D3.3 Report on the role of direct-to-consumer genetic testing companies to produce personal preventive information and measures.

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Deliverable Abstract
In this report, we provide an overview of the history of consumer genomics, the current DTC-GT landscape, the current evidence on the motivations of those that opt to have DTC-GT and the risks, benefits, limitations and concerns around DTC-GT. Furthermore we provide an overview of possible regulatory approaches to evaluate DTC-GT offers before their entry into the market and analyze criteria used to evaluate DTC-GT offers for the use of their products in Personalized Prevention. Based on the results of our literature review, we found that while many consumers undergoing DTC-GT express intentions to adjust their lifestyle based on their genetic test results, actual behavioral changes appear to be limited or moderate. Long-term studies using validated measures are needed to ascertain the magnitude and sustainability of these changes over time. Despite initial concerns regarding the potential negative impact on public health, such as downstream tests and referrals to specialists, recent data suggest that these issues have not materialized as expected. Further international research is warranted to assess the current impact of DTC-GT on the public healthcare sector, especially considering that earlier research primarily represented early adopters and may not reflect the current population undergoing DTC-GT. Several studies have documented the diverse regulatory approaches employed by various European member states concerning genetic testing, encompassing facets such as medical oversight, genetic counseling, and informed consent. Although DTC-GT could potentially fall under these legal frameworks, whether partially or entirely, there is presently no specific EU or national legislation explicitly governing DTC-GT.

Keywords
Direct-to-consumer genetic testing, impact, regulation, policy

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Executive summary

The field of genetic and genomic medicine is transitioning towards predicting risk for prevalent complex diseases, offering potential for improved disease prevention and personalized treatment. This shift has been marked by the rise of direct-to-consumer genetic testing (DTC-GT) models, where companies provide genetic testing services directly to consumers online, bypassing traditional healthcare provider involvement. DTC-GT offers a range of health-related and non-health-related tests. The popularity of DTC-GT is driven by its accessibility, affordability, and the growing demand for personalized health management. However, several concerns have been raised, including privacy, accuracy, and interpretation challenges.

Since the emergence of direct-to-consumer genetic testing (DTC-GT) in the early 2000s, the industry has undergone significant evolution driven by technological advancements and regulatory changes. Initially viewed as a disruptive force challenging traditional healthcare models, DTC-GT has transitioned to a more hybrid model where tests are still marketed directly to consumers but also require the engagement of healthcare professionals in the ordering process. DTC-GT presents a complex regulatory challenge, balancing innovation with consumer protection. In the European Union, the 'Regulation (EU) 2017/746' regulates in vitro diagnostic medical devices, including DTC-GT. The regulation has introduced a risk-based classification system and mandates independent third-party assessment for high-risk devices. However, full implementation faces challenges, leaving gaps in regulation and potential risks for consumers. Several studies have documented the diverse regulatory approaches employed by various European member states concerning genetic testing, encompassing facets such as medical oversight, genetic counseling, and informed consent. The effectiveness of these regulations however depend on factors such as enforcement, international coordination, and adaptation to evolving technologies. The role of industry self-regulation and consumer education should therefore not be overlooked.

Based on the results of our literature review, we found that while many consumers undergoing DTC-GT express intentions to adjust their lifestyle based on their genetic test results, actual behavioral changes appear to be limited or moderate. Long-term studies using validated measures are needed to ascertain the magnitude and sustainability of these changes over time. Despite initial concerns regarding the potential negative impact on public health, such as downstream tests and referrals to specialists, recent data suggest that these issues have not materialized as expected. Further international research is warranted to assess the current impact of DTC-GT on the public healthcare sector, especially considering that earlier research primarily represented early adopters and may not reflect the current population undergoing DTC-GT.

In this report, we provide an overview of the history of consumer genomics, the current DTC-GT landscape, the current evidence on the motivations of those that opt to have DTC-GT and the risks, benefits, limitations and concerns around DTC-GT. Furthermore we provide an overview of possible regulatory approaches to evaluate DTC-GT offers before their entry into the market and analyze criteria used to evaluate DTC-GT offers for the use of their products in Personalized Prevention.

Table of Acronyms

Abbreviation, Acronym	Description
AR	Autosomal recessive
cfDNA	Cell-free deoxyribonucleic acid
CE	Conformité Européenne
CF	Cystic Fibrosis
DNA	Deoxyribonucleic acid
DTC-GT	Direct-to-consumer genetic testing
EC	European Commission
EUDAMED	Database of Medical Devices available on the EU Market
FDA	Food and Drug Administration (USA)
IVD	In vitro diagnostic
HER2	Receptor tyrosine-protein kinase erbB-2
LDL	Low density lipoproteïn
NIPT	Non-invasive prenatal test
PRS	Polygenic risk score
RAT	Rapid antigen test
SNP	Single nucleotide polymorphisms
GWAS	Genome-Wide Association Study
T-DM1	Trastuzumab emtansin

Definition of Terms

Term	Description
Analytic validity	The ability of a test to accurately and reliably measure a given genotype.
Clinical validity	The ability of a test to detect of predict the relevant phenotype.
Clinical utility	The likelihood of a genetic test to result in improved healthcare management for the patient.
Consumer	Individuals targeted by DTC-GT companies, who are potentially interested in purchasing DTC-GT in order to obtain more information about their health or genetic code in general[1].
Consumer genomics	The part of the genomics industry that offers products and services to consumers, either directly or through intermediaries.
Direct-to-consumer genetic testing (DTC-GT)	Genetic testing services that are offered directly to the public without the need for involvement of a health care professional, as well as tests that are advertised directly to consumers but ordered and/or received by a health care professional[1].
Exome sequencing	Sequencing of the protein-coding fragments of an individual's genome (+/- 1% of the entire human genome).
Genotyping	Scanning an individual's genome for known genetic markers or SNPs, the presence or absence of the tested markers can support inferences about someone's risk for certain diseases.
Genome-Wide Association Study (GWAS)	Large research studies that examine the entire genome of a large number of individuals to identify genetic variations associated with a particular trait or disease.
Patient	Individuals diagnosed with a pathogenic variant and/or individuals who have entered the healthcare setting upon requesting

	consultations regarding genetic test results[1].
Predictive testing	Testing that allows the identification of pathogenic variants that increase the likelihood that an individual will develop a genetic condition.
Presymptomatic testing	Testing that allows the determination of whether an individual - without any signs/symptoms at the time of testing - will develop a genetic condition before.
Single nucleotide polymorphisms (SNP)	A variation at a single position in a DNA sequence among individuals.
Whole genome sequencing	Sequencing of the entire genome of an individual.

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Introduction

The field of genetic and genomic medicine, considered to hold substantial potential for disease prevention and personalized treatment, is increasingly transitioning from primarily focusing on rare monogenic diseases to the prediction of risk for prevalent complex diseases [1, 2]. These advancements hold potential for the introduction of novel methods in disease prediction, prevention, diagnosis, and treatment, ultimately contributing to an overall improvement in health. By providing genetic testing information on predisposition for specific diseases or conditions, citizens and patients could be empowered to proactively manage their health and potentially prevent the (early) onset of certain conditions [3]. The emphasis on lifestyle changes as a pathway for better health outcomes has also captured the attention of private companies.

Over the past two decades we have witnessed the emergence of several models to provide genetic testing information directly to the public. Commercial laboratories have been increasingly marketing and selling a wide range of genetic tests online without necessarily involving a healthcare professional [4]. The practice of direct-to-consumer genetic testing (DTC-GT) deviates from the traditional provision of genetic testing information, in which a healthcare provider is responsible for ordering, testing, interpreting, and communicating testing results [4, 5]. In the DTC-GT model, consumers usually order a test kit online after approving terms of services. Once consumers receive the test kit at home, they are asked to produce and ship a saliva sample by mail to the specific DTC-GT company for genetic analysis. Once the test results are available, they are directly communicated to the consumer via a personalized and protected web account on the internet or on a mobile app [6, 7]. Within the novel model of DTC-GT, both health-related and non-health-related genetic test are offered directly to consumers. Non-health-related DTC-GT offers include for example ancestry testing, paternity testing, traits (e.g. ability to taste bitter) etc. Health-related DTC-GT offers include susceptibility testing for multifactorial conditions (e.g. cardiovascular disease), carrier screening for autosomal recessive (e.g. cystic fibrosis)/ X-linked conditions (e.g. Fragile X syndrome) to guide reproductive decision making, pharmacogenomics tests to provide information with regard to personal drug response, etc. [8]. Yet, in some cases it might not be very easy to distinguish between these different categories with important implications for regulatory initiatives. The majority of DTC-GT offers also combine medical, genealogical and recreational information that blur the boundary between these two categories (health-related and non-health-related) even further [9]. Most recently, DTC-GT companies started offering products that combine polygenic risk scores (or genome-wide measures of individuals' genetic predispositions) with other lifestyle factors in order to market their products along general wellness products in order to be able to avoid regulatory review [10].

The online testing format has become increasingly popular due to its accessibility and affordability [3, 11]. DTC-GT offers that provide health information are currently widely available in many countries at a moderate cost [2, 11]. As of 2023, 23andMe – a prominent player in the field – has a customer base exceeding 14 million genotyped customers [12]. Surveys in the USA and Australia found that the majority (77% and 65% respectively) of those with experience with genetic testing were consumers of DTC-GT [13, 14]. While the exact

number of consumers in Europe is currently unavailable, it can be inferred from the above information that the uptake could also be significant [4]. The global DTC-GT market is expected to grow steadily and to be worth over $4 billion by 2025 because of advances in technology, increased consumer demand and the desire for personalized health management [3, 15, 16]. The rapid growth of the DTC-GT market has however raised several concerns with regard to the privacy and security of genetic data, as well as the accuracy/validity of the test results [3, 17].

The reliability of a positive test result for numerous conditions is limited, as the development of many conditions is influenced by additional factors like environmental factors, and lifestyle choices. The majority of DTC-GT also do not sequence the entire genome. Instead, they commonly employ SNP-chip genotyping, a method that examines the presence or absence of specific variants in the genetic code, including particular single nucleotide polymorphisms (SNPs) or small insertions or deletions. While SNP-chip genotyping is effective in detecting common genetic variants, it tends to produce false positives for very rare variants, indicating that these variants may not actually be present in the individual's DNA [18]. More recently, some commercial companies have also started to offer whole genome or exome sequencing and the return of raw genomic data without interpretation [4, 18]. These tests sequence nearly the entire genetic code and identify the variants within it. The capability to predict disease risk through whole genome or exome sequencing data might motivate an increasing number of healthy individuals to explore genomic technologies for personal health risk prediction in the future [19]. Yet, even though data obtained from whole-genome or exome sequencing can be valuable for understanding rare conditions in specific individuals, there is currently inadequate evidence to prove that expanding this technology to the general population, without considering personal or family history, would result in considerable benefits [20, 21]. Interpretation of genetic variants is challenging and largely depends on context [18]. The predictive significance of a "disease-causing variant" is often substantially diminished when identified without the presence of a family history linked to the relevant disease [22]. To date, the scientific understanding of genomic sequencing data remains incomplete, creating uncertainties about the real added value of this extensive information. Uninterpreted “raw” genetic data of consumers can now also be analyzed through a third-party service that offers alternative tools for interpreting, reinterpreting, or facilitating self-interpretation of individuals’ raw genetic data [3, 23]. These services might report variants and disease risk outside of the scope of the original DTC-GT test that was purchased [18]. In consequence, these services blur any distinction between genetic health risk information and non-health risk DTC-GT products even more which complicates any regulatory initiatives [24].

Within this report we provide an overview of the history of consumer genomics and the current DTC-GT landscape. We give an overview of the current evidence on the motivations of those that opt to have DTC-GT and on the risks, benefits, limitations and concerns around DTC-GT. We conclude with an overview of possible regulatory approaches to evaluate DTC-GT offers before their entry into the market and analyze criteria used to evaluate DTC-GT offers for the use of their products in Personalized Prevention.

History of consumer genomics

Following the completion of the Human Genome Project in 2003, DTC-GT companies emerged from 2006 onwards allowing consumers to access their genetic health risk information without the involvement of a health care professional [3, 6]. In the early years of its existence, the industry grew relatively slowly but this changed when DTC-GT companies emerged into the online marketplace [4]. The DTC-GT model emerged in response to traditional health care models, where genetic testing relied heavily on expert knowledge (prescribing and interpretation) and where it was structured to promote informed clinical decision making while limiting associated risks [6]. Advocates of DTC-GT argued that professional resistance to new practices resulted in prolonged innovation [6]. Several private companies saw the opportunity to introduce a new 'do-it-yourself' model where consumers could access their own personal genetic health risk information thanks to rapid advances in sequencing technology, the drop in the price of sequencing equipment and different drawbacks of traditional health care models of providing genetic testing (e.g. lack of trained genetic professionals, waiting lists, restricting genetic health risk information to medical records, expert regulation and control etc.) [3, 6].

The landscape of direct-to-consumer genetic testing (DTC-GT) has undergone significant transformations over the years, shaped by a complex interplay of technological advancements, regulatory interventions, and market forces. Since the introduction of the first direct-to-consumer genetic test (DTC-GT) in the early 2000's, companies offering DTC-GT have had to adjust their products and services to align with various changes in the regulatory environment driven by ethical concerns [3]. The dynamic and evolving DTC-GT landscape no longer strictly segregates DTC-GT and medically supervised models. There seems to be a growing agreement that the best path forward for using personal genetic health risk information is through an expert intermediary. Within this new hybrid model, tests are still marketed directly to consumers, but the ordering process involves engagement of a healthcare professional [4, 5]. This professional could either be the consumer's own physician or a health care professional from an associated company. To date, no published data clarifies the percentage of tests ordered from the consumer's regular physician versus the testing company-assigned physician [5]. The extent of the physician's engagement in the DTC-GT process could vary among different companies and among individuals. The physician's participation might be limited to approving the test order with minimal or no interaction with the consumer [4]. This new hybrid DTC-GT model of disseminating, using and interacting with genetic health data has the power to be either transformative or disruptive [6].

The following overview outlines key milestones and pivotal moments that have contributed to shaping the current landscape of the DTC-GT industry.

Early Adoption and Recognition (2006-2008)

- 2006 Pioneering companies like 23andMe and Navigenics start offering DTC-GT [3].
- 2007 deCODEme enters the DTC-GT market positioning itself as an educational resource rather than a medical diagnostic service. From the beginning, deCODEme encourages consumers to share results with healthcare professionals rather than making medical decisions solely based on the genetic health risk information provided [3].
- 2007-2008 The DTC-GT market gains recognition, with 23andMe being honored as 'Breakthrough of the year' by the scientific journal Science in 2007 and their 'Personal Genome Service' named 'Invention of the year' by Time Magazine in 2008 [3, 25].

Ambitious Goals & Regulatory Challenges (2006-2013)

- 2010 The USA Government Accountability Office publishes a report raising concerns about misleading and questionable advertising claims and the overstated value of DTC-GT in improving personal health [3, 6];
- 2010 The FDA issues warning letters to the largest DTC-GT (including 23andMe, Navigenics, deCODE) companies. They argue that their products constitute medical devices and lack the necessary premarket approval for commercial distribution of these devices [3, 6].
- 2012 23andMe announces their goal of 1 million users of their $99 DTC-GT panel [6].
- 2012 Several DTC-GT companies cease operations in the US, partly due to the impact of the 2008 financial crisis [3].
- 2013 The FDA issues cease and desist letters to several DTC-GT companies ordering them to immediately discontinue marketing and sales of their health related services until they receive FDA authorization for these specific tests [6, 26]. More evidence of the tests' accuracy is sought in addition to proof that consumers are adequately informed about the implications of the test results. Some DTC-GT companies subsequently switch to another model where they only provided raw SNP data leaving consumers to perform their own interpretations along with ancestry information [3, 9]. Consumers can still generate personal genomic reports through uploading these raw data files to free software tools with 'interpretation-only services' (e.g. promethease) which are based on publicly available scientific literature.[3]

FDA Approval and a New Regulatory Approach (2015-2018)

- 2015 The FDA provides approval for a carrier screening test for hereditary Bloom syndrome after analytical validation and user comprehension research by 23andMe [3, 6, 7].

- 2015 Mainstream molecular diagnostic companies begin to re-enter the DTC-GT market (e.g. DTC-GT spin-off Helix from Illumina) [6].
- 2017 Authorization of the FDA for the marketing of a DTC-GT for ten medical conditions, including Parkinson disease, late-onset Alzheimer disease, celiac disease, α1-antitrypsin deficiency, early-onset primary dystonia, factor XI deficiency, type I Gaucher disease, glucose-6-phosphate dehydrogenase deficiency, hereditary hemochromatosis, and hereditary thrombophilia [6, 26].
- 2017 23andMe is considered to be one of the largest repository of DNA, with a biobank that amounts to over 2 million samples [26].
- 2018 The FDA grants 23andMe marketing authorization for BRCA tests [27].

Market Growth and Investments (2018-2025)

- 2018 GlaxoSmithKline invests $300 million in 23andMe for drug development [28].
- 2019 More than 26 million consumers worldwide had taken DTC genetic tests from the four leading commercial companies, 23andMe, Ancestry, GeneByGene, and MyHeritage [29]
- 2022 New regulation of the European Parliament and the Council of the European Union on vitro diagnostic medical devices (IVD's) (Regulation (EU) 2017/746') that covers the safety and performance of IVD's when entering the European market and includes among others DTC-GT and software used for direct or indirect medical purposes.
- 2025 Global DTC-GT market is predicted to be worth over $2.5 billion.

Consumer genomics

Consumer genomics can be defined as the part of the genomics industry that offers products and services to consumers, either directly or through intermediaries [30]. DTC-GT companies differ in technologies used (sequencing-based methods vs single nucleotide polymorphism), fee type (pay-per-use, subscription, for free), level of data interpretation (no interpretation, basis interpretation or value-added interpretation), distribution channel (internet only, health care professionals only or multi-contact service), business purpose (for-profit vs non-profit), etc. [6, 11, 31]. A recent classification of the business models used by DTC-GT companies revealed a heterogenous landscape and identified six different business model archetypes, including (1) low-cost DTC genomics for enthusiasts, (2) high-privacy DTC genomics enthusiasts, (3) specific information tests, (4) simple health tests, (5) basis low-value DTC-GT and (6) comprehensive DTC-GT and low data processing [31].

DTC-GT most often do not require a recommendation or referral from a health care professional, nor are they integrated into public health initiatives. This distinguishes them from home collection kits in screening programs (e.g., bowel cancer screening), rapid antigen tests (e.g. RATs for COVID-19), or self-monitoring tests for diagnosed patients (e.g., diabetes self-monitoring) [32]. In the DTC-GT model, consumers agree to a commercial contract and pay for the purchase of a service, which includes genetic testing [7]. In comparison to conventional health care systems, where informed consent is often obtained during a medical consultation with a health care professional (e.g. clinical geneticist, genetic counselor, etc.), consumers most often agree with terms of services online when ordering the service through the internet.

Consumers purchase DTC-GT for various health and non-health related reasons [24]. Early adopters of DTC-GT were often motivated by curiosity and a keen interest in health-related information [33, 34]. Other motivating factors within this group of early adopters encompassed a willingness to lead in the adoption of new emerging technologies. In an American survey by Kaufman et. al. (2010) reasons for using DTC genetic testing were to satisfy curiosity and to learn about elevated risks of disease [35]. More recently, curiosity was also found to be a major motivation of early adopters who self-initiated the process of seeking out polygenic risk scores by sharing their DTC-GT with a third-party interpretation service [36].

Another study that studied motivators of the actual population of DTC-GT users through an exploratory study based on users' personal stories reported five major sets of motivations relating to health, curiosity/fascination, genealogy, contributing to research, and recreation [37]. As the authors also mention, the health-related motivators are noteworthy, especially since the majority of DTC-GT companies include disclaimers on their websites, explicitly stating that their services are not intended for use as medical advice or diagnostic tools. A more recent systematic review that assessed perspectives of European citizens' toward DTC-GT also identified the desire to know risk predisposition for certain serious conditions as the most common reason for undergoing DTC-GT [38]. Other studies have also shown that some consumers seem to opt for DTC-GT for various other reasons, for example to seek an explanation for current health conditions or to inform family members about an increased

familial risk for a genetic condition [39, 41, 42]. As individuals explore their genealogy, there also exists the potential to unintentionally uncover health-related information prompting some to actively seek more insights through third-party interpretation services [39, 50, 51]. Furthermore for adult adoptees, DTC-GT often serve as a primary source for both ancestry and health information in absence of consistent family history records [43].

As mentioned before both health-related and non-health-related DTC-GT offers exist. Within this report we will focus on the following subcategories that provide health-related information:

Health-related DTC-GT

Predictive and presymptomatic testing for monogenic conditions

Monogenic conditions can be passed on to future generations through different modes of inheritance. The mode of inheritance can be either recessive or dominant. Two faulty copies of a gene must be present for an autosomal recessive (AR) condition (e.g. cystic fibrosis) to develop. Only one faulty copy of a gene is sufficient to cause an autosomal dominant condition or an X-linked condition (e.g. hemophilia A) in males, as they only have one X-chromosome. Most female carriers of an X-linked condition are typically healthy and therefore not aware of the fact that they have an increased risk of having an affected son. But some may also experience mild symptoms (e.g. Fragile X syndrome). In contrast, dominant conditions (e.g. Huntington's disease) can manifest in individuals with only one copy of the disease-associated gene [52]. Predictive and presymptomatic genetic testing for monogenic conditions aims to identify the presence or risk of genetic conditions caused by a pathogenic variant in one single gene, enabling early detection and informed interventions. More specifically, predictive testing allows the identification of pathogenic variants that increase the likelihood that an individual will develop a genetic condition, while presymptomatic testing allows the determination of whether an individual - without any signs/symptoms at the time of testing - will develop a genetic condition [53].

Example: Predictive/presymptomatic genetic testing for Huntington’s disease, a lethal genetic condition that leads to the gradual degeneration of nerve cells in the brain. As a result both physical and mental abilities are progressively impacted. Huntington’s disease is an autosomal dominant condition. Therefore, an individual with Huntington’s disease has a 50% chance of passing the disease causing gene to their offspring. To date, there is neither a cure nor an effective treatment available. Thus, predictive/presymptomatic genetic testing for Huntington’s disease only serves as a means to end the uncertainty of those at-risk and to make informed life choices.

Susceptibility testing for multifactorial conditions

The following subcategory of DTC-GT entails genetic tests to determine susceptibility for multifactorial conditions. These conditions are influenced by a combination of genetic (one or more involved genes), environmental and/or lifestyle factors. More specifically these tests will evaluate the presence of specific genetic variants that increase the risk of developing a certain condition. The presence of a particular variant can increase the risk of developing the condition, but this does not mean that in all cases the condition will develop. It is important to underline that these tests are not diagnostic but only provide a risk estimation [53]. Risk information from DTC-GT is available for both high-risk disease associated variants and for polygenic risk scores (PRS). These scores are based on variants that have been identified to be implicated in many common conditions within GWAS. The clinical utility of these PRS to identify those at high risk to benefit from preventive interventions is however contested [18, 24, 54]. Moreover, the predictive accuracy of risk information for individuals without European ancestry may be diminished due to the prevailing European bias in current GWAS [24, 55].

Example: Genetic screening for type 2 diabetes - Type 2 diabetes is a complex disorder resulting from an interaction between genes and environment. Several risk factors for type 2 diabetes have been identified, including age, sex, obesity, low physical activity, smoking, ethnicity, family history, etc. There is also ample evidence that type 2 diabetes has a genetic basis. Type 2 diabetes is considered to be a polygenic disease with an inheritance ranging from 30 to 70% [56]. The generation of polygenic scores based on overall type 2 diabetes predisposition can identify individuals with a higher risk of diabetes who may benefit from targeted interventions. Yet this shouldn't be considered apart from non-genetic predictors [57].

Pharmacogenomics

Pharmacogenomics provides information on genetic variants that could impact drug metabolism, elevate the risk of adverse drug reactions, or modify an individual's response to a drug. A broader definition that has been proposed by is 'the study of genomic technologies to enable the discovery and development of novel drugs, and the optimization of drug dose and choice in individual patients to maximize efficacy and minimize toxicity' [58].

Example: Breast cancer and the drug T-DM1 - Some drugs need to attach to receptors in order to work properly. The type and amount of receptors someone has are determined by his/her DNA. This explains why some people need a lower or higher dose of a specific drug or another drug in comparison to others. The drug T-DM1, for example, will only work if a cancer tumor has a high amount of HER2 (a specific receptor that helps the cancer develop and spread). If the tumor does not have enough HER2, the drug T-DM1 will not work [59].

Prenatal genetic testing for health purposes

During pregnancy, women may be offered prenatal genetic testing to determine the likelihood of the fetus being born with a genetic condition. Two types of prenatal genetic tests exist:

screening and diagnostic genetic testing. Prenatal genetic screening tests are commonly used to identify pregnancies with an increased chance to have a baby with certain chromosomal abnormalities. However, these test are not 'diagnostic'. A positive screening test result only indicates an increased likelihood that the fetus might have the condition, but it does not confirm that the fetus will also have the genetic condition. In the case of an increased likelihood of the fetus being born with a genetic condition, further diagnostic testing is still required. Prenatal diagnostic genetic tests enable a more accurate prediction/determination of whether a fetus will develop a genetic condition by looking at cells from the fetus or placenta obtained through amniocentesis or chorionic villis sampling [60].

Example: Non-invasive prenatal screening (NIPT) - analysis of cell-free (cf) DNA in maternal blood has been shown to be highly accurate in the detection of common fetal autosomal trisomy's (Down's syndrome, Edwards' syndrome, or Patau's syndrome).

Carrier screening

Carrier screening allows for the detection of carriers of autosomal recessive and X-linked conditions in individuals who do not have an a priori increased likelihood of being a carrier based on their or their partners' personal or family history' [61]. Information gained through carrier screening can be used to make informed reproductive decisions before or after conception.

Example: Carrier screening for Cystic Fibrosis (CF) allows the assessment of whether individuals are carriers of pathogenic variants that causes CF. Carriers of pathogenic variants are typically healthy and therefore often unaware of their carrier status. CF is a genetic condition that results from a pathogenic variant in the CFTR gene. CF is a lifelong illness that most often causes problems with breathing and digestion. Currently there is not a cure available. This proactive screening could be of particular interest for prospective parents, allowing them to make informed reproductive decisions.

Other health-related assessments

Dermatogenomics

The field of dermatogenomics aims to understand the interplay between genomics and dermatology, aiming to identify predispositions to certain skin conditions with a genetic basis [62].

Example: Genetic testing for psoriasis - Psoriasis, a prevalent inflammatory skin disorder, results from the complex interaction of numerous genetic and environmental risk factors. Recent genome-wide association studies (GWAS) indicate that genetic data can differentiate subsets of psoriasis patients based on factors such as the type of psoriasis (pustular versus plaque), susceptibility to joint disease, and responsiveness to different medications. These findings hold promise for shaping personalized treatment approaches in the future, offering valuable insights into tailoring interventions for individuals with psoriasis [63].

Nutrigenomics

The field of nutrigenomics is aimed at understanding the interplay between genomics, nutrition, and health, with the goal of providing personalized dietary and lifestyle recommendations tailored to an individual's unique genetic data [3]

Example: Genetic testing for Familial Hypercholesterolemia, a genetic condition characterized by high blood levels of low-density lipoprotein (LDL) cholesterol and an increased risk to develop coronary artery disease. The condition can be caused by pathogenic variants in the LDLR, APOB, and PCSK9 genes, which affect how your body regulates and removes cholesterol from your blood. About 60-80% of people with familial hypercholesterolemia have a pathogenic variant found in one of these three genes. This also means that some people with familial hypercholesterolemia have a pathogenic variant that is currently not detected by genetic testing. Treatment for familial hypercholesterolemia typically involves lifestyle modifications such as diet and exercise, along with cholesterol-lowering medications [64, 65]

Overview of the DTC-GT market

As mentioned before, the DTC-GT market appears to be dynamic: companies come and go, and they frequently adjust their offerings. Below we provide an overview of the evolution the market went through over the past years . In addition, we have listed an overview of DTC-GT companies and the different subcategories they offer. For this report, we focus in particular on companies that offer health-related DTC-GT.

DTC-GT companies identified in our time-specific search may not encompass all available options, given that product availability is still evolving, and additional offerings may be promoted on various platforms or retailed in different ways (e.g. pharmacies). Our database of DTC-GT companies was primarily based on the list that was established by Prof. Andelka M. Phillips in 2018, which builded upon previous work of the Human Genetics Commission, the

US Government Accountability Office, and the Johns Hopkins Genetics and Public Policy Center [11]. This list was supplemented with companies identified through an additional online search.

Of the 501 initial identified companies, 375 were considered to be companies that sell or advertise genetic testing directly to consumers. The retrospective analysis of the identified companies was performed by the team of Prof. Pascal Borry in 2019 by using the Web Archive software (unpublished data). Two researchers independently gathered data on the geographical location of each DTC-GT company and assessed the status of the company's website for each year spanning from 2005 to 2019. If a company's website was operational in a given year, supplementary data were collected on the categories of DTC-GT the company offered during that year and whether the involvement of a health care professional was necessary for the test ordering.

Figure 1: Health-related DTC-GT Market Growth (2005 -2019)

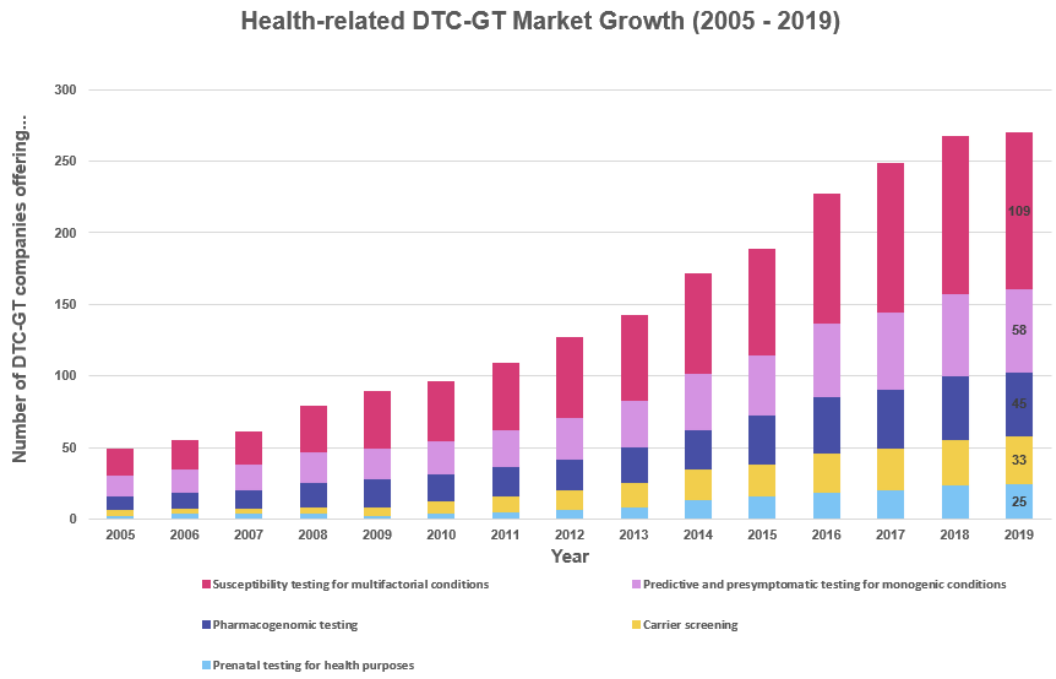

Figure 2 : Other health-related assessments DTC-GT Market Growth (2005 -2019)

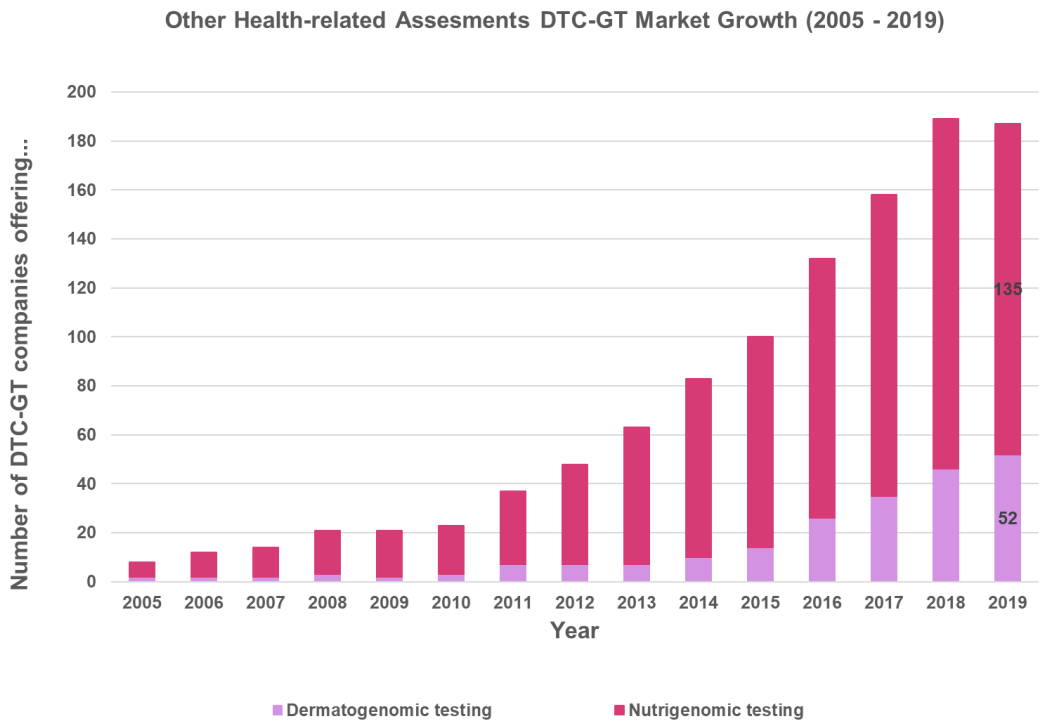

Table 1: Overview of companies offering health related DTC-GT offers (2019)

Company name	Country	Predictive and presymptomatic testing for monogenic conditions	Susceptibility testing for multifactorial conditions	Prenatal testing for health purposes	Carrier screening	Pharmaco-genomics
23andMe	USA					
23DNA	Unknown					
23mofang	China					
24Genetics	Spain					
Accu-metrics-Viaguard	Canada					
Advanced Healthcare	India					
Affinity DNA	UK					
AGS-Advanced Genomic Solutions	USA					
Ambry Genetics	USA					
Any Lab Test Now	USA					
Asper BioTech	Estonia					
Bio Logis	Germany					
Carigen Caribbean Genetics	Jamaica					
Center for Medical genetics	USA					
Centrillion Bioscience	USA					
China Life Science Holding Group	China					
Coloalert	Germany					
Color Genomics	USA					
Counsyl	USA					
Dante labs	Italy					
David Drew Clinic	USA					
DNA Diagnostics Center	UK					
DNA Plus	Germany					
DNA Power	Canada					
DNA Reference Lab	USA					

DNA Testing Centers of Canada	Canada					
DNALYSIS Biotechnology	South-Africa					
Dr. Seibt Genomics	Germany					
Dynamic DNA Labs	USA					
Eastern Biotech and Lifesciences (UAE)	United Arab Emirates					
EDGC-EONE Diagnomics genome center	South-Korea					
FitGenes	Australia					
Fitgenetix	USA					
Futura Genetics	Canada					
Future Genetic	Germany					
Gene by Gene	USA					
Genebase	Canada					
geneDecode	Hong Kong					
GeneDx	USA					
Genelex	USA					
GenePlanet	Slovenia					
Genera	Brazil					
Genetic Health	UK					
Genetic healthcare Group (geneLAB)	Malaysia					
Gene Plaza	Belgium					
Geneticure	USA					
Genetrack Biolabs	UK					

GeneWiz	Germany					
Genomic Express Inc	USA					
Genoris	Germany					
Genosense	Austria					
Genosolution	South Korea					
GenoTek	Russia					
Genova	Germany					
Gonidio	Switzerland					
Graceful Earth inc.	USA					
GTL DNA	UK					
Habit LLC	USA					
Health Check USA	USA					
Health Tests Direct	USA					
Helix	USA					
HomeDNA Direct	UK					
Human Longevity Inc.	USA					
iamYiam	UK					
Indian Biosciences	India					
Integrated Genetics	USA					
International Biosciences	UK					
Jinomz	United Arab Emirates					
Kailos genetics	USA					
Kimball	USA					
Kiragen	USA					
LabCorp	USA					
Lifecodexx	Germany					
Lifecode gx	UK					

Lineagen	USA					
Makings of me	USA					
Map My Gene	USA					
Map My Genome	India					
Medical Rogaska Slovenia	Slovenia					
Meinlabtest	Germany					
MightyDNA	USA					
Molecular Diagnostic Services	South-Africa					
MUHDO	UK					
MyDNA Health	UK					
MyGene	Australia					
Myriad	USA					
Nature Doctors	Canada					
New Life Genetics	Denmark					
Nordic Laboratories	Denmark					
Nutrigenomix	Canada					
Ome Health	UK					
Original Gene	USA					
Paternity Testing Corp	USA					
Pathway genomics	USA					
Perkin Elmer Genetics	UK					
Pillcheck	Canada					
Prenatalis	Germany					
Prenetics	Hong Kong					
Progenika	Spain					
Progenom	Germany					
Pure Genetic Lifestyle	Netherlands					
Qlu Health	United Kingdom					
Remede	Australia					
Rightangled Ltd	UK					
Selfdecode	Unknown					

Sequenom	USA					
SeqWright DNA technology Services	USA					
Skin Shift	USA					
TellmeGen	Spain					
The Wellness Brothers	United Arab Emirates					
The Wellness Gene	USA					
Theranostic Lab	New Zealand					
Toldot Genetics	Israël					
Veritas Genetics	USA					
VITAGENE-x	UK					
WellPro	South-Africa					
Who'z the daddy?	UK					
Vitagene	USA					

= Genetic test are only offered to consumers through an intermediary (e.g. physician)

Table 2: Overview of companies offering health-related assessments (2019)

Company name	Country	Dermatogenomics	Nutrigenomics
23andMe	USA		
23mofang	China		
24Genetics	Spain		
Affinity DNA	UK		
AGS-Advanced Genomic Solutions	USA		
Angelscope DNA Diagnostics	UK		
ARCpoint Labs	USA		
Asper BioTech	Estonia		
Athgene	Denmark		
Athletigen	Canada		
Atlas Biomed	UK		
BalanceDiet	USA		
Bio Logis	Germany		
Biomarker gene essence	USA		
CAligenix	USA		
Carloyn Katzin's The DNA Diet	USA		
China Life Sciece Holding Group	China		
CRI Genetics	USA		
Dante labs	Italy		
Darwin Dietitians	Australia		
DexaFit	USA		
DNA Code	Singapore		
DNA Diagnostics Center	UK		
DNA Nutricontrol	Austria		
DNA Power	Canada		
DNA Test	South-Africa		
DNA Testing Centers of Canada	Canada		
DNA Weight Control	Switzerland		
DNAFit	UK		

DNALYSIS Biotechnology	South-Africa		
Dr. Seibt Genomics	Germany		
Dynamic DNA Labs	USA		
Eastern Biotech and Lifesciences (UAE)	United Arab Emirates		
EDGC-EONE Diagnomics genome center	South Korea		
Eugene	Unkown		
Evergreen Life	UK		
FitGenes	Australia		
Fitgenetix	USA		
Fitness Genes	UK		
FitNow Health	USA		
Future Genetic	Germany		
FutureSkin	UK		
Gene2me	South Korea		
Genebase	Canada		
geneDecode	Hong Kong		
Gene Fit DNA	UK		
GenePlanet	Slovenia		
Genera	Brazil		
Genetic Balance	Germany		
Genetic Health	UK		
Gene Plaza	Belgium		
Genetrack Biolabs	UK		

Genomic Express Inc	USA		
Genopalate	USA		
Genoris	Germany		
Genosense	Austria		
Genosolution	South Korea		
GenoTek	Russia		
Genovia	Germany		
Gonidio	Switzerland		
Graceful Earth inc.	USA		
GTL DNA	UK		
Guardiome	USA		
Habit LLC	USA		
Helix	USA		
Holistic Health International	USA		
HomeDNA Direct	UK		
Home DNA Inc	USA		
iamYiam	UK		
idDNA	Switzerland		
ILLID-metachek	Germany		
Indian Biosciences	India		
International Biosciences	UK		
Jinomz	United Arab Emirates		
Kiragen	USA		
Lifecode gx	UK		
Life genetics	Slovenia		
Makings of Me	USA		
Map My Genome	India		
Meinlabtest	Germany		
MiaDNA	USA		
MightyDNA	USA		
Molecular Diagnostic Services	South-Africa		

Molecular Fitness	USA		
MUHDO	UK		
myDNA Life	UK		
MyDNA Health	UK		
MyGene	Australia		
MyInnerGo	UK		
Natgene	Italy		
Nature Doctors	Canada		
New Life Genetics	Denmark		
Nimble Diagnostics	UK		
Nordic Laboratories	Denmark		
Nutrilite	USA		
Nutrigenomix	Canada		
Ome Health	UK		
Orig3n	USA		
Original Gene	USA		
Pathway Genomics	USA		
Prenetics	Hong Kong		
Progenom	Germany		
Pure Genetic Lifestyle	Netherlands		
Qlu Health	UK		
Remede	Australia		
Rightangled Ltd	UK		
Salugen	Switzerland		
Selfdecode	Unknown		
Silverberry Genomix	USA		
Skin DNA Canada	Canada		
Skin Shift	USA		
Smart Genes	New Zealand		
Sports Gene LLC	Estonia		
TellmeGen	Spain		
The Makings of Me	Israel		
The Wellness Brothers	United Arab Emirates		

The Wellness Gene	USA		
Toldot Genetics	Israel		
Toolbox Genomics	USA		
VIAMEDEX Genetic Laboratories	UK		
VITAGENE-x	UK		
Vitaminlab	Canada		
Vitl	UK		
Wellnicity	USA		
WellPro	South-Africa		
What IF Plan	UK		
Who'z the daddy?	UK		
Verelst Genetics	Spain		
Vitagene	USA		
Genomelink	USA		

 = Genetic test are only offered to consumers through an intermediary (e.g. physician)

Benefits, risks, limitations & concerns

Since the emergence of DTC-GT, different stakeholders have voiced and debated several potential risks and benefits [1]. Proponents of DTC-GT claim that the provision of personalized genetic health information empowers consumers to take responsibility for their own health and allows them to be in charge of their health management without the mediation of health care professionals [66, 67]. Overall, study findings have shown that consumers of DTC-GT seem to have high satisfaction, low levels of regret and that they value the provision of medical information obtained through DTC-GT [24, 68]. Personalized health risk information may help consumers to be more proactive about their health and lifestyle and promote positive behavior modification [4]. Additionally, personal health risk information could be used for more tailored interventions, targeting specific populations for more effective and cost-efficient health monitoring [68]. It seems that most consumers undergoing DTC-GT also intend to modify their lifestyle based on their genetic profiles [69]. However, there seems to be only a little to moderate change in health behavior in response to DTC-GT results. While some studies reported self-reported changes in dietary behavior, exercise behavior, smoking behavior and vitamin supplements uptake in response to DTC genetic testing results, other studies did not find any significant effect change [24, 68, 70]. A meta-analysis on the effects of DTC-GT on health-related behavior change reported that overall, 24% of consumers had showed a positive lifestyle change after DTC-GT. More specifically, 16% of consumers reported improved dietary practices, while 12% reported improvement in exercise practices [68]. Furthermore, 19% of pre-test smokers reported to have quitted smoking [68]. In a large American study among DTC-GT consumer (Personal Genomics) a modest but significant effect was reported on perceived risk of breast, prostate, colorectal, and lung cancers among those consumers who received an elevated risk based on genomic test results. The increased perceived risk motivated some consumers to access healthcare/ cancer screening programs [71]. Yet, without studies assessing behavior change over time using more objective and validated measures, little is also know about the magnitude of these effects and the sustainability of these changes on the long term [68]. The motivating effect of DTC-GT alone remains unclear so far, as those making lifestyle modifications might simply be more health-motivated overall [70]. Furthermore, the motivation to improve health might also be an important factor contributing to the decision to have DTC-GT in the first place.

Supporters of DTC-GT also argue that DTC-GT allows for increased access to genomic testing due to restrictions available in the public healthcare setting (e.g. long waiting times for appointments) [4, 17]. Moreover, DTC-GT tends to be more affordable in some countries than clinical genetic testing obtained through healthcare providers [4]. Some have argued that access to personalized genetic health risk information without a gatekeeper is an individual right, and imposing restrictions is unjustified paternalism [72-74]. The choice of health care professionals to be overly cautious with genetic health risk information is very often seen as a desire of these health care professionals to preserve their professional autonomy [75]. Yet, it's important to not forget that while DTC-GT could improve access to genetic testing, consumers might still rely on input from healthcare professionals/access to the public health care system once test results are available [24]. Appointments involving DTC-GT consumers

could potentially redirect healthcare resources away from patients with a clinical indication [24]. This might present challenges to ensure equitable healthcare delivery. In 2019, the Royal College of General Practitioners and The British Society for Genetic Medicine released a position statement together to discourage referrals to clinical genetics services solely based on DTC-GT test results. Instead, they recommend conducting a comprehensive risk assessment and evaluating family medical history before considering referrals in accordance with standard clinical pathways and protocols [76].

By circumventing the public healthcare system, some believe that the privacy of genetic data may also be better protected against insurers and employers, allowing consumers to have broader control over their genetic data [77]. This may be of particular importance in countries without regulatory protections against genetic discrimination in insurance and employment. Proponents also underline the possibility to increase genetic awareness and knowledge regarding genetic risk and the opportunity to use genetic health risk information to promote preventive and individualized medicine [1, 4, 6, 72]. For example, a pharmacogenomic test that allows the identification of the optimal drug and/or dosages for an individual, which could help to reduce the likelihood of adverse drug events [78]. This could in return help to reduce unnecessary costs to individual consumers and the public health care system [6]. In addition, lessons learned from the DTC-GT marked could possibly also help to increase equity in the analysis or use of clinical genetic services where racial/ethnic disparities persist [13]. In 2017, the US National Institute of Health awarded 23andME a $1.7-million grant to sequence the genomes of African American consumers who had already bought a DTC-GT product. The project specifically aimed to address the lack of sequencing data of specific subpopulations [26]. These informative databases with genetic data from diverse populations could also significantly contribute to medical research, potentially leading to discoveries that have implications for advancing personalized medicine [4].

Alternatively, there is a different movement of diverse stakeholders that have raised several concerns, risks and limitations associated with DTC-GT and the related ethical issues. The first often-mentioned concern is the quality of the tests offered regarding clinical validity and utility. As there isn't always sufficient scientific evidence with regard to the gene-disease associations for some of the more complex disorders, results may be unreliable [4, 79]. Many of DTC-GT panels are based on genome-wide association studies which are not considered clinically robust by medical standards [6]. The available genomic datasets are also very often generated from specific populations and are therefore not sufficiently sensitive to the potential influence of ethnic and racial differences across different human populations [6]. Furthermore, DTC-GT for susceptibility for multifactorial conditions fails to take into account environmental and/or other non-genetic risk factors (e.g. family history, smoking, etc.) which can also contribute to development of a certain condition [79]. To be able to correctly interpret genetic data and to improve the scientific and medical value there still remains a need for clinical data of a patient (e.g. family health history, symptoms, age, etc.) [7, 74]. As a result, many of these tests have been considered to have dubious clinical utility and are unlikely to contribute to the healthcare management of individuals [1]. In most cases, test results only provide generic advice such as 'stop smoking' or 'exercise more'[1].

While many health care professionals (especially trained genetic professionals) doubt the trustworthiness of DTC-GT results, consumers don't always share these concerns about quality and reliability. These opposing perspectives could negatively impact the patient-clinician relationship through challenging or unsatisfactory clinical encounters [24, 80]. Disclaimers of DTC-GT companies often mention that information is neither validated for accuracy nor intended for medical use, but it remains questionable if this is understood correctly by consumers and/or non-trained genetic health care professionals [24, 74]. Recent research found that 63% (31/49) of patients that were seeking confirmatory testing of their obtained raw data through third-party interpretation services didn't receive important genetic health risk information within their original DTC-GT report [74]. In a recent American study, it was also discovered that 40% of the variants reported in DTC-GT across a range of patient samples turned out to be false positives [74]. Results were even more concerning in a survey study among Australian clinical genetics services, where fewer than 10% of variants were confirmed among DTC-GT referrals for consumers who had used third-party interpretation services [81]. Test results from different DTC-GT companies for the same condition may vary because not all DTC-GT companies test for the same sets of variants or genes related to a genetic condition [4]. Furthermore it seems that the clinical laboratory evaluation of variants in DTC-GT raw data is also subject to incorrect variant classification. Multiple cases have been described were consumers were incorrectly assigned 'an increased risk' by the commercial provider or third party interpretation service [82]. This misclassification might be due to outdated evidence that these databases use to interpret [18].

A second issue that has been subject to criticism is the absence or uncertain quality of individualized medical supervision and/or genetic counseling [72]. Prior to undergoing a genetic test, it is deemed essential that individuals receive adequate information regarding the possibilities and limitations of the test and its appropriateness. In addition, expert guidance in interpreting test results, understanding their significance and implications and providing appropriate guidance on the healthcare management of a patient is found to be equally important [1]. Some fear that consumers may experience unnecessary distress (especially in the case of false positive results) or may misinterpret test results which may lead to inappropriate healthcare management. Selling tests of undemonstrated reliability as predictive tests for medical risk factors could lead to poor diagnosis and unwarranted concerns and actions among consumers [7]. This could lead either to patients not undergoing necessary examinations in the case of false reassurance or to patients who undergo unnecessary (prophylactic) procedures in the case of over-interpretation of test results [2, 77]. Furthermore, consumers undergoing DTC-GT with very limited clinical utility might be faced with redundant follow-up examinations that could be seen as an unnecessary overburden of the public health care system [21, 77]. Over the last couple of years, more and more DTC-GT companies have included counseling and supervision of trained genetic health care professionals in their services. Yet, the above mentioned concerns remain as the neutrality of these health care professionals employed by these companies cannot be guaranteed [83, 84].

Third, it is known that several DTC-GT companies conduct further processing of consumers' genetic data for research purposes and/or sell aggregate data to third parties [4]. Given how difficult is it to obtain biological samples from a large cohort with the consent and full history

of the patients in a short space of time by the standard route, the idea of creating an interface between individuals and researchers has emerged [7]. In this model, some DTC-GT companies have become essential intermediaries between researchers and their research subjects, through the generation of large biobanks containing different samples provided for DTC-GT [7]. Yet, the terms and conditions of the future uses of genetic information aren't always very clearly communicated or are lost in the legalistic small print [1, 6, 85, 86]. While consumers might be motivated to provide their data for research, they might not fully realize that their data could potentially also be used a as source of profit for companies [7]. Improving the readability of contracts and privacy policies could enhance the consumers' understanding and in consequence the consent process. Furthermore separating the consent for testing and the consent for further uses (such as the storage, use or sale of samples for research) has also been proposed as a strategy to reduce misunderstandings. When third parties receive genetic data of consumers, individuals become vulnerable to the risks of re-identification and potential harm from actions by these external actors, which may include predatory and discriminatory practices [87]. It's important to acknowledge that the objectives of some DTC-GT companies are two-fold. On the one hand they provide DTC-GT offers at a low-cost, while on the other hand they establish a large database/biobank for research purposes [7]. Some of DTC-GT companies encourage their customers to engage through online platforms and to respond to follow-up surveys and health reports on a voluntary basis [6]. However, participants in the 23andMe research program receive supplementary information that is not accessible to individuals solely utilizing the DTC-GT service [7]. These practices give rise to ethical concerns about the way in which consumers are included in research and the acquisition and utilization of information about them [7]. Data security and privacy issues aren't only applicable to the individual who undergoes a genetic test but also applies to family members with whom they share a genetic link. Privacy advocates have long warned that sharing DNA with testing companies makes consumers vulnerable to the exposure of sensitive genetic information that can reveal health risks. Very recently, hackers gained access to almost 7 million user profiles of the company 23andMe. The comprised data that were offered for sale on the internet also included health-related information based on consumers' genetic profiles [88]. Misuse of this sensitive information could impact employment opportunities, insurance coverage and other areas of life [2, 4]. Some DTC-GT companies clearly state that third parties may have access to their databases in their privacy policies [89]. Genetic information could for example be used by police forces to identify potential suspects. In 2018, the US police used a database of a DTC-GT company to identify the California's Golden State Killer [90]. The growing trend of law enforcement using DTC-GT information may impact how people view the advantages and disadvantages of genetic testing. This could contribute to feelings of mistrust or discrimination, particularly among vulnerable social groups such as immigrants, prisoners, ex-convicts, sexual minorities, and racial/ethnic minorities. Furthermore, concerns have been raised about changes in privacy policies that can occur if a company is sold or acquired [87]. Such distrust has the potential to discourage individuals from opting for genomic medicine [91].

Fourth, concerns have been raised about the lack of adequate informed consent procedures in the context of DTC-GT [1, 6]. Information provided by DTC-GT companies is often inadequate and/or misleading [72, 92]. As consumers might solely rely on the information

provided by commercial companies that use promotional and marketing tactics, they may overestimate benefits and underestimate limitations/risks and possible consequences [1, 86]. The degree to which people are likely to read into the information provided by DTC-GT companies could also vary. As a result some citizens and patients could make uninformed decisions based on misinterpretation or misunderstanding of test results that could have serious health consequences [4]. This risk of misinterpretation is especially significant for individuals of non-European ancestry, as the tests for many screened conditions may not encompass common variants present in minority populations.

Unexpected findings could also trigger stress and anxiety in some consumers. Especially, in the case of learning about risk for unpreventable or incurable conditions [93]. The wide accessibility of DTC-GT may also favor nonconsensual testing of third parties, which occurs when an individual obtains and submits a biological sample of another person without consent [11, 94]. This becomes especially concerning when minors undergo testing, as it could result in a violation of the minor's autonomy and the confidentiality of their genetic information [95]. Based on empirical evidence it appears that objections to DTC-GT based on concerns about consumer anxiety or negative changes in health behavior may have been exaggerated [6, 68, 96, 97]. While there is evidence that some consumers experienced adverse psychological effects (e.g. anxiety, distress, worry) after receiving DTC-GT test results, overall this impact seem to be rather low and to reduce over time [68, 97]. Individuals who had DTC-GT also seem to recall test results correctly, do not interpret results in an overly deterministic way and understand that both genetics and behavior contribute to disease risk [98]. Important to mention is the fact that current evidence is based on studies that assessed the impact on consumers that were not representative for the general public, with most participants being highly educated, from high-income households and being predominantly white. Furthermore, most studies relied on self-reported data, which may not adequately measure the full range of impact [24]. More research to assess the possibility of adverse psychological effects among consumers of DTC-GT is therefore still needed.

Fifth, despite initial concerns surrounding DTC-GT and its potential impact on public health, many of these anticipated issues (e.g. downstream tests and/or procedures to address results, referral to specialists) have not manifested as expected given the most recent available data [98, 99]. DTC-GT companies often advise consumers to consult a health care professional for help interpreting and using genetic health risk information. Healthcare professionals have also voiced to feel obligated to refer patients to specialists or suggest additional screening procedures based on DTC-GT results which could pose challenges for certain populations with limited access to such services due to financial constraints and other barriers [80]. However, based on research findings it seems that only a third of consumers share their DTC-GT results with a health care professional [68]. Earlier surveys among consumers of DTC-GT found that 20-40% of participants discussed their DTC-GT results with their primary health care professionals and 1-14% discussed them with a trained genetic professional [24, 68, 85, 100-102]. The strongest predictors of seeking genetic counseling in a large American study (Personal Genomics Study) was to have had genetic counseling prior to pursuing DTC-GT, poorer self-reported health, greater uncertainty about results and a greater number of common and complex conditions (e.g. cardiovascular conditions) in the family medical history

[102]. This might indicate that some people also undergo DTC-GT to help explain an active medical condition [102]. A large survey study among primary care and specialist physicians in the US that was conducted between 2017 and 2018 revealed that 65% received zero direct-to-consumer health risk genetic test results from patients in the past year. In addition, 35% of respondents received at least one direct-to-consumer genetic test result from a patient in the last year. In 40% of these cases, physicians made a referral based on these DTC-GT results with the most frequent referrals being to clinical genetic services (78%) [103]. A different survey study that was conducted in the USA in 2017 among genetic counselors reported that while 40% had seen at least one consumer in the clinic for the sole purpose of reviewing DTC-GT results, 76% of respondents had been asked questions about DTC-GT by at least one patient [104]. This indicates a significant rise compared to an earlier survey of 2008, where only 14% of participating genetic counselors reported ever having received requests for test interpretation or discussion [105]. Another Australian study that surveyed clinical genetics services about DTC-GT related referrals over a period of 10 years (2010-2019) reported similar results. Most of the received referrals were made by general practitioners to help consumers interpret DTC-GT results correctly because they were unsure about the significance of the results that had been found [81]. While the majority of these referrals also resulted in patient appointments at a clinical genetics service, the willingness to offer appointments varied between services. Six out of ten services that participated in the study reported validation of DTC-GT results as the most common clinical post-appointment action [81]. These findings indicate that occurrences of patients sharing results from direct-to-consumer health risk genetic tests constitute a relatively small proportion of the total amount of patient visits. Nevertheless, for some DTC-GT related referrals clinical actions (e.g. carrier screening of family members) were taken which also demonstrates the clinical impact that DTC-GT could have on the public health care system [81]. Considering the ongoing rapid growth in the DTC-GT industry, there is a potential for an increased impact on the public healthcare system in the future. As more DTC-GT companies continue to develop from partnerships with physician intermediaries in the ordering and test reporting process, patients may also potentially turn to these professionals for additional health information and advice [103]. Further international research exploring the current impact on the public health care sector would be highly beneficial to gain more insights, as earlier research findings mostly represented early adopters of DTC-GT and might no longer represent the current population undergoing DTC-GT [102]. The scarcity of research data currently available predominantly concentrates on the USA context. More endeavors to gain insights about the impact of DTC-GT in other contexts worldwide (e.g. European Union) are necessary to provide more valuable insights about the implications of DTC-GT.

Regulatory approaches

Earlier events have raised crucial questions as to what degree DTC-GT should be regulated and how to reach a correct balance between promoting responsible innovation and protection consumers and public health systems [106]. For example, in 2014, more than 10.000 signatures were collected in an online petition in favor of reversing the ban the FDA had put on 23andMe [107]. DTC-GT companies have always emphasized that their primary aim is to educate and entertain their customers. As a result, they argue that regulations and legislation pertaining to clinical genetic testing should not be imposed on their activities [9]. Surveys conducted among American consumers of DTC-GT reported that less than 30% of respondents believed that the government should increase regulation of consumers' ability to directly access their genetic information. Yet, most did believe that some oversight would be beneficial [108, 109]. In an interview study where the attitudes of European clinical geneticists regarding DTC-GT were explored, most participants expressed agreement on the importance of regulatory oversight for DTC-GT. However, there were varying opinions among participants regarding the specific extent of regulation and the focal areas that require attention [110].

On a global scale, DTC-GT companies predominantly operate within broader regulatory frameworks applying to genetic testing, without being subject to any specific regulatory frameworks [70]. The regulatory oversight of DTC-GT in the United States by the Food and Drug Administration (FDA) contrasts with the absence of specific regulations for this type of testing in many other countries [11]. In Canada, the lack of regulation is partly due to DTC-GT samples being analyzed outside of Canada. While DTC-GT offers with diagnostic functions do require market authorization from Health Canada, DNA collection kits that solely transport genetic material to a testing facility outside of Canada do not mandate a license [111]. At present, there are also no specific laws directly addressing DTC-GT in China [112, 113]. The multi-layered complexity of regulating DTC-GT in Europe resides in the variation of DTC-GT offers and the coexistence of different legislations in Europe, including national legislation of member states and EU legislation [1]. Earlier studies have reported on various approaches used by different European member states to regulate genetic testing, covering aspects like medical supervision, genetic counseling and informed consent [1, 9, 114-116]. While DTC-GT may also be subject, either partially or entirely, to these legal initiatives there is currently no EU or national legislative instrument specifically regulating DTC-GT specifically [115, 116].

A risk-based approach based on proportionality, where high standards of analytical validity, clinical validity, consideration of clinical utility, adequate informed consent process, truth-in-labelling and truth-in-advertising would apply to all health-related DTC-GT offers could be way forward. In addition, additional restrictions could be imposed for DTC-GT offers that inform and impact healthcare decisions [1]. Yet, any regulatory control put in place to manage DTC-GT also has to deal with the issues of (international) enforcement given the fact that this international market is functioning through the internet [3, 117]. As a consequence, DTC-GT may still be accessible regardless of the consumer's geographical location [70].

In the following, we will provide an overview of policy and regulatory approaches that have been proposed and/or implemented to evaluate DTC-GT offers before their entry into the market.

Self-regulation of DTC-GT industry

Regulatory flexibility has facilitated the expansion of a competitive market that includes the offering of a variety of services at different price levels, and in some cases, at no cost. Some have argued that the industry could also self-regulate for the benefit of its consumers [114]. While some players in the DTC-GT market have taken steps to empower consumers with control over their own data, the absence of regulatory supervision results in large variation in policies among different DTC-GT companies. The fact remains that this relies on the voluntary goodwill of these entities [87]. An evaluation of fifteen DTC-GT companies targeting potential customers in the U.K., found that none of these companies complied with all the principles for good practice regarding consumer information that had been outlined by the UK Human Genetics Commission in the 'Common Framework of Principles for Direct-to-Consumer Genetic Testing Services (2010)' [121-123]. This set of voluntary guidelines established by the UK Human Genetics Commission (HGC) aimed to elevate standards and uniformity in the delivery of DTC- by commercial providers. These principles encompassed various aspects, including the information offered to potential consumers, counseling and ongoing support, the role of consent, laboratory procedures, the provision and interpretation of results, and procedures for handling complaints [114, 123]. Yet, the results of the earlier mentioned study suggest that the industry has not fully embraced the envisioned self-regulatory approach.

Legislation regulating the market introduction of a test

United States of America

The FDA is the regulatory agency in the USA that is responsible for evaluating the safety and performance of medical devices, including DTC-GT [124, 125]. DTC-GT are classified by the FDA based on their potential impact on medical care. Those with a low-risk (e.g. non-medical, general wellness), as well as carrier screening tests are not subject to pre-market review by the FDA [124, 126]. Yet, DTC-GT with a moderate to high risk need to undergo a review process before they are allowed to enter the market. Marketing authorization is only offered after the FDA has assessed the analytic validity, clinical validity and company claims of the specific product under review [124]. DTC-GT products that are 'substantially equivalent' to previously authorized devices are allowed to go through an accelerated approval process [127]. A test is considered to be 'substantially equivalent' if it shares the same intended use and technological features as a previously authorized medical device. Alternatively, it can be considered substantially equivalent if it serves the same intended uses but possesses different technological characteristics that do not pose distinct safety and performance concerns. In such cases, the information submitted to the FDA must demonstrate that the device is as safe and effective as the marketed device that obtained market authorization. Regarding third-

party interpretation services, the FDA currently takes the position of not classifying this software as a medical device subject to regulation. In their view this type of software only 'matches patient-specific medical information to peer-reviewed literature publications on related topics'. In consequence, third-party interpretation services remain largely unregulated in the USA at this time [10, 23]. As these services become more widespread, concerns are emerging regarding their accuracy, safety, and privacy protocols.

European Union

As of May 2022, in vitro diagnostic medical devices (IVD's) are regulated by the 'Regulation (EU) 2017/746' of the European Parliament and of the Council of the European Union [128]. The regulation applies to every IVD offered in the European market. This implies that even DTC-GT companies situated outside the EU must adhere to the regulation when providing their products to consumers residing within the EU [106, 128]. The 'Regulation (EU) 2017/746' covers the safety and performance of IVD's when entering the European market and includes among others DTC-GT and software used for direct or indirect medical purposes (e.g. prediction of disease) [1, 129]. Within the new regulation a risk-based classification system has been introduced where IVDs are classified into four risk categories:

- class A for low individual risk and low risk to public health
- class B for moderate individual risk and/or low risk for public health
- class C for high individual risk and/or moderate risk for public health
- class D for high individual and high public health risk

The new 'Regulation (EU) 2017/746', unlike the previous 'Directive 98/79 EC', assigned a high risk level (class C) to human genetic tests and all devices intended for self-diagnosis [128-130]. Before the new regulation came into force the safety and performance of IVD's was regulated by the 'Directive 98/79 EC' of the European Parliament and of the Council of the European Union. This directive underwent reform because it wasn't ensuring safe IVD's on the EU market (e.g. breast implants and hip replacement scandals) and because it was considered to be outdated in light of recent changes in the field of genetic/genomic medicine. In practice, the 'Directive 98/79' seemed to have little or no impact on the offer of DTC-GT in Europe. Moreover, concerns were expressed regarding discrepancies in the implementation of the rules among European member states [129]. Compared to its predecessor, the 'Regulation (EU) 2017/746' promotes a more comprehensive approach to the product life cycle, focusing on actively overseeing the safety and performance of the device [128]. This includes clarifying if devices are suitable for their intended purpose, if they do not compromise the safety or health of users and if they achieve analytical and clinical performance intended by the manufacturer [106, 129]. Under the 'Directive 98/79 EC', most DTC-GT offers were classified as low risk IVD's. As a result they were not subject to pre-market review by a notified body [130]. Other vulnerabilities of the previous 'Directive 98/79 EC' were considered to be the inconsistent classification system and the lack of sufficient medical supervision and genetic counseling [106]. Furthermore, this directive was criticized in comparison to other legislative initiatives in the USA, Canada and Australia where genetic tests had been classified as high-risk devices and required stronger pre-market review to obtain market authorization [106].

While 'Regulation (EU) 2017/746' enables stronger control over DTC-GT and is expected to increase overall quality of IVD's in Europe, not all its provisions have taken immediate effect after the transitional period of five years. The 'Regulation (EU) 2022/112' has prolonged the transitional period until May 2025 for class D devices, May 2026 for class C devices, and May 2027 for class B and A devices. This extension is intended to lessen the potential impact of stricter regulations, preventing a significant reduction in the availability of IVD's in Europe. The need for action was deemed necessary because of insufficient market readiness in 2021 due to shortage of notified body capacity, a low number of manufacturers applications to notified bodies and difficulties with requirements on in-house medical devices among health institutions [131]. This extended lack of implementation continues to leave grey areas/gaps in the regulation of DTC-GT, leaving patients and citizens with health and safety risks.

Within the new 'Regulation (EU) 2017/746', IVD's that are classified as class C (=high individual risk and/or moderate risk for public health), such as genetic tests, have to be assessed and certified by an independent third party (notified body) [132]. These notified bodies are private commercial entities that are appointed and supervised by a Member State's Competent Authority (often the Ministries of Health) [129]. Their role is to certify the conformity of IVD's with the essential safety requirements. Compared to the 'Directive 98/79 EC', where most DTC-GT only required self-certification by the manufacturer, a much wider range of IVD's will have to be certified by notified bodies and more performance data will be requested [132]. When manufacturers receive certification they are allowed to label their products with the "Conformité Européenne" (CE) mark, which is required to distribute and sell "CE-IVD" products on the EU market [132]. According to the new regulation these notified bodies must also carry out appropriate audits and assessments on a regular basis, at least once every 12 months, to ensure that the manufacturer is applying the approved quality management system and post-market surveillance plan [128, 129]. Manufacturers of IVD's are required to produce a periodic safety update report for each device they have marketed. This report should summarize the outcomes and findings of post-surveillance analysis, including the assessment of the benefit-risk ratio. If necessary, it's the authority of member states to prohibit or restrict market availability as there's no centralized European body similar to the FDA [129]. Article 29 in 'Regulation (EU) 2017/746' also requires genetic test manufacturers to create a document accessible to the public which should outline the essential safety and performance features of the device, along with the outcomes of the performance assessment.

Below, we will examine some of the main changes introduced by the 'Regulation 2017/746 EU'.

Clinical evidence

Compared to the 'Directive 98/79 EC', there is and added emphasis on clinical evidence in the new legislative framework of the EU. The new 'Regulation 2017/746 EU' foresees that the safety and performance of IVD's should be assessed and updated regularly. The safety and performance of each IVD should be established through the assessment of three categories of clinical evidence: scientific validity, analytical performance, and clinical performance. These

different categories of clinical evidence are defined as follow within the Regulation 2017/746 EU' [128]:

- scientific validity: 'the association of an analyte with a clinical condition or a physiological state'
- analytical performance: 'the ability of a device to correctly detect or measure a particular analyte'
- clinical performance: 'the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user'

As stated in Article 56 of the regulation, the claims made by the manufacturer in its performance assessment with regard to the purpose and clinical use of devices must be backed by appropriate clinical performance studies. Nevertheless, as the request for clinical performance studies is limited to what the manufacturer claims to be the device's intended purpose, this could still limit the protection provided to consumers [129]. Moreover, a potential vulnerability may arise from the fact that the assessment of clinical evidence is dependent on the level of evidence deemed sufficient by the manufacturer and considered acceptable by notified bodies [1]. Notified bodies have been previously criticized for their lack of uniformity in interpreting and implementing rules, as well as for displaying varying levels of expertise [1]. While there has also been suggested to incorporate clinical utility into the evaluation of DTC-GT to enhance consumer protection and to align the 'Regulation 2017/746 EU' with the Additional Protocol to the Convention on Human Rights and Biomedicine, there is no mention or consideration of clinical utility in the final text of the new regulation. During the long and animated debate among EU institutions and different stakeholders the concept of clinical utility was interpreted by many as a moving concept that could be more efficiently regulated at the level of the member states [106].

Transparency

As clarified by the 'Regulation 2017/746 EU', transparency and adequate access to information are deemed essential to empower patients and healthcare professionals, to enable individuals to make informed decisions and to protect public health. Making the European medical device database more broadly accessible (EUDAMED) is one of the key aspects of the new 'Regulation 2017/746 EU'. During the previous legislative framework, EUDAMED already enabled exchange of information between the commission and the national competent authorities to promote market surveillance, transparency and uniform implementation of the 'Directive 98/79 EC' [106]. The future goal of this database will be to enhance public and health professionals access to information, minimize redundant reporting obligations, reinforce coordination among member states, and streamline the exchange of information among manufacturers, notified bodies, and member states. EUDAMED also grants users of IVD's the ability to retrieve up-to-date information on current clinical trials as well as a summary of the safety and clinical performance reports for Class C and D devices [128].

Genetic Counselling and Informed consent

The discussion surrounding genetic counseling and informed consent raised intense debates about the potential violation of the principles of proportionality and subsidiarity if these matters were to be regulated at the EU level. These principles limit the authority of the EU to intervene only when the objectives can be more efficiently accomplished at the EU level rather than at the level of individual member states [1, 133]. Some have also argued that the mandatory provision of genetic counseling would be unworkable in the daily practice of medicine and would interfere with how clinical practice is organized at the level of the member states [134]. Furthermore, in practice problems of enforcement could arise since it would be difficult to define what qualifies as appropriate genetic counselling and when consent is truly free and informed [106]. In the preparation process of the new regulation, it was considered to include specific provisions regarding counseling and informed consent, but ultimately, these were not included in the final version of the text. The final version of the 'Regulation (EU) 2017/746' that was adopted in 2017 only mentions limited requirements, with respect to the principles of proportionality and subsidiarity [1].

As indicated in article 4 of the 'Regulation (EU) 2017/746', relevant information on the nature, significance and the implications of the genetic test should be provided to individuals undergoing genetic testing in the context of healthcare and or the medical purposes of diagnostics, improvement of treatment, predictive or prenatal testing' [128]. In addition, member states must also ensure that there is appropriate access to genetic counselling in the case of the use of genetic tests that provide information on the genetic predisposition for medical conditions and/or diseases which are generally considered to be untreatable. Yet, the regulation does not address several other elements. For example, criteria to ensure sufficient qualitative counseling and qualification of those delivering counseling, or whether this process should be supported by a written informed consent. The clear lack of these elements in the regulation could be a missed opportunity for the harmonization with regard to this matter within member states [1]. Nevertheless, member states are still allowed to regulate genetic counseling and informed consent more restrictively on an independent level under the 'Regulation (EU) 2017/746'.

Advertising

DTC-GT companies have been criticized for the potentially misleading and aggressive claims on their websites. In this context, it is noteworthy to mention that the European Parliament called for a complete ban on DTC-GT advertising during the debate for the adoption of the new 'Regulation (EU) 2017/746'. Although this amendment would have ensured a high level of protection for European consumers, it was strongly debated due to the principles of subsidiarity and proportionality. This proposal, was ultimately not retained in the final version of the text. Instead, the regulation includes Article 7 that prohibits labeling, instructions for use and advertising of IVD's that may mislead the user or the patient with regard to the device's intended purpose, safety and performance [135].

Nevertheless, regulatory bodies like the EU could play a role in implementing and enforcing "truth in advertising" standards to address concerns about inaccurate information provision.

An example is the 'Directive 2005/29/EC' on unfair commercial practices that aims to protect consumers from misleading and aggressive commercial practices [115, 136]. A practice is considered misleading if it includes inaccurate or false information or has the potential to deceive the average consumer. This remains applicable even when the information is factually correct but influences the consumer to make a decision they would not have taken otherwise. In addition, a practice is also considered misleading if information needed by the average consumer to take an informed decision is excluded or provided in an unclear or ambiguous way and is likely to cause them to take a transactional decision that they would not have taken otherwise. A transactional decision is considered aggressive if the freedom of choice of an individual is impaired due to harassment, coercion or undue influence [136].

Legislation regulating the delivery or canalization of genetic testing

European Union

Within Europe, certain aspects related to genetic testing (e.g. the role of health care professionals in prescribing genetic tests and/or providing counseling, informed consent procedures, etc) are predominantly governed by national laws as genetic testing has traditionally been offered through public health care services [115, 116]. In principle, clinical care falls under the jurisdiction of individual member states. An exemption of this rule is possible when a certain objective might be more efficiently achieved at the EU level [1]. Other aspects related to the quality of genetic testing devices are however regulated at the EU level [115].

The Convention for the Protection of Human Rights and Dignity of the Human Being in the Application of Biology and Medicine, commonly known as the Oviedo Convention, has been established by the Council of Europe in 1997. It's a significant international legal document addressing fundamental principles applicable to daily medical practice and its ratification imposes legal obligations on national legislators. Currently, 36 states have signed, and 29 have ratified the Convention [137, 138]. The Oviedo Convention imposes an obligation of obtaining patients' informed consent (ensuring particular protection of those unable to provide informed consent) and medical supervision. It also mandates genetic counseling for predictive, carrier and predisposition genetic tests for health purposes. In addition, the convention also states genetic information must not be used for any discriminatory measures [137]. In 2018, the additional protocol on genetic testing for health purposes also come into force. This protocol touches upon issues of clinical utility, medical supervision, genetic counseling and informed consent in the context of genetic testing [139]. So far the protocol has been signed and ratified by 6 members of the Council of Europe (Czech Republic, Montenegro, Norway, Portugal, Republic of Moldova and Slovenia) [138].

National member states

Across Europe, most member states have put into place national legislation that may not specifically focus on DTC-GT but that could still be applicable, either entirely or partially, to DTC-GT [116]. This might be based on biomedical and/or bioethical regulation (e.g. Norway – Bioteknologiloven 2023), laws specific to genetics (e.g Germany – Gendiagnostikgesetz 2009), laws on issues related to healthcare (e.g. Ireland – Disability Act 2005), laws related to patient rights or laws related to professionals' duties [115]. In certain instances, it is evident that these laws limit the offering of DTC-GT, but in other cases, there is uncertainty about whether the regulation encompasses genetic testing in both clinical and DTC-GT settings. Especially when it's unclear whether these tests are considered to be health services due to the absence of a clear definition of medical practice and a distinct boundary between health-related and non-health-related tests. Given that the majority of these laws are tailored for genetic testing within the conventional healthcare system, applying them to the commercial sector may introduce complexities [115]. Below we provide an overview of some of these national legislation initiatives.

(Partial) Ban of DTC-GT

One approach that has been suggested and implemented is to either partly or completely prohibit the sale of DTC-GT. Banning DTC-GT may appear drastic, but it could be an effort to provide consumers a wider and more robust scope of protection. Additionally, such a measure might lead to a more comprehensive harmonization of rules [106]. Some countries, like Germany have completely banned DTC-GT testing [115]. Under the 'German Human Genetic Examination Act', genetic tests can only be carried out after a medical doctor has provided genetic counseling and written informed consent has been obtained [140]. Some have argued that a complete ban might be disproportionate as it fails to take into account that different DTC-GT might present with different risks and benefits. A one-size-fits-all approach might therefore be overly restrictive [106]. Another approach could be to limit the number of DTC genetic tests [70]. In Austria, the 'Austria Gene Technology Act' outlines the types of genetic tests that necessitate medical oversight. This specific act restricts the offering of most health-related genetic tests to designated institutions [114-116]. While partially of completely banning DTC-GT might be an easy solution at first sight, in the international and online nature of DTC-GT market this approach could be rather difficult to enforce due to the freedom of access to the internet [7].

Focus on canalization of genetic tests through medical intermediaries

Regulating DTC-GT in such a way that consumers have to talk to a trained HCP before undergoing DTC-GT could improve informed decision making. Input from a genetics professional may alleviate the risks of misinterpretation of results, inappropriate choices for disease management or prevention, or inadequate follow up [70, 114]. However, the existing shortage of trained genetic healthcare professionals (HCPs), who are already understaffed to meet demands based on medical indications, poses a limitation.

In many European countries, medical supervision for health-related genetic testing is mandatory (e.g. France, Portugal, Italy, Austria, Hungary, Germany, Lithuania, the

Netherlands, Spain) [114-116]. For example, in accordance with Portuguese legislation, tests for genetic susceptibility are exclusively carried out by medical geneticists. This process involves genetic counseling and requires obtaining written informed consent from the individuals involved [116]. Likewise, all pre-symptomatic and susceptibility genetic tests for healthcare and healthcare-related research purposes should also be performed under medical supervision in Italy [115, 141]. Similarly, if a DTC-GT is deemed a medical practice, it can only be offered by a certified medical practitioner under Belgian regulations [114, 142]. This because a physician should always be involved in the practice of medicine. Yet, as most DTC-GT include in their terms of services that results should not be considered as medical information this leaves room for different interpretations. The 'Genetic Diagnosis Act (2009)' in Germany furthermore specifies that only physicians specialized in human genetics or other specialized physicians in their own specialist area are qualified to conduct predictive genetic examinations, while diagnostic genetic examinations can also be performed by any physician licensed to practice medicine [115, 143].

Genetic counseling

Through genetic counseling, consumers could be better informed about the accuracy, utility, and implications of a specific DTC-GT for themselves and their family members. This approach also allows to discuss emotional and social issues that could arise during the testing process and available healthcare options [1]. As stated in the before mentioned 'Oviedo Convention': "tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purpose, and subject to appropriate genetic counseling" [137]. Countries that have signed and ratified the convention (= currently 29 member states) have the obligation to implement legislation to conform with the principles mentioned in the convention. In some European member states (e.g. Estonia, Finland, Latvia, Lithuania, Slovakia) ratified international treaties are directly applicable. In consequence, genetic counseling is also mandatory for health-related genetic testing even though there is no explicit mentioning of this in their national legislation [115]. Several other European member states have legislative frameworks in place with specific requirements for the organization of genetic counseling (e.g. Austria, Cyprus, the Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Norway, Slovakia, Slovenia, Spain) [115]. For example, in Greece, Cyprus and Norway, genetic counseling is compulsory by law for carrier, predictive and predisposition genetic testing, while in Spain appropriate genetic counseling is mandatory for all health-related genetic testing [115].

Certain European member states that have not signed or ratified the Oviedo Convention also provide a comprehensive framework for genetic counseling in the context of genetic testing. In Austria, non-directive genetic counseling is mandatory for certain categories of tests. According to the 'Genetic Diagnosis Act (2009)', predictive genetic testing, fetal aneuploidy risk assessment by non-invasive methods and any prenatal genetic examination require both pre- and post-test counseling. Furthermore, while post-test counseling for diagnostic genetic examinations should be always be offered, post-test-counseling for conditions for which no treatment is available is obligatory [115]. Finally, despite genetic counseling not being

addressed specifically in some jurisdictions (e.g. Sweden), its necessity may be implied by legislation focusing on the requirement of obtaining informed consent [115]. This because consent cannot really be considered 'informed' without prior genetic counseling.

Informed consent procedures

In some European member states like Denmark and the Netherlands, there are no specific rules with regard to informed consent for genetic testing, yet other general laws do apply. For example, following the Dutch 'Medical Treatment Contracts Act', health care professionals that want to start a medical intervention have to provide information on the indication, the proposed treatment, alternatives, prognoses, risk and possible side effects. In addition, informed consent should always be obtained before starting any medical intervention [115]. Other member states like Austria, Portugal and Norway have legislation in place that mandates written informed consent in order to be able to perform a genetic test. More extensive legislation can be found in Spain, France and Germany [115].

Penalization of users or non-consensual testing

Another possible regulatory approach could be to urge individuals to refrain from ordering DTC-GT. In France, there is unique regulatory framework aiming not only to regulate the provision of DTC-GT but also to address its utilization by consumers. Article L.1133-4-1 of the French Public Health Code forbids individuals from seeking genetic tests for themselves, third parties, or for identification purposes based on their DNA profile. French consumers that do order a genetic test outside of a clinical setting could be penalized with a fine of 3750 euros [114, 144]. This type of restriction in access to personal health information is believed by some to be a significant violation of the principle of personal freedom [144]. Another way of penalizing could be to impose penalties for genetic testing with no prior written or oral consent of the donor. In the UK, the 'Human Tissue Act' (2004) that focuses in particular on the use of biological samples, criminalizes genetic analysis of human tissue without the explicit consent of the donor [114].

Permit system

The Netherlands is one of the few countries in the world where the preconditions for screening are legally established in a 'Population Screening Act' (1992). This Act provides protection against unnecessary or harmful screening programs. It outlines all the requirements that have to be met to ensure the quality of a screening program [145]. According to the Act, obtaining a license from the Dutch Minister of Welfare and Sports is mandatory for DTC-GT designed to detect cancer and diseases that cannot be treated or prevented [146]. This legal provision essentially protects the Dutch population from accessing DTC-GT with questionable validity and clinical utility. However, the act does not provide specific guidelines regarding counseling and the process of obtaining informed consent.

Regulation of laboratories

In France, laboratories are required to obtain a specific authorization from the Regional Agency for Health, following consultation with the Biomedicine Agency, to conduct genetic tests within the country [144]. Specific requirements are in place for the consent procedure, necessitating written consent after patients have been fully informed about the nature and purposes of the test, as well as for test prescription and the communication of test results. The regulatory framework places a strong emphasis on the importance and quality of the information provided, highlighting the delivery of genetic tests within a medical context. Under the current regulatory framework, it is practically unfeasible for DTC-GT companies to operate in France [144]. Similarly, the Spanish law prescribes that genetic tests need to be performed by qualified personnel in certified centers [147]. While in Belgium genetic examinations are only reimbursed by health insurance if they are carried out by a multidisciplinary team of a recognized Centre for Human Genetics based on the Royal Decree of 14 December 1987 [114].

Educational initiatives for the general public and/or health care professionals

The complexity of DTC-GT has raised concerns about whether potential consumers of DTC-GT possess the knowledge to make informed decisions about their use. One initial strategy proposed and implemented in various countries involves concentrating on educational programs aimed at either the general public or non-trained healthcare professionals. The development of educational interventions could enhance informed decision-making and the responsible utilization of genetic information. Earlier research found that exposure to an online educational module improved genetic knowledge and significantly decreased knowledge miscalibration (=the gap between consumers' actual knowledge and how much they think they know) in a positive way [118]. The authors of this study state that it might be most beneficial to use concise, simple to understand information to avoid cognitive overload and to ensure optimal learning outcomes. An information brochure on genetic tests for health purposes has also been developed by the Council of Europe in collaboration with the European Society of Human Genetics and EuroGentest in 2012. This leaflet that aims to provide general objective information on genetic tests, including their nature and the potential implications of their results has been translated in different languages [119]. Furthermore, well-informed healthcare professionals might be more equipped at assisting patients in navigating the complexities of genetic testing. As genomic medicine transitions more and more from specialized centers to mainstream medicine, there may be a growing demand for various medical specialists without expertise in clinical genetics or genetic counseling to play a more significant role in prescribing and/or interpreting genetic testing and the communication of genetic test results [80, 117]. Many health care professionals (especially primary health care professionals) have voiced they don't feel prepared to answer patients' questions about DTC-GT and show high levels or reluctance to provide information and genetic counseling to patients [80, 120]. Providing explicit instructions to healthcare professionals on whom to

consult for inquiries and when to refer to trained genetic professionals will be essential to optimize capacity and prioritize genetic test results that necessitate specialist attention [103]. The Gen-Equip project, that was co-funded by the EU Erasmus+ Program, developed a specific online program with different learning modules and tools to enable health professionals who are working in primary care to update their knowledge and skills in genetics [117].

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