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

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Abstract

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

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

1. DTC genetic testing and related services

Direct-to-consumer (DTC) genetic[1] testing (GT) encompass a wide and heterogeneous range of offers, which have been constantly evolving since the emergence of DTC GT almost two decades ago. Given the dynamic nature of the DTC GT market and how it poses (new) ethical and regulatory challenges, in this article we aim to provide overview of the current offer of health-related[2] DTC GT and the related salient ethical issues. Furthermore, as the offer of DTC GT in Europe may be affected by the recently adopted Regulation on In Vitro Diagnostic Medical Devices (the IVD Regulation), we discuss the relevant content of the Regulation in the context of DTC GT.

[1] Many of the tests discussed herein involve generating the DNA sequence for much if not all of the genome, therefore it could be considered more accurate to use the term genomic. However, for the purposes of this article, we will be using the word 'genetic' referring both to genetic and genomic testing and services.

[2] This article focuses mainly on health-related testing, excluding testing with other main purposes such as ancestry and paternity. However, it is important to note that ancestry test results may reveal health-related information to consumers, given associations between genetic ancestry and disease risks, press coverage of these relations and interest of the consumers in these issues [85]. Furthermore, the web-based interpretation services can provide health-related information on the basic of raw data received in ancestry genetic testing, which is discussed in the following sections of this article.

1.1 DTC genetic testing definition

Direct-to-consumer genetic testing is a commercial model of genetic testing provision whereby consumers can undertake a test without necessarily any involvement of a healthcare professional (HCP). A consumer can order a test via the Internet or buy it at a pharmacy, (s)he then receives a saliva or swab kit, which together with the consumer's saliva sample is sent to the genetic testing company. The results are usually delivered online to the consumer. A number of DTC GT companies however, do advertise directly to consumers, but then, require that the test be ordered by a healthcare professional and/or that the results be returned to a HCP. This broader definition of DTC GT including testing advertised directly to consumers, but involving a HCP was recognized in 'A Common Framework of Principles for direct-to-consumer genetic testing services' issued by the UK Human Genetics Commission [1] as well as by researchers [2,3]. Supporting this definition is the fact that one of the crucial characteristics of DTC GT, that is to say, advertising directly to consumers, is retained in the model of DTC GT including a HCP.

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

The first health-related genetic tests marketed directly to consumers were identified almost two decades ago [4]. In 2002, as part of research aiming at identifying the availability of DTC GT, Gollust *et al*. identified 14 companies selling health-related DTC GT [5]. A recent study by Phillips (2015) revealed that the market of health-related DTC GT has grown significantly in the last decade reaching over 100 companies [6]. Considering that these searchers were performed in English, the total number of companies offering DTC GT may be assumed to be even larger.

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

having a complex genetic background and for which development is usually the result of several genetic and non-genetic factors acting in concert (i.e. complex diseases, e.g. cancer, diabetes).

Furthermore, the DTC offer of genetic testing varies regarding the amount of data/results provided. Some companies offer single gene tests (e.g. Graceful Earth) [7], others offer the testing of a group of genes relating to a type of disorder (e.g. cardiology-panels offered by Invitae) [8], while others offer genome wide testing of hundreds of thousands of single nucleotide polymorphisms (SNP) and offer a report on over a hundred conditions and traits (e.g. 23andMe) [9]. In recent years, companies, have also been offering whole exome sequencing and whole genome sequencing [10]. Whole genome sequencing generates readouts of (almost) all the DNA present in cells, whilst whole exome sequencing provides sequence of all protein coding regions of DNA; in both cases the amount of genetic information obtained is unprecedented. Once sequenced, the exome or genome can then be analysed for specific, defined purpose(s) (e.g. using targeted gene approach where only a subset of genes is analysed), for example to identify variants relevant to a specific disease, variants related to responses to drugs, or indicating some traits.

Currently DTC GT is advertised not only to the (healthy) 'worried-well' (i.e. symptomless adults anxious about their health) and to more educated persons with disposable income. The decrease in price as well as the expansion of the types of tests offered resulted in the significant expansion of the consumer groups to which DTC GT is explicitly aimed. Namely this encompasses: couples considering having children (carrier screening, e.g. Counsyl) [11], pregnant women (prenatal testing, e.g. Veritas Genetics) [12], and individuals wanting preimplantation diagnosis/screening tests on the basis of which embryos (not) having desired genetic variants can be selected (e.g. offered by Illumina) [13]. Furthermore, parents of new-borns [14] and children [15] are being encouraged by companies, through online advertisements, to purchase the tests for their offspring.

1.3 Interpretation and data sharing services for DTC GT consumers

Some DTC GT companies (e.g. 23andMe) provide consumers not only a report describing results of the testing (i.e. the interpretation of genetic variants with respect to disease), but also non-interpreted raw data in a downloadable format [16]. These raw data can then be uploaded on

several online genomic data interpretation services, for example: Promethease [17], LiveWello [18], Genetic Genie [19], Sequencing [20]. Such online services provide consumers with health-related information based on the analysis of the raw DNA data.

Furthermore, there are also online services/platforms aimed at DTC GT consumers, to which they can upload their raw genetic data to make them accessible to others (e.g. general public or groups of researchers; for example openSNP [21], DNA.Land [22], Sequencing [20]). Apple has also announced adding a module to its ReasearchKit apps allowing consumers to share their genetic data from 23andMe with researchers [23]. Interestingly, there are also companies (Genos, Invitae, Portable Genomics) which are planning to provide consumers platforms for sharing their genetic data for which the consumers would be paid/compensated [24].

2. Ethical issues in DTC GT companies

Having originated from outside the traditional health care system, with a plethora of differences from the established clinical genetics offer of genetic testing, health-related DTC GT raises ethical, legal and social implications. These include a long list of issues: lack or problematic involvement of a HCP, adequacy of pre- and post-test counselling, scientific validity and utility of the testing, misleading advertising, potential burden on a healthcare system, testing in minors, secondary uses and privacy of consumers' data, non-consensual uses of testing, and problems related to regulation of DTC GT [25,26]. Many of these ethical issues were identified and discussed to some extent already in the beginning of existence of DTC GT [5]. In the following years, a number of authors further discussed these issues and empirical studies have been conducted to explore the offer of DTC GT and views of different stakeholders (e.g. consumers and healthcare professionals) [27,28]. Furthermore, various expert societies and advisory bodies such as the UK Human Genetics Commission [1], European Society of Human Genetics [29], European Academies Science Advisory Council [30], have issued recommendations and positions addressing DTC GT. Moreover, actions were taken by a regulatory authority, the US Food and Drug Administration, to ensure quality of the offer of DTC GT [31].

Recent literature, both more theoretical and empirical indicate that ethical issues around DTC GT are still not resolved, but rather potentially amplified as the technology is evolving and the

scope of the offer is expanding [10,32–34]. The aim of the following section is to provide an overview of the current ethical issues of DTC GT and related services, with a focus on analytical and clinical validity of the testing, adequate pre-test counselling and informed consent, potentially misleading advertising, and research uses and commercialisation of genetic data. In the subsequent section, we discuss these aspects from a legal standpoint, and in particular with respect to the changes that will be introduced by the Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices.

2.1 Analytic and clinical validity of the services

The analytic validity (the accuracy with which a genetic variant is identified), clinical validity (how well a variant can detect or predict a given disease) as well as clinical utility (whether or not any intervention/test can improve the healthcare outcome) of many of the DTC genetic tests have been seriously questioned [3]. The scientific evidence for clinical validity for which the tests are offered is very limited (especially for complex traits), therefore the commercialization of many of the predisposition tests has been criticized as being premature [35,36]. Furthermore, the disease risk predictions based on genetic data does not consider the environmental/lifestyle (e.g. diet) and family history factors which can modify the genetic risks of diseases to great extent [37]. Similar concerns about the quality of the reported results have been raised recently regarding third-party interpretation services, whose interpretation reports may not be based on the reliable scientific evidence and may not be understandable to consumers [38].

It is not only the various authors and societies that have been expressing concerns about the validity of DTC GT. In November 2013 the Food and Drug Administration (FDA), in a warning letter sent to 23andMe, expressed, among others, its lack of 'assurance that the firm has analytically or clinically validated the PGS [Personal Genome Service][3] for its intended uses' and ordered that 23andMe stop marketing its health-related tests until it obtains marketing authorization from the FDA [31]. Consequently, 23andMe limited its offer in the US to ancestry tests, at the same time applying for the FDA marketing authorization for Bloom syndrome

[3] Personal Genome Service which had been offered by 23andMe until December 2013 was providing health reports on 254 diseases and conditions including carrier status, disease predisposition, and pharmacogenomic results [31].

carrier status, which was subsequently granted to the company in February 2015 and was included in its offer together with other carrier status tests which FDA exempted from its premarket review [39]. Meanwhile, the company has been offering carrier, susceptibility and pharmacogenomic testing for a range of conditions and traits to consumers in countries where the current legal framework does not appear to pose any market barriers, such as Canada, the UK, Denmark, Finland, Ireland, Sweden, and the Netherlands [40]. Moreover, in April 2017 the FDA completed pre-market review and allowed for marketing of another 23andMe genetic test - Personal Genome Service Genetic Health Risk which provides information about predispositions for 10 diseases and conditions [41]. The validity of some of the predisposition testing results reported by 23andMe in the mentioned European countries as well as those recently approved for the offer in the US still raise important ethical and scientific questions. For example the testing for APOE variant [9] which is associated with Alzheimer's disease was described by the American College of Medical Genetics as 'not clinically recommended due to limited clinical utility and poor predictive value' together with an indication that in this context 'DTC genetic testing is not advised' [42].

Additional problems emerge regarding the interpretation of genetic results. Questions arise as who should be responsible (and liable) for the validity of the results reported as well as who (if anyone) should recontact the patient/consumer if the significance of results changes in the light of new results of genetic research. Is this responsibility of a physician (if there is one involved in the testing), the DTC GT company, the laboratory which analyse the sample, or database/platform operator used for result interpretation? These issues are regulated to some extent by professional standards (e.g. to be aware about current state of knowledge and/or care in a given profession), and may be addressed, to some extent in the company website descriptions, terms of use and submission agreements (describing the requirements and responsibilities of people adding new data to databases) [43]. This issue does not concern exclusively DTC genetic testing and interpretation services, however, it may appear more complex in this context given the lack of (adequate) involvement of a HCP in the provision of DTC GT.

One may argue that the limited clinical validity and/or utility of DTC genetic tests, are not enough grounds to prohibit their offer outright, provided that these limitations are clearly outlined to consumers. Many companies, indeed, provide this kind of statement e.g. that their services 'are for research, educational, and informational use only, and are not to be used to diagnose, prevent, or treat any condition or disease or to ascertain the state of health for any individual' [44]. Doubts arise, however, regarding whether consumers ever read these statements of limitations, given that they are often included in 'small print' documents to which consumers agree by ticking 'I agree' boxes or by default when using the services [10]. Secondly, even if consumers were well informed about these limitations (indeed, some companies provide explicit well-visible statements about the limitations of testing)[17], questions about potential implications for (public) healthcare systems remain. Should the consumer who obtained results indicating increased probability of a disease contact a HCP within the public healthcare system given that the results are of doubtful validity? Not only may this pose interpretation problems for physicians, it can also result in unnecessary follow-ups and a (financial/resource) burden on a public healthcare system [35].

2.2 Informed consent and pre-test counselling

Communicating about genetic information and obtaining valid informed consent for genetic testing is challenged by the complexity of genetic information, and in more recent years, given genomic testing, it is also challenged by the volume of data produced [45]. Therefore, pre-test counselling is recognized as a key element of the informed consent process for genetic testing, in which relevant information is provided to a person undertaking the test and her/his questions are answered [29]. The lack of involvement of (an adequately qualified) HCP in the provision of genetic testing, as well as often inadequate provision of information about offered testing suggests that DTC GT consumers may not be undergoing this important process as originally described or expected in the traditional health care system [10]. Although a number of DTC genetic tests must be ordered by a HCP, this may not ensure the presence of adequate pre-test counselling given the potential lack of genetics expertise, and potential lack of impartiality if the HCP is hired by a company [2,10]. Furthermore, a study of DTC GT company websites' sections relevant to informed consent (to which consumers agree in order to undertake the test) of

companies offering WES/WGS revealed the presence of scarce and potentially misleading information on necessary elements of informed consent for WGS (benefits, risks, incidental findings) [10].

Related to informed consent is the issue of non-consensual testing i.e. unlawful testing of a third party using his/her sample without that person's consent, for the purposes of benefiting others or for the detriment of a tested person [26]. The DTC GT context may facilitate this kind of actions given the accessibility of testing and the fact that a consumer and not a HCP is responsible for collecting samples for testing (i.e. saliva) and sending it to a company. Although in certain contexts there are laws in place [46] prohibiting this activity and sometimes contractual documents provided by DTC GT company also state the prohibition of non-consensual testing, in practice ensuring that a person whose sample is tested has voluntary agreed to this procedure poses problems [26]. These issues underline the importance of providing an adequate context for genetic testing provision so that a valid and genuine process of informed consent in which a HCP is involvement is secured.

2.3 Advertising

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

Since they appearance on the market, DTC GT companies have been criticised for the potentially misleading claims present on their websites [5]. In 2010 the report of the U.S. Government Accountability Office (2010) revealed that 10 of the 15 DTC GT companies analysed were 'engaged in some form of fraudulent, deceptive, or otherwise questionable marketing practices' [47]. Furthermore, the analysis of the content of DTC GT websites by Singleton *et al.* revealed that the information presented on the websites was weighted toward motivating consumers to purchasing the test rather that supporting informed decisions [48]. Borry *et al*. draw attention to the presence of nonpropositional content of advertisements i.e. appealing pictures and

design of DTC GT websites, which may impact consumers perceptions of value of the product and its desirability [49]. In the context of non-invasive prenatal testing advertised directly to consumers, Skirton *et al.* found that emotive language and misleading information was presented on companies' websites [50].

2.4 DTC GT for 'reproductive purposes', newborns and minors

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

Moreover, the offer to each of these groups raises specific challenges such as those related to the right not to know of minors and obtaining their assent as well as the more fundamental question of the extent of parental authority in decision making in this new era of genomics [51]. Studies surveying DTC GT companies' polices regarding testing of minors revealed that companies were performing testing on children's samples for adult onset diseases, therefore clashing with professional norms, which state, among others, that minors can be tested only if therapeutic or preventative measures are available during childhood for the condition tested [52,53]. A more recent study by Borry *et al.* indicates similar issues, although in the context of a company explicitly offering testing for newborns [33].

2.5 Research uses and commercialisation of consumers' genetic information

Genetic and genomic data are perceived as valuable and their sharing may facilitate diagnosis in patients and the progress of medical research [54]. However, potentially sensitive information about health and ancestry can be retrieved from genetic data; furthermore an entire human genome sequence is unique to each person, therefore in some cases it can be used to (re)identify a person when linked to his/her other personal information [55]. Therefore, using genetic information for research should be accompanied with adequate safeguards to protect

privacy, ensure transparency about the uses and sharing practices, and adequate informed consent [56].

Several instances of DTC GT companies performing research have been reported [57,58]. One of the best known and biggest engagement in research by DTC GT consumers has occurred with the company 23andMe, which has over 1 million customers who have consented to participate in research [59]. Consequently, the company may own the largest research databank in the world consisting of genetic information of consented re-contactable subjects.[4] The compliance of these research activities with research ethics requirements, in particular the adequacy of informed consent for participation in research and data privacy, has been questioned [57,58,60,61]. Similar issues were raised in recent studies of DTC GT websites (one of which investigated companies offering WES/WGS) exploring issues such as secondary uses of samples and data, data confidentiality and privacy. The studies revealed, among others, that some of the companies may perform research on consumers' data and/or samples for which informed consent process seemed not to comply with some of the professional guidelines [61].

Interestingly, the company 23andMe not only uses consumers' data for research, but has also sold access to consumers' data affected with Parkinson to a biotech company Genentech for research purposes [60]. Selling access to consumers' data seems to raise similar concerns to those outlined by Sterckx *et al.* (2014) when discussing patenting activities of 23andMe. In this article, the authors argued, that applying for patents seemed to contrast with company's appeals to promote the public good and, the lack of transparency about it appeared to undermine consumers trust [62]. Furthermore, gaining profit from research performed on consumers' databases, as noticed by Sharon (2016) may seem

> 'particularly problematic when public money is channeled, indirectly or directly, to their development, as has been the case with 23andMe, which recently secured a US$1.4 million research grant from the NIH to expand its database.' [63]

[4] Possibility to re-contact research subject gives the researchers opportunity of obtaining additional information which can be useful for the study as well as option to invite the subjects to participate in other studies (depending to what type of recontacting a subject has agreed).

Moreover, the problems related to commercialisation of health-related data arise, also in the context of the platforms allowing consumers to share their data and receive compensation for it. On the one hand, paying consumers to access their data may provide them with an incentive to contribute to research and may appear as a fair and respectful "compensation" for consumers given that the companies and researches (may) benefit financially from using consumers' data [24]. However, 'cash-for-DNA' approach may discourage individuals willing to contribute data for altruistic reasons, while, at the same time being potentially coercive for financially vulnerable individuals, as noticed by Roberts and co-authors (2017) [24]. Furthermore, genetic data commercialisation activities seem to challenge the ideal of open science, data sharing framework based on solidarity and it may as well lead to disparities in research [63].

3. DTC GT legislation in Europe

DTC GT in Europe[5] is currently regulated by various laws, both on the national and the European Union (EU) level. Aspects related to patients' access to GT, the role of healthcare professionals in prescribing the test and/or counselling the patient, as well as the informed consent process are regulated largely by national laws. This is mainly because GT in Europe has been traditionally offered through the public healthcare services and the conditions under which such tests are offered are considered to be part of the clinical practice [64].

The regulation of the clinical practice resides with the Member States rather than the EU, following the principles of subsidiarity and proportionality. These principles mandate that the EU may take legislative action beyond the areas of its exclusive competence, when a given objective may be more efficiently achieved on the EU rather than the national level [65]. As a result, the conditions and restrictions applying to DTC GT may vary across Europe. Currently, there are countries, such as Germany and France, which restrict the GT framework, by adopting strict laws regarding the type of tests that should be available to patients, the canalization of genetic tests through healthcare professionals, mandatory genetic counselling and requirements for informed consent in the context of GT [66]. Although these laws target

[5] For the purposes of this section, when we are using the term "Europe" we refer to the countries where relevant EU legislation apply, namely, the EU and European Free Trade Association (EFTA) Member States, as well as Turkey.

primarily the provision of genetic tests within the public healthcare system, it has been argued that they also essentially render illegal the provision of DTC GT [67]. However, there are also many countries in Europe where no specific laws on GT exist. Therefore, when it comes to restrictions related to the involvement of a HCP, genetic counselling and informed consent requirements, DTC GT companies face minimal constrains.

As opposed to aspects related to the context within which genetic tests are provided, several other aspects affecting the governance of GT in Europe are regulated on the EU level. European legislation aims, among others, to promote the harmonization of the internal market and free movement of goods [68], as well as to enhance consumer protection by promoting the fair treatment of consumers and high standards for products that enter the European market [69]. Currently, numerous EU laws are in place, aiming to protect the economic interests and rights of consumers. Such laws cover a wide set of policies, including unfair commercial practices [70], consumer contract law [71], product safety and data protection [69].

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

3.1 IVD Directive

Genetic tests with a medical purpose fall within the definition of IVD medical devices and the regulation of their safety and efficiency when entering the European market currently falls under the scope of Directive 98/79 EC on in vitro diagnostic medical devices (IVD Directive) [72]. Based on this Directive, IVD medical devices, unless considered to be ‘low risk’, have to go through a conformity assessment before entering the European market. This means that

independent commercial entities called notified bodies, assess whether such devices fulfil the essential requirements of safety and efficiency imposed by the Directive and issue a certificate of conformity (CE mark), allowing devices to circulate in the European market [73].

The impact of the IVD Directive in the effective governance of DTC GT has been questionable [74]. This may be partly because, currently, the vast majority of DTC genetic tests offered by companies are tests for predisposition to common complex disorders. However, devices for the purposes of prediction and predisposition are not explicitly covered by the Directive, creating uncertainty regarding whether such tests would actually fall within the scope of the Directive [75].

In addition, under the Directive, most genetic tests are classified as low risk devices requiring only self-assessment by their manufacturer before entering the EU market. This classification has been considered to be particularly lenient in comparison to the respective regulations in the US, Canada and Australia, where most genetic tests are considered to be moderate to high risk devices and are required to go through a pre-market assessment before being placed on the market [75].

Finally, the Directive has caused uncertainty regarding the clinical evidence that must be provided by manufacturers during the pre-market assessment of their devices. In this regard, it has been unclear whether manufacturers are required to provide evidence of clinical validity in order to prove compliance with safety and performance standards, or whether evidence of analytical validity would be sufficient [76]. A clarification on that matter would be of particular importance when it comes to DTC GT. This is because, as mentioned above, most such tests currently available on the market are susceptibility tests to common complex disorders, which often have doubtful clinical validity [35]. Therefore, requiring only evidence of analytical validity during the pre-market assessment of the tests would set the bar of performance rather low.

3.2 IVD Regulation

The revision of the IVD regulatory framework has been a long process that has given rise to an animated debate among the EU institutions and different stakeholders. After two public consultations were held, the European Commission issued in September 2012 its proposal for a

new Regulation on IVD medical devices. Following the ordinary legislative process, the European Parliament and the Council of the EU published their own versions of the proposal in October 2013 and June 2015 respectively. Finally, after negotiations among these three institutions, a compromise was reached in May 2016. After undergoing legal-linguistic review the final version of the Regulation was adopted by the European Parliament and the Council of the EU in April 2017. The regulation will apply in the member states of the EU and the European Free Trade Association (EFTA), as well as Turkey, after a 5-year transition period.

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

3.2.1 Scope of tests covered

In respect to the scope, the final text explicitly recognizes IVD devices providing information on 'predisposition to a medical condition or a disease' (Article 2(2)) as being subjected to the Regulation [77]. This amendment eliminates uncertainties regarding whether the majority of DTC GT offered (namely genetic tests for predisposition to common complex disorders) are covered by the Regulation or not. Importantly, the Regulation also clarifies that all IVD medical devices offered through the Internet to a natural or legal person established in the EU must comply with the rules set by the Regulation (Article 6) [77]. This way, it becomes clear that companies also established outside the Union should still comply with the relevant EU rules when offering their products to consumers residing within the EU.

3.2.2 Classification of IVD devices

When it comes to the classification of IVD devices, the Regulation replaces the list-based classification system adopted by the Directive with a new, risk-based classification system. The

way IVD devices are classified is particularly important, as it determines how strictly the devices may be assessed before entering the EU market. According to the Directive, the classification of devices was based on predetermined lists. These lists have been criticized as being inconsistent and outdated, and, for many products, as offering inadequate scrutiny [78]. This was particularly the case for the vast majority of genetic tests, which were considered to be low risk devices, requiring, as a result, only a minimum degree of scrutiny before being available to consumers. The risk-based classification system introduced by the Regulation, which will replace the existing list-based system, is largely inspired by the classification system introduced by the Global Harmonization Task Force [79] and aims to address the inadequacies created by the previous framework. In this regard, according to the Regulation, IVD devices may be divided in four categories based on their intended purpose and potential risks [74]. In this context, the Global Harmonization Task Force has defined risk as 'combination of the probability of occurrence of harm and the severity of that harm.'[79]. The categories vary from Class A (low risk devices), to Class D (high risk devices). Genetic tests fall under Class C, which means that they are considered to be moderate to high risk devices and they have to go through a pre-market assessment by a notified body before reaching consumers.

3.2.3 Clinical evidence

Furthermore, the IVD Regulation raises the bar for clinical evidence by stating that the assessment of conformity with general safety and performance requirements should be based on 'scientific validity, analytical and clinical performance data providing sufficient clinical evidence' (Article 56) [77]. This provision clarifies that evidence of clinical validity (incorporated in the notion of clinical performance) should be provided by the manufacturer, eliminating uncertainties created over the previous regulatory regime regarding whether providing such evidence was mandatory [75]. This amendment may make it more challenging for tests with low clinical validity (for example for many genetic tests detecting predisposition to common complex disorders) to enter the European market.

3.2.4 Advertising

A particularly interesting addition in the IVD Regulation is Article 7 under the title 'Claims'. In this article, for the first time, European legislation specifically addresses the advertising of IVD medical devices. This article provides that labelling, instructions for use and advertising of such devices must not use misleading content with regard to the device's purpose, safety or performance. Examples of misleading content for the purposes of this article are 'creating a false impression regarding treatment or diagnosis, functions or properties which the device does not have' and 'suggesting uses for the device other than those stated to form part of the intended purpose for which the conformity assessment was carried out' (Article 7) [77]. Even though the article does not seem to grant broader protection than that offered by more general laws on consumer protection [80], it grounds these laws in the specific context of IVD medical devices and its symbolic value should not be underestimated. Especially when it comes to DTC GT, the business model of which is largely relying on advertising, having a more specific definition of what may constitute misleading advertising could potentially contribute in a more efficient regulation of the way such products are promoted to the public.

3.2.5 Informed consent and genetic counselling

During the ordinary legislative process, the European Parliament, in its proposal, had supported that all genetic tests under the Regulation should be classified as prescription-only medical devices and that they must only be advertised to health care professionals and not to consumers. In addition, according to the same proposal, pre- and post-test genetic counselling should be mandatory for predictive, prenatal and diagnostic genetic tests, while informed consent should be written [81]. The above mentioned suggestions gave rise to a heated debate regarding whether regulating such issues at the EU level infringes the principles of proportionality and subsidiarity [82]. Some stakeholders argued that if such provisions were eventually adopted this would result in the Regulation going beyond its purpose (namely to regulate product efficiency and safety) and would ultimately interfere with clinical practice and the way this is organized at the national level [83]. Ultimately these provisions were not included in the final text. Instead, the Regulation acknowledges that the current divergences in

national rules on informed consent and genetic counselling do not seem to have a significant adverse impact on the smooth functioning of the internal market. As a result, the Regulation will only provide limited requirements respecting the principles of proportionality and subsidiarity. In this regard, Article 4 of the Regulation prescribes that individuals undergoing genetic tests in the context of healthcare and 'for the medical purposes of diagnostics, improvement of treatment, predictive or prenatal testing' should be 'provided with relevant information on the nature, the significance and the implications of the genetic test'. In addition, in the same context, and specifically for genetic predisposition testing for untreatable conditions and diseases, Member States shall make sure that patients have access to genetic counselling [77]. In this regard, the final text seems to attempt to strike a balance between stressing the importance of informed consent and genetic counselling while respecting the principle of subsidiarity and the right of Member States to regulate clinical practice in their territory as they see fit. This provision, however, will probably have little value for DTC GT, as it is addressed to Member States and in this regard, its impact will probably be limited to the clinical context.

Overall, it may be argued that, when it comes to genetic tests, the IVD Regulation attempts to address weaknesses and uncertainties of the existing regulatory framework, especially regarding the scope of protection, the risk-classification and requirement for clinical evidence, therefore it is addressing some of the salient ethical issues of DTC GT. In this regard, and specifically with the points discussed above, the Regulation seems to be an improvement compared to the Directive. It is now clear that predisposition tests fall within its scope and the new risk-based classification system and the requirements for clinical evidence may raise the quality bar for genetic tests entering the EU. Furthermore, the Regulation, even though it does not move to harmonize the framework within which genetic tests are offered (and potentially render DTC GT illegal within Europe)- goes beyond the Directive in specifically regulating advertising claims and referring to the need for adequate information and genetic counselling to be available in the context of health-related GT. The Regulation also shows potential for limiting the circulation of DTC GT with low quality in the EU market and deter companies from making exaggerated and unsubstantiated tests. However, it should be kept in mind that the DTC GT industry is global and operating mostly through the Internet. This means that even if such tests

fall within the scope of the Regulation, no matter where they come from, the compliance of companies sending their tests to private individuals may be hard to ensure. As a result, the real value of the IVD Regulation for DTC GT will be largely dependent on its enforcement.

4. Conclusions

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

Future perspective

The development of the DTC GT market is influenced among others by availability of new technologies, their price and the relevant regulation. Advancements in genomic sequencing technologies and increasing understanding of human genetics has been enabling obtaining more genomic information faster and cheaper. DTC GT companies have been taking advantage

of these trends and have been offering a wider range of genetic tests at lower prices. Recently, the US FDA announced its intention to facilitate quicker and least burdensome introduction of some DTC predisposition testing to the market [41]. All of these factors, as well as the general push to make genomics a more mainstream part of medicine, may help support, in the coming years the market expansion of DTC predisposition GT in the US. In the European context, however, the recent IVD Regulation which will apply in 5 years is likely to limit the offer of predisposition DTC GT including the tests offered by the providers based in the US.

Importantly, the business model of the DTC GT companies has been evolving. Selling genetic testing results is no more the only source of profit for the companies. Genomic data have been recognized as useful not only to the individual consumers, but also to researchers; some DTC companies have been taking advantage by selling consumers' data to interested third parties [63]. In this context, a novel genomic data sharing approach seeking to also entitle consumers to profit from sharing their genetic data emerged and may be further developed (e.g. Portable Genomics).

Additionally, the popularity and intake of DTC genetic testing may be dependent to some extend on the way genetics is portrayed in media and perceived by the potential consumers. For example, the story of Angelina Jolie, who underwent a preventive double mastectomy based on genetic risk and a family history of cancer, received extensive media coverage and raised some awareness about genetic testing. Media coverage, however, may not translate to the correct understanding of genetics [84]. In this context, educating about genetics, its limitations, related ethical issues and responsible communicating about science in media should be recognized as factors which may facilitate informed decisions about undertaking DTC GT and using one's genetic information. The level of genetic literacy in public may influence intake and attitudes of public towards of DTC genetic services.

Executive summary

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

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

Ethical issues in DTC GT companies

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

DTC GT legislation in Europe

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

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