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A review of the legislation of direct-to-consumer genetic testing in EU member states

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1. Introduction

The past decades have witnessed enormous progress in the field of genetic and genomics, especially after the completion of the Human Genome Project in 2003 that provided a sequencing of entire human genome for the first time in history (Collins et al., 2003). To this date, the application of genetic testing for diagnostic, predictive and treatment purposes in healthcare has been growing (de Paor and Blanck, 2016). In a traditional healthcare setting, genetic tests have been usually provided to individuals only including involvement of healthcare provider and active guidance of medical practitioners (Hogarth et al., 2008). In line with tremendous progress in genomic research, private companies have found their way of exploiting the new model of personalized healthcare by introducing genetic testing directly to the consumer (Wright and Gregory-Jones, 2010). Direct-to-consumer genetic tests (DTC-GTs) may be defined as any DNA test for a medical or non-medical trait that is advertised and sold directly to the public via Internet. Although these tests are usually delivered to customers through mailing services, numerous pharmaceutical chains are now selling these tests in the stores also. After having received the testing kit at home, the customer is usually required to collect a biological sample (either saliva or hair) and send it back to the company that will extract and analyze the genetic material. The growth of online market, which allows the general public to have direct access to vast array of genetic tests, has led to the ever-increasing availability of DTC-GTs (Gollust et al., 2003; Andelka M. Phillips, 2016).

Some of these tests are categorized as non-health-related and offer services such as paternity tests, tests of ancestral origin, athletic ability, matchmaking and testing for 'fun' traits (earwax type and eye color). However, in certain cases it is difficult to distinguish a health test from a lifestyle test, which may have important implications for the legislative initiatives (Colaiacovo and Grimaldi, 2012; Lucivero and Prainsack, 2015; Saukko et al., 2010). On the other hand, many companies are selling tests that are indeed health-related, allowing individuals to perform diagnostic testing for monogenic diseases such as cystic fibrosis, identify their predisposition to conditions such as breast cancer, heart disease, diabetes and other complex diseases (EASAC and FEAM Working Group, 2012; Andelka M. Phillips, 2016). These tests usually analyze common DNA variants, which account for only a fraction of the heritable component of multifactorial diseases including cancer (Bellcross et al., 2012; Hirschhorn and Daly, 2005). Numerous concerns have been raised about the DTC-GTs including lack of professional guidance, genetic counselling, transparency on quality control, clinical validity and clinical utility (Janssens et al., 2008).

The absence as well as inadequacy of appropriate regulation in the field of DTC-GTs poses additional challenges regarding compliance and enforcement of any laws. The vast majority of DTC-GTs on the online market originates from the USA, where the Food and Drug Administration (FDA) has been experiencing challenges in regulatory oversight. Recently, the FDA announced that DTC tests with medical indications, e.g., carrier screening for genetic conditions, require regulatory clearance due to their definition as medical devices. These USA-based online tests that have obtained marketing approval from the FDA do not necessarily have a country-specific approval elsewhere. Nevertheless, consumers can access to these tests via global online market from any country, which puts a strain on non-US authorities in enforcing local regulations of Internet-based products.

The oversight of DTC-GTs in the Asian context appears heterogeneous. Japan, in 2015, revised the Protection of Personal Information Act, which applies to DTC-GT industry, addressing privacy and confidentiality issues of genomic data, with specific regard to anonymity of data, informed consent, and sharing of genetic information (Yamamoto et al., 2018). In Korea, government approved DTC-GTs only on 42 genes related to 12 specific phenotypic traits (i.e. body mass index, cholesterol, blood pressure) in July 2016 (Jeong, 2017; Kim, 2019). Chinese Food and Drug Administration does not have clear marketing regulations for DTC-GTs, and no medical qualifications or approvals are required (Overmaat et al., 2018).

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The foundations for the regulation in Europe have been set out by the recommendations of numerous professional societies, such as European Society of Human Genetics (ESHG), Human genetics commission, European Academies of Science Advisory Council and Federation of European Academies of Medicine (Borry, 2010; HGC, 2010a; R. and V., 2013a). Overall, professional societies provided policy documents and recommendations for successful regulation, advertising and provision of predictive DTC-GTs (Borry, 2010; HGC, 2010b; R. and V., 2013b). In Europe, implementation of appropriate and unified regulatory framework for DTC genetic testing is missing. Evidence of varying and fragmented legislative and policy responses is present across individual member states (Borry et al., 2012; de Paor and Ferri, 2015; Kalokairinou et al., 2018). Recently, considering the increasing availability of DTC-GTs, initiatives have been taken in European level to understand in a comprehensive way the regulation of the these genetic tests ("IPAAC Joint Action," 2018). In this context, we performed a literature review regarding the DTC-GT legislation in the EU Member States in order to summarize the current scenario.

2. Methodology

We performed a literature search of PubMed database retrieving articles published from January 2010 to October 2018 that focused on legislation of DTC genetic or genomic testing in European countries, using the following search query: *"direct-to-consumer" AND (genetic OR genome) AND (legislative OR law OR legislation)*. We did not restrict our search according to the study type. Articles that reported information regarding any national laws or legislations in the area of DTC-GT among the European countries as well as on the EU level were considered eligible. The initial search was restricted to title and abstracts. Full text of potentially eligible articles were critically evaluated for inclusion in line with the criteria of this review. Moreover, to retrieve additional pertinent publications we hand-searched the reference lists of the included articles and screened EU commission and council website for legislative documents on genetic testing (Council of Europe Treaty Office, n.d.; "Current Directives | Internal Market, Industry, Entrepreneurship and SMEs," n.d.). From each of the included articles, we extracted the following data: first author, year of publication, objectives, timeframes, implemented methodology and the target countries. We were interested to see whether the reviews implemented a systematic approach, in terms of using multiple search databases, implementing pre-specified their search strategies, and incorporating the work of independent reviewers. Additionally, we assessed whether the articles were addressing legislation on a national or EU level. We reported the key findings through a set of country specific profiles that outline any presence of legislative frameworks towards DTC-GTs.

3. Results

3.1. Description of eligible studies

Restricting only to title and abstract, we identified 33 potentially eligible articles in the initial search. After reading full-texts in detail, 13 articles regarding legislation of DTC-GT were selected for inclusion in our review. We retrieved three additional articles throughout the reference list search (Andelka M. Phillips, 2016; Saukko, 2013; Tamir, 2010), including in total 16 eligible articles (Borry et al., 2012; Colaiacovo and Grimaldi, 2012; de Paor, 2018; Fukuda and Takada, 2018; Grimaldi et al., 2011; Kalokairinou et al., 2018, 2017; 2015; Kaye, 2008; Patch et al., 2009; Andelka M. Phillips, 2016; Saukko, 2013; Soini, 2012; Tamir, 2010; Vrecar et al., 2015; Wright et al., 2011). Considering the articles' characteristics, twelve were reviews (Colaiacovo and Grimaldi, 2012; de Paor, 2018; Fukuda and Takada, 2018; Grimaldi et al., 2011; Kalokairinou et al., 2017, 2015; Kaye, 2008; Andelka M. Phillips, 2016; Saukko, 2013; Soini, 2012; Tamir, 2010; Vrecar et al., 2015), two were commentaries (Patch et al., 2009; Wright et al., 2011) whereas, the other two reported national legislative frameworks based on expert surveys (Borry et al., 2012; Kalokairinou et al., 2018). Thirteen articles provided a legislative overview either at the EU or national level (three on national initiatives, three on EU level legislation and eight on both EU and national initiatives), and three articles focused on recommendations for improving DTC-GT regulation. The main characteristics of the eligible articles retrieved in the literature search are reported in Table 1.

3.2. EU legislative frameworks towards DTC-GT

At EU level, the basic types of legislation are directives and regulations. Regulations represents legal documents that are directly binding for all Member States, while directives set more general rules that each Member has the liberty to transpose into national legislation (EU, 2013). Generally, specific legislative instruments regulating DTC-GT have not been implemented (Kalokairinou et al., 2018). Consequently, there are certain legal instruments related to genetic testing that may provide guidance.

The Directive 2005/29/EC on unfair commercial practices (European Parliament, 2005) aims to protect consumers' rights and facilitate proper functioning of the internal market among European countries. This directive protects consumers from misleading actions and omissions, including false information, aggressive commercial practices and misleading advertising (Kalokairinou et al., 2018, 2017).

The Directive 98/79 EC represents an EU wide framework for regulation of in vitro diagnostic (IVD) medical devices in general, but also GTs with a medical purpose in particular, since they are considered as IVD medical devices (EC, 1998). The overall objective of this legislation is to guarantee an effective functioning of the European market by setting out requirements for safety and efficiency of these products. Parallel to the development of genetic and genomic fields, the EU commission acknowledged an urgent need for an updated regulatory framework. In that sense, the Directive 98/79 EC has been recently undergoing a reform that will ultimately lead to an adoption of the Regulation on IVD medical devices in spring 2022 ("EUR-Lex - 32017R0746 - EN - EUR-Lex," n.d.) – which will be directly binding and will be incorporated into national laws of all Member States (Union, 2015), (Framework Regulatory, n.d.). For this Regulation, several proposals have been made, suggesting that it should also cover aspects related to medical supervision, genetic counselling and informed consent (European Commission, 2017). However, the final text of the Regulation deals with realistic criticisms related to the difficulties in regulating clinical practice on a national level and has therefore implemented a more pragmatic approach. The Regulation places main focus on the safety and performance of IVD devices, covering GTs as products and regulating their clinical validity in order to allow the effective functioning of the internal market. Nevertheless, the Regulation allows Member States to have full control over all aspect related to the clinical practice, including medical supervision, genetic counselling and informed consent (de Paor, 2018; Grimaldi et al., 2011; Kalokairinou et al., 2018).

At **international level**, the legal documents directed to the provision of genetic tests include the Convention on Human Rights and Biomedicine (Oviedo Convention) and its Additional Protocol concerning Genetic Testing for Health Purposes.

The Oviedo Convention, elaborated by The Council of Europe in 1997, has been signed and ratified by a total of 29 countries out of 47 members of the Council of Europe: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Greece, Hungary, Iceland, Latvia, Lithuania, Montenegro, North Macedonia, Norway, Portugal, Republic of Moldova, Romania, San Marino, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, and Turkey (Council of Europe, 2016a). The Convention represents the first legally binding document on an international level that aims to protect human dignity, rights and freedoms.

Table 1
Descriptive characteristics of eligible studies retrieved in the literature search.

Author	Year	Objectives	Time frame	Law assessment	Target country	Methods	Systematic approach
Fukuda Fukuda and Takada (2018)	2018	To review regulatory requirements for DTC health-related tests in Japan within the broader context of 10 other countries	NR	National level	Austria, Belgium, France, Germany, Portugal, Switzerland, the UK, the USA, Canada, South Korea, and Japan	Review	no
Kalokairinou Kalokairinou et al. (2018)	2018	To provide an overview of laws that might impact the regulation of DTC-GT in 26 European countries	NR	National and referral to EU level legislation	Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the Netherlands, the UK	Expert reviews	NA
De Paor de Paor (2018)	2017	To evaluate main ethical, legal and regulatory issues arising within DTC-GT	NR	National level and referral to EU level legislation	Ireland	Review	no
Kalokairinou Kalokairinou et al. (2017)	2017	To examine laws regulating the advertising of GT in the EU and at a national level with suggestions on optimal ways of regulating advertising of DTC-GT	NR	EU level and referral to some national initiatives	NA	Review	no
Phillips (Andelka M Phillips, 2016)	2016	To provide an overview of current state of DTC-GT industry and challenges that different types of testing pose for regulation, with suggestions for improving regulation	NR	NA	NA	Review and suggestions	no
Kalokairinou Kalokairinou et al. (2015)	2015	To outline how regulation of DTC-GT in Europe is likely to be affected by the proposed Regulation on IVD Medical Devices	NR	EU level	NA	Review	no
Vrecar Vrecar et al. (2015)	2015	To review current situation in the field of DTC-GT, with related legal and ethical issues	searches performed in February 2014 and in October 2014	National level	Slovenia	Review through an internet search	no
Borry Borry et al. (2012)	2012	To analyze European countries' national legislation focusing on DTC-GT or other legislations that may impact the regulatory control of DTC-GT	NR	National level	Belgium, Germany, France, the Netherlands, Portugal, Switzerland and the UK	Expert reviews	NA
Colaiacovo Colaiacovo and Grimaldi (2012)	2012	To provide an overview of what regulations exist for DTC-GT and investigation of areas where more clarity is needed	NR	EU and national level	referral to France, Germany, Italy, Portugal and Switzerland	Review	no
Saukko Saukko (2013)	2012	To review academic and policy proposals on how to regulate the DTC-GT	NR	EU and national level	EU countries (France and Germany) and US	Review	no
Soini Soini (2012)	2012	To examine the legal framework governing the use of genetic tests in the clinical setting in Western Europe, with particular discussion on DTC-GT	NR	EU and national level	Austria, France, Germany, Norway, Spain, Sweden, Switzerland	Review	no
Grimaldi Grimaldi et al. (2011)	2011	To review the EU regulatory framework from the perspective of potential service providers (companies, health services and practitioners, including medical, nutritional, etc.)	NR	EU level and referral to national legislation	EU, France, Germany, Switzerland	Review	no
Tamir (Tamir, 2010)	2010	To review legal and ethical concerns of DTC-GT	NR	EU and national level	Germany and US	Review	no
Wright Wright et al. (2011)	2011	To set up an overarching framework that may be feasible for the regulation of DTC-GT	NR	NA	NA	Commentary	no
Tamir (Tamir, 2010)	2010	To review legal and ethical concerns of DTC-GT	NR	EU and national level	Germany and US	Review	no
Patch Patch et al. (2009)	2009	Points for regulatory control of DTC-GT	NR	EU and global level	NA	Viewpoint	no
Kaye Kaye (2008)	2008	To explore issues related to DTC-GT including the lack of effective regulatory controls	NR	referral to EU regulatory frameworks and US	NA	Review	no

Abbreviations:EU-European Union; NA- Not applicable; NR-Not reported.

Table 2
Extracts from the Additional protocol on genetic testing for health purposes.

Article	Text
5 - Quality of genetic services	Parties shall take the necessary measures to ensure that genetic services are of appropriate quality. In particular, they shall see to it that: - genetic tests meet generally accepted criteria of scientific validity and clinical validity; - a quality assurance programme is implemented in each laboratory and that laboratories are subject to regular monitoring; - persons providing genetic services have appropriate qualifications to enable them to perform their role in accordance with professional obligations and standards.
6 - Clinical utility	Clinical utility of a genetic test shall be an essential criterion for deciding to offer this test to a person or a group of persons.
7 – Individualized supervision	A genetic test for health purposes may only be performed under individualized medical supervision.
8 – Information and genetic counselling	When a genetic test is envisaged, the person concerned shall be provided with prior appropriate information in particular on the purpose and the nature of the test, as well as the implications of its results. For predictive genetic tests as referred to in Article 12 of the Convention on Human Rights and Biomedicine, appropriate genetic counselling shall also be available for the person concerned.
9 – Consent	A genetic test may only be carried out after the person concerned has given free and informed consent to it.

Within the Article 12 on Predictive genetic tests, the convention sets out some limitations: "*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 purposes, and subject to appropriate genetic counselling*" (Hendriks, 2004).

In 2008, The Council published the **Additional Protocol** (Council of Europe, 2016b) that provides legal and regulatory framework for genetic tests and addresses topics of scientific and clinical validity, clinical utility, medical supervision, genetic counselling as well as informed consent and potential ethical concerns (Council of Europe, 2001). The additional Protocol has been recently signed and ratified by five members of the Council of Europe: Republic of Moldova, Montenegro, Norway, Portugal and Slovenia, which allowed its entering into force. Five countries (Czech Republic, Finland, France, Iceland and Luxemburg) have only signed, but not ratified the Additional Protocol. These countries acknowledge the principles of the Additional Protocol but have no obligation to transpose its principles into national laws (Council of Europe, n.d.). Table 2 provides an overview of some of the Articles of the Additional Protocol.

3.3. Country specific legislative frameworks towards DTC-GTs

In terms of country-specific legislations, the literature on DTC-GTs addresses particularly three aspect of genetic testing process: medical supervision, genetic counselling and informed consent. Most countries have some form of national legislative on genetic testing that may partly or fully apply to DTC-GT. These legislatives have not been specifically designed to target DTC-GT, thus an analogy in interpretation is usually used. Most European countries provide some legislative frameworks in the context of genetic testing, regarding it as closely linked to healthcare services, and hence, within the conventional healthcare systems. The potential legal restrictions related to the provision of genetic testing across the EU Member States are summarized in two groups and reported in Table 3:

1. Countries that provide legislations specific to genetic testing;
2. Countries that do not provide specific legislation to genetic testing; and countries that might have certain legal instruments that can be applied in this filed;

3.3.1. Countries providing legislations related to genetic testing: Austria, Germany, Hungary, Sweden, Portugal, the Netherlands, Italy, France and Spain

The Austria Gene Technology Act is a legislation directed toward GT that provides information on which types of GT require medical supervision, limiting the provision of most health-related GTs to designated institutions. Genetic counselling about the genetic test's nature, consequences and significance should be performed by a trained medical specialist. This country requires a written informed consent for GTs determining a manifested disease based on a germ line mutation, evaluating disease predisposition and GTs for prenatal diagnosis (Borry et al., 2012; Colaiacovo and Grimaldi, 2012; Fukuda and Takada, 2018; Gentechnikgesetz, 1994; Kalokairinou et al., 2018). **German Human Genetic Examination Act** deals with diagnostic or predictive GTs for medical purposes, nevertheless it does not apply to GTs conducted for research purposes (Gendiagnostikgesetz, 2009). However, it is considered that this legislation may essentially covers some aspects of DTC-GT services. GTs in Germany may only be carried out by a medical doctor (Wright, 2009), with genetic counselling and obtaining written informed consent. The test needs to be performed after the individual has received sufficient information regarding the nature, meaning and consequences of the test, as well as after obtaining informed consent. The Act makes clear distinction regarding the qualification of medical specialists performing diagnostic genetic examinations or predictive ones: diagnostic GTs may only be performed by a physician and predictive GTs can only be undertaken by a medical specialist in the genetics. Predictive GT need to be accompanied by an obligatory pre- and post-test genetic counselling, while for diagnostic GTs post-test counselling is compulsory only when the results reveal untreatable conditions (Borry et al., 2012; Fukuda and Takada, 2018; Kalokairinou et al., 2018). The German approach has been criticized as an example of extreme genetic exceptionalism that has not been seen in other jurisdictions (EASAC/FEAM, 2012; Wright, 2009).

Hungarian Genetic Act of 2008 determines that GTs for various purposes, including prophylaxis, diagnosis, therapeutics, rehabilitation or research purposes, need to be undertaken under supervision of a licensed medical professional. A personalized genetic counselling is a mandatory step for genetic testing and screening (Act XXI, 2008; Genetikai törvény, 2008). **Swedish Genetic Integrity Act** implies that informed consent is necessary for genetic tests that are performed as part of a medical screening. Since the Genetic Integrity Act regulates the use of certain biotechnology for medical purposes, the application of this regulation in the context of DTC-GT may occur only if the services provided constitute a practice of medicine (Lag (2006:351), 2006). **The Portuguese Law** targets health information as well as genetic information and contains a set of established rules for the collection and preservation of GT for clinical or research purposes. The tests for genetic susceptibility in healthy individuals can only be performed by a medical geneticist, following genetic counselling, after obtaining written informed consent. Article 15 places responsibility on the Portuguese Government to regulate the conditions of availability and performance of genetic testing, limiting both the availability of tests offered by the laboratories without a multidisciplinary medical team in place and over-the- counter marketing of these tests (DIÁRIO DA REPÚBLICA — I SÉRIE-A, n.d.; The Portuguese Prime Minister, 2005). In **Italy,** all pre-symptomatic and susceptibility GT are restricted

Table 3
Legal regulations related to genetic testing across the EU member states.

Country	Legislation	Involvement of health professionals	Informed consent	Genetic counselling
Austria	*National legislative* - Gentechnikgesetz (1994) Gentechnikgesetz, GTG, BGBI Nr 510/1994 (the Austrian Gene Technology act)	+	+	+
Bulgaria	*International legislative:* - Oviedo convention	-	+	-
Belgium	*National legislative:* - Law on the practice of health-care professions (Royal decree n178 (B.S. 14.11.1967))	+	-	-
Czech Republic	*National legislative:* - Act No 373/2011 Coll. On Specific Health Care Services *International legislative:* - Oviedo convention - Additional Protocol, signed but not ratified	-	+	+
Croatia	*International legislative:* - Oviedo convention	-	+	-
Cyprus	*National legislative:* Law 31 (III)/2001 art. 12 *International legislative:* Oviedo convention	-	+	-
Denmark	*National legislative:* - Danish Act on Health - Danish Act on Authorisation of Healthcare Professionals *International legislative:* - Oviedo convention	+	+	+
Estonia	*International legislative:* - Oviedo convention	-	+	-
Finland	*International legislative:* - Oviedo convention - Additional Protocol, signed but not ratified	-	+	-
France	*National legislatiove:* - Code de la santé publicque (1953) Code de la santé publique (Code of Public Health) - Code Civil (2006) Code Civil - Arrêté de Bonnes Pratiques (2013) Arrêté du 20 juin 2013 relatif aux bonnes pratiques de dispensation des médicaments par voie électronique NOR:AFSP1313848A *International legislative:* - Oviedo convention - Additional Protocol, signed but not ratified	+	+	+
Germany	*National legislative:* - The Genetic Diagnosis Act	+	+	+
Greece	*National legislative:* - Law 2619/1998 art. 12 *International legislative:* - Oviedo convention	-	+	-
Hungary	*National legislative:* - Parliamentary act no XXI (2008) on the protection of human genetic data, on the human genetic studies on research and on the operation of the biobanks. - Parliamentary Act No XXI (2013) *International legislative:* - Oviedo convention	+	+	+
Iceland	*International legislative:* - Oviedo convention - Additional Protocol, signed but not ratified	-	-	-
Italy	*National legislative:* - Italian general authorisation no. 8/2014 for the processing of genetic Data *International legislative:* - Oviedo convention, signed not ratified	+	+	+
Ireland	*National legislatiove:* - Disability Act 2005	-	-	+
Latvia	*International legislative:* - Oviedo convention	-	+	-
Lithuania	*National legislative:* - Order No. V-220 issued on April 24, 2003 By minister of health. Lithuania *International legislative:* - Oviedo convention	+	+	-
Luxembourg	*International legislative:* - Oviedo convention, signed but not ratified - Additional Protocol, signed but not ratified	-	-	-
Poland	*International legislative:* - Oviedo convention, signed but not ratified	-	-	-

(*continued on next page*)

Table 3 (*continued*)

Country	Legislation	Involvement of health professionals	Informed consent	Genetic counselling
Portugal	*National legislative* - Law n112/2005 of 26 January 2005 *International legislative:* - Oviedo convention	+	+	+
Romania	*International legislative:* - Oviedo convention	-	+	-
Slovakia	*National legislative:* - Act No 122/2013 Coll. On Personal Data Protection - Act No 18/2018 Coll. On Personal Data Protection *International legislative:* - Oviedo convention	-	+	+
Slovenia	*National legislative:* - UL RS 17/98 (1998) Act ratifying the convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine, and of the additional protocol to the convention for the PRO *International legislative:* - Oviedo convention	+	+	+
Spain	*National legislative:* Boletín Oficial del Estado No159 (2007) *Boletín Oficial del Estado, No. 159 (28826–28848) (Act 14/2007 of 3 July on Biomedical Research)* *International legislative:* - Oviedo convention	+	+	+
Sweden	*National legislative:* The Genetic Integrity Act (2006) *International legislative:* - Oviedo convention, signed but not ratified	-	-	+
The Netherlands	*National legislative:* - Decree on In-Vitro Diagnostic Devices - 'Medical Treatment Contracts Act' Dutch Civil Code *International legislative:* - Oviedo convention, signed but not ratified	+	+	+
The UK	*National legislative:* - Human Tissue Act 2004	-	-	+

for healthcare and healthcare-related research purposes and should be performed under medical supervision, after obtaining a written informed consent. Italy has signed the Oviedo Convention, the formal ratification of which has not been put into place yet, despite the fact that it has been authorized by the Parliament (Italian General Authorization for the Processing of Genetic Data, 2014). **France** has a dual mode of supervision of the genetic testing, either within bioethics law or the civil code, and these legislations could apply to the DTC context (- Commission Nationale de and Libertés, 2014). The legislations limit the GT for medical or scientific research purposes only, under medical supervision, in authorized and accredited laboratories (- Commission Nationale de and Libertés, 2014), accompanied by a mandatory genetic counselling and after obtaining informed consent (Legifrance, 2013). The difference between France and other countries when it comes to genetic testing, is that France introduces penalization, a fine of 3.750 euro, to the consumers that order a test outside the clinical setting (Borry et al., 2012).

Spanish law on genetic testing, even though not directly targeting DTC-GTs, may restrict provision of these tests. Written informed consent process are strictly regulated for GT in a heath context, which need to be performed by qualified personnel in certified centers (Boletín Oficial del Estado No159, 2007).Healthcare laws regarding GT for health purposes, require appropriate genetic counselling in Czech Republic (Czech Republic, n.d.) and Cyprus (Kalokairinou et al., 2018), and mandatory medical supervision by physicians trained in human genetics in Lithuania (Civil Code of the Republic of Lithuania, 2000).

3.3.2. Countries that do not provide specific legislation on genetic testing and countries that might have certain legal instruments that can be applied in this filed

In countries without specific legislation on genetic testing, the provision of these tests might be contingent to whether DTC-GT are considered as health services or not. In **Denmark**, the application of Act on Authorisation of Healthcare Professionals to the provision of DTC-GT, relies on the fact whether to consider DTC-GT as a health service (Danish Act on Health, 2016). Similarly, in **Belgium**, Article 2 of the Belgian Law states that, if a DTC-GT is considered as medical practice, it may only be provided by a certified medical practitioner (Law on the Practice of Health Care Professions, 1967). Also, based on the Royal Decree of 2007, genetic counselling carried out by a multidisciplinary team is financed in 8 centers.

In the other hand, in UK, DTC-GT is generally not prohibited, and the tests are sold via internet and drugstore chains. There is no specific legislation addressing genetic testing in general and nothing relates to DTC-GT. The UK regulates products used in health-related genetic testing services as in vitro diagnostic medical devices. Although, if a DTC-GT company operates in UK, it has to follow a wide range of UK regulatory instruments, of which the most relevant that applies to DTC-GT comes as a voluntary set of guidelines, drawn from the Human Genetics Commission (HGC) Principles (HGC, 2010b). The UK Human Tissue Act from 2004, that focuses on the use of biological samples, regulates informed consent for GT and may impose penalties for genetic analysis of human tissue with no prior written or oral consent of the donor (Human Tissue Authority, 2004). In 2010, the HGC issued a framework of principles regarding DTC testing, recommending accurate, transparent advertising, pre- and post-test counselling by a qualified genetic counselor and regulated laboratory processes. The Netherlands have multiple regulatory barriers that, even though not directly targeting DTC-GTs, may limit their provision. The **Dutch Act** on population screening defines screening initiatives as medical examinations that detect certain diseases or risk indicators. According to the Act, a license issued by Dutch Minister of Welfare and Sports is

mandatory for DTC-GTs for detecting cancer and diseases that cannot be treated or prevented (Gevers, 2008). This legal initiative essentially protects Dutch population from accessing DTC-GTs that have questionable validity and clinical utility. However, the act does not provide indications about counselling and informed consent.

In the absence of national legislations on genetic testing, ratification of the international Oviedo Convention may impose genetic counselling as obligatory process for health-related GTs in Finland, Greece, Estonia, Romania, Latvia, Slovenia and Slovakia (Council of Europe, 2016a; Kalokairinou et al., 2018). Luxembourg and Poland, that have only signed but not ratified the Oviedo Convention, do not have specific legislative frameworks on genetic testing, hence the laws that may apply in these countries are of more general nature, regrading healthcare services and patients' rights (Kalokairinou et al., 2018). In Ireland medical supervision and genetic counselling are not obligatory in the context of genetic testing under any legislation (de Paor, 2018).

4. Discussion

The present work provides an overview of the legislations among European Member States towards DTC-GT. Overall, on the EU level, specific legal instruments regulating DTC-GT have not been implemented yet. The majority of countries have some form of national legislative, that does not necessarily target genetic testing in particular, but might be fully or partly applied to DTC-GT. Among the EU Member States, there are different levels of legislation, either national, EU and international laws, covering aspects of medical supervision, genetic counselling and informed consent. In many of EU Member States, the legislation requires the provision of GTs to be conducted under medical supervision and with genetic counselling.

A clear distinction between health-related and non-health related DTC-GTs is difficult (medical test vs lifestyle) (Grimaldi et al., 2011), which poses difficulties in deciding on national and international regulations. Goddard provides a definition of a health-related test, considering them as tests that may predict risk of disease, screen for disease, direct clinical management, identify carriers, or establish prenatal diagnoses, clinical diagnoses, or prognoses in individual people or families (K.A. et al., 2009). Majority of DTC-GT companies sell kits that simultaneously contain medical, genealogical and recreational information, further blurring the boundaries between health-related information and information about other factors (Lucivero and Prainsack, 2015). In addition, the rhetoric established and presented by the DTC-GT companies stresses the 'fun' and 'informational' aspects of these tests, while the medical complexities and limitations are often understated (Kalokairinou et al., 2017). Most DTC companies indicate under their 'terms of services' that they do not practice medicine and they offer a service with only informational purposes. DTC-GT, as an internet-based industry (Kalokairinou et al., 2017), poses great challenges for regulation because it is very difficult to clearly define where different jurisdictions begin and end. These aspects have been properly addressed by Hauskeller that stated the following: *'A globally acting, internet based industry cannot be forced to comply with laws or regulations that are binding only country by country'* (Andelka M. Phillips, 2016).

Another difficulty to be considered when applying national legislative frameworks to the context of DTC-GT is whether the tests are considered as health services and practice of medicine (C. and A.L., 2009). The lack of a comprehensive regulatory initiatives specific to DTC-GT, poses the potential consumers at risk of making inappropriate health decisions, undergoing unnecessary tests or tests with unproven significant benefit without accurate genetic counselling. The 2010 European Society of Human Genetics (ESHG) statement included recommendations about the provision of pre-test appropriate genetic counselling and post-test consultations, in order to inform and educate the potential consumers. According to ESHG, the DTC-GT should be introduced into the health care system if the criteria established by the Member States and European Union health authorities are met (Borry, 2010).

Despite our efforts to achieve comprehensive coverage of the legal instruments for DTC-GT among EU Member States, we acknowledge the fact that our study has some limits that need to be considered. The restriction of the search strategy only on title and abstract in English language in PubMed database, might have resulted in selection bias towards articles published in EU Member States national languages. However, we expanded the search by screening the references of the included articles manually as well as by screening EU institutional websites. Thus to our knowledge, our results still correctly capture the available evidence published so far, being of utmost importance for healthcare decision making. Moreover, issues of genetic privacy have not be captured in the present review. General Data Protection Regulation (GDPR) regulates, on the EU level, the protection of personal data. Certain exemptions are provided in case of genetic research purposes, but the choice of more loose or more restrictive consent processes is left on the discretion of Member state laws (Pormeister, 2018, 2017). According to recent studies, many online DTC-GT companies do not consistently respect international guidelines regarding data use, sharing and privacy (Laestadius et al., 2017). Moreover, it has been suggested that the companies are providing access to their genetic databases to third parties or using the data for research purposes probably without the consent of the consumer (Christofides and O'Doherty, 2016; Niemiec and Howard, 2016). Currently, there is also a lack of legislations that would provide guidance on what would happen after a genetic testing company goes out of business (M et al., 2011). On the other hand, people that underwent DTC testing may voluntarily make their identified genomic data public without understanding the impact of this action on themselves or their family members (Clayton et al., 2019). Hence, further analyses about the important issues of genetic privacy is warranted.

Finally, in order to protect the citizens from incompetent and harmful services, all of the aspects of DTC-GTs should be taken into consideration in the decision processes regarding the regulation of these tests both on national and international level.

5. Conclusion

The "consumer genomics" movement has reached substantial growth, both in terms of technological advances in genotyping methodologies and their availability to consumers due to the decreasing costs. However, the regulatory environment has not developed as quickly as the technology itself. DTC-GTs fall into a gap in the regulatory structure. Currently, there are different levels of legislation across the EU Member States, either national, EU and international laws.

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Declaration of competing interest

All the authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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