C.M. Witteman et al. 2008. Predicting type 2 diabetes based on polymorphisms from genome-wide association studies: a population-based study. Diabetes 57: 3122-3128.

33. Janssens A.C.J.W. and C.M. van Duijn. 2010. An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 1: 10.

34. EGAPP: http://www.egappreviews.org/about.htm

35. Grosse S.D. and M.J. Khoury. 2006. What is the clinical utility of genetic testing? Genetics in Medicine 8: 448-450.

36. Sanderson S., R. Zimmern, M. Kroese, J. Higgins, C. Patch and J. Emery. 2005. How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. Genetics in Medicine 7: 495-500.

37. Janssens A.C.J.W., M. Gwinn, R. Valdez, K.M.V. Narayan and M.J. Khoury. 2006. Predictive genetic testing for type 2 diabetes. British Medical Journal 333: 509-510.

38. Schwartz P.H. 2009. The value of information and the ethics of personal-genomic screening. American Journal of Bioethics 9: 26-27.

39. Shirts B.H. and L.S. Parker. 2008. Changing interpretations, stable genes: responsibilities of patients, professionals, and policy makers in the clinical interpretation of complex genetic information. Genetics in Medicine 10: 778-783.

40. Consumer genomics: your genes don't change, but your disease risk still might. http://journalisted.com/article/zvrp

41. Mihaescu R., M. van Hoek, E.J.G. Sijbrands et al. 2009. Evaluation of risk prediction updates from commercial genome-wide scans. Genetics in Medicine 11: 588-594.

42. Gurwitz D. and Y. Bregman-Eschet: Personal genomics services: whose genomes? European Journal of Human Genetics 17: 883-889.

43. McGuire A.L. and W. Burke. 2008. An unwelcome side effect of direct-to-consumer personal genome testing: raiding the medical commons. Journal of the American Medical Association 300: 2669-2671.

44. Kääriäinen H., M. Hietala, U. Kristoffersson et al. 2008. Recommendations for genetic counselling related to genetic testing. EuroGentest Unit 3.

45. de Wert G. and W. Dondorp. 2006. Ethical issues. In: Prenatal Medicine. M. van Vugt and K. Shulman (eds). New York/London: Taylor & Francis (pp. 575-604).

46. Cambon-Thomsen A., E. Rial-Sebbag and B.M. Knoppers. 2007. Trends in ethical and legal frameworks for the use of human biobanks. The European Respiratory Journal 30: 373-382.

47. Beauchamp T.L. and J.F. Childress. 2008. Principles of Biomedical Ethics (6th edition) New York, NY: Oxford University Press.

48. Manson N.C. and O. O'Neill. 2007. Rethinking Informed Consent in Bioethics. Cambridge: Cambridge University Press.

49. Veatch R.M. 2007. Implied, presumed and waived consent: the relative moral wrongs of under- and over-informing. American Journal of Bioethics 7: 39-41.

50. da Rocha A.C. and J.A. Seoane. 2007. Alternative consent models for biobanks: the new Spanish law on biomedical research. Bioethics 22: 440-447.

51. Council of Europe. 2008. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes.

52. McCabe L.L. and E.R.B. McCabe. 2004. Direct-to-consumer genetic testing: access and marketing. Genetics in Medicine 6: 58-59.

53. OECD. 2007. Guidelines for quality assurance in molecular genetic testing.

54. Nuffield Council on Bioethics. 2006. Genetic Screening: A Supplement to the 1993 Report. London: Nuffield Council on Bioethics (p.43).

55. McNally E., A. Cambon-Thomsen, C. Brazell et al. 2004. 25 Recommendations on the ethical, legal and social implications of genetic testing. European Commission.

56. Tutton R. and B. Prainsack. 2011. Enterprising or altruistic selves? Making up research subjects in genetics research. Sociology of Health and Illness 33(7): 1081-1095.

57. Almond B. 2006. Genetic profiling of newborns: ethical and social issues. Nature Reviews Genetics 7: 67-71.

58. Jonsen A.R., S.J. Durfy, W. Burke and A.G. Motulsky. 1996. The advent of the "unpatients". Nature Medicine 2: 622-624.

59. McGuire A.L., M.K. Cho, S.E. McGuire and T. Caulfield. 2007. The future of personal genomics. Science 317: 1687.

60. Pearson H. 2008. Genetic testing for everyone. Nature 453: 570-571.

61. Heshka J.T., C. Palleschi, H. Howley, B. Wilson and P.S. Wells. 2008. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. Genetics in Medicine 10: 19-32.

62. Pijl M., D.R.M. Timmermans, L. Claassen et al. 2009. Impact of communicating familial risk of diabetes on illness perceptions and self-reported behavioral outcomes: a randomized controlled trial. Diabetes Care 32: 597-599.

63. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534.

64. Lynch H.T. and A. de la Chapelle. 2003. Hereditary colorectal cancer. New England Journal of Medicine 348: 919-932.

65. Human Genetics Commission (HGC). 2003. Genes Direct: Ensuring the Effective Oversight of Genetic Tests Supplied to the Public. London: HGC.

66. Patch C., J. Sequeiros and M.C. Cornel. 2009. Genetic horoscopes: is it all in the genes? Points for regulatory control of direct-to-consumer genetic testing. European Journal of Human Genetics 17: 857-859.

67. Aldhous P. 2009. Gene predictions tell an ever-changing story. New Scientist.

68. Janssens A.C.J.W., M. Gwinn, R. Valdez, K.M.V. Narayan and M.J. Khoury. 2006. Predictive genetic testing for type 2 diabetes. British Medical Journal 333: 509-510.

69. Huizenga C.R., K. Lowstuter, K.C. Banks, V.I. Lagos, V.O. Vandergon and J.N. Weitzel. 2010. Evolving perspectives on genetic discrimination in health insurance among health care providers. Familial Cancer 9: 253-260.

70. Gezondheidsraad (Health Council of the Netherlands). 2008. Screening between Hope and Hype. The Hague: Health Council of the Netherlands.

71. Human Genetics Commission (HGC). 2007. More Genes Direct: A Report on New Developments in the Availability, Marketing and Regulation of Genetic Tests Supplied Directly to the Public. London: HGC.

72. Javitt G.H., E. Stanley and K. Hudson. 2004. Direct-to-consumer genetic tests, government oversight, and the first amendment: what the government can (and can't) do to protect the public's health. Oklahoma Law Review 57(2): 251-324.

73. Council for Public Health and Health Care of the Netherlands (RVZ): Screening and the Role of the Government. The Hague: RVZ.

74. Ries N.M. and D. Castle. 2008. Nutrigenomics and ethics interface: direct-to-consumer services and commercial aspects. OMICS 12: 245-250.

75. Gollust S.E., B.S. Wilfond and S.C. Hull. 2003. Direct-to-consumer sales of genetic services on the Internet. Genetics in Medicine 5: 332-337.

76. Kolor K., T. Liu, J. St Pierre and M.J. Khoury. 2009. Health care provider and consumer awareness, perceptions, and use of direct-to-consumer personal genomic tests, United States, 2008. Genetics in Medicine 11: 595.

77. Hsu A.R., J.L. Mountain, A. Wojcicki and L. Avey. 2009. A pragmatic consideration of ethical issues relating to personal genomics. American Journal of Bioethics 9: 1-2.

78. van Ommen G.B. and M.C. Cornel. 2008. Recreational genomics? Dreams and fears on genetic susceptibility screening. European Journal of Human Genetics 16: 403-404.

79. Lee S.S. and L. Crawley. 2009. Research 2.0: social networking and direct-to-consumer (DTC) genomics. American Journal of Bioethics 9: 35-44.

80. Esposito K. and K. Goodman. 2009. Genethics 2.0: phenotypes, genotypes, and the challenge of databases generated by personal genome testing. American Journal of Bioethics 9: 19-21.

81. Angrist M. 2009. We are the genes we've been waiting for: rational responses to the gathering storm of personal genomics. American Journal of Bioethics 9: 30-31.

82. Bunnik E., A.C.J.W. Janssens and M. Schermer. 2009. How attitudes research contributes to overoptimistic expectations of personal genome testing. American Journal of Bioethics 9: 23-25.

83. Green M.J., B.B. Biesecker, A.M. McInerney, D. Mauger and N. Fost. 2001. An interactive computer program can effectively educate patients about genetic testing for breast cancer susceptibility. American Journal of Medical Genetics 103: 16-23.

84. Lindor N.M., J. Sloan, R. Goldberg et al. 2004. Colorectal tumour microsatellite instability test results: perspectives from patients. Hereditary Cancer in Clinical Practice 2: 69-75.

85. Schwartz M.D., J. Benkendorf, C. Lerman, C. Isaacs, A. Ryan-Robertson and L. Johnson. 2001. Impact of educational print materials on knowledge, attitudes, and interest in BRCA1/BRCA2: testing among Ashkenazi Jewish women. Cancer 92: 932-940.

Chapter 5

The role of disease characteristics in the ethical debate on personal genome testing

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Abstract

Background

Companies are currently marketing personal genome tests directly-to-consumer that provide genetic susceptibility testing for a range of multifactorial diseases simultaneously. As these tests comprise multiple risk analyses for multiple diseases, they may be difficult to evaluate. Insight into morally relevant differences between diseases will assist researchers, healthcare professionals, policy-makers and other stakeholders in the ethical evaluation of personal genome tests.

Discussion

In this paper, we identify and discuss four disease characteristics - severity, actionability, age of onset, and the somatic/psychiatric nature of disease - and show how these lead to specific ethical issues. By way of illustration, we apply this framework to genetic susceptibility testing for three diseases: type 2 diabetes, age-related macular degeneration and clinical depression. For these three diseases, we point out the ethical issues that are relevant to the question whether it is morally justifiable to offer genetic susceptibility testing to adults or to children or minors, and on what conditions.

Summary

We conclude that the ethical evaluation of personal genome tests is challenging, for the ethical issues differ with the diseases tested for. An understanding of the ethical significance of disease characteristics will improve the ethical, legal and societal debate on personal genome testing.

Background

A growing number of personal genome testing services are presently available that estimate genetic susceptibility to multifactorial diseases.[1] Unlike genetic tests for monogenic diseases, susceptibility tests for multifactorial diseases can be obtained almost exclusively on the direct-to-consumer market. Personal genome tests are non-targeted: they determine a person's risk for a multitude of multifactorial diseases simultaneously,[2-5] including cardiovascular disease, Alzheimer's disease, osteoporosis, type 2 diabetes, schizophrenia, and many types of cancer. One of the leading personal genome testing companies is currently estimating personal risks for over two hundred diseases and other phenotypic traits in one single test.[2] The large quantity of test results will have limited clinical significance for and varying emotional impact on consumers, which are in part connected with differences between the diseases tested for.

Differences between diseases may have important implications for the ethical, legal and societal debate on genetic susceptibility testing for multifactorial diseases (for the remainder of this paper we will use the term 'susceptibility testing'), whether it is offered as part of a personal genome test or on its own, for a single disease, whether within the clinic or on the direct-to-consumer market. The offering, for instance, of susceptibility testing for less severe diseases for which there are preventive options available may be morally acceptable, whereas the same test for severe diseases in the absence of treatment options may not. Personal genome tests may comprise both severe and less severe diseases and may as a whole thus be difficult to evaluate. In recent years, a range of ethical, legal and societal issues has been touched upon in professional and academic discussions on genetic testing, such as privacy issues, psychological impact, regulatory issues, and informed consent.[6-8] These issues however may not arise in all susceptibility tests that are offered within one personal genome test. Privacy issues, for example, may be more pressing for genetic tests for psychiatric diseases than for somatic diseases, and the psychological impact of testing may be more serious in severe diseases than in less severe diseases. With this paper, we propose a systematic approach to the ethical evaluation of susceptibility testing, which considers differences between

diseases and which explains what ethical issues are to be addressed, on the basis of disease characteristics.

As in this paper we focus explicitly on *disease* characteristics and their impact on the ethical debate, we do not elaborate upon characteristics of the *test*, such as clinical validity and clinical utility. Genetic susceptibility tests differ from pre-symptomatic tests for monogenic diseases: they indicate risk rather than diagnosis and are generally of limited to moderate clinical validity and utility. Clinical validity and utility are of paramount importance to the ethical, legal and societal debate, but have already been addressed elsewhere.[8,9] Test characteristics and disease characteristics, however, are not entirely separable and may interact with one another as well as among themselves, as will be pointed out in the discussion.

The ethical debate may benefit from a better understanding of morally relevant differences between diseases. For national health care systems, policy-makers, healthcare professionals, physicians, companies or other stakeholders who are considering the offering or the regulation of susceptibility testing, it is important to be aware of differences between diseases or types of diseases, because susceptibility tests for different diseases may be connected with different ethical issues and may warrant different ethical evaluations. This poses challenges to an industry that is increasingly offering personal genome tests that consist of more and more susceptibility tests for more and more diseases rather than single susceptibility tests for single diseases. The insights offered in this paper are also anticipatory of future developments, and apply equally to susceptibility testing based on array technologies and to susceptibility testing based on exome or whole-genome sequencing technologies.

First, we will present and discuss a list of key disease characteristics that are crucial to the ethical appraisal of genetic susceptibility testing for multifactorial diseases. Then we will discuss susceptibility testing for three diseases, type 2 diabetes mellitus, age-related macular degeneration and clinical depression, and ethical issues that must be taken into account in the evaluation of such tests.

Discussion

Disease characteristics and their associated ethical issues

We have conducted a review of the biomedical and bioethical literature and identified three existing normative frameworks, one for clinical genetics [10] and two for population genetic screening programmes, namely the Wilson and Jungner criteria [11] and the ACCE model,[12] which take into account differences in disease characteristics and their impact on the ethical evaluation of testing. Not all disease characteristics or consequences of testing that are mentioned in the three frameworks, however, are applicable to genetic susceptibility testing for multifactorial diseases. For example, while characteristics such as the prevalence of the disease [13] or the population health impact [11] are relevant from a public health perspective, they are arguably less relevant for the ethical evaluation of susceptibility testing in individuals. Further, implications for relatives or availability of a follow-up plan [10] have been formulated in the context of clinical genetic testing for monogenic diseases and do not readily apply to testing for multifactorial diseases, where test results so far have been - and are likely to continue to be - of limited clinical validity and utility.

On the basis of an ethical analysis, we have identified four disease characteristics that are specifically relevant to the ethical evaluation of susceptibility testing: severity, actionability, age of onset, and the distinction between psychiatric and somatic diseases. These characteristics are morally relevant because they are directly connected with three of the four major bioethical principles: beneficence, non-maleficence and respect for autonomy.[14] Beneficence is the medical professional's duty to care, to do well, and to act in patients' interests. The principle of non-maleficence specifies that a medical professional should refrain from doing needless harm. Respect for a person's autonomy implies roughly that patients should be allowed to make their own voluntary, informed choices with regard to their health management. For the purposes of this paper, we leave aside the fourth principle, that of justice, because we focus on the justifiability of the provision of susceptibility testing to an individual rather than on societal, distributive issues that surround healthcare on a collective level.

Below, we will discuss the four characteristics and describe how they give rise to ethical issues.

It is important to note at the outset of our discussion that internationally recognised guidelines on the provision of genetic testing [15,16] demand that medical supervision and genetic counselling are made available in genetic testing. The guidelines apply to genetic testing that is 'offered in a clinical context'[15] and genetic testing 'for health purposes',[16] respectively. It is therefore unclear whether these guidelines apply also to direct-to-consumer genetic testing or to genetic testing for purposes other than health. Both guidelines do specify that the form and the extent of genetic counselling "shall be defined according to the implications of the results of the test"[16] and "should be proportionate and appropriate to the characteristics of the test, the test limitations, the potential for harm, and the relevance of test results to individuals and their relatives."[15] In our discussion, we will follow the idea that counselling requirements should be proportional and show how disease characteristics play a role in determining the appropriate level of counselling and medical care.

Disease characteristic 1. Severity

Severity of a disease refers to the morbidity and mortality brought about by the disease. In clinical genetics, the severity of the disease affects the emotional, psychological and social impact of genetic test results. Disease severity therefore has consequences for the ethical requirement to offer good care (beneficence)[14] in the form of genetic counselling and psychological support. It is recommended that extensive pre- and post-test genetic counselling is mandated in all cases of severe hereditary disease.[10] One could argue that for severe diseases, where the anticipated psychological impact and the potential for harm are greater than for less severe diseases, as a general rule, more information, guidance and care are morally required.

The severity of a disease, however, is not always easy to determine: diseases tend to express differently from one individual to the next. High levels of

phenotypic variability may cause genetic susceptibility test results to leave patients or consumers with substantial uncertainty with regard to the severity as well as the onset of the disease. These uncertainties may pose challenges for the provision of pre- and post-test information on personal genome testing and for its informed consent processes. Thus, disease severity affects the ethical issues of information, informed consent, genetic counselling, guidance and care.

Disease characteristic 2. Actionability

There are potential harms involved in genetic testing, such as health risks (e.g. unnecessary follow-up), psychological risk (e.g. anxiety) and social risks (e.g. financial costs, discrimination). Therefore, in the ethical evaluation of genetic testing and screening services, a favorable balance between risks and benefits, i.e. between the principles of beneficence and non-maleficence, has traditionally been a central criterion.[11] The availability of therapeutic interventions constitutes a major benefit and a rationale [9,11] for genetic testing or screening. With part of medicine's focus shifting from cure to prevention over the last few decades,[17] however, the notion of treatment has come to include other 'meaningful actionable options',[18] which were added primarily to include reproductive decision-making. The more contemporary ACCE framework introduces preventive options and actions as possible benefits of screening: it requires that there be "an effective remedy, acceptable action, or other measurable benefit."[12] In the context of personal genome testing, with its wide variety of diseases tested for, actionability has become a more appropriate notion than treatability.

For susceptibility testing, prevention is argued to be one of the main purposes and potential benefit.[2,3,17] Prevention may indeed constitute a benefit to both the individual and society and an argument for the moral acceptability of susceptibility testing. It should be noted that in order for preventive measures to be effective, compliance is essential. Compliance is generally promoted when preventive options are simple and morally or psychologically acceptable.[19] The daily taking of supplementary vitamins, for example, is likely to be accepted

and carried out much more easily than more intrusive measures, such as medication with side-effects or a radical change of diet.

However, it is not at all clear that susceptibility testing contributes or will contribute to the prevention of multifactorial diseases.[20] If it does not or will not, its major rationale will lack ground, and therewith, it may not be able to reach the morally required balance of benefits and risks. An alternative rationale for susceptibility testing and potential benefit could be the personal utility [19] that consumers find in knowing their genetic information. It has been found that disease risk information obtained from a screening programme may serve psychological or personal purposes, such as relief from uncertainty,[21] solace, the value of knowing. Whether personal utility on its own could provide a sufficient argument for the ethical acceptability of genetic susceptibility testing or personal genome testing, is still a topic for discussion.[22]

Disease characteristic 3. Age of onset

Through predictive genetic testing, it has become possible for individuals to know their genetic risk before the onset of symptoms of disease. Knowledge of genetic risk for late-onset disease may cause anxiety and distress. Not everyone wishes to obtain such knowledge.[23]

One of the classic ethical principles within clinical genetics is therefore the right not to know, which is derived from respect for autonomy.[24] Especially in children the right not to know is a recurrent issue, because adverse psychological and social effects of predictive genetic testing for late-onset diseases may be severe in children,[25] and also because children are considered incapable or less capable of making autonomous choices. It is generally agreed upon that in the absence of medical necessity, predictive genetic testing for late-onset diseases must be postponed until adulthood, when young adults have attained the ability to make autonomous decisions.[25] Exceptions are sometimes made when the clinical geneticist finds that the child or adolescent has sufficient cognitive ability to participate in decision-making and when the child's medical or other interests may weigh up against potential harms.[21] In

clinical genetic practice, however, children and minors are more often refused than allowed predictive genetic testing for late-onset diseases.[26] These ethical principles may be equally applicable to genetic susceptibility testing for late-onset multifactorial diseases in children or minors.

The distinction between early-onset and late-onset of disease, however, cannot be so readily made in biological reality. In the pathogenesis of most multifactorial diseases, genetic and non-genetic risk factors act and interact over time to cause evolving stages of disease. In such a 'cascade model' of disease,[27] the age of onset cannot always be pinpointed straight-forwardly. Whereas the disease itself (e.g. symptoms of type 2 diabetes) may not become manifest before adulthood or even old age, certain risk factors (e.g. overweight) or early stages of disease (e.g. pre-diabetes) may be present already in youth. Naturally, genetic risk factors are present at conception. Since the first steps towards disease may already be made before birth or in early childhood, the notion of onset of disease could become less clear. In children or minors who already demonstrate certain risk factors or early stages of disease, genetic susceptibility testing for these diseases, even though they have traditionally been considered late-onset, could arguably be morally acceptable.

Disease characteristic 4. Psychiatric/somatic distinction

There are at least three morally relevant differences between somatic and psychiatric diseases that may lead to ethical issues. Firstly, knowledge of genetic risks for psychiatric diseases could "undermine or weaken a person's sense of integrity and well-being" even before the appearance of symptoms.[28] Psychiatric diseases can change patients' perceptions of the world, their behaviours, desires, opinions and goals, their relationships, and who they are. The potentially greater psychological impact of genetic testing for psychiatric diseases may require a higher potential for medical benefit and higher standards for genetic counselling than those used for somatic diseases.[28]

Secondly, psychiatric diseases are associated with stigma to a greater extent than somatic diseases.[29,30] Stigma may lead to social and societal problems, such as

disturbed family or personal relations, or discrimination at the workplace or in the context of (health) insurance. The level of stigmatisation varies with the disease and partly determines the level of psychological and social risk involved.[31] Genetic susceptibility testing is thought capable of increasing rather than decreasing stigma associated with psychiatric diseases.[32] A high risk of stigma and subsequent psychological harm will increase the required potential for (medical) benefit as well as the need for good care and counselling.

Thirdly, it has been suggested that genetic testing itself or a positive test result may become a self-fulfilling prophecy, a 'trigger event' for the psychiatric disease tested for.[33] Moreover, the manner in which the disease is understood by the patient (e.g. "it is in my genes, therefore it is an inevitable aspect of myself") is likely to reflect on and modulate the development of the disease itself.[34] Thus, genetic testing could have unforeseen negative effects on the disease itself.

It is important to note here that the psychiatric/somatic distinction has a somewhat different status than the other disease characteristics. Modulated by actionability and severity, genetic testing for psychiatric diseases may be accompanied by a varying likelihood of adverse psychological consequences and thus bring the principle of non-maleficence into play to a varying extent. This way, disease characteristics may sometimes combine to lead to ethical issues. They should not be considered in isolation, but rather with an eye for their dynamic relations.

In conclusion, there is not yet much experience with (clinical) genetic testing for psychiatric diseases. Through personal genome testing, the practice of risk prediction for psychiatric diseases is currently taking shape, but the field and its ethical issues are largely unexplored. Due to the complexities in aetiology, and the societal and psychological sensitivities that surround psychiatric diseases, genetic testing for such diseases requires a careful approach, with special attention to ethical issues.

Three diseases: how disease characteristics affect the ethical debate

We have identified four key disease characteristics that are relevant to the ethical evaluation of susceptibility testing: severity, actionability, age of onset, and the psychiatric/somatic distinction. In this section, we analyse how these disease characteristics influence the ethical issues surrounding susceptibility testing for three multifactorial diseases, namely type 2 diabetes, age-related macular degeneration (AMD) and clinical depression. These diseases are illustrative of both the disease characteristics and the main ethical issues surrounding susceptibility testing, whether it be offered in a clinical setting or directly-to-consumer. Our main question is whether and on what conditions it would be morally justifiable to offer individual susceptibility testing to children and adults. Key elements of the discussion are summarised in Table 4.

Disease 1. Type 2 diabetes: variable severity and possibilities for early preventive intervention

Genetic susceptibility testing services for type 2 diabetes have already been made available directly-to-consumer both as targeted tests and as part of non-targeted personal genome tests.[2,35] While both physicians and consumers have been found to respond favorably to the idea of direct-to-consumer genetic testing for type 2 diabetes susceptibility,[36] experts are not convinced of its current clinical validity and utility.[37,38]

Type 2 diabetes is a somatic disease of varying severity. In its initial stages, it generally causes relatively mild symptoms, but on the long term, diabetes may cause kidney failure, blindness and neuropathy of the extremities, and it may cause premature death. As known non-genetic risk factors, such as overweight and pre-diabetes, are increasingly affecting the young,[39] type 2 diabetes can no longer simply be considered a late-onset disease. There are both therapeutic options and well-established preventive strategies available for type 2 diabetes, for children as well as for adults, at the level of lifestyle improvements.

Disease characteristic	Ethical principles	Relation characteristic/principle: Ethical issues to consider
Severity	Beneficence Non-maleficence	High severity → high potential for medical benefit, high risk of psychological harm
Actionability	Beneficence Non-maleficence	High actionability → high potential for (medical) benefit Moderate actionability → risk of psychological harm (e.g. victim-blaming or feelings of guilt) Low actionability → risk of psychological harm (emotional impact of test result)
Age of onset	Respect for autonomy	Late age of onset → right not to know in adults and children
Psychiatric/somatic	Non-maleficence	Psychiatric diseases: more risk of harm because of stigma; more risk of harm because of psychological impact

Table 4. Disease characteristics and their relations to ethical principles: Ethical issues to consider

The variability of the severity of type 2 diabetes poses difficulties for the ethical evaluation of susceptibility testing for the disease. From a precautionary perspective, it could be argued that type 2 diabetes should be viewed as a severe disease and require high levels of genetic counselling and psychological support. However, empirical research has shown that on the short term genetic susceptibility testing for type 2 diabetes hardly causes any psychological harm or emotional impact at all,[40,41] thus suggesting that consumers may not experience increased personal risk for type 2 diabetes as severe, and that requirements for counselling in order to prevent psychological harm may be less stringent. There may be discrepancies between the severity of a disease as perceived by medical professionals and the severity of the same disease as perceived by other publics. Questions regarding standards of severity may be interesting topics for further (ethical) research.

Further, the existence of preventive options for type 2 diabetes implies a potential for medical benefits to be obtained from susceptibility testing. Preventive options consist in general health recommendations, such as a healthy diet, regular physical exercise, weight loss, and smoking cessation. As a consequence, if false reassurance occurs, it may lead to harm. Individuals who are found to be at decreased risk may wrongly feel assured that they will remain free from disease, regardless of their lifestyles.[42] They may fail to understand that general health recommendations are relevant to the whole of the population, including low-risk subgroups. Low-risk individuals may ignore these recommendations and consequently put their health conditions at risk. The risk of false reassurance should be taken into account in the consideration of an offer of susceptibility testing for type 2 diabetes to adults or children.

The actionability of a test is not only a characteristic of the disease tested for, but is influenced by other factors, as well, notably the clinical validity of the test. As preventive measures in type 2 diabetes are identical to general health recommendations that apply to the entire population, it follows that it is unclear whether there is any use for susceptibility testing.[37] The actionability of susceptibility testing may nonetheless be twofold: it may motivate high-risk individuals to adhere to general health recommendations [42] and it may be used to target preventive strategies, guidance, care and monitoring by

healthcare professionals, at those who are likely to be most in need. Any clinical utility - any potential for medical benefit - will only be realised on the condition of established clinical validity, which today has not been fulfilled.

Moreover, in the context of a limited or moderate clinical validity, preventive measures ought not to be too burdensome or too strongly associated with health risks, psychological or societal risks. When the benefits of preventive action are uncertain, the risks should be minimal in order to assure proportionality. In the case of type 2 diabetes, preventive measures are likely to be acceptable to most consumers: they may not always be easy to adopt, but they do not entail health risks or side effects. Adequate post-test counselling could help to improve the implementation of behaviour change and thus actionability.

At the same time, the window of opportunity for preventive action is expanding at present. Given that childhood obesity may not only cause severe morbidity in the young,[43] but is also an independent risk factor for adult obesity [44] and subsequent diseases (e.g. type 2 diabetes), it may be sensible to start the prevention of adult obesity or type 2 diabetes already in childhood. It is still unclear whether and what childhood interventions will prove effective,[43,45] and whether genetic susceptibility testing for type 2 diabetes will gain clinical validity and will prove to be of added value over and above clinical risk factors for the identification of at-risk individuals.[38] If it can be established that early interventions yield levels of medical benefit that could not be otherwise attained, and that genetic testing can be useful for the targeting of interventions at subgroups of high-risk children, a favourable risk-benefit ration for testing in childhood might ensue. In that case it could become rational and morally justifiable to test children for their genetic susceptibility to type 2 diabetes. This will also depend on other ethical issues, such as psychological harms: at-risk children who do not adhere to lifestyle recommendations and develop the disease later in life may blame themselves or be blamed by others. Such 'victim-blaming' or feelings of guilt will not always be justified in the context of a multifactorial disease for which susceptibility testing is of moderate predictive ability: some at-risk individuals may develop the disease even if they take appropriate measures, whereas other at-risk individuals may not fall ill despite

their failing to take preventive action. These risks must be weighed against the potential medical benefits.

In conclusion, while the age of onset may be difficult to determine for type 2 diabetes and the disease is rather severe, it is actionable. There is currently insufficient evidence to support an offer of genetic susceptibility testing for type 2 diabetes to children or minors. Susceptibility tests are presently of insufficient clinical validity and utility [38] in order to justify such an offer. For adults, however, it could be argued that in the absence of clear harms, the potential for benefit need not be great in order to justify genetic testing, on the condition, naturally, of adequate ethical safeguards such as adequate information provision, informed consent, quality assurance and privacy protection, and provided the test has a reasonable predictive ability. Stringent requirements for counselling may not be necessary to protect against psychological harm, but post-test counselling may be helpful to improve actionability and to protect against the risk of false reassurance.

Disease 2. Age-related macular degeneration: very late onset

There have been optimistic reports on the feasibility of testing for genetic susceptibility to age-related macular degeneration (AMD),[46,47] and several personal genome testing services including AMD have already been put onto the direct-to-consumer market.[2,48,49] Genetic susceptibility tests for AMD are considered to be of substantial clinical validity, and are expected to eventually outperform and improve or replace existing prediction models.[50]

AMD is a leading cause of vision loss worldwide.[51] It is a somatic disease of (very) late onset that generally progresses slowly. Although end-stage AMD may entail serious vision loss and brings along a fair amount of morbidity, the disease is not life-threatening. Furthermore, there are treatment options (e.g. laser therapy) and preventive options (specific vitamin supplements, smoking cessation, the wearing of sunglasses) available for AMD.[52] Although the preventive measures are safe, they do not seem to be very effective.[53]

Given the late age of onset and the absence of opportunities for primary preventive action in childhood or adolescence, there are no medical reasons for childhood genetic testing. Therefore, it is preferable to postpone genetic testing for AMD until maturity, when young adults can make a more informed and autonomous decision whether or not to undergo testing and can provide informed consent. Thus, children's and minors' rights not to know their genetic risk can be protected.

As AMD tends not to strike until old age, psychological and social risks of genetic testing are likely to remain limited. Although there are no effective preventive options, given the availability of treatment options, the moderate severity and the (very) late onset of the disease, susceptibility testing for AMD will not give rise to very many ethical issues in consenting adults. Testing for AMD may become a morally acceptable practice in the clinic or on the direct-to-consumer personal genome testing market, depending largely on the ways in which further ethical issues are dealt with, such as quality assurance, information provision and informed consent, which are beyond the scope of this paper.

Disease 3. Clinical depression: psychiatric disease, stigma, and psychological risk

Potential consumers have expressed high interest in genetic susceptibility testing for clinical depression.[54] They have also indicated to be interested in such testing for their children.[55] Several companies are offering susceptibility testing for clinical depression directly to consumers.[56,57] The clinical validity of susceptibility testing for clinical depression has not been established.[58]

Clinical depression can present itself at any age.[52] While non-genetic risk factors for depression, such as emotional neglect or negative emotional experiences in early youth, high stress levels, major life events, and drug abuse, have been identified, they are notoriously difficult to avoid. As of yet, no feasible, effective primary preventive strategies have been established for depression, neither in children nor in adults. The disease varies in severity, but

is generally considered to be relatively severe.[52] For severe diseases, it could be argued, susceptibility tests are morally required to be of sufficient clinical validity, because low or moderately predictive testing for severe diseases would leave the tested individual with high degrees of uncertainty in the light of a fearful medical scenario. This could cause psychological harm to the patient and so violate the principle of non-maleficence. Since, as of yet, the level of clinical validity in susceptibility testing for depression has not proven sufficient, the ethical acceptability of a testing offer is not clear.

Companies are increasingly marketing pharmacogenomic testing for drug response directly to consumers, also in the context of psychiatric diseases.[2,59] One company is offering a combination of susceptibility testing and pharmacogenomics testing for anti-depressant response.[56] Such combinations of susceptibility testing and pharmacogenomic testing are a new development on the direct-to-consumer genetic testing market. Theoretically, they may increase the actionability of the test and decrease the perceived severity of the disease tested for, and thus bring more benefit and less harm to individuals than would single susceptibility tests. On the other hand, however, this development may not be without risk. In the absence of evidence of clinical validity - and there is no such evidence for pharmacogenomic testing for antidepressant response [60] - potential for medical benefit is not likely to materialise. Sensitivities and risks surrounding genetic testing for psychiatric diseases should be weighed carefully.

It has been hypothesised that susceptibility testing for psychiatric diseases be made available to children.[33] Children who are tested to be at increased risk could be provided with ‘pre-symptomatic interventions’,[33] it is claimed, consisting of advice about avoiding environmental stress, or prophylactic medication. However, in the absence of feasible primary preventive options, predictive testing is not likely to yield any medical benefit for children. Genetic information about psychiatric diseases may have an unknown effect on the child's “developing sense of self and future prospects,”[31] and may even become a self-fulfilling prophecy.[33] As long as clinical validity and utility are lacking, and taking into account moral considerations such as non-maleficence

and the right not to know, there are no convincing reasons to justify the offering of genetic testing for clinical depression risk to children or minors.

In conclusion, in addition to its variable age of onset, relatively high level of severity, and unclear preventive options, clinical depression is characterised by its psychiatric rather than somatic nature. The disease is endowed with stigma, and knowledge about one's susceptibility may cause psychological risks (see disease characteristic 4). Given the lack of 'actionability', genetic testing for depression may bring more harm than benefit onto persons. As long as uncertainty prevails regarding the psychological implications of genetic susceptibility testing for psychiatric diseases, a cautious approach may be warranted, even in consenting adults. More research into the psychological and social consequences of personal genome testing for depression and other psychiatric diseases will be needed.

Summary

We have identified four disease characteristics that are relevant to discussions on the ethical issues surrounding genetic susceptibility testing for multifactorial diseases: severity, age of onset, actionability and the somatic or psychiatric nature of the disease. These characteristics are linked to important ethical principles and work together to affect the ethical debate. For example, the potential for adverse psychological and social consequences of genetic testing for late-onset diseases (harm) is greater in the context of diseases that are both severe and have no actionable options. In such cases testing poses greater ethical challenges.

As a general ethical rule of thumb, the likelihood and seriousness of possible harms, including psychological and social harms, should weigh up against the likelihood and magnitude of the potential (medical) benefits of testing. Severity and actionability are therefore relevant disease characteristics. Moreover, severity, actionability and the somatic/psychiatric distinction affect the requirements for good pre- and post-test counselling, such that, for example, genetic susceptibility testing for psychiatric diseases will require careful

psychological counselling. In children, the right not to know must be protected, which means that late-onset disease should not be tested for, unless there is a clear advantage (a positive benefit-risk ratio) for the child.

We have discussed these disease characteristics and the resulting ethical issues for three exemplary diseases, type 2 diabetes, age-related macular degeneration (AMD) and clinical depression. First, a broader perspective may be appropriate on the age of onset in type 2 diabetes to encompass accumulating risk factors and preclinical stages of disease throughout life. Genetic susceptibility testing for type 2 diabetes may eventually become acceptable even in children and minors, depending foremost on the clinical validity of the test, but also on the actionability of the test result, and on the manner in which 'age of onset' is conceptualised. Potential for medical benefit must be weighed against psychological harms and moral wrongs, such as infringements upon the right not to know. For adults, genetic susceptibility testing for type 2 diabetes may be acceptable under certain conditions. Second, we have described AMD as a less severe somatic disease of very late onset. We have concluded that not many ethical issues are to be expected from susceptibility testing for AMD in consenting adults, whether within a clinical context or on the direct-to-consumer market. Third, clinical depression is understood to be a psychiatric disease with a variable age of onset, a relatively high level of severity and unclear actionability. Genetic information on psychiatric diseases is associated with specific ethical issues, such as stigma and possible adverse psychological consequences, that warrant a very careful consideration of genetic testing for psychiatric diseases.

As a general conclusion we contend that a critical attitude is needed towards personal genome testing services that offer 'packages' of risk estimates for a multitude of multifactorial diseases simultaneously, because, as we have argued, different ethical issues apply to different diseases, depending on their characteristics. As some personal genome testing companies are offering genetic test results for a multitude of diseases that differ from one another with regard to the disease characteristics that we have identified,[2] consumers are confronted with test results that vary in emotional impact and thus pose different requirements for pre- and post-test information and counselling. The

ethical evaluation of such broad testing is therefore highly complex. Susceptibility tests for some diseases, such as AMD, can justifiably be offered within directly-to-consumer personal genome testing. For other diseases, on the other hand, it may not even be morally acceptable to include a genetic susceptibility test at all, or only on the condition of professional counselling. Finally, many tests may not be morally justifiable in the case of children, because of a late onset of the disease and a lack of actionability. Further research will be needed in order to establish a sensible subdivision of those broad 'packages' into clusters of diseases with similar characteristics, so as to allow for parallel ethical evaluations of clusters of susceptibility tests within a single personal genome test. Such parallel ethical evaluations should point out what clusters of tests may or may not justifiably be offered, and on what conditions.

When whole-genome sequencing becomes widely accessible to patients and consumers, and yield disease risks not only for multifactorial diseases but also for monogenic diseases, these problems are likely to increase even further. It will not be easy to conduct an overall ethical evaluation of personal genome testing on the basis of whole-genome sequencing, or to determine the appropriate and morally required level of genetic counselling, care and psychosocial support.

Although other aspects of genetic susceptibility testing, such as the more technical properties of the test or specific aspects of the context in which testing is offered, may be equally important to its ethical evaluation, we think that an understanding of ethically relevant disease characteristics will prove helpful for further ethical discussions on genetic susceptibility testing and personal genome testing for multifactorial diseases.

References

1. Borry P., M.C. Cornel and H.C. Howard. 2010. Where are you going, where have you been: a recent history of the direct-to-consumer genetic testing market. Journal of Community Genetics 1: 101-106.

2. 23andme: http://www.23andme.com.

3. Navigenics: http://www.navigenics.com.

4. Genetic Health: http://www.geneticheath.com.

5. Knome: http://www.knome.com.

6. American College of Medical Genetics (ACMG) Board of Directors 2008. ACMG Statement on direct-to-consumer genetic testing.

7. European Society of Human Genetics (ESHG). 2010. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. European Journal of Human Genetics 18: 1271-1273.

8. Bunnik E.M., M.H.N. Schermer and A.C.J.W. Janssens. 2011. Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. BMC Medical Ethics 12: 11.

9. Burke W., L.E. Pinsky and N.A. Press. 2001. Categorizing genetic tests to identify their ethical, legal, and social implications. American Journal of Medical Genetics 106: 233-240.

10. Kääriäinen H., M. Hietala, U. Kristoffersson et al. 2008. Recommendations for genetic counselling related to genetic testing. EuroGentest Unit 3.

11. Wilson J.M.G. and G. Jungner. 1968. Principles and Practice of Screening for Disease. Geneva: World Health Organization.

12. Haddow J.E. and G.E. Palomaki. 2003. ACCE: A model process for evaluating data on emerging genetic tests. In: Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and

Prevent Disease. M.J. Khoury, J. Little and W. Burke (eds). New York, NY: Oxford University Press (pp. 217-233).

13. Centers for Disease Control and Prevention (CDC): Public Health Genomics: http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm.

14. Beauchamp T.L. and J.F. Childress. 2008. Principles of Biomedical Ethics (6th edition). New York, NY: Oxford University Press.

15. OECD. 2007. Guidelines for quality assurance in molecular genetic testing. OECD.

16. Council of Europe. 2008. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes.

17. Larsen L.T. 2010. Is prevention better than cure? Public health policy and the circular structure of learning. SSRN eLibrary.

18. Health Council of the Netherlands (Gezondheidsraad). 1994. Genetische Screening. The Hague: Health Council of the Netherlands [in Dutch].

19. Council of Europe. 1994. Recommendation No. R (94) 11 on Screening as a Tool of Preventive Medicine.

20. Janssens A.C.J.W. and C.M. van Duijn. 2010. An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 1: 10.

21. Robertson S. and J. Savelescu. 2001. Is there a case in favour of predictive genetic testing in young children? Bioethics 15: 26-49.

22. Grosse S.D., C.M. McBride, J.P. Evans and M.J. Khoury. 2009. Personal utility and genomic information: look before you leap. Genetics in Medicine 11: 575-576.

23. Morrison P., S. Harding-Lester and A. Bradley. 2011. Uptake of Huntington disease predictive testing in a complete population. Clinical Genetics 8(3): 281-286.

24. Council of Europe. 1996. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine).

25. Borry P., L. Stultiens, H. Nys, J. Cassiman and K. Dierickx. 2006. Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers. Clinical Genetics 70: 374-381.

26. Duncan R.E., J. Savulescu, L. Gillam, R. Williamson and M.B. Delatycki. 2005. An international survey of predictive genetic testing in children for adult onset conditions. Genetics in Medicine 7: 390-396.

27. Boenink M. 2009. Molecular medicine and concepts of disease: the ethical value of a conceptual analysis of emerging biomedical technologies. Medicine, Health Care and Philosophy 13: 11-23.

28. Nuffield Council on Bioethics. 1998. Mental Disorders and Genetics: the Ethical Context. London: Nuffield Council on Bioethics.

29. Spriggs M., C.A. Olsson and W. Hall. 2008. How will information about the genetic risk of mental disorders impact on stigma? The Australian and New Zealand Journal of Psychiatry 42: 214-220.

30. Phelan J. 2002. Genetic bases of mental illness - a cure for stigma? Trends in Neuroscience 25: 430-431.

31. Hoop J.G. 2008. Ethical considerations in psychiatric genetics. Harvard Review of Psychiatry 16: 322-338.

32. Mitchell P.B., B. Meiser, A.Wilde et al. 2010. Predictive and diagnostic genetic testing in psychiatry. Clinics in Laboratory Medicine 30: 829-846.

33. Newson A.J. 2009. Depression under stress: ethical issues in genetic testing. British Journal of Psychiatry 195: 189-190.

34. Berghmans R., J. de Jong, A. Tibben and G. de Wert. 2009. On the biomedicalization of alcoholism. Theoretical Medicine and Bioethics 30: 311-321.

35. deCODEme: http://www.decodeme.com.

36. Grant R.W., M. Hivert, J.C. Pandiscio et al. 2009. The clinical application of genetic testing in type 2 diabetes: a patient and physician survey. Diabetologia 52: 2299-2305.

37. Janssens A.C.J.W., M. Gwinn, R. Valdez, K.M.V. Narayan and M.J. Khoury. 2006. Predictive genetic testing for type 2 diabetes. British Medical Journal 333: 509-510.

38. Mihaescu R., J. Meigs, E. Sijbrands and A.C.J.W. Janssens. 2011. Genetic risk profiling for prediction of type 2 diabetes. PLoS Currents 3: RRN1208.

39. Williams D.E., B.L. Cadwell, Y.J. Cheng et al. 2005. Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999-2000. Pediatrics 116: 1122-1126.

40. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534.

41. Pijl M., D.R.M. Timmermans, L. Claassen et al. 2009. Impact of communicating familial risk of diabetes on illness perceptions and self-reported behavioral outcomes: a randomized controlled trial. Diabetes Care 32: 597-599.

42. Frosch D.L., P. Mello and C. Lerman. 2005. Behavioral consequences of testing for obesity risk. Cancer Epidemiology, Biomarkers and Prevention 14: 1485-1489.

43. Ebbeling C., D. Pawlak and D. Ludwig. 2002. Childhood obesity: public-health crisis, common sense cure. Lancet 360: 473-482.

44. Must A. 1996. Morbidity and mortality associated with elevated body weight in children and adolescents. The American Journal of Clinical Nutrition 63: 445S-447S.

45. Monasta L., G.D. Batty GD, A. Macaluso et al. 2010. Interventions for the prevention of overweight and obesity in preschool children: a systematic review of randomized controlled trials. Obesity Reviews 5: e107-118.

46. Despriet D.D.G., C.C.W. Klaver, C.C. van Duijn and A.C.J.W. Janssens. 2007. Predictive value of multiple genetic testing for age-related macular degeneration. Archives of Ophthalmology 125: 1270-1271.

47. Maller J., S. George, S. Purcell et al. 2006. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. Nature Genetics 38: 1055-1059.

48. Macula Risk: http://www.macularisk.com.

49. Genetic Diagnostic Laboratory: http://www.med.upenn.edu/genetics/core-facs/gdl.

50. Seddon J.M., R. Reynolds, J. Maller et al. 2008. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. Investigative Ophthalmology and Visual Science 50: 2044-2053.

51. World Health Organization (WHO). 2008. The Global Burden of Disease: 2004 Update.

52. Evans J. 2008. Antioxidant supplements to prevent or slow down the progression of AMD: a systematic review and meta-analysis. Eye 22: 751-760.

53. Wong I.Y.H., S.C.Y. Koo and C.W.N. Chan. 2011. Prevention of age-related macular degeneration. International Ophthalmology 31: 73-82.

54. Wilde A., B. Meiser, P.B. Mitchell and P.R. Schofield. 2009. Public interest in predictive genetic testing, including direct-to-consumer testing, for susceptibility to major depression: preliminary findings. European Journal of Human Genetics 18: 47-51.

55. Laegsgaard M.M., A.S. Kristensen and O. Mors. 2009. Potential consumers' attitudes toward psychiatric genetic research and testing and factors influencing their intentions to test. Genetic Testing and Molecular Biomarkers 13: 57-65.

56. Gene Planet: http://www.geneplanet.com.

57. Map my Gene: http://www.mapmygene.com.

58. Demirkan A., B.W.J.H. Penninx, K. Hek et al. 2011. Genetic risk profiles for depression and anxiety in adult and elderly cohorts. Molecular Psychiatry 16:773-783.

59. The Mayo Clinic: http://www.mayoclinic.org/depression.

60. Keers R. and K.J. Aitchison. 2011. Pharmacogenetics of antidepressant response. Expert Review of Neurotherapeutics 11: 101-125.

Chapter 6

Informed consent in direct-to-consumer personal genome testing: The outline of a model between specific and generic consent

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Abstract

Broad genome-wide testing is increasingly finding its way to the public through the online direct-to-consumer marketing of so-called personal genome tests. Personal genome tests estimate genetic susceptibilities to multiple diseases and other phenotypic traits simultaneously. Providers commonly make use of Terms of Service agreements rather than informed consent procedures. However, to protect consumers from the potential physical, psychological and social harms associated with personal genome testing and to promote autonomous decision-making with regard to the testing offer, we argue that current practices of information provision are insufficient and that there is a place – and a need – for informed consent in personal genome testing, also when it is offered commercially. The increasing quantity, complexity and diversity of most testing offers, however, pose challenges for information provision and informed consent. Both specific and generic models for informed consent fail to meet its moral aims when applied to personal genome testing. Consumers should be enabled to know the limitations, risks and implications of personal genome testing and should be given control over the genetic information they do or do not wish to obtain. We present the outline of a new model for informed consent which can meet both the norm of providing sufficient information and the norm of providing understandable information. The model can be used for personal genome testing, but will also be applicable to other, future forms of broad genetic testing or screening in commercial and clinical settings.

Introduction

It is generally agreed that informed consent is ethically required for biomedical research on human subjects, for medical interventions and for medical testing, including genetic testing. Outside the realm of medicine, however, the ethical requirement of informed consent is less self-evident. In the context of direct-to-consumer personal genome testing (PGT), the academic debate on the role and requirements of informed consent is still in its infancy.

PGT is a broad form of genetic testing, based on an analysis of a large set of markers across the genome, for multiple diseases simultaneously. The current generation of PGT companies offers genetic susceptibility testing for dozens to hundreds of diseases and other phenotypic traits, in one single test, on a commercial basis.[1] Consumers can order these tests online, take cheek swab samples themselves, at home, and receive their genetic test results on a secure web page a few weeks later. Some companies require that test kits are ordered through a physician,[2] others do not.[3]

Some PGT services include 'recreational genomics',[4] tests 'fun' traits such as ear wax type or the ability to smell the fragrance of asparagus in urine. Most of the susceptibilities conveyed through PGT, however, are those for common complex diseases, such as type 2 diabetes, psoriasis, schizophrenia, age-related macular degeneration, osteoporosis and many types are cancer, which are caused by an interplay of genetic and non-genetic factors. Susceptibility genes tend to explain only part of the genetic contributions to the development of diseases and tests do not include environmental or lifestyle factors. As a result, many of them are of limited predictive value and are not evidently capable of reducing disease burden or improving health or wellbeing.[5]

Over the last couple of years, however, PGT providers have been expanding their testing offers and some are now including for instance testing for APOE variants [6] that may substantially increase the individual's risk of Alzheimer's disease and have serious emotional impact on consumers. The impact on consumers will multiply when PGT becomes based on whole-genome sequencing technologies, through which not only genetic markers indicating

susceptibility to complex diseases can come to light but also, for instance, rare mutations and carrier status associated with monogenic diseases.

Over the last few years, the provision of PGT has been criticised for the lack of clinical validity and utility,[7] for direct-to-consumer access and lack of professional counselling and medical care,[8] for the enormous quantities of genetic information yielded within one PGT and as well as associated problems of misinterpretation by consumers and subsequent health risks and psychological risks.[9] These three dimensions – lack of clinical validity and utility, lack of professional supervision and quantity of information – together pose challenges to the ethical requirements of pre-test information provision and informed consent.

Informing consumers about all the diseases and traits tested for, and about the test characteristics and associated risks and limitations, involves large quantities of complex genetic information that are notoriously difficult for consumers to process,[10] especially in the absence of professional assistance, so that informed consent hardly seems possible. Overwhelming consumers with information will only undermine the attempt to adequately inform them.

More fundamental to the feasibility issues is the question whether the requirement of informed consent should apply at all in the commercial setting in which PGT is currently offered. It is not self-evident that medical-ethical concepts and practices can be translated directly to the very different commercial context of direct-to-consumer PGT.

With this paper, we aim to specify the role of informed consent in direct-to-consumer PGT. We will first present our conception of informed consent and its moral aims for PGT generally – whether offered through a medical professional or directly-to-consumers – and then discuss the question whether informed consent is morally required in the purely commercial, direct-to-consumer context of PGT. In the second part of the paper we will discuss how the information problems in PGT generally might be addressed. We will describe two leading approaches to the realisation of informed consent, and show how they fail to resolve the informational issues associated with PGT. Therefore, in the last section, we will outline an approach to informed consent that we will

argue has a fair chance of meeting the moral aims of informed consent in (direct-to-consumer) PGT.

An ethical conception of informed consent in personal genome testing

The wide usage of informed consent in many different clinical and non-clinical settings has led to a range of different conceptions of informed consent.[11] One basic classificatory distinction is that between narrow conceptions which emphasise disclosure of information and documentation of consent, and broader conceptions which stress the aspects of communication and comprehension.[12] In contrast to narrow 'narration-followed-by- signature'[13] conceptions of informed consent, the broader, ethical dimension focuses rather on patients' self-determination and self-governance, tries not only to inform but also to establish understanding,[14] and invites patients to actively participate in medical decision-making processes. This paper focuses on adequately *informed* and autonomous consent rather than on adequately *documented* consent.

The moral aims of informed consent are twofold: protection against harm, deceit or coercion,[15] and the enabling of autonomous decision-making.[16] First of all, the locus of potential harms – and 'that for which consent is given' – is not so much the taking of the test itself (the taking of a blood, saliva or cheek swab sample or the laboratory analysis of the sample) but rather *the generating and receiving* of genetic test results. On the one hand, generating genetic test results without consent would violate the individual's privacy. On the other hand, *the receiving* of genetic information may have strong emotional impact on and adverse (long-term) psychological and social consequences for patients,[17] including stigmatisation and discrimination in matters of employment or insurance, as is well-known from clinical genetics. Whereas some empirical studies suggest that the potential for harm in PGT is limited,[18] anecdotal evidence has been reported of severe and long-term anxiety following *direct-to-consumer* PGT (including predictive testing for Alzheimer's disease) outside the medically supervised research context.[19]

As many present-day PGT services include a diverse and expanding set of diseases,[20] ranging from highly complex to monogenic diseases, as well as from more and less serious diseases, the direct emotional and social impact of PGT – what we will call 'direct harm' – is no longer negligible. The level of direct harm is likely to vary with the characteristics of the tests (e.g. clinical validity) and the diseases tested for (e.g. availability of preventive or treatment options) in a given PGT.[21] Clearly, for example, PGT based upon exome- or whole-genome sequencing will be associated with a higher level of direct harm, including adverse effects on employment or insurability.

Another important concern is that in the absence of genetic counselling, consumers may misinterpret the nature of PGT test results and erroneously attribute high levels of clinical validity and utility to them.[22] Under- or over-interpretation of test results may lead to what we will call 'indirect harm', such as psychological harm (e.g. anxiety), health risks and social costs: consumers may make harmful healthcare decisions on the basis of misinformation, by taking undue action, such as the seeking of unnecessary follow-up or medications on the one hand,[23] or by refraining from due action, such as through the continuation of an unhealthy lifestyle or the foregoing of regular screening on the other hand.[24] Informed consent can inform prospective consumers beforehand about the significance and implications of possible results, and therewith mitigate indirect harms.

The second moral aim of informed consent is that of enabling and promoting autonomous decision-making or autonomous authorisation.[25] It is based on the idea (or ideal) of patients or consumers who, with sufficient understanding and in absence of the exercise of control by others, intentionally authorise providers to conduct genetic testing. Above all, informed consent aims to protect against involuntary testing and the violation of privacy. The online, private and direct-to-consumer delivery model in PGT entails an increased risk of consumers sending in biological materials from *third parties without their knowing*. A requirement of informed consent given by the very person whose sample is sent in for testing, may help to prevent involuntary testing and to promote autonomous authorisation of testing.

Moreover, from the point of view of autonomous decision-making, informed consent aims at protection against deceit,[26] and respecting patients' or consumers' autonomy. By adequately informing consumers on the nature of the service instead of, for instance, exaggerating its clinical usefulness and downplaying its limitations,[27] PGT providers would be refraining from deceit and expressing respect for autonomy. In order to 'make an understanding and enlightened decision'[28] about whether or not to undergo testing, autonomous consumers need relevant and truthful pre-test information about the PGT, and they need to comprehend that information.[29] As for very broad genetic tests it will be impossible to provide *all* information, it must be determined what information – and how much information – is 'material'[30] for informed consent in PGT.

In the literature, a distinction has been made between physician-based and patient-based standards for the contents of informed consent. In the United Kingdom, for example, physicians are required by law to 'disclose' to patients 'what a reasonable and careful doctor would disclose'.[31] In the Netherlands as well as in the United States, case law formulates that physicians are obliged to tell patients *what a reasonable patient would want to know* in order to come to a decision.[32] The idea of a patient-based standard has originally been part of an emancipation process:[33] given that information is meant to help patients make reasoned decisions in line with their own goals and values, *they themselves*, rather than 'reasonable physicians', should indicate what information they need. However, as not all patients will have the exact same informational needs, ideally, the 'reasonable person' standard should be elaborated even further, such that the individual patient – or in the case of PGT, the individual consumer – may decide what information is relevant to his or her process of decision-making and informed consent. As an 'individual person standard' will in practice not be fully feasible, it should rather be thought of as an ethical ideal.

Is there a place at all for informed consent in the context of direct-to-consumer PGT?

Given the 'imperial' historical track record of informed consent, it seems only natural that it applies also to direct-to-consumer PGT. There are however at least two reasons for scepticism with regard to the suitability of informed consent in a commercial context. First, it could be argued that commercial companies should be governed by less stringent moral standards than those of the medical profession. Commercial providers do not have a professional moral duty of care and beneficence to the same extent as do physicians. They have not taken an oath to act in the interest of consumers, or to positively promote their health and wellbeing. Their moral obligations and responsibilities consequently are much more limited than those of medical professionals. In many countries, including those of the EU and the USA, companies are legally held to meet certain standards in their advertising activities (truth-in-advertising) and in the presentation and packaging of their products (truth-in-labelling). These requirements are aimed at the protection of consumers against deceit or harm. No more, it could be argued, could or should be asked of commercial businesses.

Indeed, PGT companies tend to align with the regulatory field of commerce rather than that of medicine: they feature Terms of Service (TOS) agreements on their websites instead of informed consent.[34] Consumers are urged to tick a box before purchase: they are held to have read, understood and agreed to the TOS 'by clicking "accept" below.'[35] Although TOS are not aimed at the protection of consumers but at the legal protection of companies themselves, they can be – and in many cases they are being – used also as a tool for information provision. In their small print, TOS generally do contain disclaimers that convey information about risks and potentially adverse consequences for consumers.[36] A combination of truth-in-advertising, truth-in-labelling and TOS, it could be argued, should thus be sufficient for information provision and protection of consumers in the context of commercial PGT.

The second reason for scepticism is that it is not obvious that PGT is a form of medical testing at all. Companies are presenting themselves as providers of

informational or educational services rather than medical tests.[37] Through TOS, consumers are often explicitly advised not to act medically upon PGT test results, and to consult their physicians in case they have any questions about specific health problems.[38] From this point of view, a purchase of a PGT may be seen as a type of sales-contract, analogous to contracts for consumer goods or financial services, such as mortgages or all-in holiday packages.[39] The larger the mutual (legal) risks associated with such complex products, the higher the need for TOS. Likewise, since PGT is not a form of medical testing but a potentially risky consumer service, companies may thus claim, informed consent is not necessary and TOS should suffice.

Neither argument is convincing. To start with the latter, it would be untenable to consider PGT a purely educational or informational commercial service. Although TOS may state otherwise, the promotional slogans that are shown prominently on PGT companies' websites, such as 'take a more active role in managing your health' [40] and 'this knowledge leads to better lifestyle and health decisions',[41] are indeed suggestive of the idea that PGT is clinically valid and clinically useful and thus a form of medical testing. More importantly, in its current (and anticipated future) form, part of it is.

PGT services consist roughly of three groups of susceptibility tests:[42] firstly, tests for non-medical ('fun') traits such as alcohol flush reaction, freckling, memory or muscle performance; secondly, tests for complex diseases of limited clinical validity and utility, such as type 2 diabetes, osteoporosis, cardio-vascular diseases or schizophrenia; and thirdly, tests of higher clinical validity, such as BRCA 1,[43] some pharmacogenomic markers and carrier screening for monogenic diseases. Whereas the first group of tests (those for non-medical traits) can safely be seen as informational, educational or entertainment commercial services,[44] the third group of tests, clearly, cannot. As there are serious harms and consequences associated with tests of the third group, including direct implications for family members or for reproductive decisions, this group of tests cannot sensibly be considered 'non-medical'. There is clearly a need for informed consent to precede these tests. Strictly speaking, it may be concluded that for this group of tests, the entire testing process, including the

quality of the laboratory and the availability of specialised support and care, should meet medicine's professional standards.[45]

The applicability of medical professional standards, including informed consent, is somewhat less clear for the second group of tests, which, given their low clinical validity, may be considered to be uninformative. Two arguments in favour of the requirement of informed consent for this group are the following: firstly, the boundary lines between the second and the third groups of tests are not always clear – testing for the ApoE-variant in Alzheimer's disease, for instance, should be considered in-between the two groups. As a result of ongoing research and technological innovation, PGT is expected to gain clinical validity over the next decades and other parts of it may come to be reclassified from the clinically useless to the clinically useful.

Secondly, the problem with the second group of tests is not so much direct harm, but rather indirect harm as a result of under- or overestimation of disease risks. Informed consent can be aimed explicitly at exposing the hyperbole in companies' advertising strategies, stressing the limitations of PGT, and helping to manage consumers' expectations and protect them against the downstream risks of misinterpretation of test results.

At this point we must return to the first argument and answer the question why a combination of TOS and the protective norms of truth-in-labelling and truth-in-advertising cannot constitute a sufficient protection against misinterpretation for the second group of tests. Although truth-in-advertising and truth-in-labelling do postulate that claims made by companies on their websites, in advertisements and on packaging materials must be valid and truthful, they do not require that *specific types of information* be provided by companies. They are formulated negatively and thus do not ascribe positive informational obligations to commercial companies. Neither do TOS *demand* certain balanced types of information from companies, such as information about risks, limitations and implications of testing, or potential harms, that may lead consumers to decide against testing.

Indeed, although many present-day PGT companies are providing an abundance of information on their websites as well as in their TOS, information

about risks and limitations of testing has been found to be frequently absent or difficult to locate.[46] Moreover, TOS are not associated with the moral obligation to ensure understanding in the way in which informed consent is.[47] TOS are aimed at the legal protection of businesses rather than at the protection of consumers, and consequently, most TOS are lengthy legal documents of the kinds that are often scanned (or largely ignored) by consumers and signed (or clicked).[48] Whereas ethical informed consent presupposes understanding, TOS do not.

Finally, TOS alone do not help to protect against involuntary testing, for TOS do not verify whether the sample to be tested belongs to the customer him- or herself. They may contain a warning that it may be unethical or illegal to send in someone else's sample, but such a warning will be easily overlooked. Informed consent on the other hand would require that the consumer authorises testing his- or herself and *for* him- or herself and thus protects against involuntary testing, while TOS alone do not.[49]

In conclusion, with the blurring of boundaries between medicine and commerce, the boundaries between medical ethics and business ethics are also in flux. Medical professional standards are coming into force within commerce, because commercial standards such as TOS, truth-in-advertising and truth-in-labelling cannot do the moral work that is necessary to fulfil the aims of informed consent in the context of direct-to-consumer PGT. Medical professional standards apply not to direct-to-consumer entertainment or informational testing, but to (potentially harmful) testing for *medical risks*, of both limited and higher clinical validity, for both more and less serious diseases, also in a commercial context.

These conclusions do not necessitate the involvement of medical professionals in PGT, nor will face-to-face discussions be required. Companies can feature online modules for information provision and informed consent on their websites. Online models may not guarantee that consumers understand all information, nor that *they themselves* give informed consent, and thus leave part of the responsibility for informed consent with the consumers themselves.

Why traditional approaches to informed consent fail

We have concluded that there is a role for informed consent in PGT, but also indicated that there are hurdles to overcome in its realisation. In this section, we will examine whether two leading traditional approaches toward informed consent – specific and generic consent – are capable of solving the informational issues and meeting the moral aims of informed consent, when applied to the complexities of PGT.

Specific consent is the traditional, 'primal' model for informed consent. It refers to the original rationale of providing all relevant information needed for autonomous decision-making. It stresses the importance and the stringency of informational requirements and the high level of detail that is thought to be needed. For PGT or for other genetic tests for many diseases simultaneously, specific consent is a sheer impossibility. Detailed information about, say, dozens or hundreds of diseases and other traits, the processes of testing, the genetic variants tested, the calculations conducted, all potential outcomes, follow-up and ethical issues specific to all diseases and traits, and the uncertainties involved, can fill a bookshelf and cannot be part of any reasonable informed consent process. It has often been pointed out that it is a mistake to offer patients or research participants ever more 'numerous, highly specific propositions'[50] in the attempt to improve standards for informed consent and that 'patient understanding is inversely proportional to the page count of the [Patient Informed Consent Form]'.[51] Informed consent cannot accomplish its moral aims by containing more, or more specific, detailed information.

As a solution to the problem of increasing quantities of information, an influential generic model for informed consent has been developed for (population) screening programmes for multiple conditions simultaneously: consent should focus on 'broader concepts and common-denominator issues in genetic screening'[52] and provide detailed information 'on specific conditions only after they have been detected'.[53] This approach may be defensible for genetic screening programmes, which, unlike PGT, have been subjected to prior ethical evaluation and include only tests for actionable diseases.[54]

In PGT, a focus on broader concepts will be useful – and inevitable – during the pre-test information provision process: consumers need to know beforehand, for instance, whether the information to be purchased is medical or nonmedical and whether it is of high or low clinical validity, and the risks and implications of receiving that information, which had best be presented on a general level. Information on specific diseases or groups of diseases tested for (e.g. a list of diseases, sensibly categorised), we claim, should however *also* be part of the informed consent process in PGT and should not be withheld until after testing. Consumers should know, for instance, whether they will be confronted with genetic risks for diseases that cannot be prevented or treated. Moreover, individual consumers may attach personal meanings to certain disease risks based on personal or familial experiences with these diseases (e.g. cancers, heart diseases, carrier status for familial disorders) and may respond (strongly) accordingly.[55] If consumers do not know what information to expect – or what information they have in fact purchased – until after receiving their test results, they may be confronted with (for them) unexpected outcomes which they had rather not have known. For this reason, generic models do not suffice in the context of PGT.

Keeping the moral aims of informed consent in sight without overwhelming consumers with information, a middle way must be found between specific and generic models for informed consent, a way to provide sufficient information [56] without having to divulge too much detailed information on specific diseases.

The outline of a tiered-layered-staged model for informed consent in PGT

Both specific and generic approaches to informed consent fail to resolve satisfactorily the informational problems associated with PGT. It is however clear that if the moral aims of informed consent are to be maintained, concessions will have to be made to the level of detail in any approach suitable to PGT. We present the outline of a model that aims at adhering to the – sometimes conflicting – norms of providing complete information and providing understandable information. The model is a composite model of three

more or less existing models – tiered, layered and staged models – that have been developed in the context of biobank research. We will now briefly describe the defining features of the three models and our combined model for application in PGT.

For biobank research, differentiated or *tiered* consent has been designed to offer participants choices about the future use of their specimens.[57] During the informed consent process, biobank participants are given the opportunity to limit the future usage of their samples or information to certain types of research (e.g. for specific diseases) or to certain (e.g. non-commercial) parties.[58] Tiered consent is widely applied and claimed to be 'best practice' in biobanking.[59] A tiered model has also been proposed for neonatal screening.[60]

In PGT, a tiered model for informed consent can be used to distinguish first between the three subgroups of tests: tests for non-medical or 'fun' traits, such as bitter taste perception or iris patterns, tests for complex diseases of limited clinical validity and tests for (monogenic or other) diseases of high clinical validity. To improve the intelligibility of the information provided on the second subgroup of tests (oftentimes the largest within the PGT package), this subgroup can be subdivided further into categories of complex diseases according to relevant disease characteristics (e.g. age of onset, availability of treatment or preventive options, severity and psychiatric/somatic nature of the disease), which are connected with different psychological and social implications for consumers.[61] At a minimum, a list of disease names within each tier should be presented, so that consumers can glance through the testing offer and be given the opportunity to limit the genetic information they wish to receive by opting out of certain tiers or tests offered within the PGT-package. Through the offering of choices (and the practical necessity of having to make choices), consumers can be protected from the harms of receiving unwanted information and be encouraged to make understanding, autonomous decisions for specific tiers or diseases within the PGT-offer. One company already does this in part by requiring consumers to confirm that they wish to view certain test results (Parkinson's disease, Alzheimer's disease, breast cancer) before they are shown.[62]

Layered consent is something that Onora O'Neill calls 'extendable':[63] some information is crucial or 'material'[64] and should be offered to all consumers, whereas other, more detailed information may not be relevant to all consumers and should be made available only on individual demand. Generic consent in the context of (population) screening activities tends to be layered: it offers only basic information to all participants and refers to additional information for those who are interested.[65] In PGT, layering of information would limit the amount of information offered to all consumers (in the first layer) to a set of key messages, such as the probabilistic rather than diagnostic nature of most test results, risks and implications, the ways PGT may affect consumers in their personal lives. Consumers should understand 'what it is they are getting into' with PGT, for only on the condition that they understand *what it is to which they consent*, does their consent count as an autonomous authorisation.

In order to help make the first layer as understandable and effective as possible, this information should be kept minimal. It could be countered that, as only the first layer is offered to all consumers, only that layer can be part of the actual informed consent and that second and further layers should be considered part of a more general provision of information about the test, not of informed consent itself. Above, however, we have formulated the ideal of an 'individual consumer standard' for information provision in informed consent, meaning that prospective consumers themselves should determine what information is material to their decision-making processes. Layering of information is precisely a way to approximate that ideal, for example: some consumers may wish to know about social implications of certain tests or treatment options for certain diseases. Without that knowledge, their consent may not count as informed. Therefore, layering of information provision can help to improve informed consent not only pragmatically, in the sense that it can be a helpful tool in rendering information processes (in the first layer) manageable, but also morally, in the sense that individuals who need to know more *in order to* give informed consent, are given the opportunity to find and include the (for them) relevant information.

Many company websites do layer information,[66] but not with the aim of presenting the most important information first and improving the informed

consent process. Rather, layering of information is used for the exact opposite: whereas prominent promotional information tends to overstate the clinical validity and utility of PGT, information about risks and implications is difficult to find on company websites.[67]

Finally, the idea of *staged* consent involves the element of time and acknowledges that informed consent is a process and takes time. Strictly speaking, informed consent is given at three moments in which decisions are made throughout the testing procedure: the purchasing of the test, the viewing of the test results, and – for some providers – the viewing of updates of test results. First, the process of pre-test information provision, which precedes the first moment of consent and the purchasing of the test, can and should be extended over time. In regulations concerning biomedical research with human subjects, 'time to consider' is deemed essential to informed consent.[68] Also in clinical genetics, time is essential: 'there should be enough time between counselling and decision-making'.[69] As pre-test information may be repeated and built or elaborated upon, a staged model may constitute a learning process and improve the quality of the initial decision-making process.[70]

Second, in PGT, there is a time interval of a few weeks between the ordering of the test and the receiving of the test results. Before the test results are presented to the consumer, key information about the tiers, risks and implications can be repeated and rehearsed. The second informed consent should then be given just before the consumer views his or her test results.

Third, as genomics research is ongoing, informed consent for PGT may not hold once-and-for-all but require subsequent renewing. Some companies offer their customers updates of their risk profiles as new genetic variants have been discovered, validated and included in the company's risk calculations to improve their clinical validity.[71] Consumers are given the opportunity to decide for each update whether or not they wish to view the information, or, in other words: whether or not to consent to the receiving of further results. Again, for these subsequent occasions of consent, consumers may require time to learn and time to consider before actually giving consent.

A tiered, layered and staged model for informed consent thus combines offering choices and the prioritizing of information with allowing the time to process and to consider. PGT providers can (continue to) make use of available and rapidly evolving information and communication technologies to differentiate the testing offer, layer the relevant information and build time intervals into the information provision and informed consent procedures.

Our combined model forms a possible solution to the problems of quantity and complexity of information in PGT. At this point, however, it is no more than an outline. It points out some general directions for the development of an informed consent process that may be suitable to PGT and other broad genetic tests on the basis of exome or whole-genome sequencing, and welcomes further discussion and research on this topic.

Conclusions

There is a place for informed consent in direct-to-consumer personal genome testing (PGT). The standards of informed consent, however, vary with the type of traits tested for: whereas informed consent is not required for non-medical, 'informational' or 'entertainment' testing, we have argued, it is required for tests that may cause harm. Risk of harm is associated with highly predictive genetic tests for monogenic diseases and, to a lesser extent, with susceptibility tests for complex diseases, which are generally of more limited clinical validity and utility. The problem with susceptibility tests, especially in the context of direct-to-consumer marketing, is not so much direct psychological or physical harm, but rather over- or under-interpretation of disease risks and subsequent psychological, societal and health-related risks, as well as privacy issues and consequences for employment or insurance.

In the light of these potential harms, providers of PGT – clinical and commercial – are held by positive informational obligations, notably to inform consumers of the limitations, risks and implications of testing, also for complex diseases. Commercial norms such as truth-in-advertising, truth-in-labelling and Terms of Service do not establish a demand for relevant, truthful and understandable

information. Consumers however need this information in order to understand 'what it is they are getting into' with PGT so that they can provide autonomous authorisation of testing, and protect themselves from the harms associated with unexpected or unwanted genetic test results.

Neither specific nor generic models for informed consent are capable of meeting the moral aims of informed consent in (direct-to-consumer) PGT; a combined tiered-layered-staged model for informed consent may be more suitable. The combined model is tiered to provide consumers with options, so as to enable them to choose what types of information on what (categories of) diseases they wish to receive, and especially to opt out of receiving information they do *not* wish to receive. Layering of information will help limit the otherwise overwhelming quantity of information offered to all consumers in the first layer of the consent process, while it also strives for an 'individual consumer-based' consent, as it offers additional information for those who need that information *in order to consent*. Finally, a staged set-up of the pre-test information provision process can serve educational purposes and improve the quality of consent. Moreover, subsequent renewal of consent will be required as new test outcomes become available as a result of ongoing genomics research. A combined tiered-layered-staged model for informed consent in PGT would allow for relevant information provision that is both sufficiently complete and sufficiently understandable.

While adequate information provision is necessary to informed consent, informed consent is indispensable to a morally acceptable practice not only of direct-to-consumer PGT, but also of other forms of broad genetic testing or screening for many diseases simultaneously, in clinical or public health contexts. Further specification and substantiation of a tiered-layered-staged model for informed consent is urgently needed. For example, a definition is needed of crucial, material information to be offered in the first (minimal) layer of the informed consent process. Another problem to be resolved is that, as most PGT services offer 'packages' of different categories of tests, different standards of informed consent – but also of other aspects of provision, such as care and counselling, or the quality of the laboratory – may be applicable to one single

PGT. We hope that this paper can be a first step towards the solution of some of the informational issues involved in PGT.

References

1. Navigenics: http://www.navigenics.com; 23andme: http://www.23andme.com.

2. Counsyl: http://www.counsyl.com; Navigenics, op. cit. note 1.

3. 23andme, op. cit. note 1; deCODEme: http://www.decodeme.com.

4. Evans J.P. 2008. Recreational genomics: what's in it for you? Genetics in Medicine 10: 709-710.

5. Janssens A.C.J.W. and C.M. van Duijn. 2010. An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investigative Genetics 1: 10; Khoury M.J., C.M. McBride, S.D. Schully et al. 2009. The Scientific Foundation for Personal Genomics: Recommendations from a National Institutes of Health - Centers for Disease Control and Prevention Multidisciplinary Workshop. Genetics in Medicine 11: 559–567; Mihaescu R., J. Meigs, E. Sijbrands and A.C.J.W. Janssens. 2011. Genetic risk profiling for prediction of type 2 diabetes. PLoS Currents 3: RRN1208; Janssens A.C.J.W., A.A.M. Wilde and I.M van Langen. 2011. The sense and nonsense of direct-to-consumer genetic testing for cardiovascular disease. Netherlands Heart Journal 19: 85–88.

6. 23andme, op. cit. note 1.

7. Hunter D.J., M.J. Khoury and J.M. Drazen. 2008. Letting the genome out of the bottle: will we get our wish? New England Journal of Medicine 358: 105-107.

8. Hogarth S., G. Javitt and D. Melzer. 2008. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annual Review of Genomics and Human Genetics 9: 161-182; European Society of Human Genetics (ESHG). 2010. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. European Journal of Human Genetics 18: 1271-1273.

9. Geransar R. and E. Einsiedel. 2008. Evaluating online direct-to-consumer marketing of genetic tests: informed choices or buyers beware? Genetic Testing 12(1): 13-23.

10. Smerecnik C.M.R., I. Mesters, N.K. de Vries and H. de Vries. 2008. Educating the general public about multifactorial genetic disease: applying a theory-based framework to understand current public knowledge. Genetics in Medicine 10: 251-258; Hoffrage U., S. Lindsey, R. Hertwig and G. Gigerenzer. 2000. Communicating statistical information. Science 290: 2261-2262.

11. Manson N.C. and O. O'Neill. 2007. Rethinking Informed Consent in Bioethics. Cambridge: Cambridge University Press.

12. Ibid.

13. Pranati. 2010. Informed consent: are we doing enough? Perspectives in Clinical Research 1: 124-127.

14. Faden R.R. and T.L. Beauchamp. 1986. A History and Theory of Informed Consent. Oxford: Oxford University Press.

15. Manson and O'Neill, op. cit. note 11.

16. The Nuremberg Code. 1949. In: Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law 10: 181-182; Faden and Beauchamp, op. cit. note 14.

17. Council of Europe. 1994. Recommendation No. R (94) 11 on Screening as a Tool of Preventive Medicine. Council of Europe.

18. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534; McBride C.M., C.H. Wade and K.A. Kaphingst. 2010. Consumers' views of direct-to-consumer genetic information. Annual Review of Genomics and Human Genetics 11: 427-446.

19. Messner D.A. 2011. Informed choice in direct-to-consumer genetic testing for Alzheimer and other diseases: lessons from two cases. New Genetics and Society 30: 59-72.

20. 23andme, op. cit. note 1; Pathway Genomics: https://www.pathway.com/.

21. Bunnik E.M., M.H.N. Schermer and A.C.J.W. Janssens. 2011. Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. BMC Medical Ethics 12: 11; Bunnik E.M., M.H. Schermer and A.C. Janssens. 2012. The role of disease characteristics in the ethical debate on personal genome testing. BMC Medical Genomics 19:4.

22. Eng C. and R.R. Sharp. 2010. Bioethical and clinical dilemmas of direct-to-consumer personal genomic testing: the problem of misattributed equivalence. Science Translational Medicine 2(17): 17cm15.

23. McGuire A.L. and W. Burke. 2008. An unwelcome side effect of direct-to-consumer personal genome testing: raiding the medical commons. Journal of the American Medical Association 300: 2669-2671; Caulfield T. 2009. Direct-to-consumer genetics and health policy: a worst-case scenario? American Journal of Bioethics 9(6-7): 48-50.

24. Hunter et al., op. cit. note 7.

25. Faden and Beauchamp, op. cit. note 14.

26. Manson and O'Neill, op. cit. note 11.

27. Lachance C.R., L.A. Erby, B.M. Ford, V.C. Allen and K.A. Kaphingst. 2010. Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genetics in Medicine 12: 304-312.

28. The Nuremberg Code, op. cit. note 16.

29. Beauchamp T.L. and J.F. Childress. 1994. Principles of Biomedical Ethics (4th edition). Oxford: Oxford University Press.

30. Ibid.

31. Janssen A.J. 2006. Informing patients about small risks: a comparative approach. European Journal of Health Law 13: 159-172.

32. King J.S. and B.W. Moulton. 2006. Rethinking informed consent: the case for shared medical decision-making. American Journal of Law and Medicine 32: 429-501.

33. Gillett G.R. 1989. Informed consent and moral integrity. Journal of Medical Ethics 15: 117-123.

34. 23andme, op. cit. note 1; Navigenics, op. cit. note 1.

35. Pathway Genomics, op. cit. note 20.

36. 23andme, op. cit. note 1: Terms of Service; Pathway Genomics, op. cit. note 20: Terms of Service and Informed Consent Agreement; deCODEme, op. cit. note 3: Genetic Scan Service Agreement and Informed Consent.

37. 23andme, op. cit. note 1: 'the 23andMe services are intended for research, informational, and educational purposes only.'

38. Navigenics, op. cit. note 1; Pathway Genomics, op. cit. note 20.

39. The authors are indebted to dr. Annelien Bredenoord for the comparison.

40. 23andme, op. cit. note 1.

41. Pathway Genomics, op. cit. note 20.

42. Not all PGT services include tests of all three groups. Navigenics and deCODEme, for instance, focus exclusively on risks for complex diseases and do not offer tests for traits of the first and third groups.

43. The company 23andme provides testing for three rare mutations in the BRCA 1 gene that are associated with breast cancer and found mainly in people with Ashkenazi Jewish ancestry.

44. Some authors acknowledge that tests of the first group are not harmful, they still feel that informed consent should be required: 'Providing that non-medical genetic testing services do not inadvertently provide medical information and are not directly harmful, it is difficult to justify anything other than consumer protection and quality assurance. However, some of the established principles

that govern medical testing, such as informed consent, the protection of children from testing when it is not in their interests, confidentiality and privacy, should also be applied to these services.' Martin P. and R. Frost. 2003. Regulating the commercial development of genetic testing in the UK: problems, possibilities and policy. Critical Social Policy 23: 186-207 (p. 204).

45. It is still a matter of debate whether it is possible for the testing industry to meet these standards through a direct-to-consumer delivery model, or whether direct-to-consumer sales of tests from the third group should be banned altogether. We believe that with adequate informed consent procedures in place, this may not be necessary. However, it remains a matter for empirical study whether informed consent models such as the one proposed by us will prove effective enough to meet the moral aims stated above.

46. Lachance et al. op. cit. note 27; Singleton A., L.H. Erby, K.V. Foisie and K.A. Kaphingst. 2012. Informed choice in direct-to-consumer genetic testing (DTCGT) websites: a content analysis of benefits, risks, and limitations. Journal of Genetic Counseling 21: 433-439.

47. World Medical Association. 1964. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; Faden and Beauchamp, op. cit. note 14; Beauchamp and Childress, op. cit. note 29.

48. Böhme R. and S. Köpsell. 2010. Trained to accept? A field experiment on consent dialogs. In: Proceedings of the 28th International Conference on Human Factors in Computing Systems. New York, NY: ACM (pp. 2403–2406).

49. The difficulty here is that it remains possible for consumers to send in samples from third parties for testing. Currently, however, parents for instance may be unaware that it can be unethical to send in their children's samples. Raising awareness by making this information part of the informed consent process may thus improve current practices.

50. Manson and O'Neill, op. cit. note 11, p. 6.

51. Beardsley E., M. Jefford and L. Mileshkin. 2007. Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? Journal of Clinical Oncology 25: e13–14 (p. e14).

52. Elias S. and G.J. Annas. 1994. Generic consent for genetic screening. New England Journal of Medicine 330: 1611-1613 (p. 1612).

53. Ibid.

54. Wilson J.M.G. and G. Jungner. 1968. Principles and Practice of Screening for Disease. Geneva: World Health Organization.

55. Messner, op. cit. note 19.

56. Hofmann B. 2009. Broadening consent – and diluting ethics? Journal of Medical Ethics 35: 125-129.

57. National Bioethics Advisory Commission (NBAC). 1999. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Bethesda, MD: NBAC.

58. Wolf L.E. and B. Lo. 2004. Untapped potential: IRB guidance for the ethical research use of stored biological materials. IRB 26(4): 1-8.

59. Eiseman E., G. Bloom, J. Brower, N. Clancy and S.S. Olmsted. 2003. Case Studies of Existing Human Tissue Repositories. 'Best Practices' for a Biospecimen Resource for the Genomic and Proteomic Era. Santa Monica, CA: RAND Corporation.

60. Ross L.F. 2010. Mandatory versus voluntary consent for newborn screening? Kennedy Institute of Ethics Journal 20: 299-328.

61. Bunnik et al. 2012, op. cit. note 21.

62. 23andme, op. cit. note 1.

63. Manson and O'Neill, op. cit. note 11.

64. Beauchamp and Childress, op. cit. note 29.

65. Entwistle V.A., S.M. Carter, L. Trevena et al. 2008. Communicating about screening British Medical Journal 337: 789-791; Rijksinstituut Volksgezondheid en Milieu (RIVM). 2011. Brochure Hielprik bij Pasgeborenen [in Dutch].

66. Navigenics, op. cit. note 1; 23andme, op. cit. note 1; Counsyl, op. cit. note 2; deCODEme, op. cit. note 4.

67. Lachance et al., op. cit. note 27; Singleton et al., op. cit. note 45.

68. Ministerie van Volksgezondheid, Welzijn en Sport (VWS). 2002. WMO: De Wet Medisch-Wetenschappelijk Onderzoek met Mensen [in Dutch].

69. Kääriäinen H. et al. 2006. Summary of the Guidelines for Genetic Counselling. http://www.eurogentest.org/web/files/public/unit3/summaryofguidelinesMay06.pdf.

70. Tebbetts J.B. and T.B. Tebbetts. 2002. An approach that integrates patient education and informed consent in breast augmentation. Plastic and Reconstructive Surgery 110: 971-978.

71. Navigenics, op. cit. note 1.

Chapter 7

A tiered-layered-staged model for informed consent in personal genome testing

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Abstract

In recent years, developments in genomics technologies have led to the rise of commercial personal genome testing (PGT): broad genome-wide testing for multiple diseases simultaneously. While some commercial providers require physicians to order a personal genome test, others can be accessed directly. All providers advertise directly to consumers and offer genetic risk information about dozens of diseases in one single purchase. The quantity and the complexity of risk information pose challenges to adequate pre-test and post-test information provision and informed consent. There are currently no guidelines for what should constitute informed consent in PGT or how adequate informed consent can be achieved. In this paper, we propose a tiered-layered-staged model for informed consent. First, the proposed model is tiered as it offers choices between categories of diseases that are associated with distinct ethical, personal or societal issues. Second, the model distinguishes layers of information with a first layer offering minimal, indispensable information that is material to all consumers, and additional layers offering more detailed information made available upon request. Finally, the model stages informed consent as a process by feeding information to consumers in each subsequent stage of the process of undergoing a test, and by accommodating renewed consent for test result updates, resulting from the ongoing development of the science underlying PGT. A tiered-layered-staged model for informed consent with a focus on the consumer perspective can help overcome the ethical problems of information provision and informed consent in direct-to-consumer PGT.

Introduction

For a few years, a new generation of so-called personal genome testing (PGT) companies has been marketing genome-wide SNP analysis and whole genome sequencing directly to consumers. These companies offer personal risks for dozens of diseases simultaneously, including cardiovascular diseases, type 2 diabetes, psychiatric conditions and many types of cancer.[1-5]

Consumers can obtain this information through web-based services with [1,3] or without [4,5] the involvement of a medical professional in the signing off on the test order. Consumers take a cheek swab sample at home, send their sample to a molecular genetic testing laboratory through the mail and receive their genetic test results on a secure personal webpage.

Informed consent is an essential ethical requirement in genetic testing [6] and entails more than the signing of a consent form or the ticking of a checkbox.[7] From an ethical perspective, informed consent is a communicative process of providing intelligible, preferably tailored information, checking whether the patient—or in the case of PGT, the consumer—has understood all relevant information, complementing information found to be lacking, seeing again that all informational needs have been met, and finally, asking for informed consent. Most ethical conceptions of informed consent aim at patients' self-determination, autonomous decision-making and right to choose,[8] and at the protection against harm.[9] As such, they are much more demanding than legal 'narration-followed-by-signature' conceptions of informed consent.[10] Most ethical theories of informed consent agree that informed consent has at least three preconditions: information, comprehension and voluntariness.[11] At minimum, persons giving informed consent should be legally and cognitively capable of consenting, they should be free from external control, and they should have adequate information and understanding of what it is they are consenting to. Voluntariness as an ethical requirement may be violated when consumers send in samples from third parties without their consent. As an online health service, PGT can be vulnerable to this form of misuse, which should naturally be discouraged. For the remainder of this paper we will

however not focus on voluntariness, but on information and comprehension, which are becoming increasingly pressing issues for PGT.

A traditional ethical conception of informed consent in the context of clinical genetic testing requires consumers to receive pre-test information about the test, the disease tested for, possible outcomes and their significance, implications, limitations and risks of testing, and many other relevant aspects.[12] This conception cannot be translated directly to the very different context of PGT: it will be difficult, if not impossible, for providers to produce and for consumers - given the limited genetic health literacy among many of them - [13] to process detailed, specific information on large numbers of tests and diseases at the same time. Empirical research has not yet brought consensus on whether consumers understand important information about the (limited) clinical utility of a PGT.[14,15] Especially in a direct-to-consumer context and without the help of a medical professional, geneticist or genetic counsellor, information about PGT is likely to be misunderstood by consumers.[16,17] Therefore, the provision of adequate information and informed consent are among the main concerns in PGT.[18,19]

Current guidelines for information provision in PGT [19,20] do not distinguish between information provision and informed consent. They list a lot of information to be mentioned on providers' websites, but not all of this information pertains to informed consent. By overloading consumers with less relevant information, informational practices modelled on these guidelines may fail to convey the important information elements that are necessary for informed consent. None of the guidelines specifies how adequate informed consent can be obtained.

The quality of information provision in PGT is high for some of the leading companies, but not perfect.[21] Most companies provide abundant information, including educational materials and references to the scientific literature.[1-4] Yet, abundant information does not equal adequate or relevant information and may mislead or overwhelm consumers while failing to convey the key messages about PGT. Company websites headline 'improve your health', 'plan for the future', 'take a more active role in managing your health', or '23andme saved

my life,'[4] thereby overstating the clinical utility of a large proportion of their testing offer. They highlight the benefits of a PGT, while information about risks and limitations is often difficult to locate.[21,22] Information about risks is mentioned in 'Terms of Service' or 'Terms of Use' agreements [1,3,4] in which legal requirements are laid out and which companies use instead of informed consent procedures. Terms of Service agreements however are notoriously lengthy and are unlikely to be read completely by each customer.[20] Furthermore, these agreements can be said to aim at the legal protection of companies rather than of consumers. They are not necessarily designed to stimulate consumer understanding, nor do they automatically constitute informed consent.

There is room for improvement in information provision [21,22] and informed consent in a large proportion of PGTs offered. This paper proposes a model for informed consent that is suitable to handling the quantity and complexity of information in PGT. The model is meant for online use and can be applied to both direct-to-consumer and physician-mediated forms of commercial PGT based on either genome-wide scans or exome or whole genome sequencing. The advent of exome or whole genome sequencing technologies in PGT may further expand the testing offer and increase the clinical validity and utility of some of the findings, and may thus exacerbate the need for a new model for informed consent. We start from the assumption that it may not be necessary or desirable to legally require professional counselling or to ban direct access to PGT, and that although there is a moral obligation for providers to facilitate informed consent, the responsibility of actually making informed, autonomous decisions regarding PGT, rests with the consumer.[23]

Models for informed consent

A wide range of models for and approaches to informed consent have been developed in the history of medicine.4 Two main contrasting approaches are specific consent, which in the context of genetic testing requires consumers to be provided with elaborate and detailed information about the testing procedure, the diseases tested for and implications of testing, and generic consent, which

focuses on general information and common-denominator issues, such as general characteristics of genetics and genetic testing, and common features of the diseases tested for.[24,25] Neither approach will be completely suitable to PGT, because they both fail to promote two important ethical aims of informed consent: the enabling of autonomous choice and the protection against harms.[26] Because of the complexity and the quantity of the information offered in PGT, informed consent cannot be fully specific. It will be impossible to provide consumers with detailed information on all relevant aspects on all diseases tested for in a PGT. Overloading consumers with detailed information will undermine autonomous choice. On the other hand, informed consent should not be too generic either. Consumers should at least know what test results they will receive and be given the opportunity to opt out of receiving test results which they anticipate may harm them or which they do not wish to receive.[23]

A tiered, layered and staged model for informed consent

An ethical approach to informed consent underlines the importance of ensuring that consumers understand the clinical and emotional impact PGT may have on them, and the implications for their personal lives as well as for the lives of their family members. Informed consent in PGT should aim at the provision of both complete information (specific consent) and understandable information (generic consent). The proposed model consists of a combination of tiered, layered and staged models for informed consent, three existing approaches to informed consent [12,27,28] that all attempt to provide information which is as complete as possible while remaining understandable. Each of the three models will be described and applied to PGT.

Tiered consent

Tiered consent is differentiated consent. The broad PGT offer can be subdivided into tiers or categories of traits and diseases. Informed consent can then be given for specified categories of diseases rather than for the complete package.

Differentiation of the testing offer can help consumers make deliberate choices with regard to the information they do or do not want to receive.

Tiered consent is currently widely used for biobanks and genomic databases [27,29] and for neonatal screening programmes.[30] A few 'binning' or 'packaging' models have recently been suggested for the return of results to research participants and for the interpretation of whole genome sequencing.[31-33] A 'packages' model distinguishes a default package of research results and optional packages.[31] The 'default package' contains information that should always be reported back to participants such as directly life-saving information and other information of high clinical utility indicating serious health problems.[31] The optional packages include data of moderate clinical validity, data of reproductive significance and data of 'personal or recreational' interest. One version of the 'binning' model consists of five bins, in which the first bin contains medically actionable results, the second results that have implications for family planning, the third information that may be sensitive and unwanted (such as APOE results), the fourth information that has clinical validity for diseases for which there are no therapeutic or preventive options and the fifth bin, finally, contains all other 'results' or all data for which a clinical interpretation is lacking or uncertain.[33] In these models, the purpose of the test is used as a criterion, for example: carrier status results that can be used for reproductive decision-making are assigned a category of their own. Interestingly, in the latter model the bins are defined according to the emotional impact of results: there are separate bins for sensitive or unwanted results and results lacking actionability. For consumers, the purpose and the emotional impact of a test are likely to be important criteria in deciding whether or not to take the test - and to give informed consent. Empirical research is needed to examine what criteria consumers find important or meaningful to their decision-making processes.

In PGT, a tiered model for informed consent can be used to distinguish between categories of diseases on the basis of both test characteristics (e.g. clinical validity and utility) and disease characteristics (e.g. severity, actionability, age of onset and the somatic or psychiatric nature of the disease),[34] as these characteristics are associated with different clinical, psychological and social

implications for consumers. In a tiered process, consumers could for instance choose to obtain only testing of high clinical validity and utility for its medical value or - if they wish - only testing for non-medical traits for its informational or 'curiosity' value. Alternatively, they could choose to purchase testing for somatic diseases only and leave out psychiatric diseases, or for early-onset diseases only, not for late-onset diseases. Combinations of test characteristics and disease characteristics may also be appropriate, for example: consumers could indicate that for very severe diseases, they would only want to know their genetic risk if the test is of high clinical validity. Providers of PGT could thus structure their testing offer beforehand into tiers that are meaningful for consumers, such as purposes of testing, severity of the diseases tested for, actionability and emotional impact of test results.

At first glance, tiered consent might seem to pose practical challenges to the business models of PGT providers. It might require them to tailor their services according to consumers' preferences. Some companies have already differentiated their services and offer 'cardio scans' alongside 'complete scans'[5] or pre-pregnancy planning services alongside drug response services.[1] Alternatively, providers could conduct complete scans for all customers while offering the possibility to opt out of receiving results for certain tiers.

Layered consent

Layered consent distinguishes between different layers of information. The first layer pertains directly to informed consent and is indispensable to informed consent. This information is explicitly offered to all consumers and is kept minimal in order to increase the effectiveness of its communication. There may be other information elements that should be offered as part of a broader, general provision of information,[19-20] but these should be made available in second and further layers of the information provision process. The concept of layered consent is based upon the idea of extendable information:[9] some information is offered to all consumers, whereas other, more detailed information is accessible for consumers who actively seek it. Information provision in public screening activities is often layered.[28]

An ethical approach to informed consent in PGT acknowledges that the first layer should contain limited information in order to remain comprehensible and manageable, and to avoid information overload.[35] Many consumers will only read what is presented to them first and will not seek additional information.[36] Therefore, the first layer should contain all crucial information, all the key messages about PGT that are necessary for consumers' understanding of PGT and for their decision whether or not to take the test. For this reason, existing guidelines for information provision in PGT may be too encompassing as they include specific information such as the location of the provider, funding arrangements and the evidence on which interpretations of the test results are based.[19,20] Although this information may need to be available on PGT providers' websites, it is not part of the informed consent process itself and should not be presented in the first layer, for it will distract consumers from what they need to know in order to consent to PGT.

Informational needs for informed consent in PGT have not yet been established. Following existing guidelines for information provision in PGT [19,20] and in clinical genetic testing,7 we expect that consumers need to know at least the following eight information elements in order to give informed consent: the purpose of the test, the target group, limitations of the tests, risks and implications of testing, tiers of the PGT, potential follow-up, data protection, and where to find further and independent information (see Table 5). By way of illustration, we discuss the most important elements briefly.

Consumers should understand the purpose of a genetic test at the outset.[37] PGT services are marketed for a variety of purposes, ranging from prediction of risks for complex diseases [5] and pre-conception carrier screening [3] to pharmacogenomic information, information on other, non-medical phenotypic traits, such as ear wax type or eye colour,[4] and nutrigenomic information.[1] In order to manage consumers' expectations and help them understand correctly the nature of the PGT on offer, the purpose(s) of PGT should be clearly addressed. In tandem with the purpose, the target group(s) should be made explicit in the first layer.[37] Possible target groups are couples who intend to conceive,[3] healthy, asymptomatic adult individuals [38] who wish to know their genetic susceptibilities to complex diseases,[4,5] or consumers who are

interested in genetics and who wish to explore their genetic make-up out of curiosity.[4,39] Through an explicit definition of the target group, consumers

	Information elements	Examples
1	Purpose of the test	Prediction of disease risks Provision of information on carrier status for reproductive decision-making Education/information Entertainment
2	Target group	Adult consumers without health problems or positive family history Couples planning to conceive
3	Limitations	Probabilistic versus diagnostic information Test results may change over time
4	Implications and risks	Psychological implications (e.g. anxiety) Medical implications (e.g. unnecessary follow-up) Social implications (e.g. insurability) Implications for family members
5	Tiers	Non-medical tests Medical tests of limited versus high clinical validity and utility Medical tests subdivided into categories (tiers) of diseases tested for according to disease characteristics (e.g. severity, age of onset)
6	Follow-up	Follow-up testing and diagnostic work-up for clinically actionable test results
7	Data protection	Access by third parties (e.g. researchers)
8	Sources of independent information	Links to government/consumer/patient organisation websites

Table 5. A proposed contents of the first layer of the information provision process.

with health problems and consumers who worry about genetic conditions that run in their families can be clearly informed that they may need to see a clinical geneticist instead of purchasing a PGT. Further, in order to enhance autonomous choice, consumers should be given the opportunity to choose tiers so that they can opt out of categories of diseases (e.g. diseases for which there are no treatment options or psychiatric diseases). The company 23andme for example does this by offering test results for hereditary breast cancer, Alzheimer's disease and Parkinson's disease separately and asking separate informed consent for each of these three diseases.[4] Thus, the first layer of the information provision process contains information that is of direct relevance to the decision whether or not to proceed with PGT and to give informed consent, such as the purpose and the target group of the PGT, tiers from which to choose as well as key messages about the follow-up and general limitations, risks and implications of PGT test results.

Second and further layers may contain specific and detailed information about the tiers of the PGT and the individual diseases and traits tested for within these tiers, and about the clinical, personal and social significance and implications of test results within these tiers. Additional layers may further contain detailed information on the testing procedure, the laboratory analysis, the technology and algorithms used, the research findings on which risk calculations are based and references to the scientific literature. They may also contain additional information to improve understanding of the testing service, such as general facts about genetics, categories of complex diseases, disease prevention, genetic testing and its psychological and social implications, for those who seek explanation, explication or elaboration. Finally, they may contain legally relevant additional information such as the location of the laboratory, advertising and funding arrangements, details about policies for data security and for what will happen to the database if the company goes bankrupt. As the information offered in additional layers will be less crucial, the moral obligation to provide such information will be less stringent than the moral obligation to provide first-layer information. It follows that there may be reasons to leave the precise contents of additional layers to providers' discretion.

The proposed outline of a layered model is meant as a starting point for discussion. Geneticists, physicians, ethicists, policy-makers and commercial providers may need to work together to examine informational needs and preferences among consumers and to determine what information is material to informed consent in PGT. The aim of layered consent will now be clear: in order to avoid overwhelming consumers with information, only information that is essential to informed consent should be offered to all consumers in the first layer, whereas further layers of information provision are made available for those who desire more knowledge in order to consent. In other words: in the first layer, consumers are made aware of only the tips of all relevant icebergs, and they can find complete images of all icebergs in further layers if they wish.

Staged consent

The idea of staged consent underlines that informed consent is a process and takes time. People need time for consideration in order to come to understanding decisions.[40] In clinical genetics, time is an essential feature of informed consent: counsellors allow for time to pass between counselling and decision-making.[12] In the context of biobanks, stepwise informed consent is used to promote comprehension.[41] In PGT, a staged set-up of the information provision process is already presupposed by a tiered model for informed consent: as different risks, limitations, follow-up and implications are associated with the different tiers, these tiers require separate discussions before tier-specific consent can be given. The tiered, layered and staged dimensions of the proposed model are thus not fully separable and will intertwine.

The process of purchasing a PGT can be subdivided into three informational and decisional phases, each to be concluded with informed consent: first, informed consent to the PGT as a whole or to certain tiers prior to buying the test; second, informed consent per tier prior to receiving the test results; and third, informed consent prior to receiving subsequent updates of test results. The general contention of the idea of staged consent is that the passing of time between these informational phases may allow for learning and improve understanding.

First, the process of pre-test information provision preparing for informed consent can be extended over time. The bulk of information need not be

presented all at once, but can be subdivided into manageable portions, starting from general information about benefits and limitations of PGT, followed by introductory information about the tiers and concluded—upon demand—by specific information about the diseases tested for within selected tiers and associated risks and implications. This information may be repeated and built or elaborated upon and thus constitute a learning process. Models for a staged, integrated system of patient education and informed consent have been envisioned also in the clinical setting.[42]

PGT providers are already fulfilling part of the educational ideal of staging: they present a riches of information on their websites,[3,43] including educational materials [4,5] which can be accessed freely and repeatedly by anyone who has access to the Internet. Consumers can compare providers' websites, search for information, be taught the basics of genetics through tutorials, and in this manner compile and tailor their own pre-purchase information provision process. It remains important, however, that information material to the actual informed consent is expressly presented to all consumers (layered consent), and that informed consent is clearly requested.

Second, informed consent itself may be staged as test results may change over time. Many PGT companies offer their customers regular updates of their test results as new genetic variants come to be included in companies' risk profiles and original test results are reinterpreted, or as new associations are found between variants and diseases, thus expanding companies' testing offers.[4] Customers are given the opportunity to decide for each update whether or not they wish to view their new test results.[4] With these updates companies can rehearse or provide further information on diseases tested for, before asking customers to give renewed informed consent.

The proposed staged model emphasises that informed consent in PGT, in accordance with the science which underlies it, may undergo changes over time. Informed consent should be thought of as a process rather than a once-and-for-all-time transaction. For this reason, consumers should be able to withdraw from companies' databases and subscription lists.

In conclusion, a tiered, layered and staged model for informed consent would structure the testing offer into tiers from which consumers may choose understandingly, would prioritise information such that consumers have sufficient knowledge of PGT generally and its associated risks, limitations and implications, and would allow for time to learn and time to consider. The structure of the Internet commonly facilitates multi-layered and staged design; like many other websites, PGT company websites are already layering information (e.g. 'click here to learn more').[4,31] With the help of information and communication technologies, processes of information provision and informed consent in PGT could be improved. It is not impossible that enabling and encouraging consumers to make more well-considered decisions regarding PGT will result in a smaller proportion of them consenting to and purchasing PGT. As such, adequate procedures for informed consent may run counter to companies' business interests. It is not yet known whether conflicts of interests will arise in practice. Regardless, however, the moral obligation remains the same: to mitigate the harms of testing and of misinterpretation and to protect the value of autonomous choice.

Conclusion

Providers of PGT can be argued to have general moral obligations - also in a commercial context - to offer information about their services and to ensure that this information can be communicated effectively. In order to protect consumers against harm and to enable them to make autonomous choices, informed consent as an ethical requirement is indispensable. PGT commonly involves a lot of complex genetic information and thus poses difficulties for pre-test information provision and informed consent. This paper proposes a combined tiered-layered-staged model for informed consent that may serve as a response to widespread worries about misinterpretation and misunderstanding of PGT by consumers. The model is intended for the commercial and online context in which PGT is currently offered and in which face-to-face discussions with professional counsellors are lacking. The proposed model focuses on the consumer perspective, identifying the moments in which consumers make

decisions about PGT and the information they likely need in order to make informed decisions about whether or not to consent to (certain tiers of) a PGT. The proposed contents of the model are no more than preliminary. In order to establish adequate tiered consent, academia, providers and consumers may collaborate on the definition of categories of diseases along the lines of clinical validity, purposes of testing, level of potential harm, and personal, clinical and social implications. Also, further research is needed to establish the exact contents of the first layer of the information provision process prior to informed consent, which is meant to contain only material, indispensable information on PGT. Ideally, an interactive approach would allow providers to check whether consumers have understood the key messages of PGT. A tiered-layered-staged model for informed consent can be applied to PGT in both direct-to-consumer and professionally mediated contexts, and help overcome the challenges regarding pre-test information provision and informed consent encountered in commercial PGT, now and in the future.

References

1. Pathway Genomics: https://www.pathway.com.

2. Knome: http://www.knome.com.

3. Counsyl: https://www.counsyl.com.

4. 23andme: http://www.23andme.com.

5. deCODEme: http://www.decodeme.com.

6. Council of Europe. 2008. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes.

7. European Society of Human Genetics (ESHG). 2010. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. European Journal of Human Genetics 18: 1271-1273.

8. Faden R.R. and T.L. Beauchamp. 1986. A History and Theory of Informed Consent. New York/Oxford: Oxford University Press.

9. Manson N.C. and O. O'Neill. 2007. Rethinking Informed Consent in Bioethics. Cambridge: Cambridge University Press.

10. Pranati. 2010. Informed consent: are we doing enough? Perspectives in Clinical Research 1: 124-127.

11. Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

12. Kääriäinen H., M. Hietala, U. Kristoffersson et al. 2008. Recommendations for Genetic Counselling related to Genetic Testing. EuroGentest Unit 3.

13. McBride C.M., D. Bowen, L.C. Brody et al. 2010. Future health applications of genomics: priorities for communication, behavioral, and social sciences research. American Journal of Preventive Medicine 38: 556-565.

14. McGuire A.L., C.M. Diaz, T. Wang and S.G. Hilsenbeck. 2009. Social networkers' attitudes toward direct-to-consumer personal genome testing. American Journal of Bioethics 9: 3-10.

15. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534.

16. Howard H.C. and P. Borry. 2009. Personal genome testing: do you know what you are buying? American Journal of Bioethics 9: 11-13.

17. Berg C. and K. Fryer-Edwards. 2007. The ethical challenges of direct-to-consumer genetic testing. Journal of Business Ethics 77: 17-31.

18. Gurwitz D. and Y. Bregman-Eschet. 2009. Personal genomics services: whose genomes? European Journal of Human Genetics 17: 883-889.

19. Nuffield Council on Bioethics. 2010. Medical Profiling and Online Medicine: The Ethics of "Personalised Healthcare" in a Consumer Age. London: Nuffield Council on Bioethics.

20. Human Genetics Commission (HGC). 2010. A Common Framework of Principles for Direct-to-Consumer Genetic Testing Services. London: HGC.

21. Lachance C.R., L.A. Erby, B.M. Ford et al. 2010. Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genetics in Medicine 12: 304-312.

22. Singleton A., L.H. Erby, K.V. Foisie and K.A. Kaphingst. 2011. Informed choice in direct-to-consumer genetic testing (DTCGT) websites: a content analysis of benefits, risks, and limitations. Journal of Genetic Counseling 21: 433-439.

23. Bunnik E.M., A.C.W.J. Janssens and M.H.N. Schermer. 2012. Informed consent in direct-to-consumer personal genome testing: the outline of a model between specific and generic consent. Bioethics [Epub ahead of print].

24. Elias S. and G.J. Annas. 1994. Generic consent for genetic screening. New England Journal of Medicine 330: 1611-1613.

25. O'Neill O. 2003. Some limits of informed consent. Journal of Medical Ethics 29: 4-7.

26. Beauchamp T.L. and J.F. Childress. 1994. Principles of Biomedical Ethics (5th edition). New York, NY: Oxford University Press.

27. Eiseman E., G. Bloom, J. Brower, N. Clancy and S.S. Olmsted. 2003. Case Studies of Existing Human Tissue Repositories. 'Best Practices' for a Biospecimen Resource for the Genomic and Proteomic Era. Santa Monica, CA: RAND Corporation.

28. Entwistle V.A., S.M. Carter, L. Trevena et al. 2008. Communicating about screening British Medical Journal 337: 789-791.

29. National Bioethics Advisory Commission (NBAC). 1999. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Springfield, VA: Department of Commerce.

30. Ross L.F. 2010. Mandatory versus voluntary consent for newborn screening? Kennedy Institute of Ethics Journal 20: 299-328.

31. Bredenoord A.L., N.C. Onland-Moret and J.J.M. van Delden. 2011. Feedback of individual genetic results to research participants: in favor of a qualified disclosure policy. Human Mutation 32: 861-867.

32. Berg J.S., M.J. Khoury and J.P. Evans. 2011. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genetics in Medicine 13: 499-504.

33. Rizk C. 2011. James Evans' plan to make genetic testing data manageable for the clinic. Genomeweb.

34. Bunnik E.M., M.H. Schermer and A.C. Janssens. 2012. The role of disease characteristics in the ethical debate on personal genome testing. BMC Medical Genomics 19:4.

35. US Department of Health and Human Services (HHS). 2006. Research-Based Web Design and Usability Guidelines. Washington, DC: HHS.

36. Kaphingst K.A., C.M. McBride, C. Wade, S.H. Alford, L.C. Brody and A.D. Baxevanis. 2012. Consumers' use of web-based information and their decisions about multiplex genetic susceptibility testing. Journal of Medical Internet Research 12: e41.

37. Melzer D., S. Hogarth, K. Liddell, T. Ling, S. Sanderson and R.L. Zimmern. 2008. Genetic tests for common diseases: new insights, old concerns. British Medical Journal 336(7644): 590-593.

38. Thompson P.A. 2007. Genetic risk feedback for common disease: time to test the waters. Cancer Epidemiology, Biomarkers and Prevention 16: 1727-1729.

39. Su Y., H.C. Howard and P. Borry. 2011. Users' motivations to purchase direct-to-consumer genome-wide testing: an exploratory study of personal stories. Journal of Community Genetics 2: 135-146.

40. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: Department of Health, Education, and Welfare.

41. Mascalzoni D., A. Hicks, P. Pramstaller and M. Wjst. 2008. Informed consent in the genomics era. PLoS Medicine 5: e192.

42. Tebbetts J.B. and T.B. Tebbetts. 2002. An approach that integrates patient education and informed consent in breast augmentation. Plastic and Reconstructive Surgery 110: 971-978.

43. Map My Gene: http://www.mapmygene.com.

Chapter 8

Genomic testing and informed consent: Differentiating choice to preserve autonomy

Based on:

The new genetics and informed consent: Differentiating choice to preserve autonomy

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Abstract

The advent of new genetic and genomic technologies may cause friction with the principle of respect for autonomy and demands a rethinking of traditional interpretations of the concept of informed consent. Technologies such as whole-genome sequencing and micro-array based analysis enable genome-wide testing for many heterogeneous abnormalities and predispositions simultaneously. This may challenge the feasibility of providing adequate pre-test information and achieving autonomous decision-making. At a symposium held at the 11th World Congress of Bioethics in June 2012 (Rotterdam), organised by the International Association of Bioethics, these challenges were presented for three different areas in which these so-called 'new genetics' technologies are increasingly being applied: new-born screening, prenatal screening strategies and commercial personal genome testing. In this article, we build upon the existing ethical framework for a responsible set-up of testing and screening offers and reinterpret some of its criteria in the light of the new genetics. As we will argue, the scope of a responsible testing or screening offer should align with the purpose(s) of testing and with the principle of respect for autonomy for all stakeholders involved, including (future) children. Informed consent is a prerequisite but requires a new approach. We present preliminary and general directions for an individualised or differentiated set-up of the testing offer and for the informed consent process. With this article we wish to contribute to the formation of new ideas on how to tackle the issues of autonomy and informed consent for (public) healthcare and direct-to-consumer applications of the new genetics.

Introduction

Since the completion of the Human Genome Project in the early 2000s, worldwide research in human genetics has included the study of both specific genes (genetics) and genomes in their entirety (genomics), and has led to the development of increasingly rapid, simple and financially attractive technologies for the mapping and the scrutinizing of (parts of) the human genome, which are called the 'new genetics'. The most frequently used and promising techniques are micro-array based analysis and whole-genome or whole-exome sequencing (referred to as WGS and WES, respectively) (see Textbox 2). In the practice of (public) healthcare, these new technologies are increasingly replacing traditional test procedures. WGS is expected to be broadly implemented within the next couple of years.[1] In prenatal screening, conventional karyotyping (see Textbox 2) is being replaced by genome-wide array-based techniques,[2] and the dropping costs of the new genetics may also bring about their application in new-born screening programmes.[3] Some commentators even claim that in the near future every individual child will be 'profiled', leading to enhanced options for treatment and prevention later in life.[4] Moreover, the new genetics has found its way to the public outside of healthcare systems, through direct-to-consumer (DTC) marketing, often without the involvement of healthcare professionals.[5]

Whole-genome sequencing (WGS) refers to technologies for sequencing the whole genome: the ordering of all nucleotide bases that constitute an individual's 'genetic blueprint'. This process generates a data set of roughly three billion base pairs.

Whole-exome sequencing (WES) focuses 'merely' on the exome, being 1% of the DNA coding for the construction of proteins. Both WGS and WES require further analysis to enable the deduction of meaningful information. This analysis can be conducted on the whole genome (WGA) or whole exome (WEA), or instead focus on specific areas in the sequence only (targeted analysis).

Micro-array based technologies can simultaneously detect hundreds of thousands or millions of single nucleotide polymorphisms (SNPs, common single-base variants in the DNA molecule) across the genome. This can be done quickly, easily and at a relatively low price. SNPs are associated with genetic susceptibilities to common complex diseases. If assembled in a genetic risk profile, SNPs associated with the risk for a particular disease may indicate an overall increased or decreased personal risk for developing that disease. Personal genome tests based on genome-wide SNP-analysis commonly include a multitude of genetic risk profiles.

Conventional karyotyping allows for the reliable identification of all numerical and structural chromosome abnormalities that are visible by microscope (abnormality size > 3-5 Mega base). Karyotyping is time-consuming and labour-intensive, because it requires the culturing of foetal cells obtained by amniocentesis or chorionic villus sampling, with the aim of obtaining cells at the metaphase stage.

Textbox 2. Explanation of testing techniques

The new genetics significantly increase the chance of identifying relevant disorders, but also of revealing 'incidental' and possibly unwanted findings. In fact, whole-genome tests routinely reveal such findings, not only about the tested individual but possibly about his or her close relatives as well. Generating all this information may be welcomed insofar tested individuals are able to understand it and willing to use it for preventive strategies or reproductive decision-making. However, this information will not merely be beneficial, but may cause harm as well. If tested individuals become confused and anxious due to test outcomes, or if they are wrongly reassured by false-negative test results, this may adversely impact their health. Therefore, decisions regarding what information (not) to generate through a genome-wide test and (not) to report back to tested individuals should be made carefully and take into account both the possible benefits and burdens of receiving such information.

Genome-wide tests do not necessarily yield so much information. The analysis of the data set generated by micro-array or whole-genome sequencing technologies can be very broad in scope, but it can just as well be restricted to one single disease or to a few abnormalities only. In the public health and clinical context, there are established medical and ethical criteria for determining the scope of a responsible testing or screening offer.[6] Basically, tests should be 'meaningful: the condition screened for must be serious, the test highly predictive, and follow-up actions must be available in terms of healthcare interventions.'[7] Also, testing should be preceded by informed consent.

The aim of informed consent is to gather autonomous authorisation from the person involved for an act that would otherwise be an infringement of that person's rights.[8] Many medical interventions, including genetic testing and screening, require permission, both legally and morally. Informed consent presupposes adequate information, competence, voluntariness and comprehension.[9] The traditional model for informed consent in the context of genetic testing is derived from clinical genetics, where the person to be tested is offered extensive and non-directive pre-test counselling to enable autonomous decision-making. The individual has a right to know, but also a right not to know genetic information. Guidelines require that – before giving informed consent – the individual to be tested should receive and understand at least the following information: 'medical facts of the disorder, risk figures, (possible) benefits and harms of testing, limitations of the test, reliability of the test, implications of testing, familial implications, probabilities of inheritance, prevention and treatment, information on available support and alternative choices.'[10] Communication of all this information for one disease usually takes much time and often multiple counselling sessions. It is reasonable to assume that such a meticulous procedure will not be feasible in the context of the new genetics. The enormous quantity of information generally involved in genome-wide testing makes it difficult to meet the requirements of comprehension and competence in lay persons to be tested.

Children and young minors are often incompetent to give informed consent. Therefore, their parents are allowed to represent them and give or withhold consent for medical interventions. As we will show, the legitimacy of such

parental consent is not unlimited, since it may infringe upon the child's present and future rights, including the right not to know.

Three applications of the new genetics

Below, the (pending) implementation of the new genetics will be discussed for three areas: new-born screening, prenatal screening strategies, and DTC personal genome testing. In all three areas, a carefully designed testing offer and adequate informed consent are considered of paramount importance to respect persons' autonomy, to protect the rights of tested individuals, and to guard them from being harmed by testing (non-maleficence). As we will show, the position of (future) children deserves special attention.

New-born screening: Profiling the new-born

New-born screening was first conducted in the USA in 1962 and has since been a routine intervention performed on nearly all new-borns in many countries. The aim of new-born screening has traditionally been to discover inborn diseases which manifest early and for which safe and easy treatment is available.[11] Initially, screening aimed at detecting phenylketonuria (PKU), which is rare (but less rare than some other congenital diseases), can be reliably diagnosed and is easy to treat. Since the introduction of new-born screening, the different programmes have come to include increasingly more diseases, some of which are less obvious candidates when traditional criteria of treatability and reliability of the test are applied.[12] As a result, the screening offer has become more diverse and now includes diseases of varying seriousness, treatability and time of onset. The potential harm associated with such expansions have prompted some authors to insist that mandatory new-born screening or screening with minimal informed consent procedures, are no longer acceptable.[13] Instead, parents should be offered the option to choose whether or not (and to what extent) to have their new-born tested, at least when screening might generate information which is not of immediate medical benefit to the child.

Recent suggestions to further expand new-born screening by means of micro-array based technologies, WGS or WES, raise – with a new urgency – the question of informed consent and the standardisation of the screening offer. These new genetic technologies are likely to routinely generate incidental findings.[14] Furthermore, it has been suggested that new-born screening should be structured as a continuous process instead of a once-and-for-all affair. Such an approach would be in line with the notion of 'profiling' new-borns, which implies the possibility of creating a 'health dossier' that could be used for the prevention, diagnosis and treatment of diseases in different stages of the person's life.[15] When considering these options from the perspective of autonomy, two sets of questions stand out.

The first set of questions relates to the standardisation of the offer. On the one hand, the diversification of possible test outcomes seems to give force to the argument that parents should be offered the option of choice. On the other hand, however, the complexity of the material seems to make autonomous choices with regard to preferred test outcomes practically very difficult. How should this tension be resolved? In order to facilitate understanding and decision-making, different categories of potential outcomes could be distinguished. These categories however would be defined by – perhaps paternalistic – authorities beforehand and may thus also limit the options. Can information justifiably be withheld on the grounds that informed consent would not be possible otherwise?[16]

The second set of questions concerns the future autonomy of the child. These arise when late-onset diseases are concerned or when test results are retained and accessed later on in the child's life. Testing for late-onset diseases has traditionally been considered morally unjustified in view of children's right not to know, because it would deprive them of their right to decide (when competent to do so) whether to be tested for these conditions.[17] Other questions relate to who has access to the information and when, and for how long it should be stored. If we take seriously the possibility of new-born profiling, the accompanying informed consent procedure should address these issues.

Prenatal screening: Individualised choice

Prenatal screening strategies for detecting foetal abnormalities were introduced in the late 1960s, initially to prevent the burden and suffering caused by the birth of children affected with serious chromosomal conditions (notably Down's syndrome) and open neural tube defects. This scope has remained relatively constant for decades. Screening consisted of a standard one-step test offer that pregnant women could either accept or decline. In the course of time, the aim of prenatal screening shifted to offering pregnant women (and their partners) the opportunity to obtain information about their foetus that they may want to use for their decision whether or not to continue the pregnancy – in short, to facilitate well-informed, autonomous, reproductive choice.[18] All this time, conventional karyotyping remained the gold standard for diagnostic testing. This practice, however, is now rapidly changing due to an overall tendency towards broadening the scope of screening and diagnostic testing.[19] Micro-array based techniques are being implemented as diagnostic tests in case of ultrasound abnormalities. Some even propose to offer this technique as a one-step screening test to all pregnant women.[20]

This development challenges both the traditional scope of prenatal screening and the aim of facilitating autonomous reproductive choice. Until recently, autonomous choice in this context meant being given the opportunity to decide whether or not to accept a standard prenatal test offer, targeted at a limited number of serious conditions only. But since the scope of a standard offer is becoming less obvious, the question arises whether offering a standard test optimally meets the aim of reproductive choice. At first glance, one might assume that reproductive autonomy is best served by maximising the amount of reproductive options and thus by offering array-based techniques that enable broad-scope testing. However, it is well known that preferences regarding the scope of prenatal testing differ considerably between and amongst professionals and pregnant women.[21] Therefore, it may be preferable to differentiate the testing offer in such a way that it meets individual women's interests and wishes. Offering an ‘individualised choice’ – meaning that pregnant women themselves are allowed to determine whether they would benefit more from a comprehensive or a limited test - may thus better accord with the aim of

prenatal screening. However, the merits and feasibility of such a choice are unclear, because of the associated burdens and the difficulties of informed consent in the context of the new genetics. Whether women are offered one broad array-based standard test or a set of testing options to enable individualised choice, in either case they are confronted with a large quantity of complex information. A new approach to informed consent will thus be needed for prenatal screening.

Another problem arises in case prenatal testing identifies a late-onset disease (especially a disease that is untreatable and possibly severe) while the pregnancy is being continued: one would de facto screen a future child. This raises a similar issue to the one raised in the context of new-born screening, for the child's right not to know would then be violated. Thus, a dilemma may arise between the reproductive autonomy of the prospective parents and the future child's right not to know. In contrast with the new-born context, obtaining information about late-onset diseases in the prenatal setting may also serve a reproductive interest: prospective parents may want to use this information to decide about continuation of the pregnancy.

These issues in the prenatal context – how to serve reproductive autonomy, how to ensure informed consent and how to respect the autonomy of the future child – necessitate a reconsideration of both the aim and the scope of prenatal screening.

DTC personal genome testing: Bypassing the healthcare system

Thus far, we have discussed two public health applications, but the new genetics is also confronting the public directly through online DTC marketing by private companies. Targeted genetic tests for specific diseases have been available through online DTC services since the early 2000s.[22] As of 2007, however, a new generation of companies has been offering genetic testing services for multiple diseases simultaneously. For a few hundred dollars, consumers can can now order ‘personal genome tests’ that map hundreds of thousands of genetic variants across the genome and estimate disease risks for dozens of diseases and

other phenotypic traits. Today's testing offers include complex diseases, such as cardiovascular diseases, type 2 diabetes, rheumatoid arthritis, psoriasis, Crohn's disease, psychiatric conditions, and many types of cancer, but also pre-conception carrier screening and tests for monogenic disorders. Most services contain pharmacogenomic tests, and some offer 'entertainment' testing and ancestry testing as well. A complete personal genome test can thus be as elaborate as 243 diseases and other traits, in one single purchase.[23] Accordingly, the aim of DTC testing has shifted from the prediction of an individual's genetic risk for a single disease to something like 'getting to know as much as possible' on the basis of a genome-wide scan. Personal genome testing is thus no longer exclusively medical in nature but has become multi-purpose, and continues to expand its scope.

As a result, one personal genome test can include many different tests for many different diseases and other traits with corresponding different implications at the medical, personal, social and societal level. The standards of pre-test information provision and informed consent used in clinical genetics can hardly be met in a relatively under-regulated commercial context,[24] in which professional knowledge, skills and values are often lacking.[25] Lack of adequate information and informed consent may harm consumers both directly and indirectly: directly through the receipt of unwanted and potentially harmful information (e.g. knowing that one is at increased risk for an untreatable or unpreventable disease, such as Alzheimer's disease), and indirectly through misunderstanding or misinterpretation, and associated personal, social and health risks.[26] The inclusion of potentially harmful tests (e.g. for untreatable conditions) goes against the ethical criteria for a responsible screening offer.[27]

Informed consent is needed not only to help prevent the potential harms associated with personal genome testing, but also to help ensure that genetic testing is the result of an autonomous decision rather than the 'inconsiderate' acceptance of a commercial offer. Given the unequalled quantity, complexity and diversity of the information involved in personal genome testing, however, the construction of adequate informed consent and the enabling of autonomous decision-making will be a major challenge. We suggest that it could be helpful to differentiate the testing offer, to make the aim(s) of testing explicit to the

consumer as part of the pre-test information provision process, and to have the scope of testing correspond with these aims. This means that separate informed consent could be asked for (categories of) tests that are associated with different aims – and preferably also for (categories of) tests that are associated with a higher potential for harm.

A further issue arises when additional stakeholders are taken into account, namely children. Parents are increasingly interested in ordering (DTC) genetic testing for their children, also for late-onset diseases,[28] and diseases for which there are no treatment options.[29] It has been found that many providers do indeed perform genetic testing in children and minors.[30] This practice runs against the broad consensus among researchers, clinicians and policymakers that predictive genetic testing of children should not be allowed unless there is clear medical benefit to be obtained through early interventions in childhood, which cannot otherwise be attained.[31] Professional guidelines indicate that testing should be deferred until adulthood.[32] It would be inconsistent to allow private companies to act differently in this regard.

Discussion: Informed consent and the new genetics

We have discussed three contexts of the new genetics and their implications for the principle of respect for autonomy. Although the neonatal, prenatal and DTC testing contexts each raise different sets of questions, common issues can be identified. Three main issues merit further ethical reflection and discussion: first, the original aims of testing and screening are subject to change and tend towards increasing choice while not necessarily increasing well-considered, autonomous choice. Second, the notion of individualised choice needs fleshing out in the different contexts, with special attention to the variety of stakeholders involved, including (future) children. And lastly, the interpretation and practice of informed consent needs adjustments to meet the challenges raised by the introduction of the new genetics.

Since the scope of genetic testing and screening offers both within and outside of healthcare is expanding, the aims of testing and screening are shifting

accordingly. In new-born screening, direct medical benefit seems no longer the single aim of screening. Parents may benefit from knowing early that their child will develop a disease in childhood or is carrier of a mutation, as they can use this information to decide about future pregnancies. Also in DTC personal genome testing, the aims of testing seem to include broader notions of utility. Testing for incurable diseases such Alzheimer's disease, for example, may help at-risk individuals to prepare for the future.[33] In all three contexts, however, it holds that more choice is not necessarily better than less, because choices imply costs as well as benefits: they require time and resources, and they entail burdens and responsibilities.[34] As a result, maximising information or choice is not always beneficial, but may undermine comprehension and autonomous decision-making.[35] Respect for autonomy and adequate informed consent thus seem to demand a trade-off between maximising choice on the one hand, and keeping information relevant and comprehensible on the other hand.

The notion of individualised choice requires serious ethical consideration. Irrespective of whether tests have a narrow or broad scope, a standard offer means that the scope of testing is determined by others than the tested individuals themselves (by 'tested individuals' or 'persons to be tested' in this context we mean pregnant women or couples, parents of new-borns or adult individuals to be tested). On the one hand, standard offers may fail to take into account the different preferences of persons to be tested. Ignoring the technological possibilities to enable individuals to take some control over the scope of testing and screening and opting for a traditional 'take it or leave it' approach would be difficult to justify, as it would disregard opportunities to improve autonomy. On the other hand, it will not be feasible nor desirable to give individuals complete control over the testing process. In the prenatal setting, for instance, not all parental wishes regarding genetic testing of their unborn children should be granted, as they may run counter to the principle of respect for the autonomy of the future child. The (legitimate) purpose of prenatal screening is not to offer limitless insight into the genetic make-up of a future child. A similar issue applies to new-born screening programmes: parental control over the screening offer could and should be limited, in cases of harm to the child or disrespect for the autonomy of the adult-to-be. It is our

general contention that the right to self-determination of the child may trump parental choice.

When considering individualised choice, it is important to acknowledge all stakeholders involved, particularly the future child and the adult-to-be. Thus, the principle of respect for autonomy may be best served through a middle way between a standard offer and individualised choice: a differentiation and pre-structuring of the testing or screening offer, a 'menu of options'[36] from which persons to be tested may legitimately choose. With regard to (the aim of) prenatal screening this means that testing options should be limited to conditions that meet a clear reproductive interest of the prospective parents,[37] in order to avoid harming the future child's autonomy rights. A form of 'conditional access' would be needed and would require thorough genetic counselling. Pregnant women should be strongly discouraged from having their foetus tested for late-onset disorders if they are not willing to terminate the pregnancy in case a mutation is found. Conditional access would mean that the traditional non-directive character of counselling should be abandoned. Obviously, however, it would not only be difficult, but also undesirable to enforce abortion in case of a positive test result. Ultimately in these matters, voluntariness remains a basic ethical requirement. But it should be clear that testing for (genetic susceptibilities to) late-onset diseases should preferably not be conducted in pregnancies which – regardless of test outcomes – will be carried to term, that is to say: not in future children.

Finally, the notion of informed consent itself may need revision in light of the new genetics. There are important differences between the tests included in broad testing or screening offers, both in terms of clinical validity and utility (some may be highly predictive and have implications for clinical decision-making, others less so) and in terms of characteristics of diseases tested for.[38] For example, not everyone will want to know their genetic risk for diseases for which there are no treatment or preventive options,[39] or for psychiatric diseases.[40] In the DTC context, such information may come as a terrible surprise for consumers who have purchased a very broad personal genome test without much thought as to its precise contents, without having given informed consent, and thus without (mental) preparation for the receiving of such test

results.[41] Differentiation of the testing offer and adequate procedures for informed consent will be indispensable protective shields against the potential harms of expanding genetic testing and screening offers, whether offered within (public) healthcare or outside.

The aim of informed consent in the context of the new genetics should in our opinion be to improve informed and autonomous decision-making with regard to genetic testing and screening. As a consequence of the quantity, complexity and diversity of information possibly involved, detailed and specific consent will simply not be possible. Therefore, informed consent requires a new model. Generic consent, which focuses on general concepts and common-denominator issues, seems a viable and often-mentioned alternative.[42] But ideally - and in line with the proposed differentiation and pre-structuring of the testing offer - a generic consent process should also be differentiated, for if pre-test information is too generic, it may fail to constitute informed consent. The aim is to render pre-test information manageable and comprehensible in order to maximise understanding, without failing to convey important messages about the different versions of testing offers and to enable considered and informed decisions with regard to the scope of testing to be conducted. Generic but differentiated consent should allow persons to opt out of receiving information about themselves or their children that they may not wish to receive or that may harm them. The facilitation of informed consent for an 'individualised' version of a testing or screening offer is a minimal condition for any responsible offer of a genetic (screening) test. Empirical research will be needed to determine effective ways of designing adequate consent procedures in the context of the new genetics.

Concluding Remarks

New genetic and genomic technologies such as micro-array and whole-genome or whole-exome sequencing technologies are technical means to generate genetic and genomic data, not medical tests in themselves. They have, however, brought along a tendency to expand the scope of testing and screening. We have discussed three areas in which new genetics technologies are currently gaining

ground – new-born screening, prenatal screening and DTC personal genome testing – and the implications of expansions of testing offers for the principle of respect for autonomy and informed consent. We have seen that an expansion of testing offers may yield valuable information and medical benefits, and may enhance autonomous (reproductive) choice. There are however moral limits to these expansions. When testing (unborn) children, the right not to know and the right to self-determination of the (future) child should be respected. This means that the scope of new-born screening should be restricted to childhood diseases only, and that access to prenatal testing for late-onset diseases should be conditional. DTC personal genome testing should not be conducted on children or minors.

The new genetics enable persons to be tested to have a say in determining the scope of testing and screening offers, and thereby to improve autonomous decision-making with regard to genetic testing or screening. To achieve this, standardised approaches to the design of testing and screening offers may need to be replaced by differentiated or individualised approaches that take into account individual informational preferences. In the context of new-born screening programmes, for instance, this means that there are strong ethical arguments for allowing parents to choose whether or not to have their new-born child tested for childhood diseases for which there are no therapeutic or preventive options.

Still, due to the quantity, complexity and diversity of the information involved in genome-wide tests, the new genetics may threaten comprehension of pre-test information and thus hinder informed decision-making. The traditional model of detailed informed consent is no longer tenable for genome-wide genetic tests. Therefore, we support instead a generic but differentiated approach to informed consent, which aims to convey important information about (categories of) diseases tested for and to enable informed and autonomous decision-making for or against specific versions of the testing offer. By placing limits on the scope of testing and by requiring generic but differentiated consent, a morally responsible design of genetic testing and screening practices – respecting the individual autonomy of both adults and (future) children – may be possible.

References

1. Davies K. 2010. The $1,000 Genome: The Revolution in DNA Sequencing and the New Era of Personalized Medicine. New York: Free Press.

2. de Jong A., W.J. Dondorp, S.G.M. Frints, C.E.M. de Die-Smulders and G.M.W. de Wert. 2011. Advances in prenatal screening: the ethical dimension. Nature Reviews Genetics 9: 657-663.

3. Solomon B.D., D.E. Pineda-Alvarez, K.A. Bear, J.C. Mullikin and J.P. Evans. 2012. Applying genomic analysis to newborn screening. Molecular Syndromology 3: 59-67; Tarini B.A. and A.J. Goldenberg. 2012. Ethical issues with newborn screening in the genomics era. Annual Review of Genomics and Human Genetics 13: 381-393.

4. Collins F.S. 2010. The Language of Life: DNA and the Revolution in Personalized Medicine. New York: Harper .

5. 23andme: http://www.23andme.com; Navigenics: http://www.navigenics.com; deCODEme: http://www.decodeme.com; Pathway Genomics: http://www.pathway.com.

6. Dondorp W. and G. de Wert. 2010. The 'Thousand-Dollar Genome': An Ethical Exploration. The Hague: Health Council of the Netherlands.

7. European Commission. 2004. 25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing. Brussels: European Commission.

8. Brownsword R. and D. Beyleveld. 2007. Consent in the Law. Oxford: Hart Publishing.

9. Faden R.R. and T.L. Beauchamp. 1986. A History and Theory of Informed Consent. Oxford: Oxford University Press.

10. Wertz D., J. Fletcher and K. Berg. 2003. Review of Ethical Issues in Medical Genetics. Geneva: World Health Organization; Kääriäinen H., M. Hietala, U. Kristoffersson et al. 2008. Recommendations for genetic counselling related to genetic testing. EuroGentest Unit 3.

11. Khoury M.J., W. Burke and E.J. Thomson (eds). 2000. Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease. Oxford: Oxford University Press .

12. Wilson J.M. and Y.G. Jungner. 1968. Principles and Practice of Screening for Disease. Geneva: World Health Organization.

13. Ross L.F. 2006. Screening for conditions that do not meet the Wilson and Jungner criteria: the case of Duchenne muscular dystrophy. American Journal of Medical Genetics 140A: 914-922 .

14. Solomon et al., op. cit. note 3.

15. Human Genetics Commission (HGC). 2005. Profiling the Newborn: A Prospective Gene Technology? London: HGC.

16. Nijsingh N. 2007. Informed consent and the expansion of newborn screening. In: Ethics, Prevention, and Public Health. Dawson A. and M. Verweij (eds). Oxford: Oxford University Press (pp. 198-213).

17. Dondorp W. B. Sikkema-Raddatz, C. de Die-Smulders and G. de Wert. 2012. Arrays in postnatal and prenatal diagnosis: an exploration of the ethics of consent. Human Mutation 33: 916-922.

18. van El C., T. Pieters and M. Cornel. 2012. Genetic screening and democracy: lessons from debating genetic screening criteria in the Netherlands. Journal of Community Genetics 3: 79-89; Gezondheidsraad (Health Council of the Netherlands). 2001. Prenatal Screening. Down's Syndrome, Neural Tube Defects, Routine-Ultrasonography. The Hague: Health Council of the Netherlands .

19. De Jong et al., op. cit. note 2.

20. Dondorp et al., op. cit. note 17.

21. Bui T-H., A. Vetro, O. Zuffardi and L.G. Shaffer. 2011. Current controversies in prenatal diagnosis 3: Is conventional chromosome analysis necessary in the post-array CGH era? Prenatal Diagnosis 31: 235-243; Grimshaw G.M., A. Szczepura, M. Hultén, F. MacDonald, N.C. Nevin, F. Sutton and S. Dhanjal.

2003. Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities. Health Technology Assessment 7: 1-146.

22. DNA Direct: http://www.dnadirect.com.

23. 23andme: http://www.23andme.com.

24. Hogarth S. 2010. Myths, misconceptions and myopia: searching for clarity in the debate about the regulation of consumer genetics. Public Health Genomics 5: 322-326; Borry P., R.E. van Hellemondt, D. Sprumont et al. 2012. Legislation on direct-to-consumer genetic testing in seven European countries. European Journal of Human Genetics 20: 715-721.

25. Bunnik E.M., A.C.J.W. Janssens and M.H.N. Schermer. 2012. Informed consent in direct-to-consumer personal genome testing: the outline of a model between specific and generic consent. Bioethics Nov 8. doi: 10.1111/bioe.12004 [Epub ahead of print]; Lachance C.R. Lachance C.R., L.A. Erby, B.M. Ford, V.C. Allen and K.A. Kaphingst. 2010. Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genetics in Medicine 12: 304-312.

26. Messner D.A. 2011. Informed choice in direct-to-consumer genetic testing for Alzheimer and other diseases: lessons from two cases. New Genetics and Society 30(1): 59-72; Leighton J.W., K. Valverde and B.A. Bernhardt. 2012. The general public's understanding and perception of direct-to-consumer genetic test results. Public Health Genomics 15: 11-21.

27. Wilson and Jungner, op. cit. note 12.

28. Tercyak P.K., S. Hensley Alford, K.M. Emmons, I.M. Lipkus, B.S. Wilfond and C.M. McBride. 2011. Parents' attitudes toward pediatric genetic testing for common disease risk. Pediatrics 127: 1288-1295.

29. Tarini B.A., D. Singer, S.J. Clark and M.M. Davis. 2009. Parents' interest in predictive genetic testing for their children when a disease has no treatment. Pediatrics 124: 432-438.

30. Borry P., H.C. Howard, K. Sénécal and D. Avard. 2010. Health-related direct-to-consumer genetic testing: a review of companies' policies with regard to genetic testing in minors. Familial Cancer 9: 51-59; Howard H.C., D. Avard and P. Borry. 2011. Are the kids really all right? Direct-to-consumer genetic testing in children: are company policies clashing with professional norms? European Journal of Human Genetics 19: 1122-1126.

31. de Wert G.M.W.R. 1999. Met het Oog op de Toekomst: Voortplantingstechnologie, Erfelijkheidsonderzoek en Ethiek. Amsterdam: Rozenberg Publishers [in Dutch]; Borry P., G. Evers-Kiebooms, M.C. Cornel, A. Clarke and K. Dierickx. 2009. Genetic testing in asymptomatic minors: background considerations towards ESHG recommendations. European Journal of Human Genetics 17: 711-719.

32. American College of Medical Genetics (ACMG). 1995. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Journal of Human Genetics. 57: 1233-1241.

33. Rahman B., B. Meiser, P. Sachdev, K. Barlow-Stewart, M. Otlowski, E. Zilliacus and P. Schonfield. 2012. To know or not to know: an update of the literature on the psychological and behavioral impact of genetic testing for Alzheimer disease risk. Genetic Testing and Molecular Biomarkers 16: 935-942.

34. Schwartz B. 2004. The Paradox of Choice: Why More is Less. New York: HarperCollins Publishers.

35. Ormond K.E. M. Iris, S. Banuvar, J. Minogue, G.J. Annas and S. Elias. 2007. What do patients prefer: informed consent models for genetic carrier testing. Journal of Genetic Counseling 16:539-550 .

36. Rothstein M.A. 2006. Tiered disclosure options promote the autonomy and well-being of research subjects. American Journal of Bioethics 6: 20-21; Bredenoord A.L., N.C. Onland-Moret and J.J. van Delden. 2011. Feedback of individual genetic results to research participants: in favor of a qualified disclosure policy. Human Mutation 32: 861-867.

37. Dondorp et al., op. cit. note 17.

38. Bunnik E.M., M.H. Schermer and A.C. Janssens. 2012. The role of disease characteristics in the ethical debate on personal genome testing. BMC Medical Genomics 19:4.

39. Morrison P.J. 2010. Accurate prevalence and uptake of testing for Huntington's disease. Lancet Neurology 9(12): 1147.

40. Laegsgaard M.M., A.S. Kristensen and O. Mors. 2009. Potential consumers' attitudes toward psychiatric genetic research and testing and factors influencing their intentions to test. Genetic Testing and Molecular Biomarkers 13: 57-65.

41. Messner, op. cit. note 12.

42. Elias S. and G.J. Annas. 1994. Generic consent for genetic screening. New England Journal of Medicine 330: 1611-1613.

Chapter 9

Personal utility in genomic testing: Is there such a thing?

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Under review

Abstract

In ethical and regulatory discussions on new applications of genomic testing technologies, the notion of 'personal utility' has been mentioned repeatedly. It has been used to justify direct access to commercially offered genomic testing or feedback of individual research results to research or biobank participants. Sometimes research participants or consumers claim a right to genomic information with an appeal to personal utility. As of yet, no systematic account of the umbrella notion of personal utility has been given. This paper offers a definition of personal utility that places it in the middle of the spectrum between clinical utility and personal perceptions of utility, and that acknowledges its normative charge. The paper discusses two perspectives on personal utility, the healthcare perspective and the consumer perspective, and argues that these are too narrow and too wide, respectively. Instead, it proposes a normative definition of personal utility that postulates information and potential use as necessary conditions of utility. This definition entails that perceived utility does not equal personal utility, and that expert judgment may be necessary to help determine whether a genomic test can have personal utility for someone. Two examples of genomic tests are presented to illustrate the discrepancies between perceived utility and our proposed definition of personal utility. The paper concludes that while there is room for the notion of personal utility in the ethical evaluation and regulation of genomic tests, the justificatory role of personal utility is not unlimited. For in the absence of clinical validity and reasonable potential use of information, there is no personal utility.

Introduction

Over the past decade, commercial companies have started to market broad genomic tests that estimate genetic susceptibilities to various types of complex diseases in adults [1] or screen for carrier status for recessive monogenic disorders in prospective parents.[2] Some of these tests contain risk estimates for non-medical information as well, such as information about ancestry, paternity or other phenotypic traits, such as freckling and eye colour.[1] Broad genomic tests have given rise to ethical and regulatory discussions, in which concerns are expressed with regard to quality assurance, psychological and social risks and implications of testing, and informed consent. Moreover, it is not clear whether commercially offered genomic testing leads to health benefit.[3] Lately, however, health benefit no longer seems to be prerequisite to what is considered a morally responsible genomic testing offer. Other, non-clinical benefits are gaining in importance.

In ethical and regulatory discussions of emerging genomic testing applications, the notion of personal utility has been mentioned repeatedly,[4, 5] often in a normative manner. Sometimes it is used as a moral justification of direct access to commercially offered genomic testing,[6] or as a basis for a moral claim right to feedback of individual genomic test results in the context of research.[7, 8] Personal utility has been suggested as a complement to traditional criteria in the (ethical) evaluation of genetic or genomic testing.[4, 5] The notion of personal utility is an umbrella term which may serve different, even opposing agendas. For instance, whereas proponents of direct access to commercially offered genomic testing consider personal utility to be a valid rationale for the provision of testing, those thinking from a medical perspective may feel that in policy decisions with regard to the provision or reimbursement of genomic tests within the healthcare system, personal utility should have no role. This paper explores the contested notion of personal utility in the context of genomic testing, and not only demarcates the notion, but also discusses whether it can justify the (direct-to-consumer) provision or reimbursement of genomic testing.

Traditional assessment of genomic testing

Genetic and genomic tests are generally systematically assessed before policy decisions are made regarding clinical or public health implementation and reimbursement. Evaluative frameworks for the assessment of genomic tests may vary, but have a set of key criteria in common: analytic validity, clinical validity and clinical utility (see Textbox 3).[9] Roughly, analytic validity is the ability of a test to detect the intended genetic variant(s). Clinical validity is the ability of a test to identify individuals with the intended phenotype, i.e. a disease or a risk factor for a disease (predictive ability). And clinical utility is the ability of a test to lead to improved health outcomes. Traditionally, it is thought that a morally responsible genetic or genomic testing or screening offer should meet all three criteria.

Analytic validity
How accurately and reliably the test measures the genotype(s) of interest.

Clinical validity
How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.

Clinical utility
How likely the test is to significantly improve patient outcomes.[10]

Textbox 3: Traditional assessment of genetic and genomic (screening)tests

Many new commercially offered broad genomic tests are of high analytic validity, for the sequencing or microarray-based technologies used are often accurate and reliable.[4] However, evidence for the clinical validity of many tests is lacking.[11] Most complex diseases, such as cardiovascular diseases, psychiatric disorders, auto-immune diseases and many types of cancer, are caused by an interplay of many genetic and non-genetic factors. Currently

available genomic tests for complex diseases map only a limited set of genetic factors per disease, and fail to take environmental factors into account. As a consequence, these tests will generate risk estimates that cannot distinguish reliably between individuals who are likely and individuals who are unlikely to develop such diseases. Monogenic diseases and phenotypic traits that are caused largely by a single mutation on the other hand can be predicted much more reliably through genomic testing.

The assessment of the clinical utility of a genomic test is complex, and allows for disagreement.[5] Clinical utility traditionally requires that the test affects patient management and that preventive or therapeutic options are available, accessible and effective. Also, the test should be (cost-)effective compared to existing tests or approaches.[4] This notion of clinical utility excludes genomic tests from which only general health recommendations (e.g. physical exercise, smoking cessation, a healthy diet) can be derived, and tests for diseases for which there are no preventive or therapeutic options. Current commercially offered genomic testing services largely consist of these types of tests.

Alternative, wider notions of the clinical utility of present-day genomic tests have been proposed, which embrace the full range of the effects, positive and negative, that tests may have on patients.[12] For example, if a genomic test for obesity may increase the motivations of at-risk individuals to lose weight, this can be considered a positive behavioural effect of testing, thus ceteris paribus rendering the genomic test clinically useful. Wider notions of clinical utility also encompass emotional effects, such as reassurance or anxiety, social effects, such as changing family dynamics and stigmatisation, and cognitive effects, such as improved disease understanding.[12] As they cover 'the full range of effects' they will also cover effects on reproductive decision-making. However, in our view, to include emotional and social effects or the aim of enhancing reproductive autonomy in a notion of clinical utility is to overstretch the notion. The ethical and regulatory debate is better served by a narrower notion of clinical utility covering foremost clinical or medical harms and benefits and a complementary notion of personal utility encompassing non-clinical dimensions of testing.

Two perspectives on the notion of personal utility

In the ethical and regulatory debate, the notion of personal utility has been used at various occasions and in various ways. It usually covers personal rationales for and effects of testing, some of which may be health-related and some of which may not. Two prominent and recurring perspectives on personal utility are the following:

The healthcare perspective: meaningful options

The notion of personal utility is not foreign to traditional clinical genetic testing. In specialised clinical genetics centres in many countries, genetic testing is offered and reimbursed also when there is limited potential to improve health outcomes (no clinical utility), for instance in Huntington's disease, for which no preventive or therapeutic options are available. Although genetic testing will not alter the clinical management of Huntington's disease, it may have major psychological, social and practical benefits - and thus personal utility - for at-risk individuals.[9] Some current commercial genomic tests include testing for Alzheimer's disease,[1] which, in contrast to genetic testing for Huntington's disease, does not offer a pre-symptomatic diagnosis but a risk estimate. Still, a 'negative' test result may offer relief and reduce uncertainty and anxiety, whereas consumers with a highly increased risk may undertake psychological and practical preparations for a possible future. Research participants have reported that genomic testing for Alzheimer's disease may be a coping strategy,[13] and a source of valuable information for making important life decisions,[14] for tested individuals themselves as well as for their family members. It is a matter of debate whether such psychological and personal options fit within the goals of medicine. If so, personal utility can serve as a criterion in the (ethical) evaluation of genomic tests, also in the clinical setting. It will however not be overriding. The weight of personal utility in the overall assessment of a genomic test will depend *inter alia* on the disease tested for (e.g. the severity of the disease) and on the clinical validity of the test. For example, genomic testing for Alzheimer's disease is not (yet) offered through the clinic because of its moderate clinical validity. Thus, from a healthcare perspective,

personal utility can (but need not) be a reason to provide and/or reimburse genomic testing, when clinical utility (i.e. treatment) is lacking.

Likewise, in the field of public health, notions of utility have evolved and expanded. Central to the evaluation of population screening programmes is the principle that the benefits of a programme must outweigh the harms and burdens (e.g. false positives).[15] The benefits of screening were traditionally defined in terms of preventive or curative options. However, as opportunities for prenatal screening increased, the view arose that lack of treatment does not necessarily mean that screening is not worthwhile.[16] Screening can be aimed at informed choices regarding reproduction,[16] at the offering of 'meaningful action options.'[17] The criterion of clinical utility evolved from treatability to 'actionability,' and actionability became a justification of population screening. Strictly speaking, since reproductive options do not lead to improved health outcomes (in the foetus), they are not part of the clinical utility of a prenatal screening test. Rather, they are an example of (health-related) personal utility for the parents.

Notions of personal utility that have arisen within the healthcare perspective retain their associations with the goals, norms and values of healthcare. For instance, while one article defines personal utility as "those benefits or harms that are manifested primarily outside medical contexts,"[5] its examples are reinforced compliance, awareness of health risks, personal accountability for health-related choices and increased health-seeking behaviours. From a healthcare perspective, personal utility often remains health-related utility and tends to remain based on the medical-ethical principle of beneficence. Genomic information has personal utility, for instance, on the condition that it is "relevant to well-being."[5] The healthcare perspective on personal utility may be too narrow, however, for there are other (than health-related) ways in which genomic information can be personally useful.

The consumer perspective: my genome, my self

In contrast to the healthcare perspective, the consumer perspective is characterised by autonomy as a leading moral principle. "For better or for worse, people will want to know about their genomes,"[18] because people will want to know about themselves. Many consumers do not turn to commercially offered genomic testing for specific health problems. Rather, they seek such testing 'out of curiosity,' for the 'fun factor,'[19] because they self-identify as early adopters of new technologies, or because they wish to contribute to genomics research. There appears to be a trend of 'appropriation' or ownership and control of genomic information among research participants and consumers. People feel they should be able to own their genomic data, and wish to "know as much as possible" about their genetic make-up.[20] They even claim a "sense of personal entitlement to that knowledge."[21] The consumer perspective implies that there is personal utility in the sheer possession of one's genomic data. Participation, access and self-determination are its core values.

The notion of personal utility is repeatedly referred to in the recent literature on preferences of research participants regarding the return of findings from genomics studies or biobanks. Research participants often prefer to receive a wide set of individual test results, even when these results are not validated or have little clinical significance.[8] While researchers and clinicians often feel that results of unclear significance should not be reported,[22] participants indicate that 'information is information' and point out that the results have personal utility.[8] Seen from the consumer perspective, consumers or research participants themselves should decide whether or not a genomic test has personal utility, on the basis of their subjective experiences. The consumer notion of personal utility is not restricted to well-being, and may even be wider than the psychological, social and emotional benefits of testing. Genomic testing is not required to bring benefits at all - it may just bring entertainment or satisfy curiosity. Personal utility may reside even in something like 'the value of information per se.'[23] The consumer perspective on personal utility will not be tenable across the board, for, as will be argued, there is no such thing as personal utility in 'information per se,' especially when its significance is unclear.

What is personal utility? A definition

An adequate definition of personal utility should seek a middle ground between the healthcare perspective and the consumer perspective to do justice to both components of the term. It should also take note of the implicit normative charge of the term, for the claim that a test has personal utility implicitly suggests that it has value. It is a positive evaluative judgment. Because of this normative charge, inflation of the term should be avoided: if genomic tests are attributed personal utility whenever someone takes any form of interest in them, the term can no longer be used in ethical or regulatory discussions to distinguish between useful tests and useless (or less useful) tests.

This paper proposes the following tentative definition: genomic information has personal utility if and only if it can reasonably be used for decisions, actions or self-understanding that are personal in nature. It can be personally useful to know that one is carrier of a mutation that causes Huntington's disease. In theory, it can be personally useful to know, for instance, about one's paternity, muscle type, memory, baldness, carrier status or metabolism – on the condition that these traits can be reliably predicted (oftentimes, they cannot). Personal utility can be (indirectly) related to health and disease, but is distinguished from clinical utility because it does not affect clinical management or lead to improved health outcomes.

The proposed definition of personal utility presupposes two things: that a genomic test delivers information (i.e. meaningful information) and that this information can be used or put to use in some reasonable way. This means that raw data do not have personal utility, since data themselves do not yet constitute information. Furthermore, a genomic test of limited clinical validity, which fails to consistently and accurately predict a phenotype of interest, does not convey meaningful, informative results and thus cannot have personal utility. In fact, it cannot have any utility at all, neither clinical nor personal. Research participants have been found to prefer 'even uninterpretable information'[24] to be reported back, with an appeal to personal utility. According to our definition, there can be no personal utility in uninterpretable information, for uninterpretable information is a contradiction in terms.

Second, genomic information of personal utility should have a purpose. According to the proposed definition, 'just wanting to know' is not a form of personal utility. Neither are mere entertainment or curiosity value. An exemplary case is the Asparagus Metabolite Detection test,[1] which estimates an individual's ability to detect the distinct smell of a metabolite called methanethiol, a sulfur-containing compound which is found in urine after eating asparagus. As the test is of limited clinical validity, it cannot determine whether or not someone has this ability, but only indicates slightly increased or decreased odds. Although consumers may perceive some sort of value in such testing (e.g. they may simply 'enjoy knowing' that their odds of having the ability to smell asparagus in urine are slightly increased, or they may wish to tell their friends about their testing experience), the 'information' conveyed does not answer the question: 'do I have this ability?', nor is it actionable in any reasonable way. The Asparagus Metabolite Detection test thus has no personal utility, for there is no 'reasonable personal use' for it.[25]

From the proposed definition it follows that not all claims to personal utility are equally valid. Consumers or research participants may not always be in the best position to judge whether a genomic test has personal utility. Expert judgment, especially of clinical validity, is indispensable.[26] Although consumers should be free to decide what values or goals (if any) they seek to attain through genomic testing, experts should determine whether a particular genomic test can provide the (clinical or personal) utility sought. Individual consumers or research participants may claim or perceive personal utility where there is none. Perceived utility does not equal personal utility. If genomic information is not valid and/or cannot be used in any reasonable way, there is no utility in that information.

Do genomic tests have personal utility? Two examples

There is no single answer to the question whether genomic tests have personal utility. Personal utility comes in degrees and can be established only on a case-by-case basis, for it relies upon a fit between test characteristics (e.g. clinical validity) and the individual context of testing, notably on the purpose of testing

or on the question for which testing is sought. Expert judgment may be required to assess whether or not there is personal utility in a particular genomic test in a particular context. Two examples serve to illustrate this point.

Muscle Performance testing: clinical validity

Mr. A wants to take up sports, but is unsure whether to start training for a marathon or play squash. To learn which of the sports best suits him, Mr. A orders a Muscle Performance test from a direct-to-consumer company that maps a gene called ACTN3,[1] which encodes for the production of alpha-actinin-3 in fast-twitch muscle cells and is associated with power and sprint performance in Olympic athletes. Can the Muscle Performance test tell mr. A whether he is a sprinter or a marathoner? Mr. A turns out heterozygous for the ACTN3 gene. The one study that has been conducted in non-professional athletes showed no or very small effects of the ACTN3 gene on running performance.[27] Testing for the ACTN3 gene in non-professional athletes like Mr. A thus has little clinical validity. Further, whether mr. A is a sprinter or a marathoner is determined by a variety of factors besides alpha-actinin-3, ranging from the condition of his heart and the capacity of his lungs to his personal history of exercise and training, and above all else, his personal preferences. The Muscle Performance test is unable to answer Mr. A's question regarding sports suitability, for it has insufficient clinical validity in this context. And in the absence of clinical validity, there is no personal utility.

Testing for BRCA 1: context of testing

Mrs. B orders a Hereditary Cancer DNA Insight^{SM} test from an Internet-based commercial company [28] to find out whether she has an increased risk for hereditary breast cancer. Although breast cancer has not occurred among her many female relatives, Mrs. B has been reading about the disease and feels a pressing need to be reassured. The test is of high analytic and clinical validity: if the company finds a mutation in the BRCA1 or BRCA2 genes, Mrs. B will know that her risks of developing breast and ovarian cancer are very high. There are preventive options for hereditary breast cancer, such as surveillance and prophylactic surgery. Does the Hereditary Cancer DNA Insight^{SM} test have personal utility for Mrs. B?

As Mrs. B does not have a personal or family history of breast or ovarian cancer, the odds that she carries a BRCA1 or BRCA2 mutation are very low. The test is likely to come back negative. Mrs. B will feel relieved and perceive (personal) utility of testing. However, if Mrs. B's reason for purchasing the test was to be reassured about breast cancer (generally), not about a set of specific mutations that can cause hereditary breast cancer syndromes in affected families, this test has no utility for her. In feeling relieved after receiving negative test results, Mrs. B may not understand that she still has an average risk of 1 in 8 of developing breast cancer in her lifetime. She might even have a different mutation causing breast cancer that was previously unknown and therefore not covered by the test. In a worst-case scenario, Mrs. B, falsely reassured, may ignore a developing lump and see a doctor when it is too late for effective treatment. Notwithstanding Mrs. B's perception of utility, it must be concluded that the Hereditary Cancer DNA Insight℠ test has little personal utility for Mrs. B. To the contrary, Mrs. B had better not use this test for the purposes of reassurance with regard to breast cancer.

It should be noted that measures of utility may be different for Miss C, who does not know her family history because she has been adopted as a young girl. Miss C has witnessed the impact of hereditary breast cancer on the life of a close friend. Miss C wants to know whether she might be affected by a similar hereditary condition. Although Miss C's odds of having a BRCA1 or BRCA2 mutation are low, they are not absent, and a test will reliably detect these mutations if they are present. It is not unreasonable for Miss C to order genomic testing. Testing may have personal utility for her.

Conclusions: Limits of personal utility

Genomic sequencing is on its way to become widespread, through research, in the clinic and on the direct-to-consumer market. Around the world, researchers, clinicians, ethics committees and participant representatives are directing their efforts toward policies for the interpretation and feedback of genomic data in the context of genomics or biobank research. Although understandably, research participants, consumers and patients may wish to know 'all there is to know' or

'as much as possible,' these preferences do not automatically justify a claim right based on personal utility. From the fact that consumers or participants perceive (clinical or personal) utility in genomic information it does not follow that this information has utility. There is no utility in uninterpretable, meaningless or useless information or in information that cannot answer the question with which testing was initiated. Consumers and research participants may need expert assistance to determine whether genomic information can have clinical or personal utility for them.

Many currently offered genomic tests for complex diseases and other traits are neither informative nor useful for decision-making - whether clinical or personal. Consumers may find entertainment value in such tests, or seek ownership of genomic information, which may be perfectly good reasons for consumers to pursue them. But entertainment value is not the same as utility. It need not follow that such genomic testing should be restricted, but it does follow that its provision cannot simply be justified on the basis of - perceived - utility (for there is none).

Although personal utility does not provide an overriding argument for (direct) access to genomic testing, expert judgment of personal utility can serve as a criterion in the ethical evaluation and regulation of genomic tests. It can function as an addition or alternative to the traditional criterion of clinical utility. After all, there are reasonable uses of genomic information that are personal rather than clinical in nature (e.g. paternity testing or testing for certain phenotypic traits). Personal utility can be weighed differently from one individual testing context to the next. Where there is sufficient clinical validity and little risk of harm, personal utility may constitute a net benefit and might work to justify a direct-to-consumer genomic testing offer. And just like clinical genetic testing for Huntington's disease, genomic testing that improves well-being and meets the goals of medicine may be eligible for provision and reimbursement through the healthcare system, even in the absence of clinical utility. An appeal to personal utility is well-founded however only on the conditions of clinical validity and reasonable use.

References

1. 23andme: http://www.23andme.com.

2. Counsyl: http://www.counsyl.com.

3. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534.

4. Khoury M.J., C.M. McBride, S.D. Schully et al. 2009. The Scientific Foundation for Personal Genomics: recommendations from a National Institutes of Health - Centers for Disease Control and Prevention multidisciplinary workshop. Genetics in Medicine 11: 559-567.

5. Foster M.W., J.J. Mulvihill and R.R. Sharp. 2009. Evaluating the utility of personal genomic information. Genetics in Medicine. 11: 570-574.

6. Vayena E. and B. Prainsack. 2013. The challenge of personal genomics in Germany. Nature Biotechnology 31(1): 16-17.

7. McGuire A.L. and J.R. Lupski. 2010. Personal genome research: what should the participant be told? Trends in Genetics 26(5): 199-201.

8. Daack-Hirsch S., M. Driessnack, A. Hanish et al. 2013. 'Information is information': a public perspective on incidental findings in clinical and research genome-based testing. Clinical Genetics 84(1): 11-18.

9. Grosse S.D., L. Kalman and M.J. Khoury. 2010. Evaluation of the validity and utility of genetic testing for rare diseases. Advances in Experimental Medicine and Biology 686: 115-131.

10. ACCE: http://www.cdc.gov/genomics/gtesting/ACCE/ [Accessed 7 February 2014].

11. Kalf R.R., R. Mihaescu, S. Kundu, P. de Knijff, R.C. Green and A.C. Janssens. 2013. Variations in predicted risks in personal genome testing for common complex diseases. Genetics in Medicine [Epub ahead of print].

12. Bossuyt P.M., J.B. Reitsma, K. Linnet and K.G. Moons. 2012. Beyond diagnostic accuracy: the clinical utility of diagnostic tests. Clinical Chemistry 58(12): 1636-1643.

13. Gooding H.C., E.L. Linnenbringer, J. Burack, J.S. Roberts, R.C. Green and B.B. Biesecker. 2006. Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. Patient Education and Counseling 64: 259-267.

14. Kopits I.M., C. Chen, J.S. Roberts, W. Uhlmann and R.C. Green. 2011. Willingness to pay for genetic testing for Alzheimer's disease: a measure of personal utility. Genetic Testing and Molecular Biomarkers 15: 871-875.

15. Wilson J.M.G. and G. Jungner. 1968. Principles and Practice of Screening for Disease. Geneva: World Health Organization.

16. Nuffield Council on Bioethics. 1993. Genetic Screening: Ethical Issues. London: Nuffield Council on Bioethics.

17. Van El C.G., M.C. Cornel, T. Pieters and E.S. Houwaart. 2010. Witness Seminar: Debatteren over Genetische Screeningscriteria. Houten: Prelum Uitgevers [in Dutch].

18. Pinker S. 2009. My genome, my self. New York Times Magazine (7 January 2009).

19. Vayena E., E. Gourna, J. Streuli, E. Hafen and B. Prainsack. 2012. Experiences of early users of direct-to-consumer genomics in Switzerland: an exploratory study. Public Health Genomics 15(6): 352-362.

20. Levitt D.M. 2001. Let the consumer decide? The regulation of commercial genetic testing. Journal of Medical Ethics 27(6): 398-403.

21. Geransar R. and E. Einsiedel. 2008. Evaluating online direct-to-consumer marketing of genetic tests: informed choices or buyers beware? Genetic Testing 12(1): 13-23.

22. Kohane I.S. and P.L. Taylor. 2010. Multidimensional results reporting to participants in genomic studies: getting it right. Science Translational Medicine 2(37): 37cm19.

23. Grosse S.D. and M.J. Khoury. 2006. What is the clinical utility of genetic testing? Genetics in Medicine 8: 448-450.

24. Facio F.M., H. Eidem, T. Fisher et al. 2013. Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. European Journal of Human Genetics 21(3): 261-265.

25. Roundtable on Translating Genomic-Based Research for Health. 2010. The Value of Genetic and Genomic Technologies: Workshop Summary. Washington, DC: The National Academic Press.

26. McGuire A.L., L.B. McCullough and J.P. Evans. 2013. The indispensable role of professional judgment in genomic medicine. Journal of the American Medical Association 309(14): 1465-1466.

27. Moran C.N., N. Yang, M.E. Bailey et al. 2007. Association analysis of the ACTN3 R577X polymorphism and complex quantitative body composition and performance phenotypes in adolescent Greeks. European Journal of Human Genetics 15(1): 88-93.

28. Pathway genomics to launch Next-Generation Sequencing (NGS) comprehensive cancer panel including BRCA1 and BRCA2. In: Pathway Genomics Newsroom (13 June 2013).

Chapter 10

General discussion

Whereas genetics bears on relatively few families with rare heritable disorders, genomics touches all of us. Genomics teaches us about the complex diseases to which we are all - to lesser or more degrees - susceptible. As sequencing technologies are replacing SNP-based scanning technologies, genomics is quickly becoming clinically relevant to more and more people. Up close and personal. For we all carry with us a handful - or a few dozen - of Achilles' heels.

Over the past fifteen years, as genomic technologies have emerged and evolved, they have alternatively sparked hope and scepticism. On the one hand, they have shattered the crystal ball DNA was thought to be: we now know that the greater part of the genome has little predictive value. Observers fear that all the promises of genomics will get lost somewhere between bench and bedside.[1] Others feel, to the contrary, that 'the train has left the station', and that genomics will change the face of healthcare.[2] Truth usually hides in the middle. Genome interpretation is a major challenge. Even if sequencing soon becomes affordable to all, our genomes may not immediately flood us with useful information. In all likelihood, however, there will already be one or two things worth knowing in each and every one of us: our carrier status for autosomal recessive disorders that may guide our reproductive decisions, some sporadic or inherited mutations that may increase our disease risks significantly, or some pharmacogenomics markers that may help tailor our drug prescriptions. Everyone's genomes will contain a few 'breath-taking' mutations.[3] Base-pair by base-pair, I expect, we will proceed with the interpretation of our genomes.

Today, commercial companies have pre-emptively been marketing genomic testing to healthy individuals. This runs counter to one of the four classic principles of bio-medical ethics: non-maleficence. *Primum non nocere*: first, do no harm. Genomic testing - for the purposes of disease prediction - may bring harm beside good. It turns healthy persons - who are free from symptoms - into persons carrying all sorts of genomic health risks, into patients-to-be or 'unpatients'.[4] By disclosing disease risks, genomic testing 'generates' potential health problems where there were none before. Medical professionals are trained to regard predictive testing in healthy people with suspicion. Moreover, genomic risk prediction - for now - is wrapped in a high degree of uncertainty. Also, there is little evidence to suggest that people will profit from learning

about their genomes,[5] as they have not been found willing or able to adopt healthier lifestyles. There is no indication that any benefits of testing will outweigh potential psychological, social, financial and health-related costs and burdens. Especially in the light of limited clinical validity, it goes against traditional medical-ethical intuitions to offer genomic testing to the - healthy - public at all.

But what if people want to know about their genomes? Achilles knew about his weakness and had the opportunity to lead his life accordingly. Human beings have always wondered what the future has in store. The desire to know - and to control - our fates is deeply ingrained in our natures. Should people not decide for themselves whether they wish to access their genomes, whether to use their genomic information, and in what ways? If they are willing to pay for genomic testing out of pocket, must we withhold it from them? Must we keep consumers waiting until the genome is better understood? Must we let the perfect be the enemy of the good?[1]

Theoretical background and guiding principles

This thesis offers ethical guidance for the responsible provision of genomic testing, whether through commercial channels or within the context of healthcare systems. For there must be a middle way between a total ban on genomic testing and a policy of complete non-intervention. This middle way - our practical ethical approach toward genomic testing - is the topic of this general discussion.[2]

This research project has been led by four main questions: first of all, as the field of genomic testing is wide and manifold, any fruitful ethical examination of it

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[1] The expression is from Voltaire ("le mieux est l'ennemi du bien").[6] I am not the first to use it in the context of genomic testing.[7]

[2] Chapters 2-9 of this thesis have been written in close collaboration with my supervisors prof. Cecile Janssens and prof. Maartje Schermer. When referring to findings or insights derived from these chapters, I use the words 'we' and 'our'. In this general discussion, however, where I express my personal views, I sometimes make use of the words 'I' and 'me'. I apologise for any inconvenience this may cause to the reader.

stands in need of definition and demarcation (research question 1: What is genomic testing?). Then, it demands a typology of tests and their associated ethical issues (research question 2: What are the ethical issues?). Further, a central ethical issue that is common to genomic tests - of limited clinical validity - is what we have called the 'information problem', which flows from the quantity, complexity, disputability, fluidity and diversity of the information they yield. A model for informed consent is presented as a solution to this problem (research question 3: How should informed consent be made possible?). Other important ethical issues are the value - or utility - of genomic testing and its values (research question 4: What is personal utility?): the moral values and principles that are associated with its provision.

Before proceeding to discuss the four research questions, I will explain some of my own normative starting-points and principles: liberalism, respect for autonomy and protection against harm. These principles and positions underlie the approach taken within this research project and are *leitmotifs* throughout this thesis.[3] Together, they function as a framework for this general discussion, in which I attempt to present an interpretation and an ethical evaluation of genomic testing.

Liberalism

This research project has started from the broadly shared assumption that freedom is a vital value. By derivation, it endorses the values of liberty of choice, ease of access and autonomous decision-making. In this thesis we therefore assume that outright prohibition of commercially offered genomic testing is not desirable - or necessary.

[3] We pay ample attention to three of the four principles of bio-medical ethics - beneficence, non-maleficence and respect for autonomy - but less to the fourth, justice. We have focused mainly on the individual relationships between providers and consumers of testing. Justice plays an important role in various ethical and regulatory issues surrounding genomic testing (equity of access, clinical implementation and reimbursement, issues of discrimination and stigmatisation), which have not been the primary topics of our research project.

From a liberal starting-point, it may sometimes be advisable for the state, the healthcare system, professional organisations or functionaries, to restrict individual or corporate liberties, most notably when others may be harmed.[8] And especially when the interests of vulnerable groups, such as (unborn) children, are at stake (see chapter 8). In the context of genomic testing, restrictive measures may be aimed at the protection against the harms of misunderstanding, or at the enhancement or reinstallation of autonomy (see chapter 6). From a liberal point of view, restrictive measures should - at minimum - be proportionate and subsidiary.[4]

In many countries, including Germany, France, Switzerland and Portugal, it is illegal to offer genomic testing directly to consumers.[10] Through such legislation, healthcare systems retain or reclaim a monopoly on genomic testing. National legislators apparently presume that healthcare systems offer unique safeguards, standards, quality assurance, professional care and support, etc. Responsible provision of genomic testing, they apparently presume, is warranted by the involvement of medical professionals, who are endowed with fiduciary responsibilities and mores. This warranty, however, may be passing its expiration date.

Today, boundaries are blurring between healthcare providers and commercial companies, clinicians and researchers, consumers and research participants, physicians and patients.[11-13] Consumers are increasingly bypassing healthcare systems: they are seeking health information and medication online, through commercial companies, and pursuing health services across borders.[14-16] It may no longer be possible to halt these developments - to confine healthcare to the realm of the medical-professional.

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[4] The principle of proportionality is a traditional legal 'container' principle that states, for instance, that the seriousness of a restrictive intervention should befit the seriousness of the risk of harm associated with the restricted practice, or that a criminal sentence should befit the gravity of the crime committed. Subsidiarity is the idea that from a set of effective interventions, the least invasive is the most preferable, or the idea that regulatory tasks had best be taken up by the least centralised authorities. These two principles are part and parcel of the legislative processes of the European Union.[9]

Thus, genomic testing may continue to be offered by non-professional parties. If non-professionals do provide healthcare or health services, these parties need to take on some the mores and standards of healthcare, if they are to operate in a morally responsible manner. For this reason, we have posited general moral obligations for the provision of genomic testing (e.g. adequate pre-test information), which are not exclusive to - and need not be carried out by - healthcare professionals. Our practical ethical solutions (e.g. a tiered-layered-staged model for informed consent) do not necessitate the presence of healthcare professionals, and can be applied in an online, direct-to-consumer context as well as in a clinical or public health context. Non-professionals can ask informed consent, too. If need be, they can be forced to do so by law. Otherwise, standard-setting or self-regulation may be subsidiary, effective alternatives.[17]

Thus, the ethical guidance provided in this thesis applies to genomic testing generally, whether it is offered through healthcare professionals or by commercial companies. We do argue that highly predictive medical tests (e.g. BRCA testing) should be offered according to the norms and standards of medicine, such as quality control, analytical validity, genetic counselling and professional medical supervision. For less predictive genomic tests, the implementation of what we have called 'proportionate protective measures', such as differentiation of the testing offer and tiered informed consent, may currently suffice. It is important to note that not all not-so-predictive testing will be innocent: tests for personal traits such as ethnicity, sexual orientation or tendency to criminal behaviour might need to be (self-)regulated more carefully, because of the privacy issues and possible social implications associated with misinterpretation (i.e. over-interpretation) of test results.

Finally, this background liberalism entails that in a commercial context, consumers take up some of the responsibility for decision-making with regard to genomic testing. This presupposes faith in the capacities of consumers to understand - the limitations of - genomic information and to make informed decisions about a testing offer. Although genomic 'illiteracy' is widespread, I am not too sceptical about the possibilities of conveying key messages to lay people through adequate information and communication.[18]

Respect for autonomy

Autonomy has been a topic of philosophical debate for decades. As there are many notions of autonomy in circulation, I briefly wish to expound on the 'thin' conception of autonomy employed in this thesis. Autonomy is the capacity for personal self-governance: "personal rule of the self by adequate understanding while remaining free from controlling interferences by others and from personal limitations that prevent choice."[19] Autonomous decision-making with regard to genomic testing thus requires - no more than - decisional capacities, information and comprehension ('full understanding')[20] of that information, and freedom from external constraints.

The claim that autonomous decision-making regarding genomic testing is important, is not based upon what is known as 'genetic exceptionalism'. I do not hold that genomic information is essentially different from other information: it is not uniquely predictive, uniquely personal or uniquely familial.[21] However, to many people, DNA is something special. DNA is 'an identifier in itself',[22] which can mark, follow and trace us. At the same time, we pass half of it to our children, and share on average 25% of it with each of our siblings. DNA expresses our family ties and connects us to our histories. Also, it embodies part of the explanation of the way we look, smell, eat, mate and vote. It is a looking glass, through which we can find and assess our weaknesses and strengths. To an extent, it has predictive powers, and knows our Achilles' heels.

Genomic testing should ideally be the result of an autonomous choice, that is: an informed and considered choice, not necessarily a rational or authentic choice. This means, first and foremost, that it is a violation of someone's autonomy to conduct genomic testing without their consent - behind their back or against their will. Second, people should preferably know 'what it is they are getting into' when they decide to undertake genomic testing. This is not exclusive to genomic testing: it comparable to consumers' interest to know relevant information - including the snags - about a financial product they are about to commit to or a house they are about to buy. Genomic testing may be one of those things that shape human lives. If human beings are to lead their own

lives,[23] they should be able to make important life decisions themselves, in full understanding.

This justifies a demand for proportionate measures (i.e. informed consent) from (commercial) providers as an expression of respect for autonomy, and as a means to achieve autonomy.[24] A liberal starting-point therefore need not be incompatible with the placing of limits on the provision of genomic testing. It need not equal a complete laissez-faire approach. In our view, it entails an active attempt to enable or enhance autonomous decision-making.

Assessment of the harm question

Two of the four principles of bio-medical ethics - beneficence and non-maleficence - converge in the principle of protection against harm. Apart from respect for autonomy, the principle of protection against harm, in my view, is a central reason for healthcare authorities to intervene in the commercial provision of genomic testing (see chapter 6). Many of the moral judgments or policy solutions offered in this thesis aim at the lessening of the risk of harm. However, the harms involved in genomic testing have so far remained mostly hypothetical, because no evidence of harm has been found,[5, 25-29] not even at long-term follow-up.[30] The empirical evidence may thus seem to displace or disarm a large part of our argumentation. In this section, I will argue that it need not do so: based on the available evidence, it is too early to draw the conclusion, as some do,[27, 31, 32] that genomic testing is harmless. The significance and generalisability of the evidence are not clear-cut for four reasons:

First, the results cannot be applied straight-forwardly to the public at large. Most studies have been conducted in well-educated participants with 'greater-than-average scientific acumen'[5, 27, 29] While research participants with graduate degrees in the life sciences generally understand that genomic information is not deterministic and that an increased risk does not constitute a diagnosis, among the general public, there are gaps in genetic and genomic literacy.[33] Knowledge of underlying genetic and genomic concepts - or lack thereof - is expected to influence consumers' (mis)understanding and response to the receiving of genomic test results,[33] especially in the absence of adequate information. Second, the genomic tests that were used in most of these studies

were especially adapted to be less broad compared to the tests that were actually marketed at the time.[27, 28] Actual commercially offered genomic tests include myriad more conditions and are - at least partially - much more predictive. Today's testing offers are thus much more likely to seriously impact consumers. Third, the circumstances under which research studies are conducted are highly dissimilar to the direct-to-consumer context through which actual genomic testing has been confronting consumers. Research studies generally involve extensive information beforehand and informed consent, as well as professional post-test care and medical supervision.[5, 27] This kind of information and support is not made available to most consumers. Variations in information provision, communication and counselling may hugely affect consumers' interpretation and (psychological) response to test results.

Fourth and finally, the impact of genomic testing might not be adequately captured by measures of psychological distress. Not even predictive genetic testing for major gene disorders, such as BRCA 1 and 2 testing, seems to lead to measurable - transitory or enduring - negative emotions.[34-36] But most women in whom a BRCA 1 mutation was detected through direct-to-consumer genomic testing, sought clinical follow-up, and some opted for prophylactic surgery.[36] Numerous online support groups, personal statements,[37] and documentaries [38] can bear witness to the size of the impact of genetic risk information about hereditary breast cancer on women's lives. Although people are resilient and psychologically adaptive, and may not be blown off their feet easily by genetic information, the consequences of genetic testing may nonetheless change and even dominate a person's life.[38] This applies to a much lesser extent to not-so-predictive genomic testing, where the potency of test results will vary with their predictive value as well as with the characteristics of the diseases they pertain to.

On the basis of the available evidence, it can be concluded that genomic testing of limited clinical validity for a limited set of conditions in genetically literate research participants in a research context does not lead to significant measurable psychological distress. This is not surprising. But neither is it sufficient to conclude that genomic testing in general is harmless.[26] Nor does it realistically portray the benefits and harms in (a group of) actual consumers of

commercially offered genomic testing.[39-41] Often, harm is brought about by misinterpretation: having the ApoE-ε3/ε4 genotype, after all, is not nearly a 'death sentence'.[40] When pre-test information, informed consent and professional help with the interpretation of test results are lacking, misinformation can persist and lead to psychological problems, such as depression.[40] These effects may not be detected in large research studies carefully and responsibly set up for the genetically savvy.

In conclusion, I contend that the harm question is unresolved. While there is little evidence of benefits or harms associated with commercially offered genomic testing, absence of evidence is not evidence of absence. Especially in the light of recent and expected developments in genomic testing, notably the expansion of genomic testing offers and the advent of genomic sequencing, the question of harm among the general public should not be discarded as non-existent. The principle of protection against harm therefore remains of continuing relevance for an ethics of genomic testing.

Together, liberalism, respect for autonomy and the principle of protection against harm form the ethical framework for our general ethical discussion of genomic testing. But before we proceed to answer the research questions, I will first make some methodological remarks.

Methodological remarks

The ethics of genomic testing has not been laid down exhaustively in this thesis. There are other ethical issues, of trust, privacy, confidentiality, access, patenting and licensing, which have not been discussed in detail. This is not without reason, for example: long-standing concerns about discrimination and stigmatisation [42] are lacking ground in testing of limited clinical validity, for not-so-predictive information is simply not useful for the purposes of risk stratification. On the condition that all parties involved do not over- or under-interpret genomic test results, these are not likely be a potent source of discrimination or stigmatisation. Genomic testing as of yet does not seem to have major implications for consumers' eligibility for mortgages or life

insurance.[43-45] Also, I have not elaborated on long-term societal issues surrounding genetic and - to a lesser extent - genomic information (e.g. social pressures to participate in genomic screening programmes, or the effects of genomic risk information on societal solidarity with those who fall ill), because I tried to contribute to the current ethical debate rather than anticipate hypothetical futures.

Multidisciplinary research projects place special demands on researchers. This project took place on the crossroads of philosophy, bioethics, epidemiology, genomics and genetics, and called not only for sound ethical reasoning, but also for a clear grasp of the field of genomic testing - of the technical aspects (and limitations) of genomic tests and technologies, as well as the societal and regulatory context in which these are offered. I have sought regular interaction with a wide range of genetics and genomics researchers, clinical geneticists, public health experts, policy-makers, consumers and commercial providers of genomic tests, through interviews, expert meetings, conferences, teaching sessions and workshops. From these interactions, I have learned to make ethics work, i.e. to make it relevant and useful. Through a series of publications in genetics journals (chapters 2, 5, 7) and in bioethical journals (chapters 4, 6, 8), we have managed to reach both our intended audiences. I am happy that our work on informed consent in particular (chapter 7) has gained traction among - and has been found useful by - (public health) genetics and genomics experts, practitioners and policy-makers.

Answers to the four research questions

In this thesis, I have set out to answer four leading research questions:

1). What is genomic testing?
2.) What are the ethical issues?
3.) How should informed consent be made possible?
4.) What is personal utility?

Question 1: What is genomic testing?

We have tried to show that the first research question is not a purely descriptive question. Rather, it is deeply connected to ethical and regulatory standpoints. Seemingly descriptive claims about the nature of genomic testing can be used to support normative claims regarding whether or not it should be subject to the regulatory safeguards of healthcare. I will recount our argumentation and our clarifications of the key concepts 'testing', 'medical testing' and 'screening'.

We have raised the question whether genomic testing is a *test* at all. Commercial providers have frequently answered negatively to this question, so as to evade regulatory action (see chapter 3). Most commercial providers, however, do not deliver only vast and inhospitable data sets containing millions or billions of SNPs. Rather, they try to *interpret* these data, turn them into information: they use these data for testing. Whereas mapping the genome itself is thus not a test, it allows - in principle - for countless interpretations, countless tests, ranging from genetic susceptibility to multiple sclerosis to the percentage of Neanderthal DNA in one's genome.[46] Moreover, most 'genomic tests' are not single tests, but rather sets of tests, or test packages: they consist of dozens or hundreds of tests offered as packages. Many different test packages have been made available over the past fifteen years.

Genomic testing is a heterogeneous and evolving field, which has been difficult to define. For want of a clear-cut definition of our research topic, we have offered the following 'family resemblances' definition of the term 'genomic testing' (see chapter 3): genomic tests are broad genome-wide sets of tests, based on SNP-genotyping or sequencing technologies, with the purpose, among other things, of risk prediction for multiple complex diseases and other traits, which are currently but not necessarily available through commercial companies, with or without professional medical supervision or counselling. There are overlapping similarities between genomic tests, but none of these features are common to all tests.[47] Although a 'family resemblances' definition may leave room for dispute, it is not useless: mostly, we recognise a genomic test when we see one, just like we recognise a game - Wittgenstein's well-known example - [47] when we see one. Our wide and open-ended definition not only captures

the various and ever-changing genomic tests that are available at present, but can also accommodate possible future applications (e.g. screening tests based on sequencing technologies).

A definition is not complete without a fitting name. In chapters 2 and 3, we have shown that a wide range of names have been used to refer to - the variety of - genomic tests over the years. What is more, we have ourselves failed to be consistent in our terminology throughout our research project, and throughout this thesis. As our research topic has been new and rapidly changing, it did not have a fixed name. In the literature, names have come and gone (see chapter 3). Over five years ago, in the original research proposal, the term 'multiple genetic testing' was used, while we experimented with the term 'genomic risk profiling' in early drafts of some of our chapters. In later publications (2011-2012), we used the term 'personal genome testing'. In the final stages of this research project, however, we put naming itself on the research agenda, and found that the term 'personal genome testing' is morally charged (see below). For the purposes of this general discussion, we have settled on the term 'genomic testing', as it best expresses our definition and delineation of our research topic.

In chapter 2, we have explained the normative effects of name-giving and framing: names and other (e.g. visual) modes of presentation may emphasise one or more features of a genomic test and conceal other features, and thus suggest a certain interpretation - a frame - of the test. What we have called 'the medical frame' emphasises the medical benefits and costs of genomic testing and draws attention to its clinical application. Names such as 'direct-to-consumer genomic testing' and 'personal genome testing', by contrast, highlight the outside-of-healthcare delivery model and the non-medical value proposition. Thus, what we have called 'the personal frame' presents genomic testing as an informational or consumer service.

Over the past few years, I have observed an inclination among bioethicists and social scientists to name and frame genomic testing foremost as a personal, informational or consumer service - rather than a medical test - and to presume the risks and implications of testing to be minimal.[27, 31, 32] In response to this trend, we have warned, in chapter 2, against the - intended or unintended -

effects of the personal frame, which may downplay expectations of finding potentially meaningful medical information in the genome and may direct the attention away from potential harms. The personal frame refers to the values of liberty of choice and ease of access, and favours a laissez-faire approach to genomic testing. 'Anything goes', we have argued, is a morally problematic adage, given the potential for harm associated with clinically valid genomic testing.

Instead, the medical frame should be used as a basis for evaluation and regulation of genomic testing. There are reasons for presenting and perceiving genomic tests as medical tests. Few people will deny that genomic testing based upon sequencing technologies that allow for the detection of rare variants of potentially serious effect sizes [48] is a form of medical testing. Clearly, genomic tests of moderate to high clinical validity, such as ApoE testing for Alzheimer's disease or BRCA 1 testing for hereditary breast cancer, should be considered medical tests. It is less self-evident that genomic tests of limited clinical validity are medical tests. However, many not-so-predictive genomic test packages consist primarily of health-related traits, and are undertaken mainly for health-related reasons. A genomic test that indicates that I have a 1,43 times increased risk for Primary Biliary Cirrhosis compared to the average Caucasian population, for instance, or a 0,80 times decreased risk for Esophageal Squamous Cell Carcinoma (I do, apparently),[5] may not be very informative. But as it estimates genetic susceptibilities to diseases, it should be seen and evaluated as a medical test. Likewise, commercially offered full body scans or health checks, which aim at detecting risk factors or early-stage diseases, should be considered medical tests, even if they lack clinical validity or are offered outside of the healthcare system. This conclusion is - deliberately - normatively formulated and normatively charged: it implies that the norms and standards of healthcare are applicable to genomic testing. It steers toward a more restrictive position with respect to regulatory issues.

[5] The company 23andme has estimated my risk of Esophageal Squamous Cell Carcinoma on the basis of data from two studies among Asian populations. The SNP-disease association has not been studied in Caucasian populations. Consequently, it is not at all clear whether my risk is correctly estimated.

Of course, not all genomic testing is medical testing. This depends largely on the purpose of the test. The purpose of the test is a characteristic of the context in which testing is undertaken, and is partly determined by the motivations and plans of the tested individual.[6] In genomic testing, the purpose of the test is a crucial moral variable:[49] different purposes are associated with different ethical considerations.[7] Consumers may purchase specialised genomic testing for purely non-medical purposes, such as the assessment of ancestry or paternity, the prediction of 'inborn talents' or the entertainment value. Human DNA holds many meanings. The norms and standards of healthcare do not apply to all genomic technologies or tests: they hold no sway over paternity testing or testing for - say - ear wax type or the ability to smell the fragrance of asparagus in urine.

In chapter 3, we have discussed the differences between online direct-to-consumer advertisements for genomic testing and state-offered screening programmes that are - publicly perceived as - legitimised by healthcare authorities. Given that the initiative to undertake testing lies with consumers themselves, it is reasonable, from a liberal point of view, to place some of the moral responsibility for the testing process on them - the responsibility to be informed, to evaluate the offer, to weigh benefits and costs, to decide whether or not to proceed with testing, etc., according to their own values and interests. Therefore, we have concluded, a commercial genomic testing offer need not adhere to the stringent and widely accepted criteria for morally responsible population screening by the healthcare system.[8] Genomic testing differs

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[6] For this reason, it is not part of our lists of test characteristics or disease characteristics.
[7] It is part of what we have identified as 'material' information in the informed consent process (see chapter 7).
[8] Notwithstanding the ethical asymmetry between genomic testing and screening programmes, there are lessons to be learned from the ethics of screening. Screening criteria have always limited the scope of screening offers for moral reasons. The criterion 'suitability of the test'[50] entails that the scope of the test must align with the purpose of the test (see chapter 8). As the purpose of prenatal screening is reproductive autonomy, for instance, screening offers ought only to include life-threatening or serious diseases, for which women or couples may consider termination of an affected pregnancy. The purpose of the test is part of the pre-test information we have identified as 'material' to informed consent in genomic testing. Also, the criterion that an accepted treatment should be available [50] implies that the scope of a new-born screening offer should be

decisively from population screening programmes, and leads to a different distribution of moral responsibilities. Therefore, I would advise against subjecting commercial provision of genomic testing to the Dutch 'Wet op het bevolkingsonderzoek' [the Population Screening Act], notwithstanding the current viewpoint of the Dutch Health Council.[51][9]

In conclusion, it is hardly possible to maintain descriptively that genomic testing is a form of medical testing. It need not be. Neither is it a form of screening. But when it comes to the kinds of genomic tests that have been the topic of this thesis, 'medical testing' is the most suitable frame and the preferable basis for evaluation and regulation, also in a commercial context. Genomic testing for disease risks had best be understood as a form of medical testing.

Question 2: What are the ethical issues?

In written academic or popular articles about genomic testing, authors often list a handful or a dozen ethical issues, ranging from quality assurance, professional supervision, counselling and informed consent to privacy, confidentiality and data protection, and from family dynamics, psychological burdens and health risks to patenting and licencing, equitable access, healthcare system implications, and societal issues, such as concerns about eugenics, stigmatisation and discrimination. Oftentimes, ethical concerns do not apply to the whole field of genomic testing. For different tests tend to give rise to different ethical, legal and societal issues.

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restricted to childhood diseases for which there are effective preventive or therapeutic options. Treatability or 'actionability' is on our list of morally relevant disease characteristics.

[9] The act pertains to screening or the "medical examination which is carried out in response to an offer made to the entire population or to a section thereof and which is designed to detect diseases of a certain kind or certain risk indicators either wholly or partly for the benefit of the persons to be examined".[52] I would argue that a direct-to-consumer advertisement does not constitute an 'offer' in the sense of an offer made by the healthcare system or associated parties.

To help clarify the ethical debate on genomic testing, we have systematically distinguished test characteristics and disease characteristics and connected these characteristics with ethical issues. Test and disease characteristics function as moral variables: when test characteristics or disease characteristics vary, other ethical issues come into play. In our identification of test and disease characteristics, we have drawn from guidelines for genetic counselling,[53] which represent the ethics of clinical genetics, and the evaluative frameworks for genetic and genomic testing [54] and screening.[55]

Our list of four test characteristics (see chapter 4) comprises analytic (or analytical) validity as a precondition to any morally responsible testing offer, although it is currently no longer at the centre-stage of the ethical debate.[10] The test characteristic clinical validity, on the other hand, continues to be of unabated urgency. Clinical validity (roughly: predictive value) is not easy to determine objectively, nor is it fixed or constant. First, clinical validity is not an all-or-nothing but a gradual measure. Second, judgments about whether a test's predictive capacity is sufficient or insufficient are not factual but normative. Consequently, there may be disagreement about thresholds of clinical validity to be set for a responsible testing offer. Third, as the science underlying genomic testing proceeds and more and more validated SNPs - and, theoretically, environmental factors - come to be incorporated into risk profiles, the clinical validity of risk profiles will change, or improve. Our third test characteristic, that of clinical utility, is likewise difficult to establish - let alone to quantify - firstly because of diverging views on what clinical utility entails (see below), and secondly because the clinical utility of a test may change over time as new preventive or therapeutic measures or other action options are discovered, developed or deployed. Our list of relevant test characteristics concludes with the distinction between targeted and non-targeted testing, which bears on multiple aspects of testing. First, it refers to the context of testing: whereas targeted genomic testing is conducted for diagnostic purposes, non-targeted genomic testing is usually not aimed at finding the cause of a particular disease,

[10] Since the early 2000s, many commercial providers of genomic testing have begun to make use of state-of-the-art microarray technologies (e.g. gene chips), which are highly accurate.

but rather at finding multiple risk factors or even at finding 'as much as possible'. Second, it refers to what we have called 'the information problem' associated with non-targeted genomic testing, which yields *inter alia* exceptional numbers of test results. These numbers count morally, for they may seriously complicate the process of informed consent (see below).

Our list of four morally relevant disease characteristics comprises the severity of the disease and its age of onset, 'actionability' of the test result and the distinction between psychiatric and somatic diseases (see chapter 5). We have used the term 'actionability' because it is more encompassing than the traditional screening criterion of availability of an accepted treatment [50] or 'treatability': it includes preventive options and reproductive options, and even comprises other forms of utility, such as relief from uncertainty [21] or solace. The severity and age of onset of the disease are existing implicit or explicit variables in the ethics of clinical genetics.[53, 56] Age of onset also features in the ethical debate surrounding genetic testing in children and minors: as a general rule, predictive testing for adult-onset diseases should be postponed until adulthood in order to avoid infringing upon a child's right to future autonomous decision-making with regard to testing.[56] We have added the distinction between somatic and psychiatric diseases, because genomic testing for psychiatric disorders is a rather new and sensitive phenomenon. As of yet, uncertainty has prevailed with regard to the psychological impact of testing, the issue of stigmatisation [57] and potential effect of genomic testing on the development of a disorder (e.g. trigger effects).[58, 59] For as long as these uncertainties are waiting to be resolved, a cautionary approach is most appropriate. After all, when new medical technologies are introduced into clinical practice, we tend to tread carefully and closely monitor the impact of these technologies, before we unleash them.

Test and disease characteristics may work together to create ethical problems and, subsequently, to demand certain regulatory responses. For instance, testing of high clinical validity for a severe, late-onset disease for which there are no treatment options (the paradigmatic example for which is Huntington's disease), is likely to have major psychological impact on tested individuals and their family members (e.g. emotional distress, depression, so-called 'survivor guilt'),

and - according to most - should preferably be offered through specialised clinical genetics centres and on the condition of professional counselling and psychosocial support. On the other end of the spectrum, testing of limited clinical validity for conditions that are less severe and treatable (e.g. type 2 diabetes, hypertension), are likely to have less impact (see chapter 5.3). Against a liberal background, the general principles of proportionality and subsidiarity suggest that the involvement of professional genetic counsellors may not be necessary in testing of limited clinical validity: adequate pre- and post-test information provision may suffice to avert potential harms. Clinical validity is a pivotal moral variable that determines the nature of the regulatory response needed for a responsible testing offer.

As different tests for different diseases pose different ethical problems and require different levels of care, supervision, counselling and other safeguards, currently available packages of genomic tests - sometimes comprising hundreds of diseases - pose a major regulatory challenge. There are various possible solutions to the problem of genomic test packages: first, regulations can be designed to apply to the whole of the test package, with an eye to the most potent of sub-tests. Recently, the FDA seems to have taken this route, when it forced the company 23andme to stop its direct-to-consumer sales of genomic tests, referring in particular to some "particularly concerning" tests included in the company's Personal Genome Service, notably BRCA-testing and certain pharmacogenomic tests, "because of the potential health consequences that could result from false positive or false negative assessments for high-risk indications such as these."[60] In response, 23andme has decided to refrain from health-related testing altogether, and now provides only raw genetic data and ancestry testing. Thus, the FDA forbade 23andme's Personal Genome Service in its entirety because it deemed two or three among its over 250 tests potentially harmful. Submitting the provision of relatively innocent genomic tests (e.g. testing for freckling and type 2 diabetes) to the most stringent of regulations (e.g. a ban) - in my view - is disproportionate. Moreover, I believe that in the long run, this type of solution is ill-equipped to handle the growing desire among patients and consumers to learn as much as possible from their genomes.

People prefer to know more, not less about their health.[11] Moreover, technological imperatives and financial incentives point toward the expansion of the scope of testing and screening. Broad-scope screening and testing, I think, are becoming a fact of life.[12] We had better learn to deal with the information problem, with the quantity and diversity of health-related information flowing from broad-scope testing.

Second, regulations can be designed to apply to the whole of the test package, with an eye to the least potent of sub-tests. This type of solution will entail not subjecting the provision of impactful tests (e.g. ApoE or BRCA-testing) to any requirements because the (vast) majority of the testing offer is much less potent. This, in turn, may pose too large a danger to patients or consumers.

Another possibility is differentiation of the testing offer, and concurrent differentiation of the regulatory response, so that different policies come to apply to different parts of a genomic testing offer. Although this solution may put up practical hurdles for the provision of genomic testing, in my view, it is the most suitable way to move forward. It maximises access to genomic testing while it minimises avoidable harms. It avoids unnecessary and disproportionate practical costs (e.g. the involvement of medical professionals) on the part of the provider, and it leverages the power of the online environment in which genomic tests are offered. Also, it constitutes an experimental arena - and possibly a model - for dealing with the much more general problem of the growing availability of large quantities of health-related data within or outside of the healthcare setting. The following section contains an example of a differentiated regulatory response.

[11] Unless, of course, it turns out that most genomic information has so little informative value, that people lose interest in genomic testing.
[12] On the condition that broad-scope genomic testing and screening is or becomes capable of delivering sufficient valuable information.

Question 3: How should informed consent be made possible?

Genomic test results can be so numerous and their status can be so unclear, that it is difficult to interpret them. It is also difficult - if not impossible - to inform oneself adequately about genomic testing beforehand: indeed, informed consent has come under serious threat. Informed consent serves as a safeguard against involuntary testing and the violation of privacy. Also, it promotes well-considered decision-making and aids consumers in protecting themselves against the potential harms of unwanted predictive testing. Presenting consumers with detailed information about dozens or hundreds of genomic tests for equally many diseases and traits tested for, possible test outcomes, follow-up and ethical and practical implications of so many tests, would simply overwhelm them and compromise autonomous decision-making. Traditional, specific informed consent is no longer possible (chapters 6-8). This, we have argued, is one of the most urgent ethical problems in - commercially offered - genomic testing: the information problem. The information problem is caused by the complexity, disputability, fluidity, quantity and diversity of the information - possibly - generated through genomic technologies. I will first rehearse each of these features of genomic information.

Genomic testing yields information that is complex, disputable, fluid, numerous and diverse. It is complex because it is probabilistic: it is usually based on the analysis of multiple SNPs, which increase or decrease an individual's susceptibility to complex diseases only slightly. People are notoriously helpless when it comes to interpreting statistical risk,[61] and tend to view genetic risk dichotomously, as either 'high' or 'low', 'increased' or 'decreased', 'good news' or 'bad news',[62] and are thus prone to over- or under-interpretation of test results. Even for the genetically and numerically literate, it will be difficult to make sense of genomic tests that - say - turn the average lifetime risk of 13% of developing type 2 diabetes into 10% or 17%.[63] It is not at all clear whether and how such results can be meaningful.

Genomic test results are disputable not because of the analytical validity of the tests, which is often impeccable, but because different companies either select different SNPs to include in their algorithms for risk prediction or use different

formulae for risk prediction.[64] Over the years, consistency among commercial testing providers has improved.[65, 66] Temporary inconsistencies are to be expected from emerging and evolving technologies. Also in clinical practice, nowadays, as standardised protocols for clinical exome or whole-genome sequencing are only just being promulgated,[67] practices and policies still differ among laboratories.[68]

Genomic information is fluid in the sense that the interpretation of SNP-data may change over time,[69] as more and more correlations between SNPs and diseases come to be discovered and validated. On the basis of the same sample and the same set of SNP-data, different tests can be run - or test can be run differently. A few years ago, a company may have calculated the risk of type 2 diabetes on the basis of one SNP that was known at the time, whereas by now, it may have added 17 newly replicated SNPs to the risk profile. Chances are that through such updates, customers' estimated risks will have changed from increased to decreased risk, or vice versa.[70] Although again, initial erraticism may be inescapable in emerging technologies, the 'fluidity' of genomic test results begotten in the early years of commercial companies' existence does cast severe doubts on their utility.

Genomic information can be numerous and diverse. One of the leading companies has offered genomic test packages containing over 250 diseases and other phenotypic traits, ranging from cardio-vascular diseases, auto-immune diseases and psychiatric disorders to ApoE and BRCA 1 testing, from carrier screening for over fifty monogenic disorders to estimates of the percentage of Neanderthal DNA, from testing for ear wax type and muscle performance to susceptibility to the beneficial effects of breastfeeding on IQ-scores.[46]

It will have become clear that traditional, specific informed consent is not feasible for broad-scope genomic testing. As an alternative, a model for generic consent has gained ground, in which the focus of pre-test information provision lies on general aspects of testing and detailed information on specific conditions is withheld until after testing.[71] In chapter 6, we have argued that neither specific nor generic consent are fit for commercially offered genomic testing. Consumers should not be burdened with excessive information, but neither

should pre-test information about specific diseases be held back. Consumers should be able to view the list of diseases tested for, to ensure that they will not proceed without knowing 'what it is they are getting into'. For they may prefer not to receive certain genomic information, either because of test characteristics (e.g. clinical validity) or disease characteristics (e.g. severity, lack of therapeutic or preventive options, psychiatric disorders), or because of contextual characteristics (e.g. personal or family experiences with specific diseases). They should be given the option not to receive unwanted test results, and should not be invited to proceed without their consent to all tests that are part of the testing package.

A feasible model for informed consent in genomic testing requires an optimal trade-off between the norm of providing complete information and that of providing understandable information, and asks for an innovative solution. In chapter 7, we have presented a model between specific consent and generic consent, which is tiered, layered and staged. The model can be used in an online environment, and as it does not presuppose the involvement of a healthcare professional, it can be applied to both physician-mediated and direct-to-consumer forms of commercial genomic testing.

Our model advocates differentiation of the testing offer into tiers or categories of tests. Consumers should be given the opportunity to prepare for possible test outcomes and - ideally - to select tiers of tests to which (not) to consent. At the very minimum, consumers should be able to opt-out of certain tests, in order to protect themselves against potential harms of unwanted testing. This means that providers should organise their testing offer into tiers that are meaningful to consumers, that are organised along the lines of *inter alia* (medical or other) purposes of testing, clinical validity, the severity of the diseases tested for, actionability and the potential emotional impact of testing.

Informed consent should be layered firstly in order to render the pre-test information process manageable and comprehensible, and secondly in order to tailor the process to the informational needs of individual consumers. In the first layer, 'material' information is offered to all consumers, key information that is crucial to autonomous decision-making. In chapter 7 we have presented a

provisional list of material information in commercially offered genomic testing. Importantly, information about limitations, risks and implications of testing should be conveyed clearly to all consumers as part of the informed consent process. All too often, such indispensable information has been found lacking on company websites.[72, 73]

Further, layered consent enables a more personalised approach to informed consent: some consumers may need more information than others in order to make considered autonomous choices with regard to the testing offer. The online context in which many genomic tests are advertised and marketed perfectly allows for a layered, maximally personalised organisation of the pre-test information process, in which further, more detailed information can be accessed easily by those who desire more knowledge in order to consent. Staged consent, lastly, exploits the given that genomic testing is a process, involving at least three moments in which decisions must be made: the ordering of the test, the receiving (and viewing) of test results and the receiving (and viewing) of updates. At all three moments, informed consent can be asked and consumers' understanding of the test itself and its implications deepened. Staged consent utilises the passing of time as a facilitator for well-considered decision-making.

Chapter 6 addresses the question whether there is a place at all for - our model for - informed consent in commercially offered genomic testing. It discusses the intuition that commercial companies may be bound by other, less stringent moral responsibilities than healthcare professionals. In the commercial trading of goods and services, the norms of truth-in-labelling and truth-in-advertising are meant to protect consumers from misleading marketing claims. Further, companies make use of Terms of Service (TOS) agreements, in which mutual rights and obligations between the provider and its customers are laid down. It is not self-evident that over and above these general norms, the medical-ethical norm of asking informed consent would be necessary or desirable. We have argued that commercial providers are not free from the moral obligation to inform consumers about their genomic testing offer. Further, we have shown that the norms of truth-in-labelling or truth-in-advertising and TOS are inadequate means to meet these obligations. These norms do not demand certain information (notably information about risks and implications of

testing), nor do they compel providers to ensure and optimise understanding in consumers - the lengthy, hardly legible legal documents of TOS being testimony. The moral aims of informed consent - the mitigation of harms and the enabling of autonomous choice - will thus not be met by the general legal and moral norms of commerce. Some form of informed consent, we have concluded, remains necessary, also in a direct-to-consumer context.

In chapter 8 we have broadened the reach of our model for informed consent by comparing commercially offered genomic testing to other applications of what is sometimes [74, 75] called 'the new genetics': prenatal screening and new-born screening. In all three contexts, some form of organisation is essential to the endeavour of 'making sense' of the vast amounts of information generated by genomic testing. In line with chapters 6 and 7, chapter 8 proposes differentiation of the screening or testing offer. Since autonomous decision-making entails much more than mere liberty of choice, a pre-structuring of choices by the provider may be necessary to ensure a workable process of informed and considered decision-making.

In contrast to commercially offered genomic testing, prenatal screening and new-born screening are clearly bound by the criteria for morally responsible screening programmes, such as the availability of an accepted treatment (in new-born screening) or more generally, a positive balance of costs and benefits.[50] This places limits on the scope of a responsible prenatal or new-born screening offer right from the start. Moreover, in both areas of public healthcare, the interests of unborn babies or newly born children are at play. Children have a so-called 'right to an open future':[76] they should be enabled to make their own decisions with regard to genetic self-knowledge. Where possible, genomic testing should be postponed until adulthood. Consequently, testing for diseases that will not affect parental reproductive decisions should not be part of prenatal screening, and testing for diseases that will not manifest during childhood or do not merit early medical interventions should not be part of new-born screening. If one ever starts to doubt the importance of respect for the future autonomy rights of children, one may be reminded of a - to me, always - startling figure: of those who know they have 50% chance of carrying a Huntington's disease mutation, only about 15% choose to proceed with pre-

symptomatic testing.[77, 78] Decisions about predictive (or pre-symptomatic) genetic testing are highly personal. Thus, predictive testing of children and minors for adult-onset disorders has no place in a morally responsible commercial genomic testing offer. This piece of ethical guidance runs counter to current practice, in which most companies are unscrupulously testing children and minors.[79] Companies should (be reminded to) take heed of existing professional and industry guidelines on genetic testing in children.[80, 81]

Question 4: What is personal utility?

Despite promotional slogans suggesting genomic testing to be a catalyst to behaviour change,[82] there is no empirical evidence to suggest that genomic testing improves consumers' health status.[5, 25, 30] In fact, research participants have been found to become even less motivated to change their lifestyles for the better after having made aware of individual genetic susceptibilities.[83] If genomic testing does not lead to health benefit - if it lacks clinical utility - what, then, is the value of genomic testing? What do consumers seek in genomic testing?

In ethical and regulatory discussions on genomic testing, the notion of 'personal utility' has been proposed repeatedly as an alternative to the traditional criterion of clinical utility. Personal utility generally refers to the non-medical value of a genomic test and covers, among other things, psychological and social effects of testing. The notion has been used not only to describe wider rationales for testing, but also in justificatory ways: to justify direct access to commercially offered genomic testing,[84] or feedback of individual research results to research participants.[85] Sometimes research participants claim a right to genomic information with an appeal to personal utility.[85] Participants usually prefer to be reported back as many individual genomic test results as possible, including test results of unclear clinical significance, for, they feel, these results may be personally meaningful.[86]

Although it is a factual given that consumers or research participants take an interest in genomic information, 'personal utility' is not always a valid basis for

that interest. In chapter 9 we have argued that perceived utility does not equal personal utility. When individual consumers or research participants claim that - for them - genomic testing has personal utility, they may be wrong. First, the 'information' may have insufficient informative value. Without clinical validity (the ability of the test to predict the phenotype in question), we have claimed, there is no personal utility. One of my test results from the company 23andme indicates that I have a 5,2% instead of a 4,2% lifetime risk of developing Restless Legs Syndrome.[13] It is doubtful whether such a test result is information at all, let alone useful information. Second, even if genomic information would be clinically valid, it may or may not be personally useful, depending on the individual context of testing. Knowing that my genetic risk of prostate cancer or male pattern baldness is increased or decreased, for instance, has no personal utility for me, because I am a woman. And if I believe that a genomic test for the three most common mutations responsible for hereditary breast cancer in Ashkenazi Jews has personal utility because it may take away my worries about developing breast cancer, I am simply mistaken. Such a mistake (false reassurance) can have serious implications, if from now on I feel free from risk and decide in future not to attend regular breast cancer screenings.

Clinical validity and 'reasonable potential use', therefore, are preconditions to a sensible notion of personal utility. Advocates of direct access to genomic testing might retort that they feel that it may not be useful, but it is fun or fascinating to know that they have a 5,2% instead of a 4,2% lifetime risk of developing Restless Legs Syndrome. Consumers list various reasons for purchasing genomic testing, ranging from health and genealogy, to curiosity and fascination, recreation and the desire to contribute to genomics research.[87] Why cannot curiosity or 'the fun factor'[29] be a form of personal utility? And what is more, why should consumers need to explain themselves: why cannot they have personal reasons for wanting to know this information. Should it not be up to the person - and only the person - him- or herself to determine what personal utility means?

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[13] The test is based on one SNP (rs3923809) with an odds ratio of 1,26. The test has two possible outcomes: 4,2% or 5,2%. As a predictive test for Restless Legs Syndrome, this test has very little clinical validity. It the range of possible outcomes were between 4,2% and - say - 84% (instead of 5,2%), the test would have had clinical validity, and my risk of 5,2% would have been informative.

To this 'anything goes' stance I would reply that we will not deny that this 'information' may have personal value for someone - as a form of entertainment, as a starting-point for further study, as an exotic experience. Further, as the 'information' pertains to an individual's own DNA, there is a case to make for allowing this individual access to genomic services that uncover this information. I understand the desire to learn or to 'own' this information about oneself. But from this desire it does not follow that genomic information has personal utility. Personal utility is not the same as 'personal satisfaction'.[88] Someone may derive personal satisfaction from a ride on the ferris wheel, but that is not to say that the experience is personally useful.

Clarification of the concept of personal utility, I think, is a valuable contribution to the ethical and regulatory debate. Personal utility, in our more technical definition, highlights important values, such as self-determination, access and wider notions of well-being. Further, it can rightfully be considered in the overall evaluation of a genomic test: it may even be a reason to provide and reimburse genomic testing within the healthcare system, depending *inter alia* on the clinical validity of the test (e.g. testing for Alzheimer's disease). It may also work to justify the offering of genomic tests on the direct-to-consumer market (e.g. ancestry testing). Its role, however, is not unlimited: it surely does not in itself or by itself morally justify direct access to genomic testing.

We have demarcated a notion of personal utility that occupies a space between the more or less objective criterion of clinical utility and the personal, subjective claim to meaning. This space in-between can be useful for wider discussions in healthcare. Discrepancies between expert judgments of utility and patients' or proxies' judgments of utility are widespread, for instance in the context of prenatal screening [89] or new-born screening.[90] Patients and proxies generally want to know more than clinicians or researchers think would be advisable to tell them. Everywhere in the world, from Denmark to Brazil, it is said, patients have become more demanding or assertive ("mondig" in Dutch).[91, 92] Our notion of personal utility may help to explain that a preference to know - a preference to be tested or screened - in patients or proxies does not automatically imply a valid claim to personal utility of testing or screening. As a tool to help curb patient- or consumer-induced demand, while

acknowledging wider notions of utility than strictly clinical ones, the concept of personal utility merits further study.

The future of genomic testing

Genomic testing enables us to look at ourselves up close and personal. The looking glass of genomics will continue to be both alluring and - in part - relevant. It is true that direct-to-consumer sales of genomic tests may be coming to a halt (although tests are still *advertised* directly to consumers): in response to pressure from professional and regulatory bodies, most companies now require physicians to sign off on the testing order. Experts and professional organisations, such as the European Society of Human Genetics and the American College of Medical Genetics, have pressed for healthcare systems to take genomic testing under their wings or for banning it altogether, and now seem to be succeeding. Genomic testing, however, will not easily be brought to a standstill. In regions other than the EU or the US, research groups have much vested interest in genomics: for instance, there are 178 state-of-the-art next-generation sequencing machines in one research facility in Beijing which produces at least a quarter of genomic data worldwide.[93] Moreover, there is sustained public and expert interest in genomic testing, and there are ways around existing regulations and legislations. The FDA, for instance, does not regulate the (direct-to-consumer) provision of genetic or genomic data. Consequently, data can still be purchased directly from commercial companies.[46] Research groups are developing genome interpretation tools, most of which are freely available online.[94, 95] Consumers can study their own genomes on the Internet - although most parts of those genomes may be not-so-predictive, and even the most wonderful interpretation tools will not be able to turn meaningless data into meaningful information.

The online and commercial provision of genomic testing or data raises the ethical issue of equity of access, to which I may have paid too little attention in this thesis. While the commercial availability of genomic testing enables affluent consumers to scrutinise and utilise genomic information for the purposes of disease prevention, it may be out of reach for poorer consumers. And while

Millennials have little trouble navigating the Internet, older generations may get lost in translation. Although most of us are not morally troubled by all discrepancies in the ability to purchase goods and services between richer and poorer consumers, we do tend to object to health inequalities based on socio-economical or generational differences. So long as little health benefit is derived from genomic testing (as is currently the case), the commercial provision of genomic testing for complex diseases is unlikely to lead to any substantial health inequality. If in future, genomic testing attains sufficient clinical validity to improve the health of tested individuals, policy-makers and health insurers should consider clinical and/or public health implementation and reimbursement of - clinically useful - genomic testing (e.g. within primary care or through population screening programmes), to ensure equitable access to genomic testing.

Indeed, genomic technologies are already finding their way to clinical and public health implementation: microarray technologies are increasingly replacing conventional karyotyping in prenatal diagnostic testing,[96] non-invasive techniques (NIPT) for prenatal screening for Down syndrome and other chromosomal anomalies are in the process of being introduced in the Netherlands,[97] and the clinical genetics laboratory at my own university medical centre will soon offer exome sequencing as a diagnostic test for certain indications. Across the world, researchers and clinicians are grappling with questions regarding the scope of testing, the reporting of incidental - or ancillary or secondary - findings and the feasibility of informed consent, in the clinical setting as well as in the research context. There is no consensus yet on how to deal responsibly with any additional information yielded through genomic technologies,[98, 99] or on how to reconcile the sometimes conflicting duties of protection against harm and respect for individuals' right (not) to know genomic information.

Many of the insights offered in this thesis can be brought to bear on these questions. For instance, clinicians or researchers are sometimes pressed by patients or research participants to report any ancillary individual 'results'. Because the significance of ancillary findings is often unclear, clinicians and researchers may be apprehensive (and rightfully so) about reporting such

findings. The normative notion of personal utility we have developed in chapter 9 may come in handy: personal utility, we have argued, presupposes clinical validity and reasonable potential use. Thus conceived, individual research findings of unclear clinical significance cannot have personal utility for patients or research participants. Consequently, research participants cannot claim a right to clinically unclear individual research findings with an appeal to personal utility. This conclusion may strengthen unilateral expert decisions not to report such findings. Likewise, our notion of personal utility may assist healthcare authorities in rebutting increasing public demands for medical self-testing and screening.

Further, our model for informed consent may be used to improve existing models. Across the regular healthcare system, generic consent is often used or suggested as a model, for instance in the context of clinical genomic testing or screening on the basis of sequencing technologies (see chapter 6). We have argued that it is preferable, when possible, to present beforehand - a list of - the diseases included in the (screening) test, to enable patients to opt out of certain tests. Our proposed tiered-layered-staged model for informed consent may be more suitable from an ethical point of view, as it approximates the ideal of personalised informed consent - more so than do current models for generic consent - and strengthens autonomous choice.

The future of genomics - inside or outside of healthcare - raises many ethical issues, ranging from privacy and data security issues [100] and shifting medical-professional responsibilities (e.g. a potential duty to re-contact patients with updates of test results) to the - future - autonomy rights of (unborn) children.[96] Also, the ubiquitous expansion of testing and screening offers across healthcare generally, flies in the face of current ethical guidelines that resist expansion of testing or screening 'packages'. These guidelines prescribe a proven favourable balance of risks and benefits (and even something like a 'necessity criterion')[99] for each test to be added to a testing or screening offer. It is unknown whether this restrictive ethical approach will hold up in the age of big data - especially since many patients, consumers and prospective parents prefer to control and to widen the scope of screening and testing.[101] When through the use of evolving genomic sequencing technologies, enormous quantities of genomic

data can be generated easily and cheaply, many of us may be tempted to obtain these data and have computer programmes crunch them to see if they contain anything useful.[94, 95] Targeted genetic or genomic testing might then become part of history.[14]

Computer programmes for the interpretation of genomes will contain a great deal of normativity: they must distinguish between information and non-information, between useful and useless information, between information to report and information not to report. Such distinctions are deeply normative in nature. Automated genome interpretation tools ought to be carefully designed and monitored to ensure the clinical validity and utility of the test results they generate. It is not yet clear what parties should be (made) responsible for the quality assurance of such services - who, among those who design, produce, distribute, sell or use these tools, bears responsibility for the test outcome? Can designers be held responsible for having missed clinically relevant findings? Can hospitals? Or laboratories? Or physicians, who may try to assist their patients in making sense of their genomes? Also: should there be processes for regular updates of the algorithms used by these tools to interpret DNA-data? After all, new associations between genetic variants and diseases continue to be discovered or validated every month. Should governments require such updates from producers and distributors? All these questions are unresolved. In future, the normativity and the distribution of moral responsibilities in data-based medicine are likely to become important topics for applied ethical research.

Concluding remarks and recommendations

On the basis of our ethical interpretation and evaluation of genomic testing for disease susceptibilities, we have effectively come to quite restrictive conclusions and recommendations:

[14] Recent guidelines from the American College of Medical Genetics and Genomics (ACMG) are already pointing in that direction: they suggest that in all diagnostic exome or whole-genome sequencing, laboratories should actively and systematically screen for a set of actionable mutations in 57 genes.[98] These guidelines are presently vividly debated.

- Genomic testing for disease susceptibilities should be named and framed as a form of medical testing.
- Its provision - also when offered commercially - should largely adhere to the norms and standards of healthcare.
- For the purposes of (ethical) evaluation and regulation, genomic testing should be differentiated. Different policies may apply to different parts of a genomic testing offer.
- Genomic tests should thus not be offered as heterogeneous 'package deals' - not if these deals include dozens or hundreds of very diverse tests. Broad testing offers should be differentiated into categories or tiers that are meaningful to consumers and reflect their personal considerations and interests.
- Highly predictive tests for severe diseases should not be offered as part of genomic testing packages, but separately, as targeted tests, and require genetic counselling.
- Pre-test information and informed consent are essential ethical requirements. Test providers - whether they are medical professionals, institutions or commercial companies - are responsible for enabling consumers to make autonomous decisions with regard to the testing offers.
- Consumers should give tiered consent to broad genomic testing, and should be able to opt out of particular tests for particular diseases. Pre-test information should be layered and staged.
- Non-targeted genomic testing for late-onset diseases and diseases for which there are no actionable options during childhood, should be discouraged in children and minors.

When Watson and Crick had discovered the double-helical structure of DNA in 1953, they were thought to have found the basic building block of all life. In reality, our capacity to make predictions based on genomic information may in effect not surpass that of oracles. When we consult an oracle, we seek control over something which we cannot fully command - in this case: our future health. A similar motivation may drive consumers to commercially offered genomic testing. But when such testing lacks clinical validity, the sense of control it may convey, will be no more than an illusion. Should consumers be protected against self-sought illusions? Clearly, the state should not offer, recommend, authorise or reimburse illusions. Instead, it may inform consumers, and encourage or require (commercial) providers to adhere to a set of moral norms and principles (e.g. informed consent) for a morally acceptable as well as accessible genomic testing offer. In the end, our genomes are ours, up close and personal. And what we wish to learn - or not to learn - from our DNA, is a matter of individual autonomy.

References

1. Wald N.J. and J.K. Morris. 2012. Personalized medicine: hope or hype. European Heart Journal 33(13): 1553-1554.

2. Hsu A.R., J.L. Mountain, A. Wojcicki and L. Avey. 2009. A pragmatic consideration of ethical issues relating to personal genomics. American Journal of Bioethics 9(6-7):1-2.

3. Angrist M. 2010. Here is a Human Being: At the Dawn of Personal Genomics. New York: HarperCollins.

4. Jonsen A.R., S.J. Durfy, W. Burke and A.G. Motulsky. 1996. The advent of the "unpatients". Nature Medicine 2(6): 622-624.

5. Bloss C.S., N.J. Schork and E.J. Topol. 2011. Effect of direct-to-consumer genomewide profiling to assess disease risk. New England Journal of Medicine 364: 524-534.

6. Voltaire. 1772. La Bégueule, Conte Moral.

7. MacArthur D. 2010. A sad day for personal genomics. In: Genomes Unzipped: Public Personal Genomics.

8. Mill J.S. 1859. On Liberty. Oxford: Oxford University.

9. European Union. 2008. Protocol (No 2) on the Application of the Principles of Subsidiarity and Proportionality.

10. Borry P., R.E. van Hellemondt, D. Sprumont et al. 2012. Legislation on direct-to-consumer genetic testing in seven European countries. European Journal of Human Genetics 20: 715-721

11. Prainsack B., J. Reardon, R. Hindmarsh et al. 2008. Personal genomes: misdirected precaution. Nature 456: 34-35.

12. Howard H.C., B.M. Knoppers and P. Borry. 2010. Blurring lines: the research activities of direct-to-consumer genetic testing companies raise questions about consumers as research subjects. EMBO Reports 11(8): 579-582.

13. Prainsack B. 2010. Guest post: Barbara Prainsack on public attitudes to DTC genetic testing. In: Genomes Unzipped: Public and Personal Genomics.

14. van Dam F. and L. Stalpers. 2012. Geef commerciële bodyscans geen kans. Medisch Contact 31-32: 1814-1816 [in Dutch].

15. Hanefeld J., D. Horsfall, N. Lunt and R. Smith. 2013. Medical tourism: a cost or benefit to the NHS? PLoS One 24(8): e70406.

16. Weiss AM. 2006. Buying prescription drugs on the internet: promises and pitfalls. Cleveland Clinic Journal of Medicine 73(3): 282-288.

17. Hogarth S. 2010. Myths, misconceptions and myopia: searching for clarity in the debate about the regulation of consumer genetics. Public Health Genomics 13(5): 322-326.

18. Smerecnik C.M. 2010. Lay responses to health messages about the genetic risk factors for salt sensitivity: do mass media genetic health messages result in genetic determinism? Psychology, Health and Medicine 15(4): 386-393.

19. Beauchamp T.L. 2007. The 'four principles' approach to health care ethics. In: Principles of Health Care Ethics. R.E. Ashcroft, A. Dawson, H. Draper and J.R. McMillan (eds). West Sussex, UK: John Wiley & Sons Ltd.

20. Faden R.R. and T.L. Beauchamp. 1986. A History and Theory of Informed Consent. New York, NY: Oxford University Press.

21. Manson N.C. and O. O'Neill. 2007. Rethinking Informed Consent in Bioethics. Cambridge: Cambridge University Press.

22. Lunshof J.E., R. Chadwick and G.M. Church. 2008. Hippocrates revisited? Old ideals and new realities. Genomic Medicine 2(1-2): 1-3.

23. Dworkin G. 1988. The Theory and Practice of Autonomy. Cambridge: Cambridge University Press.

24. Schermer M.H. 2001. The Different Faces of Autonomy: A Study on Patient Autonomy in Ethical Theory and Hospital Practice. Amsterdam: University of Amsterdam.

25. Roberts J.S. and J. Ostergren. 2013. Direct-to-consumer genetic testing and personal genomics services: a review of recent empirical studies. Current Genetic Medicine Reports 1(3): 182-200.

26. Goldsmith L., L. Jackson, A. O'Connor and H. Skirton. 2012. Direct-to-consumer genomic testing: systematic review of the literature on user perspectives. European Journal of Human Genetics 20(8): 811-816.

27. James K.M., C.T. Cowl, J.C. Tilburt et al. 2011. Impact of direct-to-consumer predictive genomic testing on risk perception and worry among patients receiving routine care in a preventive health clinic. Mayo Clinic Proceedings 86(10): 933-940.

28. Kaphingst K.A., C.M. McBride, C. Wade et al. 2012. Patients' understanding of and responses to multiplex genetic susceptibility test results. Genetics in Medicine 14: 681-687.

29. Vayena E., E. Gourna, J. Streuli, E. Hafen and B. Prainsack. 2012. Experiences of early users of direct-to-consumer genomics in Switzerland: an exploratory study. Public Health Genomics 15(6): 352-362.

30. Bloss C.S., N.E. Wineinger, B.F. Darst, N.J. Schork and E.J. Topol. 2013. Impact of direct-to-consumer genomic testing at long term follow-up. Journal of Medical Genetics 50(6): 393-400.

31. Saukko P. 2013. State of play in direct-to-consumer genetic testing for lifestyle-related diseases: market, marketing content, user experiences and regulation. Proceedings of the Nutrition Society 72: 53-60.

32. Vayena E. and B. Prainsack. 2013. Regulating genomics: time for a broader vision. Science Translational Medicine 5(198): 198ed112.

33. Lea D.H., K.A. Kaphingst, D. Bowen, I. Lipkus and D.W. Hadley. 2011. Communicating genetic and genomic information: health literacy and numeracy considerations. Public Health Genomics 14(4-5): 279-289.

34. Heshka J.T., C. Palleschi, H. Howley, B. Wilson and P.S. Wells. 2008. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. Genetics in Medicine 10(1): 19-32.

35. Beran T.M., A.L. Stanton, L. Kwan et al. 2008. The trajectory of psychological impact in BRCA1/2 genetic testing: does time heal? Annals of Behavioral Medicine 36(2): 107-116.

36. Francke U., C. Dijamco, A.K. Kiefer et al. 2013. Dealing with the unexpected: consumer responses to direct-access BRCA mutation testing. PeerJ 1:e8.

37. Jolie A. 2013. My Medical Choice. The New York Times (14 May 2014).

38. Maassen H. 2013. Documentaire: Nieuwe Tieten - Sacha Polak. Medisch Contact 40: 2026.

39. Corpas M. 2012. A family experience of personal genomics. Journal of Genetic Counseling 21(3): 386-391.

40. Messner D.A. 2011. Informed choice in direct-to-consumer genetic testing for Alzheimer and other diseases: lessons from two cases. New Genetics and Society 30(1): 59-72.

41. Lebel R.R. 2011. That personal touch. Hastings Center Report 41(3): 6-7.

42. Lee C. 1993. Creating a genetic underclass: the potential for genetic discrimination by the health insurance industry. Pace Law Review 13: 189-228.

43. Bunnik E.M. 2012. Erfelijk risico goed te verzekeren. Medisch Contact 67(48): 2728-2730.

44. Joly Y., I. Ngueng Feze and J. Simard. 2013. Genetic discrimination and life insurance: a systematic review of the evidence. BMC Medicine 11(25).

45. Caulfield T., S. Chandrasekharan, Y. Joly and R. Cook-Deegan. 2013. Harm, hype and evidence: ELSI research and policy guidance. Genome Medicine 5(3):21.

46. 23andme: http://www.23andme.com.

47. Wittgenstein L. 1953. Philosophical Investigations. Oxford: Basil Blackwell Ltd.

48. Cirulli E.T. and D.B. Goldstein. 2010. Uncovering the roles of rare variants in common disease through whole-genome sequencing. Nature Reviews Genetics 11(6): 415-425.

49. Zimmern R.L. and M. Kroese. 2007. The evaluation of genetic tests. Journal of Public Health 29(3): 246-250.

50. Wilson J.M.G. and G. Jungner. 1968. Principles and Practice of Screening for Disease. Geneva: World Health Organization.

51. Gezondheidsraad. 2009. Wet Bevolkingsonderzoek: Knelpunten in de Toepassing - Voorstellen ter Verbetering. Den Haag: Gezondheidsraad [in Dutch].

52. Gezondheidsraad. 1994. Genetische Screening. Den Haag: Gezondheidsraad [in Dutch].

53. Rantanen E., M. Hietala, U. Kristoffersson et al. 2008. What is ideal genetic counselling? A survey of current international guidelines. European Journal of Human Genetics 16(4): 445-452.

54. Haddow J.E. and G.E. Palomaki. 2003. ACCE: A model process for evaluating data on emerging genetic tests. In: Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease. M.J. Khoury, J. Little and W. Burke (eds). New York, NY: Oxford University Press (pp. 217-233).

55. Andermann A., I. Blancquaert, S. Beauchamp and V. Déry. 2008. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization 86: 317-319.

56. Bunnik E.M. 2010. Why not order genomic testing for your children? Genomics, Society and Policy 6(3): 68-70.

57. Bortolotti L. and H. Widdows. 2011. The right not to know: the case of psychiatric disorders. Journal of Medical Ethics 37(11): 673-676.

58. Berghmans R., J. de Jong, A. Tibben and G. de Wert. 2009. On the biomedicalization of alcoholism. Theoretical Medicine and Bioethics 30: 311-321.

59. Newson A.J. 2009. Depression under stress: ethical issues in genetic testing. British Journal of Psychiatry 195: 189-190.

60. Food and Drug Administration (FDA). 2013. Warning Letter 23andMe, Inc. (22 November 2013).

61. Hoffrage U., S. Lindsey, R. Hertwig and G. Gigerenzer. 2000. Communicating statistical information. Science 290(5500): 2261-2262.

62. Hunt L.M., H. Castañeda and K. de Voogd. 2006. Do notions of 'risk' inform patient choice? Lessons from a study of prenatal genetic counseling for latinas. Medical Anthropology 25(3): 193-219.

63. van Ommen G.B. and M.C. Cornel. 2008. Recreational genomics? Dreams and fears on genetic susceptibility screening. European Journal of Human Genetics 16: 403-404.

64. Kalf R.R., R. Mihaescu, S. Kundu, P. de Knijff, R.C. Green and A.C. Janssens. 2013. Variations in predicted risks in personal genome testing for common complex diseases. Genetics in Medicine [Epub ahead of print].

65. Government Accountability Office (GAO). 2006. Nutrigenetic testing: Tests purchased from four web sites mislead consumers. GAO.

66. Government Accountability Office (GAO). 2010. Direct-to-consumer genetic tests: Misleading test results are further complicated by deceptive marketing and other questionable practices. GAO.

67. Rehm H.L., S.J. Bale, P. Bayrak-Toydemir et al. 2013. ACMG clinical laboratory standards for next-generation sequencing. Genetics in Medicine 15(9): 733-747.

68. Jamal S.M., J.H. Yu, J.X. Chong et al. 2013. Practices and policies of clinical exome sequencing providers: analysis and implications. American Journal of Medical Genetics 161A(5): 935-950.

69. Shirts B.H. and L.S. Parker. 2008. Changing interpretations, stable genes: responsibilities of patients, professionals, and policy makers in the clinical interpretation of complex genetic information. Genetics in Medicine 10(11): 778-783.

70. Mihaescu R., M. van Hoek, E.J. Sijbrands et al. 2009. Evaluation of risk prediction updates from commercial genome-wide scans. Genetics in Medicine 11: 588-594.

71. Elias S. and G.J. Annas. 1994. Generic consent for genetic screening. New England Journal of Medicine 330: 1611-1613.

72. Lachance C.R., L.A. Erby, B.M. Ford, V.C. Allen and K.A. Kaphingst. 2010. Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genetics in Medicine 12: 304-312.

73. Singleton A., L.H. Erby, K.V. Foisie and K.A. Kaphingst. 2012. Informed choice in direct-to-consumer genetic testing (DTCGT) websites: a content analysis of benefits, risks, and limitations. Journal of Genetic Counseling 21: 433-439.

74. Harrison C. 2011. New genetics and diagnosis of childhood B-cell precursor acute lymphoblastic leukemia. Pediatric Reports 3: Suppl 2:e4.

75. Hudziak J.J. and S.V. Faraone. 2010. The new genetics in child psychiatry. Journal of the American Academy of Child and Adolescent Psychiatry 49(8): 729-735.

76. Feinberg J. 1980. The child's right to an open future. In: Whose child? Children's Rights, Parental Autonomy, and State Power. W. Aiken and H. Lafollette (eds). Littlefield, NY: Adams & Co. (pp. 124-153).

77. Morrison P.J. 2010. Accurate prevalence and uptake of testing for Huntington's disease. Lancet Neurology 9(12): 1147.

78. Tibben A. 2007. Predictive testing for Huntington's disease. Brain Research Bulletin 30(72): 2-3.

79. Howard H.C., D. Avard and P. Borry. 2011. Are the kids really all right? Direct-to-consumer genetic testing in children: are company policies clashing with professional norms? European Journal of Human Genetics 19(11): 1122-1126.

80. European Society of Human Genetics (ESHG). 2009. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. European Journal of Human Genetics 17(6): 720-721.

81. Human Genetics Commission (HGC). 2010. A Common Framework of Principles for Direct-to-Consumer Genetic Testing Services. HGC.

82. Pathway Genomics: https://www.pathway.com/.

83. Smerecnik C.M., I. Mesters, N.K. de Vries and H. de Vries. 2009. Alerting the general population to genetic risks: the value of health messages communicating the existence of genetic risk factors for public health promotion. Health Psychology 28(6): 734-745.

84. Vayena E. and B. Prainsack. 2013. The challenge of personal genomics in Germany. Nature Biotechnology 31(1): 16-17.

85. McGuire A.L. and J.R. Lupski. 2010. Personal genome research: what should the participant be told? Trends in Genetics 26(5): 199-201.

86. Daack-Hirsch S., M. Driessnack, A. Hanish et al. 2013. 'Information is information': a public perspective on incidental findings in clinical and research genome-based testing. Clinical Genetics 84(1): 11-18.

87. Su Y., H.C. Howard and P. Borry. 2011. Users' motivations to purchase direct-to-consumer genome-wide testing: an exploratory study of personal stories. Journal of Community Genetics 2(3): 135-146.

88. Green R.C. 2011. FDA Public Meeting "Direct to Consumer Genetic Testing"

89. de Jong A, W.J. Dondorp, A. Krumeich et al. 2013. The scope of prenatal diagnosis for women at increased risk for aneuploidies: views and preferences of professionals and potential users. Journal of Community Genetics 4(1): 125-135.

90. Plass A.M., C.G. van El, T. Pieters and M.C. Cornel. 2010. Neonatal screening for treatable and untreatable disorders: prospective parents' opinions. Pediatrics 125(1): 99-106.

91. Schmidt M.J. 1996. Consumers' healthcare rights in Brazil. International Nursing Review 43(5): 139-141.

92. Traulsen J.M. and M. Noerreslet. 2004. The new consumer of medicine - the pharmacy technicians' perspective. Pharmacy, World and Science 26(4): 203-207.

93. Specter M. 2014. Letter from Shenzhen: the gene factory. The New Yorker (6 January 2014).

94. Daneshjou R., Z. Zappala, K. Kukurba et al. 2014. Path-scan: a reporting tool for identifying clinically actionable variants. Pacific Symposium on Biocomputing 229-240.

95. Karczewski K.J., R.P. Tirrell, P. Cordero et al. 2012. Interpretome: a freely available, modular, and secure personal genome interpretation engine. Pacific Symposium on Biocomputing: 339-350.

96. de Jong A., W.J. Dondorp, M.V. Macville et al. 2013. Microarrays as a diagnostic tool in prenatal screening strategies: ethical reflection. Human Genetics [Epub ahead of print].

97. Gezondheidsraad. 2013. NIPT: Dynamiek en Ethiek van Prenatale Screening. Den Haag: Gezondheidsraad [in Dutch].

98. Green R.C., J.S. Berg, W.W. Grody et al. 2013. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in Medicine 15(7): 565-574.

99. van El C.G., W.J. Dondorp, G.M.W.R. de Wert and M.C. Cornel. 2013. Call for prudence in whole-genome testing. Science 341(6149): 958-959.

100. Gymrek M., A.L. McGuire, D. Golan, E. Halperin and Y. Erlich. 2013. Identifying personal genomes by surname inference. Science 339(6117): 321-324.

101. De Jong A. 2013. Prenatal screening à la carte? Ethical reflection on the scope of testing for foetal anomalies. Maastricht: Maastricht University.

Summary

Summary

Genomically speaking, human beings are much alike: they differ from one another less than 1%. Still, there are a few million differences between most people - after all, DNA contains about three billion base-pairs. These differences largely determine how we look (different), how we speak, eat and move our bodies, how we think, love and vote, and how we remain healthy or fall ill. By using new technologies to look into our genomes, we can gain insight into our strengths and weaknesses. Such insight may benefit us: our genomes can be tested for genetic susceptibilities to diseases, which we may then try to avoid by changing our lifestyles or through early medical interventions. But we can also be harmed by such insight: not everyone will want to know their Achilles' heels, in particular when these Achilles' heels concern diseases for which there are no preventive or therapeutic options. Our genomes are up close and personal. But given that the genomic looking glass is rather new to us, we may not yet know what to do with it, or how to use it responsibly.

Over the past few decades, a great deal of funding and effort has been directed worldwide towards genomics research and technology. Research groups and entrepreneurs have developed so-called (micro)array technologies that are capable of quickly, easily and inexpensively generating information about a large number of interesting segments of the genome - segments that contain common variation. Sequencing technologies, which map the entire DNA molecule - base-pair by base-pair - are rapidly developing, too, and are finding their way toward clinical implementation. However, the interpretation of genomic information is often laborious and uncertain: for many genomic variants, the biological effects and the interactions with other genetic and environmental factors are completely unclear. Moreover, the genome has turned out to be less predictive (of much more limited clinical validity) than was previously thought - and hoped.

Nevertheless, genomic tests have been spreading across the developed world over the past fifteen years, both within regular healthcare systems and outside

of these. Genomic tests have propelled numerous ethical and regulatory discussions among researchers, clinicians and policy-makers, about the quality and the clinical utility of genomic test results, about informed consent and genetic counselling, about the risks of expanding testing offers and about the merits and perils of direct access to genomic tests through commercial providers. This thesis discusses ethical issues in genomic testing against a liberal ethical framework. It provides practical ethical guidance for the responsible provision of genomic testing, in a clinical setting, in the context of direct-to-consumer marketing and in the context of biomedical research.

Chapter 1 comprises a general introduction of the biological and technical mechanisms that underlie genomic testing, and of current commercial delivery models. It offers a quick overview of the developments within accompanying ethical and regulatory discussions. It describes our applied ethical and pragmatic research approach and the four leading questions that have driven this project.

Our first research question pertains to the nature and definition of genomic testing. **Chapter 2** shows how seemingly descriptive claims about the nature of genomic testing are deeply connected to underlying normative positions with respect to regulatory issues. Naming and framing are often used - deliberately or unintentionally - to present genomic testing a certain light, and to suggest certain problem definitions and avenues for their solutions. Notably, medical names and frames emphasise health-related aims and motivations of genomic testing, and focus on its (lack of) clinical validity and utility. Contrarily, personal names and frames put forward other, non-medical uses and purposes of testing, and refer to the values of liberty, access, convenience, personal utility and self-determination. In this chapter, we warn against uncritical usage of the personal frame, for it may downplay and conceal the risks and implications of genomic testing.

Chapter 3 elaborates on frame theory and showcases a long list of names that have been used to refer to genomic testing over the years. A case study elucidates the workings of three prominent frames - the technical, medical and personal frames - and shows how frames advance associated normative

positions within the ethical and regulatory debate. Further, chapter 3 proffers a family resemblances definition of genomic testing and a brief history of the field of commercially offered genomic testing. It clarifies three key concepts within the ethical debate (testing, medical testing and screening), and argues that genomic testing for complex diseases should be considered a form of medical testing. Contrarily, the well-established ethical framework for the evaluation of screening tests is not directly applicable to commercially offered genomic testing. To overcome the - distracting - normative effects of definitions, name-giving and framing, we propose the reduction of harm as a guiding principle to settle regulatory disputes. Roughly, where there is potential for harm, there is a reason for protective regulatory action, regardless of (possibly conflicting) underlying perceptions of the nature of genomic testing.

Our second research objective is to map the ethical issues associated with genomic testing and relate these issues to characteristics of the test and characteristics of the diseases tested for. **Chapter 4** distinguishes four test characteristics: targeted vs. non-targeted testing, analytical validity, clinical validity and clinical utility, and singles out clinical validity as a crucial morally relevant test characteristic. Different levels of clinical validity are connected with their own ethical issues, notably: whereas genomic testing of high clinical validity raises issues because of its strong impact on tested individuals and their families, testing of limited clinical validity does so because its impact is frequently unclear. Because of the uncertainties that surround it, not-so-predictive genomic testing may give rise to misunderstanding (i.e. over- or under-interpretation of the significance of test results). Thus, whereas the ethics of genetic testing of high clinical validity traditionally centres around the minimisation of harm (the medical-ethical principles of beneficence and non-maleficence), the ethics of not-so-predictive genomics concentrates on information, communication and education.

Chapter 5 distinguishes four disease characteristics: severity, age of onset, 'actionability' and psychiatric vs. somatic. These characteristics function as moral variables, for instance: genomic testing for late-onset diseases should preferably not be conducted in children or minors. Another example is genomic testing for (very) severe diseases, especially diseases for which there are no

preventive or therapeutic options (e.g. Huntington's disease). Because of its potentially tremendous impact on the lives of tested individuals and their relatives, such testing requires high levels of quality assurance, professional pre- and post-test counselling, clinical follow-up and psychosocial support.

In the bioethical and bio-medical literatures, myriads of ethical issues have been mentioned, which usually do not apply to all genomic tests. Our typology of genomic tests on the basis of test and disease characteristics can thus be used to explain why some issues bear on some genomic tests, and other issues bear on others - or, more anticipatory: to determine what ethical issues are to be expected from a particular (type of) genomic test.

Our third research question concerns one of the pivotal ethical issues associated with genomic testing, that which we call 'the information problem': because of the quantity, disputability, complexity, fluidity and diversity of the data generated through genomic technologies, informed consent seems hardly possible. **Chapter 6** argues that although informed consent may be exacting, it should continue to precede genomic testing, also in a direct-to-consumer context. Informed consent entails much more than simply accepting the 'Terms of Service': it presupposes a voluntary, adequately informed and considered choice. The requirement of informed consent is grounded in the principles of respect for autonomy and the prevention of harm. Although commercial companies may not be straight-forwardly bound by the moral and professional standards of healthcare, they are not free from basic informational obligations. Consumers should at minimum be enabled to know the limitations, risks and implications of genomic testing and be given some control over the information they do and do not wish to receive. As neither traditional specific informed consent nor generic consent are suitable for (broad) genomic testing, a different model for informed consent must be devised.

Chapter 7 presents a proposal for a so-called tiered-layered-staged model for informed consent, which is meant to meet both the norm of providing sufficient information and that of providing understandable information. Genomic tests should not be presented as packages, consisting of dozens or hundreds of (very) diverse tests, but differentiated into separate tiers. In the process of pre-test

information provision, these tiers ought to be defined along the lines of morally relevant test and disease characteristics, such that - say - testing of high clinical validity for severe diseases is clearly distinguished from testing of limited clinical validity for less severe diseases, and psychiatric testing and/or testing for diseases for which therapeutic or preventive options are lacking, are discussed separately. Ideally, consumers should give informed consent not to the (broad) testing package as a whole, but to separate tiers, so that they optimally know 'what it is they are getting into' with genomic testing. Our model further proposes that pre-test information is provided in a layered fashion to tailor to individual informational needs and to maximally personalise the informed consent process. Information provision should also be staged to make optimal educational use of the passing of time between the key decisional moments within the testing process. Our model can be implemented online, in a clinical as well as a commercial context. The layered and staged organisation of pre-test information, combined with the differentiation of the testing offer itself into tiers, should render the process of pre-test information provision and informed consent feasible, also for very broad genomic tests.

In **Chapter 8**, we compare commercially offered genomic testing to two areas of (public) healthcare in which genomic technologies are making their entrance: prenatal screening and new-born screening. In all three areas, the technological possibility of generating ever more genomic information tends to lead to an expansion of testing and screening offers. Such expansion does not necessarily enhance (reproductive) autonomy, for increasing quantities of information may only overwhelm consumers or (prospective) parents and undermine autonomous decision-making. A restriction or a pre-structuring - differentiation - of screening or testing options may sometimes be indispensable to a workable process of informed consent. Further, there are moral limits to the scope of a responsible testing or screening offer: providers - whether within the public healthcare system or on the consumer market - should avoid violating the (anticipated) autonomy rights of children by subjecting them to undue and unnecessary genomic testing.

The fourth and final research objective of this thesis is to critically analyse the notion of personal utility. In the bioethical debate, personal utility is often

equated with subjective experiences of value, (health-related) benefit or satisfaction among consumers, patients or research participants. Often, the notion is deployed normatively to advocate (direct) access to or disclosure of genomic information. **Chapter 9** distinguishes between perceived personal utility and actual personal utility. It proposes a normative definition of personal utility, which subjects it to the preconditions of clinical validity (or predictive value) and what we call 'reasonable potential use'. Consequently, genomic tests that lack clinical utility but are (still) pursued by consumers or participants, should not automatically be considered to have personal utility. Also, consumers' or participants' claims to genomic information with reference to (perceived) personal utility may not always be valid - for there may be no (real) utility. Although personal utility does have a role to play - beside clinical utility - in the (ethical) evaluation of genomic testing with an eye to its clinical or public health implementation or reimbursement, its role is not unlimited.

Chapter 10 contains a general ethical discussion of the main findings and insights presented in this thesis. It argues that providers of genomic testing - whether these are healthcare professionals, institutions or commercial parties - should deliver the fruits of emerging genomic technologies while seeking to minimise harm, and implement adequate pre-test information and informed consent. Genomic testing or screening offers should be carefully designed and differentiated, and enveloped in proportionate protective measures.

Genomic information is up close and personal. Therefore, we should be allowed to decide - in privacy and in freedom - what genomic information we do and do not wish to receive about ourselves, and to what parties we wish to disclose any of it. Still, there are moral limits to the ways in which our genomic information is made accessible to us. This thesis offers insight in some of these limits, and seeks to guide our ethical management of genomic testing.

Samenvatting

In genomisch opzicht verschillen mensen maar weinig van elkaar: minder dan 1%. Toch zijn er in het DNA (dat uit zo'n drie miljard baseparen bestaat) tussen mensen onderling enkele miljoenen verschillen te vinden. Die bepalen grotendeels hoe we er (anders) uit zien, hoe we spreken, eten en bewegen, hoe we denken, liefhebben en stemmen, hoe we gezond blijven en ziek worden. Dankzij nieuwe technologieën waarmee we in ons genoom kunnen kijken, kunnen we inzicht verkrijgen in onze krachten en onze zwakheden. Dat inzicht kan ons verder brengen: we kunnen ons genoom testen op erfelijke aanleg voor ziekten, en proberen deze ziekten te voorkomen, bijvoorbeeld door onze leefstijl aan te passen of door vroegtijdig in te grijpen met medische behandelingen. Dat inzicht kan ons ook schaden: niet iedereen zal zijn of haar Achilleshiel willen leren kennen, zeker niet als het gaat om ziekten die niet te voorkomen of te behandelen zijn. Ons genoom is dichtbij en persoonlijk, maar omdat genomische 'spiegels' betrekkelijk nieuw voor ons zijn, weten we wellicht nog niet wat we ermee willen doen - of hoe we deze spiegels op een verantwoorde manier kunnen inzetten.

De afgelopen decennia is er wereldwijd veel geïnvesteerd in genoomonderzoek en in technologieën om het DNA in kaart te brengen en te analyseren. Onderzoeksgroepen en entrepreneurs hebben zogeheten (micro)array technologieën ontwikkeld, die op snelle, gemakkelijke en betaalbare wijze informatie genereren over een flink aantal van de meest interessante gedeelten van het genoom - gedeelten die veelvoorkomende onderlinge verschillen bevatten. Ook sequencing technologieën, die alle baseparen van het DNA één voor één in kaart brengen, ontwikkelen zich razendsnel en worden langzaam maar zeker geïmplementeerd in de kliniek. Echter, de interpretatie van genomische informatie is vaak bewerkelijk én onzeker: van veel genomische varianten zijn de biologische effecten en de interacties met andere varianten en omgevingsfactoren nog volstrekt onduidelijk. Bovendien is het genoom minder voorspellend gebleken (de klinische validiteit is lager) dan voorheen werd gedacht - en gehoopt.

Desalniettemin hebben genoomtests zich gedurende de afgelopen vijftien jaar verspreid over de westerse wereld, zowel binnen de reguliere gezondheidszorg als daarbuiten. Genoomtests hebben talloze ethische discussies losgemaakt onder onderzoekers, artsen en beleidsmakers, met name over de kwaliteit en de klinische bruikbaarheid van genoomtestresultaten, over geïnformeerde toestemming en counselling, over de risico's van een groeiend testaanbod en over de voor- en nadelen van directe toegang tot genoomtests via commerciële aanbieders. Dit proefschrift bespreekt ethische kwesties rond genoomtests tegen een liberaal-ethische achtergrond. Het biedt een praktisch ethisch kader voor een verantwoord aanbod van genoomtests, in een klinische setting, in de context van zogeheten direct-to-consumer marketing en in de context van medisch-wetenschappelijk onderzoek.

Hoofdstuk 1 bevat een algemene inleiding in de biologische en technische mechanismen die ten grondslag liggen aan genoomtests, in de bestaande commerciële kanalen waarlangs genoomtests worden aangeboden en in de ontwikkelingen binnen de bijbehorende ethische discussies en beleidsdiscussies. Ook bevat het hoofdstuk een bespreking van onze toegepast-ethische, pragmatische aanpak van onderzoek en beschrijft het de vier onderzoeksvragen die leidend zijn geweest bij het schrijven van dit proefschrift.

Onze eerste onderzoeksvraag luidt: Wat zijn genoomtests? **Hoofdstuk 2** laat zien hoe schijnbaar descriptieve uitspraken over genoomtests sterk zijn verbonden met onderliggende normatieve posities ten aanzien van beleidsproblematiek. Naamgeving en framing worden vaak ingezet - bewust of onbewust - om genoomtests in een bepaald licht te presenteren, om bepaalde problemen en/of oplossingsrichtingen te suggereren en de aandacht weg te leiden van andere problemen. In het bijzonder zullen medische namen en frames de nadruk leggen op aan de gezondheid gerelateerde doelen en beweegredenen met betrekking tot genoomtests, en op (het gebrek aan) klinische validiteit en bruikbaarheid. Daarentegen zullen persoonlijke namen en frames andere, niet-medische doelen en toepassingen van genoomtests naar de voorgrond schuiven, en verwijzen naar de waarden vrijheid, toegang, gemak, zelfbepaling en persoonlijke bruikbaarheid. Het hoofdstuk sluit af met een waarschuwing voor het kritiekloos gebruik van het persoonlijke frame, omdat

dit frame de neiging heeft de risico's en implicaties van genoomtests te verdoezelen en verbergen.

Hoofdstuk 3 bevat een uitgebreider bespreking van frame theorie en een lange lijst van namen die de afgelopen jaren zijn gebruikt in discussies over genoomtests. Een casusbespreking laat de werking zien van drie prominente frames - technische, medische en persoonlijke frames - die bijbehorende normatieve posities binnen het ethische debat naar voren schuiven. Verder geeft hoofdstuk 3 een zogenoemde 'familiegelijkenissen definitie' van genoomtests en een kleine geschiedenis van het veld van commercieel aangeboden genoomtests. Het verheldert drie belangrijke concepten binnen de ethische discussie (te weten: test, medische test en screening) en beargumenteert dat genoomtests voor complexe aandoeningen moeten worden beschouwd - en behandeld - als een vorm van medisch testen. Het breed gedragen ethische kader voor de evaluatie van screeningstests echter is niet van toepassing op een commercieel aanbod van genoomtests. Teneinde weerstand te kunnen bieden aan de normatieve effecten van definities, naamgeving en framing, wordt het minimaliseren van schade voorgesteld als richtinggevend principe bij beleidsproblematiek rond genoomtests. Daar waar kans op schade bestaat, zijn beschermende beleidsmaatregelen benodigd, ongeacht (mogelijk conflicterende) onderliggende ideeën over het wezen van genoomtests.

Onze tweede onderzoeksvraag betreft het identificeren van ethische kwesties rondom genoomtests, en het relateren van deze kwesties aan de kenmerken van de test en de kenmerken van de aandoeningen waarop wordt getest. **Hoofdstuk 4** onderscheidt vier testkenmerken: gericht/ongericht testen, analytische validiteit, klinische validiteit en klinische bruikbaarheid, en richt zich met name op klinische validiteit als cruciaal moreel-relevant testkenmerk. Verschillende niveaus van klinische validiteit zijn verbonden met hun eigen ethische problemen, bijvoorbeeld: terwijl genoomtests van hoge klinische validiteit ethische problemen oproepen vanwege hun zwaarwegende gevolgen voor de geteste personen, zullen tests van lage klinische validiteit juist ethische problemen oproepen vanwege de heersende onduidelijkheid met betrekking tot de betekenis - en de gevolgen - van de test. Omdat aan niet-zo-voorspellende genoomtests zoveel onzekerheden kleven, kunnen zij gemakkelijk leiden tot

misverstanden, zoals over- of onderschatting van de (klinische) betekenis van testresultaten. Terwijl het in de ethiek van genetisch testen van hoge klinische validiteit traditioneel gaat om het minimaliseren van schade (de medisch-ethische principes van weldoen en niet-schaden), gaat het in de ethiek van niet-zo-voorspellende genoomtests met name om informatie, communicatie en voorlichting.

Hoofdstuk 5 onderscheidt vier ziektekenmerken, te weten: ernst, age of onset (de leeftijd waarop de ziekte zich voor het eerst manifesteert), actionability (de aan- of afwezigheid van handelingsopties) en het onderscheid psychiatrisch/somatisch. Deze vier kenmerken opereren als morele variabelen, bijvoorbeeld: genoomtests voor ziekten met een late age of onset moeten - waar mogelijk - niet worden aangeboden aan kinderen en minderjarigen. Een ander voorbeeld vormen genoomtests voor (zeer) ernstige ziekten, met name ziekten waarvoor geen behandeling of preventieve opties bestaan, zoals de ziekte van Huntington. Vanwege de mogelijk levensgrote impact op de levens van de geteste personen en hun familieleden, vereist het aanbod van dergelijke tests een hoge mate van kwaliteitsborging, professionele counselling voorafgaand aan en volgend op de test, medische follow-up en psychosociale begeleiding.

In de bio-ethische en biomedische literatuur is melding gemaakt van legio ethische kwesties, maar deze kwesties zijn niet allemaal van toepassing op alle genoomtests. Onze typologie van genoomtests op basis van test- en ziektekenmerken kan worden gebruikt om te verklaren waarom bepaalde ethische kwesties spelen bij bepaalde tests en andere kwesties spelen bij andere tests - of, meer anticiperend, om te bepalen welke ethische kwesties verwacht kunnen worden van een bepaald type genoomtest.

Onze derde onderzoeksvraag heeft betrekking op één van de meest centrale ethische kwesties rondom genoomtests, namelijk het probleem van informatie: vanwege de kwantiteit, betwistbaarheid, complexiteit, veranderlijkheid en diversiteit van de informatie die wordt gegenereerd bij het testen van het genoom, lijkt geïnformeerde toestemming vrijwel onmogelijk. **Hoofdstuk 6** betoogt dat geïnformeerde toestemming vooraf moet blijven gaan aan genoomtests, ondanks eventuele praktische struikelblokken, ook in een direct-

to-consumer context. Geïnformeerde toestemming is méér dan het instemmen met de gebruikersvoorwaarden, en veronderstelt een vrijwillige, adequaat geïnformeerde keuze. Deze morele vereiste is gegrond in de medisch-ethische principes van respect voor de autonomie en niet-schaden. Hoewel commerciële bedrijven niet zonder meer onderhevig zijn aan de morele en professionele regels en standaarden van de gezondheidszorg, zijn zij niet geheel vrij van basale informationele verplichtingen. Consumenten moeten tenminste in staat gesteld worden kennis te nemen van de beperkingen, risico's en implicaties van genoomtests, en een zekere controle hebben over welke genomische informatie zij wel of niet zullen ontvangen. Omdat traditionele, specifieke geïnformeerde toestemming noch generieke toestemming geschikte opties zijn voor (brede) genoomtests, moet worden gezocht naar een ander model voor geïnformeerde toestemming.

In **Hoofdstuk 7** wordt een voorstel gepresenteerd voor een gedifferentieerd-gelaagd-gefaseerd model voor geïnformeerde toestemming, dat poogt tegemoet te komen aan zowel de norm van het geven van voldoende informatie als de norm van het geven van begrijpelijke informatie. Genoomtests moeten niet aan consumenten of patiënten worden gepresenteerd als pakketten, bestaande uit tientallen of honderden (zeer) uiteenlopende tests, maar moeten worden opgedeeld in verschillende onderdelen. Bij de informatievoorziening voorafgaand aan de test moet het testaanbod worden gedifferentieerd langs de lijnen van relevante test- en ziektekenmerken, zodanig dat bijvoorbeeld tests van hoge klinische validiteit voor ernstige ziekten duidelijk worden onderscheiden van tests van lage klinische validiteit voor minder ernstige ziekten, en dat bijvoorbeeld psychiatrische tests en/of tests voor onbehandelbare aandoeningen apart worden besproken. Idealiter geven consumenten geïnformeerde toestemming niet voor de (brede) genoomtest in zijn geheel, maar voor specifieke onderdelen, zodat zij zo goed mogelijk weten 'waar zij aan beginnen' wanneer zij een genoomtest bestellen. Verder stelt het model voor de informatie voorafgaand aan de test te presenteren op een gelaagde manier, zodat zij kan worden toegespitst op de individuele informatiebehoeften van de consument en het toestemmingsproces zoveel mogelijk wordt gepersonaliseerd. De informatie moet ook gefaseerd worden voorgelegd, om zodoende optimaal gebruik te maken van de tijdspannen tussen belangrijke beslissingsmomenten in het

testproces en een leercurve te bewerkstelligen. Ons model kan online worden toegepast, en zowel in een klinische setting als in een commerciële context worden geïmplementeerd. Dankzij de gelaagde, gefaseerde organisatie van informatie voorafgaand aan de test, gecombineerd met de differentiatie van het testaanbod zelf in moreel onderscheiden onderdelen, moet het mogelijk zijn het proces van informatievoorziening en geïnformeerde toestemming werkbaar te maken, ook voor zeer brede genoomtests.

Hoofdstuk 8 vergelijkt commercieel aangeboden genoomtests met andere gebieden van de (publieke) gezondheidszorg waarin genoomtechnologieën hun intrede doen: prenatale screening en neonatale screening. Op alle drie de terreinen leiden toenemende technologische mogelijkheden om steeds meer genomische informatie te genereren tot een uitbreiding van het test- en screeningsaanbod. Een dergelijke uitbreiding komt de (reproductieve) autonomie niet altijd ten goede, omdat grote hoeveelheden informatie consumenten of (toekomstige) ouders kunnen overspoelen en daarmee de autonome besluitvorming kunnen ondermijnen. Een beperking of een voorstructurering (differentiatie) van (screenings)testopties zal soms onontbeerlijk zijn om een werkbaar proces van geïnformeerde toestemming mogelijk te maken. Bovendien zijn er morele grenzen aan een verantwoord test- of screeningsaanbod: aanbieders - of het nu gaat om aanbieders binnen het reguliere gezondheidszorgsysteem of op de commerciële markten - moeten schending van de (toekomstige) autonomie van het kind voorkomen door hen niet bloot te stellen aan ongeschikte en onnodige genoomtests.

De vierde en laatste onderzoeksvraag van dit proefschrift betreft een kritische analyse van het begrip persoonlijke bruikbaarheid of persoonlijk nut (personal utility). In bio-ethische discussies wordt persoonlijk nut vaak gelijkgesteld aan de subjectieve ervaring van waarde, (wel of niet aan de gezondheid gerelateerd) voordeel of tevredenheid onder consumenten, patiënten of deelnemers aan medisch-wetenschappelijk onderzoek. Veelal wordt het begrip normatief ingezet om te pleiten voor (directe) toegang tot of kennisgeving van genomische informatie. In **Hoofdstuk 9** wordt een onderscheid gemaakt tussen waargenomen nut en werkelijk nut. Het hoofdstuk stelt een normatieve definitie voor van het begrip persoonlijk nut, die nut onderwerpt aan de

randvoorwaarden van klinische validiteit (of voorspellende waarde) en redelijke mogelijke toepassing (bruikbaarheid). Dientengevolge mag aan genoomtests zonder klinisch nut, die (toch) worden nagejaagd door consumenten of onderzoeksdeelnemers, niet automatisch persoonlijk nut worden toegeschreven. Ook zijn de claims die consumenten of deelnemers maken op genomische informatie, met een beroep op het (waargenomen) persoonlijk nut van die informatie, niet altijd valide. Soms heeft die 'informatie' immers geen werkelijk nut. Alhoewel het begrip persoonlijk nut een rol kán spelen - naast klinisch nut - bij de (morele) beoordeling van genoomtests met het oog op de implementatie binnen de klinische of publieke gezondheidszorg, zal die rol niet grenzenloos zijn.

Hoofdstuk 10 bevat een algemene ethische discussie naar aanleiding van de belangrijkste bevindingen van dit onderzoek. Wij pleiten ervoor dat aanbieders van genoomtests - ongeacht of het gaat om medische professionals, gezondheidszorginstellingen of commerciële partijen - de baten van genoomonderzoek beschikbaar stellen aan het publiek en de gevaren minimaliseren, en zorg dragen voor adequate informatievoorziening en geïnformeerde toestemming. Het aanbod van genoomtests moet met zorg worden ingericht (o.a. gedifferentieerd) en gepaard gaan met proportionele beschermende maatregelen.

Genomische informatie is dichtbij en persoonlijk. Daarom moeten wij in alle vrijheid en privacy kunnen beslissen over welke genomische informatie (over onszelf) wij willen beschikken, en aan welke andere partijen wij die informatie kenbaar willen maken. Desondanks zijn er morele grenzen aan de wijze waarop deze informatie voor ons toegankelijk wordt gemaakt. Dit proefschrift geeft inzicht in een aantal van deze grenzen, en poogt richting te geven aan de wijze waarop wij omgaan met genoomtests.

Dankwoord

Dankwoord

Het was dr. Medard Hilhorst die mij, afgestudeerd in de filosofie, zag zitten tussen de eerstejaars geneeskundestudenten aan het Erasmus MC. Zonder enige aarzeling bood hij mij een bijbaantje aan als onderzoeker op de afdeling Medische Ethiek en Filosofie van de Geneeskunde. Onder zijn wijze leiding publiceerde ik mijn eerste stukken over de ethische toetsing van dierproeven, en mocht ik onderdeel worden van onze warme en groeiende afdeling.

Aan het hoofd van deze afdeling staat onze hoogleraar Inez de Beaufort, oprecht en rechtvaardig, bezield en visionair. In 2012 heeft zij de gehele internationale gemeenschap aan bio-ethici bijeengebracht in Rotterdam, voor een legendarisch, onvergetelijk congres. Ik ben Inez dankbaar voor de kansen die zij mij bood en biedt, vanuit een ongekend vertrouwen in haar jongere medewerkers: binnen de kortste keren mocht ik hoorcolleges geven aan honderden geneeskundestudenten en zelfverzonnen onderwijsprogramma's verzorgen voor medisch-specialisten in opleiding. Ik ben één van die mensen die gedijt bij het in het diepe worden losgelaten, en heb enorm genoten en geleerd van de vrijheid die Inez mij heeft geboden, om ethiek-onderwijs te geven.

Verreweg de meeste dank ben ik verschuldigd aan Cecile Janssens en Maartje Schermer, mijn begeleiders en promotoren. Cecile en Maartje zijn zo tegengesteld als maar mogelijk is, maar zij hebben mij allebei al die jaren opgeleid en aangestuurd, aangemoedigd en teruggeroepen, gedisciplineerd en gesteund, elk op hun eigen manier. Cecile is expressief en ambitieus, extravert en gedreven, ontwapenend en enthousiast. Cecile is slim, snel en veerkrachtig, en heeft een uitzonderlijke ontvankelijkheid voor nieuwe ideeën. Zij heeft een groot, genereus hart. Maartje is verstandig en kalm, zorgvuldig en helder, betrouwbaar en integer. Als Maartje spreekt, dan maakt zij altijd het meest belangrijke punt dat kan worden gemaakt. Maartje is naar alle waarschijnlijkheid de enige promotor op de hele wereld die de e-mails van haar promovendus altijd beantwoordt. Wij zijn samen op reis geweest naar Atlanta,

een verrassende week, waarin ik aan haar gehecht ben geraakt. Maartje is een denker: zij kan écht nadenken.

Het commentaar dat ik van Maartje en Cecile kreeg op stukken die ik had geschreven, was ook altijd tegengesteld van aard: waar Cecile een paar *sweeping statements* in de kantlijn krabbelde en rode strepen trok door technische onjuistheden, kwam Maartje met constructieve, conceptuele oplossingen. Allebei onontbeerlijk. Cecile en Maartje hebben enorm vormgegeven aan mijn promotieonderzoek, niet alleen aan de producten ervan, maar ook aan mijn beleving. Promoveren is een steile leercurve, ondanks het feit dat het tevens een hoop geploeter is, laat ik eerlijk zijn. Mensen zeggen weleens dat promoveren een oefening in nederigheid is, een proces van karaktervorming. Het is inderdaad een vormende ervaring. Mooi, zwaar en dierbaar, maar ik weet niet of ik het iedereen zomaar zou aanraden. Tijdens dit proces heb ik niet alleen veel geleerd van Maartje en Cecile: zij hebben ook heel sterk hun stempels gedrukt, hun sporen achtergelaten in mijn geest, in mijn persoon.

Ik ben het Centre for Society and the Life Sciences (CSG) dankbaar voor het financieren van mijn promotieonderzoek, voor de organisatie van talloze onderzoekersdagen en andere bijeenkomsten, voor de aanstekelijke opdracht een verbinding te leggen met de maatschappij en beroepspraktijk, en voor het bij elkaar brengen van onderzoekers, Met een aantal CSG-onderzoekers heb ik in vriendschap en met succes samengewerkt aan zowel academische als op een breder publiek georiënteerde publicaties. Ik vertrouw erop dat deze waardevolle contacten zich in de toekomst zullen voortzetten. Tevens wil ik onze Principal Investigators bij het CSG, tevens leden van de leescommissie, professor Martina Cornel en professor Guido de Wert, bedanken voor hun inzet.

Aan de landelijke Onderzoekschool Ethiek (OZSE) heb ik een opleiding in de ethiek gevolgd. Ik heb het altijd een ongelooflijke luxe gevonden dat een deel van mijn betaalde werk erin bestond cursussen te volgen. Op deze cursussen, winterscholen, zomerscholen en in mijn tijd als lid van de Promovendiraad van de OZSE, heb ik allerlei bevleugelde mensen leren kennen van allerlei universiteiten, die ik overal terugzie op bijeenkomsten en congressen. Als promovendus leid je in eerste instantie een vrij geïsoleerd werkend bestaan,

maar door het net dat de OZSE als het ware over alle ethici in Nederland heeft gelegd, ontwikkelde zich in mij langzamerhand een ervaring van ingebed-zijn in een gemeenschap. Mijn dank gaat ook uit naar de Netherlands Association for Community Genetics and Public Health Genomics (NACGG), die mij in contact heeft gebracht met bijzondere mensen en inzicht heeft gegeven in de publieke gezondheidszorg.

Aan de afdeling Klinische Genetica van het Erasmus MC heb ik jarenlang met veel plezier ethiek-onderwijs gegeven, en heb ik op mijn beurt kennis mogen nemen van de morele problemen die spelen in de praktijk van de klinische genetica. Ook van geneeskundestudenten, onderzoekers en artsen - ik ben dol op artsen - binnen het Erasmus MC blijf ik leren.

Ik ben de lieve mensen op mijn afdeling dankbaar voor hun vriendelijkheid, interesse, *tips & tricks*, commentaar bij *work in progress*, koffies en opstekers, en voor allerlei momenten van menselijkheid, plezier en tranen van vreugde, op het werk of buiten het werk om. Sommigen zijn reeds uitgevlogen, anderen zijn net nieuw, maar de meesten blijven waar ze zijn, op onze afdeling. In het bijzonder wil ik Annemieke van Tintelen bedanken voor het draaiende houden van de hele machinerie, Frans Meulenberg voor zijn taaltalent, en Hannie Aartsen voor haar energie en strategisch advies.

Dan zijn er de mensen in mijn persoonlijke leven, die zo ook hun bijdrage hebben geleverd aan de totstandkoming van dit proefschrift. Mijn schoonmoeder, Oma Petra, die iedere maandag met zoveel liefde en plezier op onze kinderen past, en die onwaarschijnlijk sterk en positief is. Mijn lieve schoonzussen Marijn, Sara en Jenny en zwager Olivier, die gehecht zijn aan onze kinderen en die ons zo nu en dan bijstaan - deze grote, hechte, bijna-Italiaanse familie. Onze vrienden en vriendinnen, oud en jong, in binnen- en in buitenland, die - genood of ongenood - komen eten of praten of feestvieren of dansen. Mensen op de school van mijn dochter. Mensen in onze buurt. Mijn meest dierbare vriendinnen, met wie ik al een groot deel van mijn leven ben verbonden. Fenneke, Sabine, Saskia. Mijn nichtje Nicole. We praten meestal over leven en liefde en ouders en kinderen en avontuur en tragedie en de toekomst en de belangrijkste keuzes. Maar jullie vragen ook naar mijn werk, dóór naar

mijn werk. Er zijn maar weinig mensen echt geïnteresseerd in of begaan met de levens van anderen. Jullie zijn dat, met mijn leven. Ik vind dat prachtig, en ik ben jullie daarvoor erg dankbaar. Mijn broertje Thomas en zijn vrouw Kellie, die samen drie kinderen op de wereld hebben gezet: wonderschone Oxo, Zia en Amé. Jullie zijn ongelooflijk en ik heb jullie alle vijf lief.

Mijn ouders, papa en mama, die mij hebben gemaakt en gedragen, die mij hebben leren lopen, lezen en spreken. Die mij manieren hebben bijgebracht, kracht, zorgvuldigheid en doorzettingsvermogen, maar ook opmerkzaamheid en empathie. Die mijn nieuwsgierigheid en leergierigheid hebben gevoed. Die mij vertrouwen hebben gegeven. Die altijd voor mij hebben gezorgd, tot op de dag van vandaag. Die zo betrokken zijn bij ons leven, en dat van onze kinderen. Gelukkig zijn jullie er allebei. Gelukkig zijn jullie samen. Gelukkig zijn jullie zo gelukkig met elkaar… Wat hebben wij toch veel geluk.

Het is heel precair, een mensenleven, daar ben ik mij vaak van bewust. Ik hoop dat het geluk nog een hele tijd aan onze zijde blijft. Ik houd heel veel van jullie.

Mijn lieve kindjes. Drie stuks. Best veel. Maar jullie zijn zo onbeschrijflijk lief. Ik ben heel erg blij dat ik zoveel tijd met jullie kan doorbrengen. Jullie maken mij op een gemiddelde dag zo'n veertig tot vijftig keer extreem gelukkig. Ik ben natuurlijk heel erg trots op jullie alle drie, Liztophe omdat je zo apart, getalenteerd, fijngevoelig, wijs en ruimhartig bent, Tiberius omdat je woest en oplettend, toegewijd en hardnekkig bent, zoals je vader, en Abel omdat je nog zo klein en zacht en heerlijk bent, en toch al dapper. Ik hoop met heel mijn hart dat ik jullie alle drie mag zien opgroeien tot volwassen mensen, en dat jullie zo vrolijk blijven als je nu bent.

Mijn liefste Tim. Ik heb nog steeds geen andere naam voor jou. Jij bent alles wat ik nodig heb. Ik heb genoeg aan jou.

About the author

Curriculum Vitae

Eline Bunnik was born on October 14th 1982, in a hospital in Leidschendam, the Netherlands. In secondary school in Rotterdam, Eline completed all the courses (biology, chemistry, mathematics, physics) required for medical school. But upon graduation, she decided to study philosophy and literature instead at the University of Amsterdam (UvA). She obtained a bachelor's degree (cum laude) in Philosophy in 2003, and then the very first UvA research master's degree (cum laude) in Philosophy in 2005. Eline received a Talent Grant from the Dutch Nuffic foundation to pursue further studies in London, but she soon returned to the Netherlands to have her first child, Liztophe, in 2006. Eline enrolled in medical school at Erasmus MC in Rotterdam in 2007, where she received a first-year diploma (propedeuse). That same year she also took a part-time job as a research assistant at the Department of Medical Ethics and Philosophy of Medicine, where she collaborated with dr. M.T. Hilhorst on a research project on animal ethics. In late 2008 she started the research PhD-project (part-time) for her thesis Up Close and Personal, Ethical Issues in Genomic Testing, supervised by promotores prof.dr. M.H.N. Schermer and prof.dr. A.C.J.W. Janssens. The project was funded by the Centre for Society and the Life Sciences (CSG) as part of the Netherlands Genomics Initiative. Eline has been an active member of the CSG, the PhD-Council of the Netherlands School for Research in Practical Philosophy (OZSE) and the Netherlands Association for Community Genetics and Public Health Genomics (NACGG). She has taught medical ethics and bioethics at undergraduate, graduate and post-graduate levels at Erasmus MC and at Leiden University Medical Centre (LUMC). Through publications and lectures, Eline sought to communicate her work to both academic and professional or public audiences. She was awarded the NACGG Innovation Prize for her publications on informed consent in genomic testing in 2012. Eline married in 2010, and has had two more children, Tiberius and Abel. Eline is currently working on a ZonMW post-doc project at Erasmus MC, on the ethics of incidental findings in brain MRI research.

List of selected publications

Bunnik E., A.C.J.W. Janssens and M. Schermer. 2009. How attitudes research contributes to overoptimistic expectations of personal genome testing. *American Journal of Bioethics* 9(6): 23-25.

Cornel M.C., E.M. Bunnik en G. de Wert. 2010. Van hielprik naar persoonlijke DNA code? 1. Tien jaar genetische screening in Nederland. Een terugblik. *Tijdschrift voor Gezondheidszorg en Ethiek* 20(2): 38-43.

Bunnik E.M., G. de Wert en M.C. Cornel. 2010. Van hielprik naar persoonlijke DNA code? 2. De uitdagingen van 2010: Een inventarisatie van maatschappelijke en ethische implicaties. *Tijdschrift voor Gezondheidszorg en Ethiek* 20(2): 44-50.

Bunnik E.M., M.H.N Schermer and A.C.J.W. Janssens. 2011. Personal genome testing: Test characteristics to clarify the discourse on ethical, legal and societal issues. *BMC Medical Ethics* 12:11.

Bunnik E.M. 2011. Personal genome tests: Ethische en maatschappelijke implicaties. *NVBe-Nieuwsbrief* 18(2): 32.

Bunnik E.M. 2011. Why not order direct-to-consumer genetic testing for your children? *Genomics, Society and Policy* 6(3): 3-5.

Bunnik E.M., M.H.N. Schermer and A.C.J.W. Janssens. 2012. The role of disease characteristics in the ethical debate on personal genome testing. *BMC Medical Genomics* 5:4.

Bunnik E.M., A.C.J.W. Janssens and M.H.N. Schermer. 2012. Informed consent in direct-to-consumer personal genome testing: The outline of a model between specific and generic consent. *Bioethics* doi: 10.1111/bioe.12004 [Epub ahead of print].

Bunnik E.M. 2012. Erfelijk risico goed te verzekeren. *Medisch Contact* 67(48): 2728-2730.

Bunnik E.M. 2012. IAB Congres in Rotterdam, 2012. Van apen en mensen: Op naar een globale bio-ethiek. *Podium voor Bio-ethiek* 19(3): 4-7.

Bunnik E.M. 2012. Commerciële genetica: Waar gaat dat naartoe? *Podium voor Bio-ethiek* 19(3): 7-9.

Bunnik E.M., A. de Jong, N. Nijsingh and G.M. de Wert. 2013. The new genetics and informed consent: Differentiating choice to preserve autonomy. *Bioethics* 27(6): 348-355.

Bunnik E.M., A.C.J.W. Janssens and M.H.N. Schermer. 2013. A tiered-layered-staged model for informed consent in personal genome testing. *European Journal of Human Genetics* 21(6): 596-601.

Bunnik E.M., M.H.N. Schermer and A.C.J.W. Janssens. 2014. Naming and framing in genomic testing. *Trends in Molecular Medicine* 20(2): 63-65.

Bunnik E.M. 2014. Consumenten: Ziekte op bestelling? In: *Genen en Gezondheid.* Stichting Biowetenschappen en Maatschappij 33(1): 54-59.

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio

Eline M. Bunnik Erasmus MC Department of Medical Ethics and Philosophy of Medicine	PhD period: 2008-2014 Promotores: prof. dr. A.C.J.W. Janssens and prof. dr. M.H.N. Schermer

PhD training

	Year	Workload (ECTS)
General courses		
Course 'Research Integrity' (Department of Medical Ethics, Erasmus MC)	2009	0,5 ECTS
Course 'Systematisch literatuuronderzoek' (Medical Library, Erasmus MC)	2012	0,2 ECTS
Specific courses		
Course 'Ethics & Technology' (Landelijke Onderzoekschool Ethiek (OZSE))	2009	6 ECTS
Summerschool 'Bioethics and Ethical Theory' (OZSE)	2009	6 ECTS
Course 'Ethics & Health Care' (OZSE)	2010	6 ECTS
Winterschool 'Ethical Theory and Moral Practice' (OZSE)	2011	6 ECTS
Course 'Introduction to Clinical and Public Health Genomics' (NIHES)	2009	1,9 ECTS
Erasmus Winter Programme 'Genetic Analysis in Clinical Research' (NIHES)	2009	1,9 ECTS
Course 'SNPs and Human Diseases' (MolMed)	2009	1,4 ECTS

Summerschool 'Clinical Ethics Support Services' (ECEN, Italy)	2012	3 ECTS
Seminars and workshops		
Working group Ethics & Technology (OZSE)	2008-2014	0,6 ECTS
Working group Ethics & Health Care (OZSE)	2008-2014	0,2 ECTS
PhD-seminars (OZSE)	2008-2013	3 ECTS
Researchers' Days and Researchers' Meetings (CSG)	2009-2012	2 ECTS
Meetings (NACGG)	2009-2014	0,5 ECTS
Workshop 'Open tentamenvragen maken' (Desideriusschool)	2011	0,1 ECTS
Presentations and invited lectures		
Ethics Department of the Dutch Ministry (VWS)	2008	0,1 ECTS
Clinical geneticists and genetic counsellors in training	2009	0,1 ECTS
'From researching to publishing' (CSG)	2009	0,1 ECTS
33e Nederlands-Vlaamse Filosofiedag (TU Delft)	2011	0,5 ECTS
Jaarsymposium Nederlandse Vereniging voor Bio-ethiek (NVBe)	2012	0,5 ECTS
Debate-night 'Voorbestemd voor Goud' (Lux, Nijmegen)	2012	0,3 ECTS
Centre for Medical Systems Biology (CMSB) Symposium	2012	0,5 ECTS
'A personalised model for informed consent' (NACGG)	2012	0,5 ECTS
Workshops Landelijk Medisch Studenten Overleg (LMSO)	2012	0,2 ECTS
Congress 'Wat worden we wijzer van genetisch testen?'(Jaarbeurs Utrecht)	2013	0,3 ECTS
'Genetics and insurability' at information meeting for Peutz-Jehgers syndrome patients (Utrecht)	2013	0,3 ECTS

Presentations at (inter)national conferences		
1st Annual Dutch Conference in Practical Philosophy, Doorn (OZSE)	2009	1 ECTS
European Society for Human Genetics (ESHG), Amsterdam (poster)	2011	1 ECTS
European Society for Philosophy of Medicine and Healthcare (ESPMH), Zürich: 'Personal genome testing: The basic questions'	2011	1 ECTS
3rd Annual Dutch Conference in Practical Philosophy, Amsterdam: 'The information problem in personal genome testing: A layered-staged-tiered model for informed consent'	2011	1 ECTS
ESRC Genomics Network conference: Genomics and society: Facts, fictions and cultures, London	2012	1 ECTS
Symposium 'The new genetics and informed consent' and symposium 'DTC genetic testing' at IAB World Congress, Rotterdam	2012	1 ECTS
International workshop 'Genetics goes online: Practices, policies and possibilities', Maastricht	2012	1 ECTS
4th Annual Dutch Conference in Practical Philosophy, Eindhoven (OZSE)	2012	1 ECTS
American Society for Bioethics and Humanities (ASBH), Atlanta, Georgia, US: 'Naming and framing in genomic testing'	2013	1 ECTS

Teaching

	Year	**Workload (ECTS)**
Lectures 'Animal ethics' (bachelor)	2009-2014	1 ECTS
Lectures 'Animal ethics' (post-academic), Erasmus MC and LUMC	2009-2014	8 ECTS
Lecture 'Genetics and Parkinson's disease'	2013	0,5 ECTS

(continuing professional development) Supervision discussion groups medical students (bachelor and master) on various ethical topics (e.g. euthanasia, the use of human subjects in biomedical research, responsible parenthood, prenatal screening, academic writing, argumentation, professional development, introductory classes medical ethics, etc.)	2008-2014	8 ECTS
Post-academic ethics classes (continuing) for clinical geneticists and genetic counsellors in training	2009-2014	8 ECTS
Development of self-study assignment (ZO) 'Geavanceerd genoomonderzoek'	2011	0,5 ECTS
Guest lectures on DTC genetic testing in minor-courses Clinical Genetics and Health Policy and Management (iBMG)	2011-2012	0,3 ECTS
Supervision thesis minor Clinical Genetics	2012	0,3 ECTS
Lectures and courses (primary) physicians in training	2013-2014	2 ECTS
Other		
Membership PhD Council (OZSE) and organisation of PhD-seminars	2010-2013	
Editor NACGG Newsletter	2010-2011	
Organisation of Expert Meeting on informed consent in genomic testing (Utrecht)	2010	
NACGG Innovation Award 2012	2012