TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies

Marilin Tukia 163398YVEM

MARKET RESEARCH ON DIRECT-TO-CONSUMER HEALTH, WELLNESS, AND LIFESTYLE GENETIC TEST PROVIDING COMPANIES, THEIR COMPLIANCE WITH QUALITY INDICATORS AND ASSESSMENT

Master's thesis

Supervisor: Peeter Ross
MD, PhD

Co-supervisor: Tõnu Esko
PhD

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Marilin Tukia 163398YVEM

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Juhendaja: Peeter Ross
MD, PhD
Kaasjuhendaja: Tõnu Esko
PhD

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Marilin Tukia

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Abstract

Background: As a result of rapid developments in genomics, wide variety of direct-to-consumer (DTC) genetic testing has become available to the public. Health, wellness, and lifestyle DTC genetic tests are believed to have a positive impact on one's health. On the other hand, this sector is highly unregulated and the value of DTC genetic tests has been questioned. *Aim:* The aim of this thesis is to map and describe available DTC health, wellness, and lifestyle genetic testing companies on the market and to assess their transparency and compliance with the quality indicators. *Method:* Two methods were used in this thesis: the market research, that consisted a checklist assessing quality indicators and the questionnaire, that gathered additional information about the quality criteria. *Results:* According to the checklist, the mean number of criteria satisfied was 3.7 out of nine, which means that the overall quality requirements were met 41% of the time. The questionnaire indicated that the companies have very different methods for genetic testing and transparency issues could be prevalent. *Conclusion:* The overall compliance with quality indicators is poor and there are several differences regarding genetic testing procedures among DTC genetic testing companies. The development of a harmonized regulated approach is recommended as well as the improved transparency regarding genetic testing quality among all companies.

This thesis is written in English and is 64 pages long, including 5 chapters, 3 figures and 5 tables.

Annotatsioon

Ülevaade kommertsiaalselt mittemeditsiinilisi geeniteste pakkuvatest ettevõtetest, nende kvaliteedikriteeriumite täitmine ja hinnang

Kommertsiaalsete geenitestide levik on saanud võimalikuks tänu laialdastele arengutele geneetika valdkonnas. Turul on teste mitmetest erinevatest valdkondadest ning teenusepakkujate arv aina kasvab. Arvatakse, et tervise, heaolu ning elustiiliga seotud geenitestidel on suur potentsiaal inimese tervisekäitumise muutmisele ning seeläbi elukvaliteedi ning tervisenäitajate paranemisele. Peab aga meeles pidama, et kommertsiaalsete geenitestide valdkond on oma uudsuse tõttu vähe reguleeritud, ning enamike testide kvaliteet turul on teadmata, mis omakorda põhjustab ohtu testi usaldusväärsusele.

Töö eesmärk: Koguda andmeid kommertsiaalselt pakutavate tervise, heaolu ning elustiiliga seotud geenitestide kohta ning hinnata nende kvaliteedikriteeriumite täitmist ning kvaliteedinäitajaid.

Meetod: Andmete kogumiseks ning kvaliteediindikaatorite täitmise hindamiseks viidi läbi veebipõhine uuring. Lisaks koostati ning saadeti ettevõtetele küsimustik, millega koguti lisainfot tähtsamate kvaliteedinäitajate kohta.

Tulemused: Veebipõhisest uuringust selgus, et keskmiselt täitsid ettevõtted nelja kvaliteedikriteeriumit üheksast, mis viitab kvaliteedikriteeriumite täitmisele keskmiselt 41% ulatuses. Küsimustiku tulemused näitasid, et ettevõtted kasutavad väga erinevaid meetodeid geenitestide analüüsimisel ning probleemid vastuste saamisel võivad viidata kvaliteediga seonduva läbipaistvuse puudujäägile.

Kokkuvõte: Kommertsiaalselt pakutavate tervise, heaolu ning elustiiliga seotud geenitestide läbiviimine ning tarbijatele pakutava info mitmekesisus varieerub suurelt erinevate firmade seas. Teenusepakkujate kvaliteedi läbipaistvust suurendaks ühtlustatud õigusliku raamistiku väljatöötamine.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 64 leheküljel, 5 peatükki, 3 joonist, 5 tabelit.

List of abbreviations and terms

A	Adenine
ACCE	The Analytic Validity, Clinical Validity, Clinical Utility and Ethical, Legal and Social Issues Framework
ASHG	American Society of Human Genetics
C	Cytosine
CAP	The College of American Pathologists
CLIA	The Clinical Laboratory Improvement Amendments of 1988
DNA	Deoxyribonucleic Acid
DTC	Direct-to-Consumer
ESHG	European Society of Human Genetics
FDA	The Food and Drug Administration
FTC	The Federal Trade Commission
G	Guanine
GAO	The US Government Accountability Office
GWAS	Genome-Wide Association Studies
HGC	The UK Human Genetics Commission
HGP	The Human Genome Project
ISO	The International Organization for Standardization
IVD	In Vitro Diagnostic
NIH	National Institutes of Health
RNA	Ribonucleic acid
SNPs	Single Nucleotide Polymorphisms
ToS	Terms of Service
T	Thymine
WES	Whole Exome Sequencing
WHO	World Health Organization

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Introduction

Over the last years, precision medicine has become increasingly widespread. The term "precision medicine" refers to individualized medical treatments and reaching optimal health outcomes through genomics, medical information technology and patient empowerment, all while minimizing medical expenses [25].

The Human Genome Project (HGP), completed in 2003, has made it possible to understand the human genome and has discovered more than 1800 genes that are associated with the occurrence of various diseases. According to the Human Genome Project, humans have between 20,000 and 25,000 genes. The HGP has revealed detailed information about the organization, structure and function of human genome, all of which can be thought of as "instructions" for the development of human being. This has paved the way to researchers to identify genes that are causing different diseases [30].

The completion of HGP has also opened the market for direct-to-consumer (DTC) genetic testing services. DTC genetic tests are sold directly to consumers, without the involvement of health-care specialist [40]. The industry is rapidly evolving, growing from 54 million U.S dollars in 2014 to 140 million U.S dollars in 2018 and is expected to reach 340 million U.S dollars by the year 2020 [47]. However, there are still many people (67% of survey respondents), who are not aware that genetic testing is directly available to the public [38].

Due to the novelty and complexity of DTC genetic testing, various risks and limitations – especially within regulatory environment – have arisen [16]. For example, it has been found that the value of DTC genetic testing is questionable due to the high risks for misleading results and unproven and invalid tests. On the other hand, consumers generally assume that the effectiveness and safety of medical products are assessed before they can be sold commercially to consumers [3].

The predictive power of genetic tests and quality indicators have been studied in the past, however solely within a broad context. Additionally, the transparency of DTC genetic

testing companies has been a studied topic, but the compliance with quality indicators specifically, have not been evaluated widely.

The aim of this thesis is to provide a broad overview of the various companies that offer DTC health, wellness and lifestyle genetic tests on the market and their compliance and transparency regarding quality indicators. In order to achieve these goals, a market overview was conducted and the checklist based on most important quality indicators was composed. To get additional information regarding the quality of genetic testing, a questionnaire was conducted among DTC health, wellness and lifestyle genetic testing companies. The outcomes of this thesis will give an overview of the scope of information provided to customers about the quality indicators. Based on the outcomes of these analyses, recommendations will be made both to consumers to aid in decision-making as well as to providers to improve the transparency of quality indicators.

This thesis consists of three main sections, where the first provides background information about the research topic. The second section defines the aims, sub-aims, and the research methodology. The third section includes results of the study, discussion and conclusions.

1 BACKGROUND

The rapid developments in the field of science and the completion of HGP have made it possible to study the human genome and discover associations between different genes and diseases [30].

1.1 Overview of Genetics

Cells are building blocks for all living things. Cells also hold the genetic material of the body and can make copies of themselves. Cells also consist of organelles, each with a specific yet important function. One of the most crucial organelles, in the eyes of genetics, is the nucleus. The nucleus contains deoxyribonucleic acid (DNA), the genetic material of the cell and sends commands to the cell to grow, mature, divide, or die. Outside the nucleus lies the nuclear envelope, which is a membrane that protects the DNA and separates the nucleus from the cell. Another organelle that contains genetic material is the mitochondria. The role of the mitochondria is to convert food into a form of energy that the cell can use. Mitochondria have their own genetic material and can make copies of themselves [13], [29].

DNA is the hereditary material in humans and almost all other organisms. Most DNA molecules consist of two polynucleotide strands, that are composed of monomers called nucleotides. A nucleotide is composed of one of four nitrogen-containing nucleobases which are called adenine (A), guanine (G), cytosine (C), and thymine (T). Each nucleotide contains a sugar group, a nitrogen base, and a phosphate group. Human DNA contains about 3 million bases, and these are 99% identical in all humans. DNA nucleobases pair up and form base pairs, A with T and C with G. The particular order of these nucleobases constitutes the long chain of the DNA molecule and ultimately determines the information for building an organism [13], [29].

A gene is unit of heredity and a sequence of nucleotides inside a DNA molecule. It contains instructions to make proteins (sequences of amino acids). Every cell of a human

contains identical genetic material. This genetic material within each cell is the human genome. The human genome is packaged in chromosomes, which are separate molecules that range in length from 50 to 250 million base pairs. Chromosomes come in pairs, one set inherited from each parent. Humans have 23 pairs of chromosomes, consisting of 22 autosomes and one pair of sex chromosomes (X and Y) [13].

1.2 Overview of Genetic Testing

Genetic testing refers to the analysis of human DNA, ribonucleic acid (RNA), chromosomes or protein to discover abnormalities. Genetic tests look for changes in heritable sequences which can predict significant health effects or to rule out suspected genetic conditions. Direct testing refers to specifically examining the DNA or RNA that make up a gene to identify mutations or variation that could indicate a particular genetic disorder. Linkage testing is examining markers that are coinherited with a disease-causing gene. Biochemical testing is examining the activity level or amount of proteins, which could both cause changes in the DNA. Cytogenic testing indicates examining entire chromosome to detect genetic changes, for example, an extra copy of a chromosome [39].

Genetic tests are also meant for determining a person´s chance to develop or pass a genetic disorder inside their family. There are more than one thousand genetic tests in use and new tests are being developed every day. Genetic testing is voluntary because despite its numerous benefits, there are significant limitations and risks. Genetic counsellors can advise and provide information about both the benefits and risks of genetic testing. Moreover, a crucial part of genetic counselling is discussing the emotional and social aspects of genetic testing [13].

Other types of genetic testing:

- Newborn screening is used to identify and treat genetic disorders after birth, in particular, disorders that can be treated early in life.
- Diagnostic testing is used to confirm or rule out a specific and suspected genetic disorder. Diagnostic testing is performed in all ages and if necessary, before birth. The limitation of diagnostic testing is that it is not available for all genetic conditions.

- Carrier testing is used to identify if someone is carrying a copy of a gene mutation, which will cause a genetic disorder if two copies of gene mutation are present. It is offered to people with family history of genetic conditions and some ethnic groups with an increased risk of genetic disorder.
- Prenatal testing is meant to detect abnormalities in a fetus´s genes before birth.
- Preimplantation testing is conducted in embryos that were created using assisted reproductive techniques in order to detect any genetic abnormalities.
- Predictive and pre-symptomatic testing are for detecting genetic mutations that appear later in life. These tests can be helpful for people who have a family member with genetic condition, but do not have the disorder themselves. Predictive testing can identify mutations which increase the risk of developing a condition with genetic basis (some types of cancer) and help to make decisions about medical care.
- Forensic testing is used to identify an individual for legal reasons. It is not meant to detect mutations and abnormalities in genes. [33]

1.3 Direct-to-Consumer Genetic Testing

Direct-to-Consumer (DTC) genetic testing refers to genetic tests that are sold directly to customers through different distribution channels, including the Internet, television and other channels independent of health care specialists. DTC genetic testing is a rapidly evolving industry, which is starting to draw attention from governments, scientists, and consumers [40]. Traditionally, genetic tests were only available through healthcare specialists like physicians and genetic counsellors. When a person purchases a DTC test, the testing kit will be mailed to the consumer instead of being ordered by a healthcare specialist. The testing kit usually involves collecting a DNA sample at home, typically saliva sample, and mailing it back to the laboratory. There are some companies that offer DTC genetic testing based only on raw data. In that case, consumer sends previously analyzed data directly to the provider and no testing kit is involved. There are also some tests on the market which require going to a health clinic and taking a blood sample. After taking a test, consumers are informed of the results usually via email, mail, or over the telephone. Some companies offer genetic counselling to explain the results to customers. The price for DTC genetic test ranges from approximately fifty euros to several thousand euros [34]. Genetic tests that are sold directly to consumers are usually predictive and

pre-symptomatic tests. There are several different types of DTC genetic testing, for example, tests that can predict athletic talents, provide information about nutrition, disease risk, ancestry, food intolerance, fertility, as well as neonatal services and paternity testing.

Sequencing an individual´s entire genome is still too expensive despite the fact, that the cost of sequencing has fallen from 2.7 billion U.S dollars when the first whole human genome was sequenced to less than 1000 U.S dollars now and continues to fall [31]. Thus, these companies use an "SNP chip" to target specific single nucleotide polymorphisms (SNPs) in genetic material [43].

Mutations in genes can occur in different ways during cell division. Base pairs could be rearranged in a gene, or genetic information could be added or deleted from a gene. During copying, nucleotides could also be miscoded (for example, guanine could be replaced by thymine) which leads to SNPs. SNPs are inherited from parents and research is finding correlations between the specific SNPs and different health-related measures, including the receptivity to some diseases or responsiveness to certain drugs. DTC companies who offer health, wellness and lifestyle genetic tests rely on these SNPs to provide inexpensive testing. DTC genetic testing companies provide individualized information to the customer by linking current research associating specific SNPs with susceptibility to disease. SNP chip is used by each type of genetic test to get genetic information and then relies on previous research to make potentially useful conclusions [43]. Genome-wide association studies (GWAS) have made it possible to perform genetic testing this way. GWAS test the genome for hundreds of thousands of SNPs to discover the association between complex diseases and specific SNPs [1].

The growth of DTC genetic testing may encourage people to take a more proactive role in their health and wellbeing. At the same time, DTC genetic testing can have significant limitations and risks. For example, consumers are unprotected from misleading results or invalid and unproven tests. Without genetic counselling, consumers can make important decisions about their treatment based on inaccurate or misunderstood results. Additionally, DTC genetic testing companies could use the genetic information in an unauthorized way without consumers permission [13].

1.4 Testing for Mendelian and Non-Mendelian Diseases

Genetic tests work to assess both Mendelian and non-Mendelian diseases. In case of Mendelian or single-gene disorders, the “defective” gene indicates that there is a 100 percent probability the condition will occur (for example, Huntington´s and cystic fibrosis) or a significant increase in the probability (‘‘breast cancer genes’’ BRCA1 and BRCA2). Mendelian disorders usually occur in defined and often small populations, with a prevalence of one in one thousand or fewer; they are often classified as rare diseases. Testing for Mendelian diseases is usually conducted in a medical setting and test results are clinically useful [35].

In contrast to Mendelian diseases, non-Mendelian or multi-gene (complex or polygenic) diseases are common and include Alzheimer´s disease, diabetes, and cardiovascular diseases. Polygenic diseases do not exhibit Mendelian inheritance patterns and are thought to emerge due to complex interactions of many environmental and genetic influences. Tests for multigene disorders are commercially available through direct-to-consumer genetic testing companies. The frequency of these complex disorders, the interest to health and the wish to control have increased the demand for DTC genetic testing. Unlike genetic tests for Mendelian diseases, multi-gene genetic tests only predict the current risk of developing a disease and do not have significant utility to modify the treatment plan [15], [35].

1.5 Risks and Benefits of Direct-to-Consumer Genetic Testing

There are many benefits, as well as limitations associated with DTC genetic testing. Compared to traditional genetic tests, DTC genetic tests are more accessible and affordable. There are no geographical restrictions to order a genetic test because it is mailed to the consumer’s home address after ordering the test online. Many companies state that genetic testing will lead people to make healthier choices and to live a preventive lifestyle [40]. However, it is unsure what effect DTC genetic testing could have on healthcare costs. It is possible that it could encourage people to change behavior, increase early detection and intervention, which could result in reduced costs. On the other hand, if more people are genetically-tested, the results could lead these people to seek more medical help and other preventive measures, which consequently would lead to increased costs [35].

As a consumer, an informed choice to receive a DTC genetic test requires knowledge about potential benefits, limitations, and risks of DTC genetic testing. It is important that the consumers can sufficiently understand the benefits as well as risks and limitations to make an informed decision without consulting health care specialist [46].

1.5.1 Predictive Value of Direct-to-Consumer Genetic Testing

It is expected that advantages in genomics can help us to understand the etiology and pathogenesis of common diseases like cardiovascular disease, type 2 diabetes, and cancer better. Genetic testing is also thought to help with prevention, treatment and early detection of common diseases. However, complex interactions between environmental and genetic causes of most common diseases are not well understood and therefore, the usefulness of genetic testing is unclear. Nevertheless, there are many companies that offer personalized lifestyle health recommendations based on consumers´ genomic profiles [19].

Due to an arguably underdeveloped regulatory environment for genetic tests, it is possible that the quality and accuracy of tests offered on the market is inadequate. A good quality test has to be performed in the laboratory that ensures the reliability of the test results. Moreover, there has to be enough scientific evidence that supports the relation between a specific health condition and a genetic variant [16].

The predictive value of genetic testing in common diseases may be insufficient to provide lifestyle recommendations because most of these diseases are caused by complex interactions of genetic and environmental factors [15], [19], [35], [50]. In addition, it has been found that the average number of SNPs analyzed by companies differ as well as the sets of SNPs selected, which as a result, will lead to different predicted risks by different companies [20], [36]. In general, DTC genetic testing companies have agreed to use clinically validated markers, but not certainly the same markers or number of markers, which leads to different results between companies [36].

Another factor that is influencing the differences in risk scores is how the absolute risk is derived. Absolute risk is depending on two parameters: “relative risk” and “average population risk”. When the relative risk is derived from an individual´s genetics then the average population disease risk could vary, depending on the definition by the company. For example, some companies distinguish population disease risk between men and

women (women are less likely to have heart attacks compared to men), whereas some companies only consider age (probability of rheumatoid arthritis increases with age). When interpreting the results, the ambiguity in the definition of a population needs to be take into account [36].

Janssens *et al.* assessed the scientific evidence of DTC genetic tests by reviewing meta-analyses of gene-disease associations for the genetic variants in the profiles. They analyzed seven companies, who tested at least 69 different polymorphisms in 56 genes. From the 56 genes, 24 (43%) were not reviewed in meta-analyses. For the other 32 genes, many meta-analyses were identified that examined 160 associations, however, only 60 (38%) were detected to be statistically significant. They concluded that there is insufficient scientific evidence to claim that genomic profiles are useful to determine the genetic risk for common diseases or in developing personalized lifestyle recommendations for preventing these diseases [19] Moreover, it is found that there is a wide variation in susceptibilities in complex diseases among different ethnic groups. Despite that, genome-wide association studies have been conducted mainly on European populations [1].

Additionally, it has been found that DTC genetic testing could have a high false-positive rate [36], [49]. The recent study conducted by Tandy-Connor *et al.,* found a distressingly high false-positive rate (40%) for variants reported in the raw data. According to this study, the reason could be analyzing SNPs, which they claim not to be a comprehensive analysis method [49]. Furthermore, the markers that have been discovered do not explain the majority of genetic heritability of diseases, which means that the marker set used, could miss unknown genetic factors and lead to false negatives [36]. Although DTC genetic tests are not intended to have an impact on developing a clinical intervention, the information obtained from interpreting genetic data could lead to unnecessary changes in the medical management. It is possible, that the DTC genetic tests could be misinterpreted or misused by the consumer, which could lead to unnecessary medical procedures, testing of family members or unnecessary stress [49].

The US Government Accountability Office (GAO) investigated DTC genetic testing companies in 2006. To assess whether these tests are misleading to consumers, GAO purchased 10 tests, each from four different companies. The prices varied from $299 to $999 per test. After purchasing the tests, five donors were selected and two DNA samples

from each donor were sent back to the company. They used factual information for one sample and the fictitious information (like persons age and race) for the other. Donors received risk predictions for 15 diseases and additionally, GAO made undercover calls to ask health advice from these companies´ genetic counsellors. To evaluate whether the provided information from these companies was medically useful, genetic experts were consulted. They found out that the received test results were misleading and had little or no practical use at all. The disease risk predictions varied across four companies, which means that identical DNA samples had contradictory results. For example, one donor's results from the companies ranged from having an above-average, average and below-average risk for hypertension and prostate cancer. In addition, donors received DNA-based disease predictions that were conflicting with their real medical conditions. For example, the person who had a pacemaker for 13 years because of an irregular heartbeat, received the result that he has a decreased risk of developing this condition. After receiving the results, follow-up consultations were offered and three of the companies were not able to provide expert advice. GAO also found many examples of deceptive marketing, for example, one company claimed that their supplements could cure disease and repair damaged DNA. Two companies allowed a customer to secretly test another person´s DNA, which is restricted in many countries and in 33 U.S states. After these findings, GAO informed the Food and Drug Administration (FDA) and Federal Trade Commission (FTC) to take appropriate action, which was followed by alerts to warn consumers [26].

The fact that DTC genetic tests are sold over the internet and the report is also sent via the internet or the mail, raises a concern that consumers will not receive sufficient counselling – either before taking the test to understand the consequences as well as after taking the test to ensure that consumers comprehend all the information provided [16]. As found by the GAO, even if the genetic counselling is provided, the quality of the service could be questionable [26].

Moreover, some companies provide genetic testing to predict sports performance and talent identification. Specifically, these tests claim to be able to predict children´s athletic talents and to assess the potential for future sports performance. Based on the published scientific evidence, it is found that the information provided when predicting sports performance is virtually meaningless. It is stated that there is no evidence that genetic

testing can provide meaningful information to predict training response, predisposition for some sport or predisposition to exercise-related injury [17], [53], [54].

1.5.2 Motivation and Behavior Change Regarding Direct-to-Consumer Genetic Testing

The motivations to use DTC genetic tests can be categorized into three different groups. The first one is identity seeking that includes testing to identify paternity, ancestry, and ethnicity. The second group is disease risk testing that complements health care. These types of tests are usually ordered by physicians but can be ordered by patients themselves as well. It is highly contested area in DTC genetic testing due to the lack of regulations. The last group is curiosity-driven testing/searching for a better lifestyle, which is one of the most common reasons for genetic testing. Nowadays people are interested in changing their life in a healthier way and want the lifestyle-related genetic tests to define this direction [40].

Roberts *et al.* examined consumers´ interests, decision making and responses after obtaining DTC genetic testing services. This study of consumers examined two DTC genetic testing companies with the goals of finding out who obtained DTC genetic testing and what benefits and limitations were detected after testing. Consumers were most interested in ancestry (74%), trait information (72%) and disease risks (72%). Among disease risk, greatest interests were heart disease (68%), breast cancer (67%), and Alzheimer disease (66%). 38% of consumers did not consider the potential unwanted information before taking the test. After obtaining the results, 59% of respondents claimed that test results would influence the management of their health, 2% said that they regret taking the test and 1% reported harm from receiving the test results. Most of the respondents were satisfied and said that results made them feel controlling their health more (65.8%) and this information helped to improve their health (61%). Nevertheless, 38% of respondents said that they were disappointed about the superficiality of genetic test results [44]. Many people believe that this information can help to improve their health, but on the other hand, there are several studies that have found the opposite – people are not changing their behavior after receiving test results [2], [4], [5], [51]. Despite the fact that people are not changing their health behavior, most people are still satisfied with the DTC genetic testing experience [4], [5], [44], [52].

There are many studies that assess behavioral changes after DTC genetic testing. For example, Ahn and Lebowitz made an experiment to assess whether personalized feedback about genetic susceptibility to obesity can have beneficial effects on diet and exercise. This study was conducted to manipulate the type of genetic feedback participants received. They studied how learning that someone is not genetically predisposed to obesity could affect the attitude towards eating, exercise and how it could affect choosing their meals. It was demonstrated that when people were told that they were not genetically predisposed to obesity, they judged adherence to a healthy diet and physical exercise to be less effective for controlling their weight. In addition to that, they found out that these participants, who had been told they were not genetically susceptible to obesity were more likely to select unhealthy food options. These results suggest that finding out they are not genetically predisposed to obesity could encourage people to this kind of health behaviors that could place them at greater risk of obesity than they would face if they would not have received this information [2].

There are also studies that have found some positive effects with DTC genetic testing on health behavior [6], [37]. For example, Nielsen and El-Sohemy assessed the disclosure of genetic information on the change in dietary intake. Unlike many studies, this study was conducted to find out about short- and long-term effects of disclosing genetic information for personalized nutrition in younger adults using a randomized controlled trial. The results showed that at the 3-month follow up there were not any changes in nutritional intakes. At the 12-month follow-up, these participants who were carrying a risk version of the ACE (sodium-sensitivity) gene, reduced their mean sodium intake significantly. No significant changes were observed in caffeine, vitamin C or added sugars at either follow-up assessments [37].

1.6 Marketing Genetic Testing

Singleton *et al.* conducted a study to analyze 23 health-related DTC genetic testing company websites and to understand the information that potential customers of DTC genetic testing are receiving on company websites. It was found that there are many benefits stated on websites, the average number was 26.3 (range 3–155). Most often described benefits were patient education, personalized medicine, prevention, and capability to make informed decisions based on test results. The most common benefit

stated, which was present on 96% of websites, was the potential of testing to prevent the onset of a disease or reduce the morbidity of a health condition. The average number of risks stated was 1.04 (range 0–7). Thirty-five percent of DTC genetic testing company websites mentioned at least one risk, while 65% did not mention any risks associated with testing. In fact, two companies only mentioned "risks" to state that there are no risks in genetic testing. The most common risk, that was stated on 26% of websites, was the potential for worry and anxiety due to genetic testing. The average statements of limitations were found to be 3.17 (range 0–30). 78% of DTC testing websites stated at least one limitation of DTC genetic testing. 74% of websites disclaimed regulatory statements, for example, that they do not provide medical advice, treatment, and diagnosis. In addition to that, 70% of DTC testing websites said that consumers should consult with their physician in order to make decisions about health-related concerns [46]. This study indicates that DTC genetic testing companies often mention various benefits, whereas limitations and risks are mentioned rarely.

There have been several studies that have addressed the transparency of DTC genetic testing companies. They have concluded that the transparency guidelines and recommendations are poorly met [14], [27], [28].

1.7 Regulations of Direct-to-Consumer Genetic Testing

Genetic testing industry is still in its infancy and there are few regulatory controls in place at national and European levels to evaluate the clinical validity of these tests before they are sold to consumers. In Europe there is no EU or national legislative instrument that particularly regulates genetic testing. Due to the fact that the industry is unregulated, there are some legal documents that influence the regulation of various aspects of genetic testing. The laws that influence genetic testing on the EU level involve consumers protection laws and in vitro diagnostic (IVD) medical devices laws. Some individual countries have determined mandatory medical supervision and other restrictions on genetic testing [21]. For example, in France genetic tests can be performed only for healthcare purposes and must be medically prescribed [7]. Additionally, in Hungary, genetic testing must be done by healthcare provider and only for some specific purposes [12]. In Italy, predictive tests are also only allowed for healthcare purposes and healthcare research [18]. Different countries have different approaches and follow various

procedures when it comes to genetic testing. There are some countries limiting access to genetic testing, but, at the same time, there are countries that do not provide any specific legislation on genetic testing. There are 16 EU countries that require genetic counselling for some types of genetic tests. In some countries, genetic counselling as well as providing consumers with risk and consequence information is mandatory for all genetic tests (France, Spain, Hungary). Several countries require written informed consent of a person who is requesting genetic testing [21].

Most of these regulations also apply only for genetic testing in clinical setting. It would be more complicated to apply the same laws in the commercial DTC genetic testing sector. Another challenge is that DTC genetic tests are usually sold through the internet and companies can be based anywhere in the world. Even if the test is sent to some specific European country, regulation of testing service may still fall outside of the national jurisdiction [21].

The current regulatory framework has brought up the question of whether it is necessary to have harmonized European regulation in order to make DTC genetic testing more reliable. This question has been a topic during the revision of the Medical Devices Directives [10]. This process led to the Regulation on IVD medical devices, that is replacing the IVC Directive. During the procedure, the European Parliament proposed a suggestion that this instrument should also regulate DTC genetic testing (medical supervision, informed consent and genetic counselling) [8]. Adopting these conversions would ban most of DTC genetic testing services on the market, which is why this proposal received criticism from some stakeholders and got rejected [21].

The lack of a proper regulatory system in the US is also prevalent. The number of DTC genetic testing companies is increasing, but there remains no cohesive federal mechanism to ensure the quality of tests before being marketed. Although a regulatory system at a federal level is not available, state bodies in New York and California are trying to regulate DTC genetic testing companies. For example, California issued in June 2008 “cease-and-desist” letter to 13 DTC genetic testing companies demanding to stop providing genetic tests to residents of California. These letters insisted companies to provide evidence to prove the quality of their laboratories and that all tests sold were requested by physicians [23]. Additionally, New York requires data about clinical validity for all laboratory tests performed for residents of New York. The Food and Drug

Administration (FDA) regulates and requires the information about clinical validity only for some tests [32]. In July 2006 the FTC issued a consumer alert to inform consumers about questionable value of some genetic tests after GAO investigated genetic testing companies. Nevertheless, these kinds of approaches do not affect the availability of genetic tests with questionable clinical validity [22].

In addition, FDA considers a genetic test as medical device only if it is manufactured as freestanding kit and sold to laboratory. Right now, most DTC genetic tests are manufactured in-house by laboratories themselves, which means the laboratory decides whether the test has adequate clinical validity [54].

1.8 The Quality Requirements

Currently, genetic testing is not widely available, but the industry is expanding very quickly. Maintaining quality standards for genetic testing is challenging, taking into account the complexity of genetic information and the changing value of genetic tests currently available. Due to lack of standardization and regulation, it is very hard to determine the quality of a genetic test for multi-gene disorders. Genetic tests that are meant to predict the common diseases have questionable value, because these diseases are a product of complex interactions between genes and environmental factors and it is often not clear what role genes play in these disorders [15], [19], [35].

According to WHO (World Health Organization) and NIH (National Institutes of Health) quality is a broad concept when we are talking about genetic testing. Quality standards should apply to all the processes, from the decision to take a genetic test to receiving results about the provided test. Three of the most important measures of quality regarding to genetic testing are analytical validity, clinical validity and clinical utility.

- Analytical validity indicates how well can the laboratory test detect the presence or absence of genetic variant that this test was designed to measure, indicating that the laboratories executing genetic testing have to be competent performing these tests. The physical test itself has to be validated and evaluated for effectiveness.
- Clinical validity refers to the need of validating the tested genes to be associated with a disease or an outcome, which ensures the meaningfulness of genetic test.

In DTC genetic testing it is more relevant, because of the complexity of multi-gene disorders and the results indicating solely the probability of a disease.

- Clinical utility indicates whether the test result can provide information that could be used in developing a clinical intervention. For example, whether the result can inform patient about diagnosis, treatment of prevention of a disease. Some tests that provide clinically useful information can help a person to take more responsibility in their own health but on the other hand, some diseases have no treatment. In the absence of cure, the test is still relevant when the quality of life can be improved with social interventions like education and counselling. Also with complex disorders, additionally to the analytic phase of genetic testing, counselling is equally important in order ensure the quality by consumer to understand the consequences and conveying the results clearly. [32], [55]

In addition, there are different models and recommendations to ensure the quality of DTC genetic testing. For example, one approach to evaluate genetic tests has been the analytic validity, clinical validity, clinical utility and ethical, legal and social issues framework (ACCE), which was developed in 2000 and completed in 2004. ACCE framework stands for analytic validity, clinical validity, clinical utility and ethical, legal and social issues [42]. The ACCE framework is also in accordance with the most important quality measures put forward by WHO and NIH [32], [55].

Analytical validity is largely addressed in laboratory certifications. In the US, the most common laboratory certificates are the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and The College of American Pathologists (CAP´s) Laboratory Accreditation Program. CLIA determines only basic requirements, such as personnel qualifications, quality-control standards, validation and documentation of tests and procedures performed. CLIA does not set the requirements for clinical validity of genetic tests [16]. In Europe, the most common standards are different standards by the International Organization for Standardization (ISO), that prove the laboratory to be competent to perform specific genetic testing [45].

The American Society of Human Genetics (ASHG) and The European Society of Human Genetics (ESHG) have both developed recommendations for DTC genetic testing in order to make genetic testing processes more efficient. These policies include recommendations about different aspects, for example clinical utility, analytical validity, clinical validity,

laboratory quality, proper qualifications of personnel, consumer education, genetic counselling, privacy and transparency [11], [16].

The quality issues of DTC genetic testing are so acute because DTC genetic testing has lack of provider supervision as well as the complex information consumers need to understand in order to make an informed decision. Consumers are at a very high risk of choosing tests with unproven benefits, deciding without accurate genetic counselling and receiving a test of questionable quality [16].

1.9 Previous Studies

There are few previous studies that have researched the quality indicators of DTC genetic testing companies only. There are articles that explore the predictive power of health and lifestyle genetic tests in general but do not address specific companies and tests sold on the market. However, there are several studies that evaluate the transparency in general.

For example, Hall *et al*. assessed the transparency of DTC health, wellness, and lifestyle genetic testing services. Specifically, they evaluated the information that is provided to customers at the pre-purchase stage which could affect the decision of a consumer. This study assessed 15 DTC genetic testing companies in the UK by creating a checklist of 28 assessment questions that were composed and modified based on The UK Human Genetics Commission (HGC) pre-consumer transparency guidelines. HGC guidelines include specific recommendations related the information for consumers before making the purchase. The results showed that there was not any provider that would have complied all the principles and the companies had very different levels of compliance. They found that the transparency indicators are poorly met and it was common to not provide support services to customers in order to understand tests results after receiving them [14].

In addition, Lewis *et al.,* evaluated similarly to Hall *et al*., transparency among DTC genetic testing companies. They assessed 25 DTC genetic testing companies in the US. The assessment was based on ASHG transparency recommendations. ASHG principles are divided into three categories: transparency, provider education, and test and laboratory quality. They found that the overall transparency standards were met 41% of the time. Only six of 25 companies complied with 70% or more recommendations [28].

Laestadius *et al.* assessed the transparency of 30 DTC genetic testing companies in the US. More specifically, the companies that were investigated use the results for research purposes. They developed a codebook by synthesis of seven DTC genetic testing guideline documents with the emphasis on privacy, security, confidentiality and secondary use of data. They concluded that DTC genetic testing companies did not consistently meet the transparency guidelines [27].

2 AIM OF THE STUDY

The aim of this thesis is to map and describe available DTC health, wellness, and lifestyle genetic testing companies globally and to assess the compliance and transparency in relation to various quality indicators.

Sub-aims

- To map and describe available somatic DNA based genomic services on market.
- To describe the quality indicators provided on DTC genetic testing webpages.
- To conduct a questionnaire among DTC health, wellness, and lifestyle genetic testing companies on the market to obtain additional information regarding quality indicators.

3 MATERIALS AND METHODS

In order to achieve the aims, two different methods were used. Firstly, descriptive market research was conducted to gather information on DTC health, wellness, and lifestyle genetic testing companies´ websites. In addition to market research, a web-based questionnaire was conducted among companies that offer DTC health, wellness, and lifestyle genetic tests to gather additional information about the quality aspects of genetic tests.

3.1 Market Research

The market research was conducted to gather general information and assess the compliance with quality indicators of companies that offer DTC health, wellness, and lifestyle genetic testing. This was done by composing a database of DTC genetic test providers, by describing available DTC health, wellness, and lifestyle genetic tests on the market, and by gathering information about their predictive power, scientific relevance and other data about the quality.

In order to map DTC health, wellness, and lifestyle genetic testing companies, a web-search was conducted. The author searched DTC genetic testing companies and different tests offered. The collected data contained information about target groups, price, whether the company offers complex only testing, whether the company accepts a raw data file from the customer, if the company offers genetic counselling, and details regarding quality criteria. All the questions were composed in order to receive a comprehensive understanding of the companies and the information they provide online to consumers.

3.2 Questionnaire

The questionnaire was formed in collaboration with Estonian Genome Centre, because of the complexity of the topic and the lack of studies using the questionnaire on the same issue. The aim of the questionnaire was to obtain a broader understanding of the quality indicators of genetic tests among different DTC health, wellness, and lifestyle genetic testing companies globally. The questionnaire was composed in English and consisted of five sections. The first section was about general information and consisted of fields with company name and type. In addition to general fields, there were 10 questions. The

second section was regarding genotyping technology. The third section was regarding genetic profile development. The fourth section gathered information about the nature of genetic risk scores. The final section, examined whether the feedback to customers is evidence-based and how often are the algorithms updated in accordance with new scientific evidence. The questionnaire was sent twice at a one-week interval to 67 DTC genetic testing companies.

3.3 Market Research– Participants and Procedures

The objective of the market search was to gather information from DTC health, wellness, and lifestyle genetic testing companies´ websites and to assess the information provided. Market research is the process of gathering as well as analyzing the information about a market and a product [24]. Market research was conducted online due to the fact the main sales channel of DTC genetic tests is a webpage. The search was made through Google search with the search results between the years 2010–2018. The search words included: "direct-to-consumer genetic testing", "genetic testing companies", "direct-to-consumer testing", "genetic testing", "health genetic testing", "lifestyle genetic testing", "wellness genetic testing", "fitness genetic testing", "direct-to-consumer genetic testing company".

Each website was reviewed in order to determine whether it met the inclusion criteria. The search led to few websites that provided an overview of DTC genetic testing companies, but these lists were not including all the companies on the market and were insufficient when providing information on the number of currently active DTC genetic testing companies. In addition to web search, academic literature from university and international databases was searched (Google Scholar, PubMed, Tallinn University of Technology library databases) for articles in English. One article was found which stated that there are 246 DTC genetic testing companies providing tests to consumers, but the list of companies was not provided [41].

Because of the lack of information about active genetic testing companies, the list of DTC genetic testing companies used in this thesis was independently consolidated. The inclusion criteria included: offering health, wellness, and lifestyle DTC genetic tests and do not require the involvement of health-care specialist. Hall *et al*. defined health, wellness, and lifestyle DNA tests as all health, wellness, and lifestyle-related tests excluding neonatal services, ancestry and paternity testing [14]. Health, wellness, and

lifestyle tests include nutritional, athletic performance, skincare, stress, talent, mental health and genetic predisposition tests for different diseases [28]. The author found 67 DTC genetic testing companies that met the inclusion criteria.

Many companies were found that offered only genetic testing for ancestry, neonatal services or paternity testing, and were excluded. In addition, all companies that required the involvement of a physician or other healthcare specialist were also eliminated. This physician involvement included ordering the test through a physician but still taking the test by the consumer themselves. The role of the physician, in that case, is the genetic counselling after receiving results. The second option of physician involvement is taking the DNA sample, which is usually a blood sample. Finally, the author excluded companies which do not have active websites. The data collection took place between 1 October 2017 and 30 April 2018.

Information queries from companies' websites were as follows:

- Which tests the company is offering?
- Where is the company based?
- Who is the target group?
- What are the prices of DTC genetic tests?
- Is the service complex only (genomic test with interpretation)?
- Do they accept data files form consumers?

In addition to general information about DTC genetic testing companies, a checklist was composed to assess compliance with quality indicators. The checklist with quality indicators was composed based on the most important quality measures by WHO, NIH, ACCE model, recommendations by ESHG and ASHG and the checklists from similar previously made studies [11], [14], [16], [27], [28], [32], [42], [55]. The checklist had to be composed and modified by the author, due to the nature of the aim and the fact that the assessment was web-based. The objective of the checklist in this study is to evaluate the information about the quality of genetic testing. The created checklist for the transparency regarding quality consists of nine questions.

To assess the analytical validity, it was determined whether companies have any laboratory certificates and, if they do, then which specific certificates. This is important for determining if the tests are handled carefully. In order to evaluate the clinical

validity, the information about scientific evidence was derived from companies´ websites. In addition, it was searched, whether the information about analyzed genes, was present. To assess clinical utility, the feedback that companies provide to customers was evaluated, if possible. It was also determined if the company provides genetic counselling to customers and whether the company requires written consent before testing.

The checklist criteria:

- Does the laboratory have any certificates? Which certificates?
- Do they provide information about which genes are analyzed?
- Do they refer to specific scientific literature?
- Do they provide an overview of limitations/risks?
- Do they use phenotypic information when providing risk assessments (e.g. age, gender, environment, lifestyle factors)?
- Do they provide information about privacy?
- Does the company have a sample report on their website (i.e. information on what results and recommendations they are providing)?
- Do they provide genetic counselling?
- Do they require consumers written consent before testing?

3.4 Questionnaire– Participants and Procedures

Participants were all 67 DTC health, wellness, and lifestyle genetic testing companies that were identified in the market research. The questionnaire was formed in Google Forms. The contact information of the companies was found from companies' websites. Some of the companies did not have email addresses on their websites. The author found 50 companies email addresses from their websites. There were 15 websites where the only way to contact the company was via a contact form on the website. One website had neither an email address nor a contact form. One email was not delivered. In total, 65 international DTC health, wellness, and lifestyle genetic testing companies received the questionnaire either on their email address or via the contact form on their website.

The study was carried out from 7 March 2018 until 28 March 2018. On the 7th March 2018, all participants received the personalized email or a message via a contact form

containing the link of the questionnaire. These companies, whose email address was known, received an email where the questionnaire was already attached. Those that received a message via contact form, received a letter and a link to the questionnaire. The email or letter started with the clarification of the reason why it was sent, followed by the introduction of the author of the thesis, the thesis topic, the approximate time of taking the questionnaire and short description of the questionnaire. A reminder letter was sent one week after the first email or letter via contact form was sent. It has been found that reminders in web-based studies are effective on response rates [48]. Because of the low response-rate after sending reminder letters, these companies were contacted by phone, if possible.

The goal of the questionnaire, which was composed in cooperation with Estonian Genome Center, was to gain an overview of the quality of DTC genetic tests. The purpose of the first question, about the genotyping technology, was to get an overview of the technology used to infer DNA sequence variants and ultimately, the thoroughness of genome sequencing. The second question asks about whether the genotyping is performed in-house, in which case the service could be more reliable. The third question is meant to find out which databases are used. The fourth question is about the number of mutations that are included in risk scores; the more variants, the more informative. The fifth question asks how many SNPs algorithms are used on average. The more SNPs companies include in their risk model will lead to the higher predictive ability [20]. The sixth question is regarding imputed SNPs, which also increase the quality of the genetic test [56]. The seventh question is about phenotypic information. If an algorithm uses also phenotypic information when providing risk assessment, then the results will be more accurate because phenotypic information has an important role in developing multigene disorders [15], [19], [35]. The two last questions are about scientific relevance. It is asked, whether the provided feedback is evidence-based and how often are the algorithms updated in the light of new scientific discoveries.

4 RESULTS

The results from the market research, including the checklist and the questionnaire are complementary to each other. The checklist collected only publicly available information, whereas the questionnaire was targeted directly to DTC genetic testing companies.

4.1 Market Research

67 companies were included in the market research. There were companies from Australia, Finland, France, Greece, Israel, Netherlands, Slovenia, Denmark, India, Estonia, Canada, UK and US. The majority of companies were based in US (28%) and UK (31%) (Table1).

Table 1. Number of companies by region.

Country	Number of companies
Australia	1
Finland	1
France	1
Greece	1
Israel	1
Netherlands/UK	1
Slovenia	1
Denmark	2
India	2
Estonia	4
Canada	5
UK	21
USA	19
Unknown	7

244 health, wellness, and lifestyle genetic tests were identified. The prices range from 8€ to 1999€, with average of 233€. Raw data test prices range from 8€ to 78€, with the average of 30€. Complex only genetic testing prices range from 23€ to 1999€, with the average of 247€. The year of company establishment was not found for 22 companies,

but the majority of other 45 companies were established in 2014–2016 (21 companies) (Table 2). Most of the companies (87%) used saliva as the source for their DNA tests. There was one company that used blood, one company used hair and one company used saliva or hair (Table 3). The 72% of the companies did not accept a data file from the consumer and offered complex only genetic testing, while 28% of the companies accepted a raw data file, of which four companies accepted raw data only.

Table 2. The year of establishment by the number of companies.

Year of establishment	Number of companies
Unknown	22
2005	2
2006	2
2007	1
2008	4
2009	1
2010	2
2011	3
2012	4
2013	3
2014	6
2015	6
2016	9
2017	1
2018	1

Table 3. Source of DNA analysed by the number of companies.

What material is the source for DNA?	Number of companies
No information	1
Blood	1
Hair	1
Raw data company	5
Saliva/blood	1
Saliva	58

Based on the checklist, it was found that 62 companies offer complex genetic testing (genomic test with interpretation), of which 24 (39%) companies have laboratory certificates. Specifically, 11 companies have ISO standards, 17 companies have CLIA certificate and 11 companies have CAP certificate. 27 companies (40%) companies, provide an overview of genes that are being tested. In addition, 13 companies (19%) refer to scientific articles to justify the choice of genes that are being tested. 42 companies (63%) provide details about the limitations of genetic testing on their website. Only five companies (7%) use phenotypic information when providing risk assessments (e.g. age, gender, environment, lifestyle factors). 57 companies (85%) had information about their privacy measures. 22 companies (33%) provided the sample report on their website. 17 companies (30%) offered genetic counselling to consumers. 39 companies (58%) specified that they require informed consent for the testing service. See Table 4 below for the full list of criteria addressed and the number of companies.

Table 4. Addressed criteria by number of companies and the compliance score.

Criteria	Number of companies	Compliance score
Privacy/security	57	85%
Limitations	42	63%
Informed consent	39	58%
Mention Genes	27	40%
Certifications	24	39%
Sample report	22	33%
Genetic counselling	17	30%
Scientific references	13	19%
Phenotypic information	5	7%

As illustrated in Table 5, none of the DTC genetic testing companies complied with all the criteria in the checklist. According to the checklist, the mean number of criteria satisfied was 3.7 out of nine and the overall quality requirements were met 41% of the time. There was only one company that complied with eight out of nine criteria. The only criteria missing was providing genetic counselling to their customers. In addition, there were two companies that fulfilled seven out of nine criteria. The missing criteria in this case were mentioning the specific genes tested and using phenotypic information when providing the risk assessment. The majority of companies (64%) complied with three to five criteria (the full list of companies and addressed criteria is provided in Appendix 1).

Table 5. The number of criteria addressed by the number of companies.

The number of criteria addressed	The number of companies
9	0
8	1
7	2
6	6
5	13
4	16
3	14
2	6
1	5
0	4

4.2 Questionnaire

The questionnaire was sent to 67 DTC genetic testing companies. Two emails were not received. Out of 65 DTC genetic testing companies that received the questionnaire, nine companies answered the web-based questionnaire (Dynamic DNA Labs, Fututest OÜ, Futura Genetics, Suisse Life Science Group, Sports Gene OÜ, Atlas Biomed, MyInnerGo/Geenitestide Labor, Diagfactor, FitnessGenes). The response rate was 14%. Six answers were received after the first email sent to the companies. Only two questionnaires were filled in after sending the reminder email to DTC genetic testing companies. The most common answers from the companies that were reached by phone were the following: the questionnaire does not fit the company policy or that they will review the questionnaire and if they find it appropriate they will fill it in. One questionnaire was filled in after phone calls to DTC genetic testing companies. All questionnaires were considered in analyses and were fully completed. Three of the companies that filled in the questionnaire were from Estonia, three from UK, one from US and Canada, and one from Finland. The additional feedback was received via email from five companies, who did not fill in the questionnaire. All these companies answered to the email saying that they will not answer this questionnaire because the required information is confidential.

Three of the nine companies that filled in the questionnaire conduct the genotyping in-house whereas the remaining companies subcontract the genotyping from major service providers. Two of the companies are using Known Mutation Detection (TaqMan/Sanger sequencing), four are using Whole Genome Genotyping arrays (Illumina/Affimetrics) while two companies use Gene Panel Sequencing (10–200 genes) and one Whole Exome Sequencing (WES), gene panel sequencing and target gene sequencing (Figure 1). Four companies use genomic imputation do enhance Genomic Profiles (three don’t use genotyping array) and two companies do not use genomic imputation to enhance Genomic Profiles (the full questionnaire is provided in Appendix 2, the results of questionnaire are provided in Appendix 3).

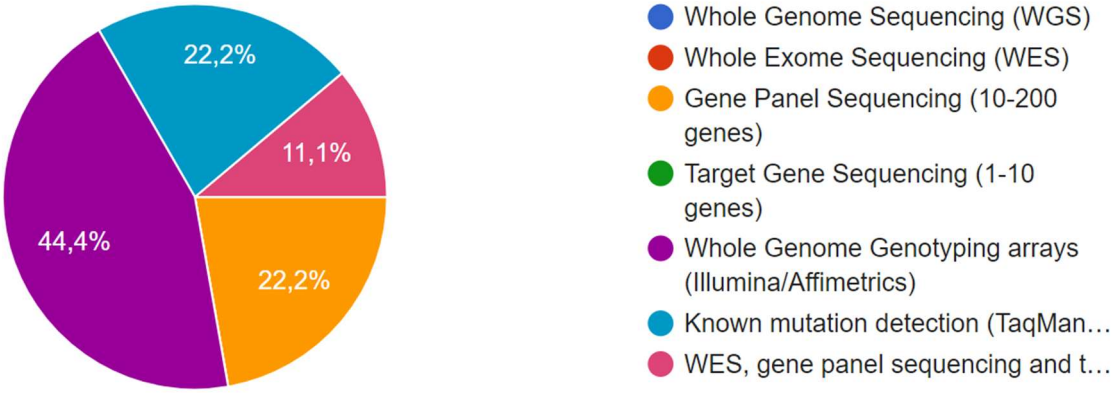

Figure 1. Genotyping technology.

Two companies, among the four that use genomic imputation to enhance Genomic Profiles, are using 1000 Genome panel and two other companies are using their own global reference. Two companies stated that the reported genetic risks are based on single mutation, while other seven companies answered that genetic risks are based on polygenic scores constructed using multiple DNA sequence variants from scientific literature.

It was found out that one company did not use polygenic scores. Among these companies that use polygenic scores, two companies reported that their algorithms use 2–10 SNPs on average, two companies reported 26–100 SNPs on average, one company reported 101–500 on average, and three companies reported 501+ on average.

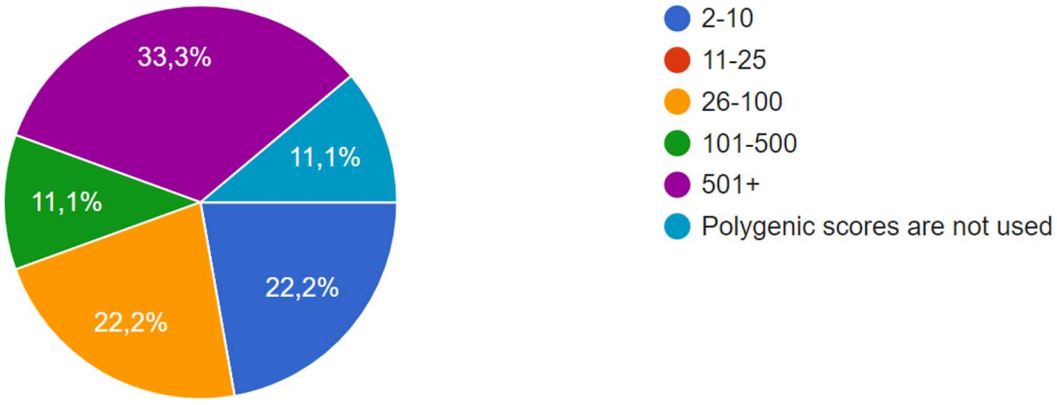

Figure 2. The number of SNPs used by the algorithms.

Among these eight companies that use polygenic scores, four companies use imputed SNPs by the algorithm. Six from nine companies claimed that their algorithms use also

phenotypic information when providing risk assessments (e.g. age, gender, lifestyle factors). One company stated that their feedback is not evidence-based, while others said that their feedback is based on scientific literature. Three companies update their algorithms once per year, three companies once per six months, and the remaining three companies update their algorithms, in the light of scientific discoveries, once per month.

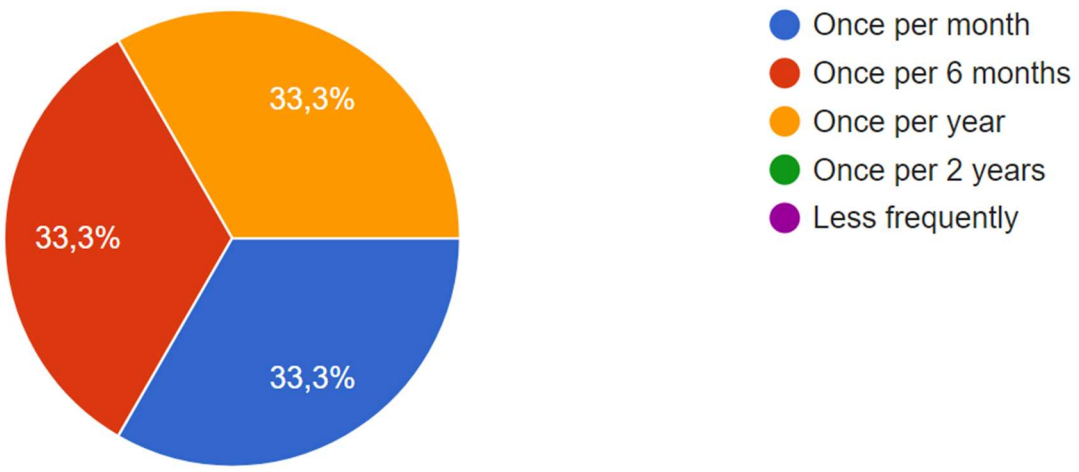

Figure 3. Frequency of updating the algorithms in the light of scientific discoveries.

5 DISCUSSION

There are numerous DTC genetic testing companies in the market offering several types of DTC genetic tests. Due to the lack of regulations and wide range of DTC testing methods, test quality can vary greatly. The quality indicators of these tests are not yet well-studied. There are studies that evaluate the transparency of some DTC companies, which include the quality, but also many other factors. DTC genetic testing is a rapidly evolving industry, which was also seen in this study by the high number of companies founded in last five years.

This thesis explored the DTC genetic testing market and the companies that offer genetic tests directly to consumers via the internet without involving healthcare specialists. Two different methods were used. The first method was market research and included 67 DTC genetic testing companies. The market research was made based on the information companies provide on their websites, of which general and quality information was gathered. The second method was a questionnaire and included 65 DTC genetic testing companies.

Based on the checklist, which consisted of nine quality criteria, it was found, that most of the companies complied with four criteria, which is only 41% of all criteria assessed. Some criteria were widely met by DTC genetic testing companies, while others were rarely satisfied. The mean number of criteria addressed was very low, although this scoring is generous, considering that the assessed criteria do not hold equal weight. For example, providing information about the scientific relevance and predictive value of genetic test are among the most important factors related to the quality of genetic testing, whereas disclosing the information about laboratory requirements seems to be more a marketing tool on DTC genetic testing websites.

The most highly satisfied criterion in this study was providing information about privacy, which was addressed by 57 out of 67 companies. DTC genetic testing companies handle health-related sensitive information and ensuring privacy is essential. It is recommended that DTC genetic testing companies should keep the data confidential, give explanations to consumers about what happens to the DNA sample, and inform consumers about security procedures [11].

The second most satisfied criterion was disclosing information about the limitations of genetic testing. The fact that these genetic tests are health-related makes educating consumers about risks and limitations of genetic testing imperative. In this study, 63% of the companies informed consumers about risks and limitations, although many of them just reported that genetic testing is not for diagnosing and medical advice. In contrast, some of the companies provide very comprehensive list of information about risks and limitations. Additionally, these tests are marketed to impact positively one´s health and are meant for changing the lifestyle in a healthier way. At the same time, some companies´ websites report that the information provided is solely informative and when considering lifestyle changes, consumers should see a personal doctor, should not rely on test results and should not change their lifestyles upon test results. Controversially, one company stated that there are no known health risks and side effects involved and that genetic testing is extremely safe and harmless.

In addition, the reason why companies provide minimal information about the testing process and scientific relevance of the test could be because the information is complex and consumers may find it too complicated to understand. Consumers should have access to information that promotes understanding about all aspects of genetic testing and not solely more disclosure of complex facts. Comprehending the various aspects of genetic testing and understanding the benefits and limitations of the test is important in order to make an informed decision whether to get tested. According to ESHG, a health-related genetic test may be only carried out after the informed consent from the customer has been obtained [11]. This is the one aspect of genetic testing where it is possible to explain the consumer about the details of genetic testing. This thesis found that 58% of the companies mentioned that they require the informed consent before genetic testing. Some of these companies specified this in their Terms of Service (ToS) that when customers purchase the service, then they agree with ToS and have given informed consent for testing. This approach does not ensure that the customer can understand the details of genetic testing. Hall *et al.* found similarly that many companies use this kind of approach to obtain consent from their customers [14]. As stated by ESHG, although signing an informed consent could be a necessity for documenting the process, it should not replace the process that is ensuring that the consumer can understand the disclosed information and give their agreement to all aspects involved. In addition, it should be made clear that if the company uses samples for research, separate consent should be obtained [11].

In order to understand the complex testing information as well as the limitations and risks, genetic counselling could have an important role in genetic testing process. It has been found that without the genetic counselling, consumers lack full comprehension of their results [52]. Moreover, this lack of comprehension negatively affects the utility of genetic testing. In this study, it was found that only 30% of the companies offered genetic counselling to their consumers. WHO has suggested that genetic counselling and the content of informed consent should be based on standards. Genetic counsellors should have appropriate qualifications to provide genetic counselling. After taking the test, genetic counselling should be conducted to inform customer about interventions [55]. When genetic counselling is provided to customers, it is important that the quality and the value would be ensured. For example, during the investigation by the GAO, it was found that genetic counsellors provided misleading information for customers. For example, it was claimed that their supplements could cure a disease and repair damaged DNA. Moreover, one company told a customer that an above average risk prediction for breast cancer means that the individual is "in the high risk of pretty much getting" the disease, which is highly misleading and suggests that the test is diagnostic [26]. The investigation, conducted by GAO, demonstrates that providing genetic counselling does not ensure that the counsellor will provide quality information to consumers. In addition, ESHG states that individuals are entitled to genetic information, but it needs to be delivered while ensuring the appropriate procedures. They add that this is only possible with adequate pre-test counselling, psychological support, and medically-relevant tests. An informative website does not replace appropriate pre-test and post-test genetic counselling. It would be preferable if genetic counselling would not be provided by counsellors who are employed by or connected to the same company which conducted the test. Due to this interdependence, a conflict of interest may arise and the quality of health advice could be compromised [11].

Analytical validity is one out of the three most important quality indicators related to DTC genetic testing. It refers to the ability of a laboratory to detect the presence or absence of genetic variant that the test was designed to measure. It means that the laboratory that is performing the test has to be competent for genetic testing processes. To ensure the competence of the laboratory, there are several laboratory certifications. In this study, 39% of companies had laboratory certificates. It is important to note that some of the companies do not have their own laboratory and thus, they are obtaining the service

through subcontracting to a major service provider. This could be the reason why the company does not provide the information about laboratory certifications. However, this does not guarantee by any means that the laboratory is not certified. Nevertheless, there are few companies that mention whether the testing is performed in-house of obtained through subcontracting from major service provider. That question was addressed also in the questionnaire and it was found that most of the companies (six out of nine) were obtaining genotyping service through subcontracting major service provider. Performing genotyping in-house could indicate a more reliable and scientifically-relevant genetic testing. [1]

According to both ASHG and ESHG, clinical validity is one of the most important quality measures and indicates how a genetic variant is analyzed related to the presence, absence or a risk of a disorder. Analytical validity emphasizes the importance of the association between the tested variants and the outcome or disease [11], [16]. The clinical validity includes information about which genes are being tested and the scientific evidence to justify testing specific genes. In this study, it was found that 40% of the companies had the overview about the tested genes on their websites and the scientific references were provided by only 19% of the companies. It is recommended that companies disclose the specific tested genes to consumers in the pre-purchase stage and also refer to scientific basis to justify why they will be testing those genes. In this study, many companies claimed that they only test the most researched genes and their tests are evidence-based, but did not provide any specific details. Because the variety of genetic testing services on the market, a total list of tested genes and the related scientific-evidence would be recommended to improve the transparency and ultimately to help the consumer make an informed decision.

Furthermore, the markers that have been discovered do not explain the majority of the genetic heritability of disease, which means that the marker set used could miss unknown genetic factors and lead to false negatives. It is recommended that the DTC genetic testing companies should report the proportion of the genetic contribution of a disease that can

[1] Tõnu Esko, EGV, personal communication

be attributed to the used markers and the proportion of genetic contribution that is unknown [36].

The third quality indicator is clinical utility, which refers to whether the test result can provide useful information that could be used to increase one's quality of life. In case of DTC genetic testing, most tests are lifestyle-related and will not disclose information that could be used to develop a clinical intervention, as in case of single gene disorders. Due to that, it is even more important to make sure whether the results will have an impact on, or even have the possibility to improve, the quality of life. For the recently developed genetic tests, evidence for clinical utility is not available [11] or has limited evidence [51]. In this case, it would be beneficial for consumers to know exact details about the information they will receive with test results. Previous studies have found that many people (38% of respondents) are disappointed with the superficiality of genetic test results [44]. In this thesis, it was found that 33% of the companies provided the sample report on their website. It is essential for the customer to see the explanation, as well as the sample report, to understand how and what information will be delivered with their results. On the other hand, the motivations to take the genetic test can be very different. Some people may do it just for interest and fun, while having no intention to change their health behavior [51].

It is widely recognized that environmental factors play an important role in the emergence of complex diseases [15], [19], [35], [50]. DTC genetic testing would be more accurate if phenotypic information was included in the algorithms, including age, gender and lifestyle factors into risk assessments. From conducting the checklist, it was found that only 7% of the companies use phenotypic information when providing risk assessments. Three of these companies clarified on their website that customers have to fill in a questionnaire, which is designed to gather information about different aspects of health, life and well-being. From the questionnaire, it was found that six out of nine companies used phenotypic information when providing risk assessments. Due to the high contribution of environmental factors, it is recommended for the companies to use phenotypic information in their risk assessments.

It is highly recommended to consumers that when considering purchasing a DTC genetic test, to take in account all the quality indicators mentioned in this thesis. Consumers should read carefully all the details provided by the company, including the ToS,

frequently asked questions, and the privacy statement. Consumers should determine whether the company provides genetic counselling and what information is received with results, to ensure their motivation to be tested is being satisfied. Additionally, consumers should ensure they know which genes are tested and if the company provides scientific evidence that supports analyzing those particular genes. It is also advised to consult with a genetic counsellor before purchasing a test and obtain pre- and post-test counselling. A genetic counsellor is preferred because a primary care provider could lack in-depth knowledge of DTC genetic testing [52].

Conducting a questionnaire evoked difficulties due to minimal company contact information and a low response rate. There could have been several reasons why the response rate was low. There were five companies who gave feedback that the information required in the questionnaire is confidential and they are not able to answer the questionnaire. It is possible that this was also the main reason for not answering the questionnaire for other companies. The questionnaire consisted of basic questions about the quality and how the company is analyzing the samples and providing feedback to customers. That raises the question of why companies do not want to make this kind of information available, which describes transparently the details about their genetic testing processes. The unwillingness to answer the questionnaire and to disclose the information about the quality of genetic testing highlights the lack of transparency with DTC genetic testing companies. Moreover, Hall *et al.,* Laestadius *et al.,* and Lewis *et al.* studied the transparency of DTC genetic testing companies and all concluded that DTC genetic testing companies lack transparency [14], [27], [28]. In addition, ESHG has stated, that they are concerned about how DTC genetic testing companies are marketing genetic tests to consumers and to the market of consumers outside the scope of healthcare system. Overstatement of effectiveness and aggressive marketing strategies might exaggerate the predictive power of genetic testing and to overrate the benefits for one's health. It has been suggested that advertisements should conform to the same standards that apply for advertisements of drugs and medical devices [11]. Today, the average prescription medicine bottle lists 70 side effects [9], while most genetic tests do not even inform their customers about which genes are being analyzed. All details about the genetic tests offered should be transparent when providing genetic testing services.

Several studies and investigations have been conducted in order to assess the quality of DTC genetic testing in general. Many studies have pointed out the dubious value of some

DTC genetic tests offered on the market [17], [19], [26], [53], [54]. The questionable value of genetic tests offered and thus the unwillingness to expose the details about their testing processes could be another reason to not fill in the questionnaire. Despite the fact that DTC genetic testing has no healthcare specialist involvement, most of the tests included in this study are rather health-related, which makes the quality of tests even more imperative. After receiving test results, consumers may change their health behavior, and therefore, in case of poor-quality testing, may lead to deterioration of their health or missed opportunities.

The questionnaire indicated that companies can use various technologies to infer DNA sequence variants and the compliance with different quality indicators widely ranges. For example, two companies said that their algorithms use only 2–10 SNPs on average, while three of the companies said, that they use 501+ SNPs on average. It appears that companies use very different number of SNPs in their algorithms, which will lead to different predicted risks. This finding was also confirmed by Kalf *et al.* [20]. The lack of consensus about which markers to test, could be avoided if companies were regulated or standardized to only include markers that have better estimates [36]. A positive finding was that many companies update their algorithms in the light of scientific evidence often, which can help to improve the tests in accordance with new discoveries. This is very important in this sector, because studies are conducted constantly and new associations between genetic variants are discovered. Of the seven companies that stated that their genetic risks are based on polygenic scores constructed using multiple DNA sequence variants from scientific literature, two stated that the reported genetic risks are based on a single mutation. This is worrisome because of the limited predictive value of relying on single genetic markers when testing for multigene disorders [19].

When comparing the checklist and the questionnaire, it was found out that many companies that complied with indicators that refer to good quality, did not present these indicators on their websites. Therefore, it is not possible to determine, based on the checklist, which quality indicators are actually met. It is only possible to assess the presentation of quality indicators on the DTC genetic testing companies´ websites. It is recommended that companies provide more information to consumers about the predictive power, scientific evidence, and other indicators that are referred to in this study. On the other hand, there was a company who complied with seven criteria in the checklist,

but it was found by the questionnaire that all their provided feedback is not evidence-based.

Many shortcomings related to DTC genetic testing are due to the fact that DTC genetic testing market is largely self-regulated [21], [23]. This shifts the control from healthcare specialist into the hands of consumers. There have been some restrictions and alerts warning customers about the risks and limitations of DTC genetic testing, but this has not stopped DTC genetic testing companies to sell their tests directly to consumers. Some countries have banned DTC genetic testing without the involvement of healthcare specialist or without providing genetic counselling. However, in most countries DTC remains unregulated. The lack of regulation is the main reason for the wide range in test quality. A standardized regulatory approach to genetic counselling, medical supervision, and most importantly informed consent for testing may endorse the oversight of DTC genetic testing and minimize the risks.

5.1 Limitations

There are, however, several limitations in this study. Firstly, the publicly available information was examined in a specific period of time. The content of the websites could have changed or it is possible that after placing the order, more detailed information will be provided to the customer. Secondly, the focus of the checklist was primarily on transparency, thus in-depth analysis of the specific procedures was not conducted. In addition, by independently analyzing information from company websites (for example ToS, privacy policies, frequently asked questions), some errors could have occurred. For example, if the author did not find all the provided information or misinterpreted the details provided on the websites.

Furthermore, the questionnaire was not based on the previously used ones, because the author did not find any studies that have used similar questionnaires. Moreover, the response rate was very low, and it is not possible to make any conclusions based on the questionnaire about the quality indicators of DTC genetic tests on the market. Additional efforts are needed to examine the compliance with quality-indicators in-depth. Future research should examine the quality of genetic tests, especially clinical validity, among different DTC genetic testing providers. In addition, more studies about monitoring the behavior change after DTC genetic testing should be conducted to identify the benefits to

an individual´s health. Finally, this thesis was not intended to highlight any specific companies in a bad light, but instead to address concerns in the DTC genetic testing industry as a whole.

Conclusion

DTC genetic testing, which is becoming increasingly popular, is found to have many risks and limitations. The novelty of the industry has led to gaps in the regulatory environment and standardization of DTC genetic testing. The oversight could be endorsed and the risks could be minimized if a harmonized regulatory approach is taken.

One of the limitations is the variable quality of DTC genetic tests and the transparency of the quality of genetic testing. The aim of this thesis was to provide an overview of the various companies that offer DTC health, wellness, and lifestyle genetic tests on the market and assess their compliance and transparency regarding quality indicators.

Based on the checklist, which included 67 health, wellness, and lifestyle DTC genetic testing companies, it was found that the quality indicators are poorly met. None of the companies complied with all quality criteria assessed. The mean number of quality criteria addressed by the companies was 3.7 out of nine, which shows that the overall quality requirements were met only 41% of the time. The questionnaire showed that it is extremely difficult to obtain the quality information when addressing the companies directly, which could imply an intentional lack of transparency regarding the quality of DTC genetic testing. In addition, it was found that the companies offering DTC genetic tests could have a wide range of testing processes and methods which leads to variable quality and differing predictions.

It is highly recommended that the companies provide a transparent overview and as many details as possible about their genetic testing processes and methods. Customers are advised to carefully read all the information provided about the test and to discuss the benefits and risks of DTC genetic testing with a genetic counsellor.

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Appendix 1 – Checklist

	Privacy	Limitations	Informed consent	Tested genes	Certifications	Sample report	Cenetic counselling	Scientific references	Phenotypic information
1	x	x	x	x	x	x	0	x	x
2	x	x	x	0	x	x	x	x	0
3	x	x	x	x	x	x	x	0	0
4	x	x	x	0	x	x	x	0	0
5	x	x	x	x	x	x	0	0	0
6	x	x	x	x	x	0	0	x	0
7	x	x	x	x	x	x	0	0	0
8	x	x	x	x	0	x	0	x	0
9	x	x	x	x	x	x	0	0	0
10	x	x	x	x	x	0	0	0	0
11	x	x	x	x	0	0	0	0	x
12	x	x	0	0	x	x	x	0	0
13	x	0	x	x	x	x	0	0	0
14	x	0	x	x	0	0	x	x	0
15	x	x	x	0	x	x	0	0	0
16	x	x	0	x		x	0	x	0
17	x	x	x	x	x	0	0	0	0
18	x	x	x	0	0	0	x	x	0
19	x	x	x	x	x	0	0	0	0
20	x	x	x	0	0	x	0	x	0
21	x	x	x	x	x	0	0	0	0
22	x	x	x	x	x	0	0	0	0
23	x	0	0	x	0	0	x	x	0
24	x	0	0	x	0	0	x	x	0
25	x	x	x	0	0	0	0	x	0
26	x	x	x	0	0	0	0	0	x
27	x	0	x	x	0	x	0	0	0
28	x	x	x	0	0	0	0	x	0
29	x	0	0	0	x	x	x	0	0
30	x	0	x	x	0	x	0	0	0
31	x	x	0	0	0	x	x	0	0
32	x	x	0	0	0	0	x	0	x
33	x	x	x	0	x	0	0	0	0
34	x	x	x	0	x	0	0	0	0
35	x	x	x	0	x	0	0	0	0
36	x	x	0	0	x	0	x	0	0
37	x	x	x	0		0	x	0	0
38	x	x	x	0	x	0	0	0	0
39	x	0	0	x	0	0	x	0	0
40	x	x	x	0	0	0	0	0	0
41	x	0	0	0	0	x	x	0	0
42	x	0	x	0	x	0	0	0	0

43	x	x	x	0	0	0	0	0	0
44	x	0	x	x	0	0	0	0	0
45	x	x	x	0	0	0	0	0	0
46	x	0	x	x	0	0	0	0	0
47	x	x	x	0		0	0	0	0
48	x	0	0	x		x	0	0	0
49	0	x	0	x	0	x	0	0	0
50	0	0	0	x	0	x	x	0	0
51	x	x	x	0	0	0	0	0	0
52	x	x	x	0	0	0	0	0	0
53	x	0	0	x		0	0	0	0
54	x	x	0	0	0	0	0	0	0
55	x	x	0	0	0	0	0	0	0
56	0	x	0	0	0	x	0	0	0
57	x	0	0	0	0	0	0	0	x
58	x	0	0	0	0	0	x	0	0
59	0	0	0	0	x	0	0	0	0
60	x	0	0	0	0	0	0	0	0
61	x	0	0	0	0	0	0	0	0
62	0	x	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	x	0
64	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0
	85%	63%	58%	40%	39%	33%	30%	19%	7%

Criteria addressed	x
Criteria not addressed	0
Criteria not applicable	

Companies that filled in the questionnaire are marked in red.

Appendix 2 - Questionnaire

Questionnaire to DTC genetic testing companies

1) General information

- Company name

- Type of the company

  - Direct-to-consumer fitness
  - Direct-to-consumer nutrition
  - Direct-to-consumer health-risks
  - All of these
  - Other:

2) Genotyping technology

- Is the genotyping performed in-house

  - Performed in-house
  - Obtained through subcontracting from major service provider

- What technology is used to infer DNA sequence variants?

  - Whole Genome Sequencing (WGS)
  - Whole Exome Sequencing (WES)
  - Gene Panel Sequencing (10-200 genes)
  - Target Gene Sequencing (1-10 genes)
  - Whole Genome Genotyping arrays (Illumina/Affimetrics)
  - Known mutation detection (TaqMan/Sanger sequencing)
  - Other:

2) Genetic profile development

- If genotyping array is used, do you use genomic imputation do enhance Genomic Profiles.

  - Yes
  - No
  - Genotyping array is not used

-If genomic imputation is used to enhance Genomic Profiles, which of the following panels you use?

  - 1000 Genome
  - Halotype Reference Consortium

- Company own global reference
- Genomic imputation is not used
- Other:

3) Nature of genetic risk-scores

- The reported genetic risks are based on:

- Single mutation
- Mutation aggregation within a gene (eg any pathogenic mutation in disease-causing gene [APOB/LDLR])
- Polygenic scores constructed using multiple DNA sequence variants from Scientific Literature.

- If polygenic scores are used, how many SNPs your algorithms use on average?

- 2-10
- 11-25
- 26-100
- 101-500
- 501+
- Polygenic scores are not used

-If polygenic scores are used, are also imputed SNPs used by the algorithm?

- Yes
- No
- Polygenic scores are not used

- Do your algorithms use also phenotypic information when providing risk assessments (eg age, gender, lifestyle factors)

- Yes
- No

4) Scientific evidence

- Is all your provided feedback evidence based

- Yes
- No

- How often are the algorithms updated in the light of scientific discoveries

- Once per month
- Once per six months
- Once per year
- Once per two years
- Less frequently

Appendix 3 – Questionnaire results

Company name	Type of the company	Is the genotyping performed in-house or obtained through service provider?	What technology is used to infer DNA sequence variants?	If genotyping array is used, do you use genomic imputation do enhance Genomic Profiles?	If genomic imputation is used to enhance Genomic Profiles, which of the following panels you use?	The reported genetic risks are based on:	If polygenic scores are used, how many SNPs algorithms use on average?	If polygenic scores are used, are also imputed SNPs used by the algorithm?	Do your algorithms use aphenotypic information for risk assessments?	Is all your provided feedback evidence based?	How often are the algorithms updated in the light of scientific discoveries?
Dynamic DNA Labs	All of these	Performed in-house	Known mutation detection (TaqMan/Sanger sequencing)	Genotyping array is not used	Genomic imputation is not used	Single mutation	2-10	No	No	Yes	Once per 6 months
Fututest OÜ	Direct-to-consumer health-risks	Obtained through subcontracting from major service provider	Whole Genome Genotyping arrays (Illumina/Affimetrics)	Yes	1000 Genome	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	501+	Yes	No	Yes	Once per year
Futura Genetics	All of these	Performed in-house	Gene Panel Sequencing (10-200 genes)	No	Genomic imputation is not used	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	101-500	No	Yes	Yes	Once per 6 months
Suisse Life Science Group plc	Direct-to-consumer fitness, Direct-to-consumer nutrition, B2B technologies for genetic interpretation	Obtained through subcontracting from major service provider	Whole Genome Genotyping arrays (Illumina/Affimetrics)	Yes	Company own global reference	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	501+	Yes	Yes	No	Once per month
Sports Gene OÜ	Direct-to-consumer fitness, Direct-to-consumer nutrition	Performed in-house	Known mutation detection (TaqMan/Sanger sequencing)	Genotyping array is not used	Genomic imputation is not used	Single mutation	Polygenic scores are not used	Polygenic scores are not used	Yes	Yes	Once per year
Atlas Biomed	All of these	Obtained through subcontracting from major service provider	Whole Genome Genotyping arrays (Illumina/Affimetrics)	Yes	Company own global reference	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	26-100	No	Yes	Yes	Once per month
myInnerGo OÜ/Geenitestide Labor	Direct-to-consumer fitness, Direct-to-consumer nutrition	Obtained through subcontracting from major service provider	Gene Panel Sequencing (10-200 genes)	Genotyping array is not used	Genomic imputation is not used	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	2-10	Yes	No	Yes	Once per year
DiagFactor Oy	Genetic counselling on all of above plus Whole Exome Sequensing (WES)	Obtained through subcontracting from major service provider	WES, gene panel sequencing and target gene sequencing	No	Genomic imputation is not used	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	501+	Yes	Yes	Yes	Once per 6 months
FitnessGenes	Direct-to-consumer fitness, Direct-to-consumer nutrition	Obtained through subcontracting from major service provider	Whole Genome Genotyping arrays (Illumina/Affimetrics)	Yes	1000 Genome	Polygenic scores constructed using multiple DNA sequenoe variants from Scientific Literature	26-100	No	Yes	Yes	Once per month