

Legal regulations on health-related direct-to-consumer genetic testing in 11 countries

Rei Fukuda, Fumio Takada

Department of Medical Genetics and Genomics, Kitasato University Graduate School of Medical Sciences

Objective: Direct-to-consumer (DTC) genetic testing is offered worldwide and via the Internet. The study reviews the current situation of regulatory requirements for DTC health-related tests in Japan within the broader context of 10 other countries, in order to recommend further steps to improve and develop genetic testing regulations and provisions.

Method: This study reviewed the current regulatory status for health-related DTC genetic testing in 11 countries (Austria, Belgium, France, Germany, Portugal, Switzerland, the United Kingdom, the United States of America, Canada, South Korea, and Japan) focusing on an overview of policies and the legal landscape. This review included the quality of tests, such as laboratory accreditation, provision of genetic testing, and protective regulations regarding genetic information, all of which impact DTC genetic testing services.

Results: More than half of the countries surveyed have legal frameworks that apply fully or in part to make DTC genetic testing services strict, while Japan has the least regulatory legal frameworks.

Conclusion: There is a range of possible legal approaches to DTC genetic testing. Assessment procedures addressing the usefulness of various genetic testing and their legal regulations warrant further development in Japan.

Key words: direct-to-consumer, genetic testing, legal, regulation

Introduction

Due to rapid scientific and technological advances, genetic testing and counselling have long been used by health systems to help individuals and families respond to the inherited diseases that may affect them. In contrast, direct-to-consumer (DTC) genetic testing, allows people to personally find out what disease-associated genes they may be carrying, outside the scope of the traditional health care system.¹ DTC genetic testing has been making available a wide variety of both health-related and non-health-related genetic tests directly to the public,¹ using various business models and including different types of services. Some commercial companies require the involvement of a healthcare professional for ordering and/or receiving such tests, while others do not.² Since 2014, Japan has been marked by the emergence of several major companies, with services offering hundreds of multifactorial disease tests as well as non-health tests over the internet. Because there are separate private

service institutions involved in kit production, sales, and analysis, the provision of DTC genetic testing is complicated.

While DTC companies cite test results benefits ranging from greater consumer autonomy and encouraging healthier behaviors to positive lifestyle choices, such as changes in diet or the use of nutritional supplements, critics are concerned about a range of questions and problems: accuracy of the tests (analytical and clinical validity, as well as clinical utility), misinterpretation of testing claims and test results, the lack of qualified genetic counselling and informed consent procedures, research activities conducted by DTC companies, and the potential burden on the healthcare system.^{1,3}

Major changes in genetic technologies in recent years have led to worldwide debates about how to respond to DTC genetic testing services. These concerns have resulted in regulatory scrutiny of DTC genetic testing services, e.g., the United States (US) Food and Drug

Received 21 December 2017, accepted 4 January 2018

Correspondence to: Rei Fukuda, Department of Medical Genetics and Genomics, Kitasato University Graduate School of Medical Sciences 1-15-1 Kitasato, Minami-ku, Sagami-hara, Kanagawa 252-0373, Japan
E-mail: dm13030a@st.kitasato-u.ac.jp

Administration (FDA) has recently taken a more active role in regulating such DTC services. In November 2013, the US FDA sent a letter to stop 23andMe from marketing its DTC services without the FDA approval because of the marketing of its health-related genetic tests due to misleading marketing.⁴ The FDA indicated in the letter that its aim was to protect the public from the "unreasonable risk of harm if the tests are not analytically and clinically accurate so that individuals are misled by incorrect test results or unsupported clinical interpretations."⁴ Despite being forbidden by the FDA from selling it in the USA, 23andMe launched its service in Canada from October 2014,⁵ and in the United Kingdom (UK) from December 2014.⁶ This highlights discrepancies between different countries, with identical tests being banned in the USA and at the same time being allowed in the UK and Canada.

The differences in DTC genetic testing services between countries may be due to the present regulatory requirements. When discussing appropriate responses to provide better DTC services to the public, it is essential to identify the different regulatory approaches for DTC genetic testing by comparing different countries. Unfortunately, although various publications have focused on the regulations of DTC genetic testing activities in the USA¹ and Europe,^{7,8} there are scant published studies about the current challenges and impacts in relation to the regulations of DTC health-related genetic tests in Japan. Therefore, the present study expands on previous research to focus specifically on the conditions in Japan, while including South Korea for purposes of comparison. The study reviews the current situation of regulatory requirements for DTC health-related tests in Japan within the broader context of 10 other countries to recommend steps to improve and develop genetic testing regulations and provisions.

Materials and Methods

To compare legal approaches between the countries, the study examines the laws and policies on regulating DTC health-related genetic testing offered without health professionals' involvement in 11 countries: Austria, Belgium, France, Germany, Portugal, Switzerland, the UK, the USA, Canada, South Korea, and Japan. We focused on health-related testing because this will likely continue to become more widespread as sequencing costs decrease. To identify and compare the current legal approach governing DTC genetic testing between the countries, we examined and analyzed specific legislation and policy guidance governing genetic testing and

applying the DTC context. Our survey terms for the regulations of genetic testing services were: the quality of the tests such as laboratory accreditation, provision of genetic testing such as performing under medical supervision, genetic counseling, and consent requirements in the process of genetic testing, all of which impact DTC genetic testing services.

Documents explicitly addressing the use of DTC genetic testing were eligible for inclusion if they were available as a position paper, report, guidelines, or consensus statement produced by international or national governmental or non-governmental health organizations, bioethics committees, or professional organizations. Documents written in English or officially translated into English were eligible for inclusion, but also documents written in Japanese or Korean were included, even if there was no official English translation available.

Results

Legal regulations for genetic testing

The study reviewed an overview of the general legal and policy landscapes in 11 countries regarding DTC genetic testing services. Regarding the specific legal act of genetic testing, the study found that explicit laws in the area of bioethics were enacted in France and South Korea that contain several provisions related to genetic testing. In France, the Civil Code states that genetic tests can only be performed for an individual for medical or scientific research purposes (Art. 16-10). In 2005, South Korea introduced the Bioethics and Biosafety Act (partially modified in 2016)⁹ aiming to contribute to the promotion of citizens' health and the improvement of their quality of life by preventing the violation of human dignity, as well as regulating research involving embryos and genes (Art. 1).

Some countries have adopted specific laws on genetics, such as Austria, Germany, Portugal, and Switzerland. In Austria, the Gene Technology Act of 1995¹⁰ stipulates that a genetic test for medical purposes is only to be performed to further new scientific knowledge and technical progress (Art. 65). The Portuguese Law n°12/2005 of 26 January 2005¹¹ aims to protect health information and genetic information and sets rules for the collection and preservation of genetic testing for clinical or research purposes (Art. 1). The Act states that government has a responsibility for regulating the conditions of availability and performance of genetic testing of heterozygosity status, presymptomatic, predictive, prenatal, and preimplantation tests to avoid possible over-the-counter marketing of these types of tests (Art. 15.1).

In Switzerland, genetic testing is regulated under the Federal Act on Human Genetic testing 2007,¹² covering the scope of medical context, identification, determining descent, and the insurance and employment sectors (Art. 1). In 2009, Germany introduced the Human Genetic Examination Act¹³ covering a range of medical purposes, and the intent of this Act is to determine the requirements for genetic examinations and to prevent any discrimination and disadvantage based on genetic characteristics (Sec. 1-1). The UK regulates products used in health-related genetic testing services as *in vitro* diagnostic medical devices.¹⁴ The USA, Canada, and Japan treat genetic tests that fall within the *in vitro* diagnostic medical device regulations as moderate-to high-risk and, therefore, generally require premarket review.^{15,16}

The regulations for laboratories

To ensure the analytical accuracy of tests performed by laboratories, in Austria, France, Germany, Portugal, Switzerland, and South Korea laboratories must legally comply with the country's requirements. The Austrian Act requires the head of the facility to appoint a laboratory manager for each laboratory (Art. 68a). In South Korea, the Bioethics and Biosafety Act stipulates that only medical institutions are legally permitted to conduct genetic tests in connection with the prevention, diagnosis, or treatment of disease. The exception to this rule gives allowance to other institutions to conduct genetic testing related to the prevention of disease, at the request of a medical institution and/or as the Minister of Health and Welfare deems it necessary (Art. 50-3). In the USA, all laboratories performing clinical testing services, except for research purposes, are regulated for analytical validity under the Clinical Laboratory Improvement Amendments of 1988.¹⁷

Some countries have a legal framework in the clinical setting. Belgium has 8 centers for human genetics recognized by the Minister of Public Health under the Royal Decree of December 14, 1987 (modified in 2007).¹⁸ The Decree sets requirements for laboratories performing genetic tests for reimbursement. In the UK, Canada, and Japan, there are no specific legal standards for genetic service laboratories, but they do have to comply with other regulatory factors. In the UK, laboratories funded by the National Health Service are required to seek accreditation with Clinical Pathology Accreditation or the UK Accreditation Service.¹⁹ In Canada, the regulation of laboratories does not fall under federal jurisdiction but rather provincial jurisdiction.²⁰ In Japan, genetic testing is performed at medical institutions, as well as at clinical and research laboratories, but there are no specific

standardized regulatory frameworks.²¹

The provisions of genetic testing

National legislations in Austria, France, Germany, Portugal, and Switzerland state that genetic tests for medical purposes should only be offered under medical supervision. Article 69 of the Austrian Gene Technology Act stipulates that genetic testing of genetically based disease or the determination of a carrier status are only to be performed after obtaining informed consent along with the provision of genetic counseling. Article 16-10 of the French Civil Code also stipulates about obtaining informed consent after providing information on the nature and purpose of the tests. In Germany, the Act stipulates that a diagnostic genetic examination may only be performed by a physician and that a predictive genetic test can only be undertaken by a medical specialist in the field of human genetics or another physician within their specialist area (Sec. 7) with genetic counselling (Sec. 10) and obtaining written informed consent (Sec. 8). The Portuguese Act regulates that the detection of the heterozygosity status of recessive diseases, the presymptomatic diagnosis of monogenic diseases, and the tests for genetic susceptibility in healthy persons can only be performed by a medical geneticist, following genetic counseling and are subject to obtaining written consent prior to testing. For late-onset diseases with no cure or treatment, the performance of any presymptomatic or predictive testing must be preceded by psychological and social evaluation including follow-up support (Art. 9). The Swiss Act stipulates that genetic testing may be performed only under medical supervision. Informed consent for a genetic test should be obtained verbally for diagnostic testing and in written form for presymptomatic or prenatal purposes or for family planning (Art. 18). Moreover, genetic testing for presymptomatic and prenatal purposes has to be ordered by physicians with appropriate postgraduate training after proper genetic counselling (Art. 14,15).

In South Korea, the Act also stipulates that written informed consent of the subject must be obtained before conducting genetic testing, and information must be given regarding the objective and management of the test; in addition, procedures for the withdrawal of consent and protections must be in place (Art. 51). However, genetic counseling is not structured and there is no legislation for genetic counseling in South Korea.²²

In Belgium, based on the Royal Decree of June 7, 2007, genetic counseling carried out by a multidisciplinary team is financed in 8 centers.²³ In the UK, clinical genetic services are generally based on professional guidelines

from the Royal College of Physicians and the Clinical Genetics Society.²⁴ The UK Human Tissue Act 2004 regulates informed consent for genetic testing.²⁵ This declares as genetic theft the collection or analysis of an individual's genetic data without their consent. In the USA, regulations for genetic testing vary among the 50 states. More than 10 states have laws requiring a physician or other healthcare professional to order the tests and receive the test results.²⁶ In Canada and Japan, informed consent for medical treatment in general falls under general medical law, and professional organizations have made recommendations specific to informed consent for genetic testing and counseling.^{27,28}

The regulations for DTC genetic testing

The study explored an overview of the general legal and policy landscape in 11 countries, regarding DTC genetic testing services offered without the involvement of health professionals. As shown in Table 1, none of them have legislation created specifically to regulate DTC genetic testing services. The present survey discovered several different legal approaches used nationally to regulate genetic testing, which also affects the current status of DTC genetic testing services.

First, there are legal regulations that integrate the provision of genetic tests in a medical relationship. National legislation in Austria, France, Germany,

Portugal, and Switzerland state that genetic tests for medical purposes should only be offered under medical supervision with informed consent obtained after genetic counseling. Thus, the legislation prohibits medically purposed DTC genetic testing services without the involvement of medical professionals in those countries.

Second, there is national legislation such as that in the USA and South Korea, which gives more attention to the analytical and clinical validity of tests and which limits certain genetic testing. In the USA, the FDA has legal authority to regulate the safety and effectiveness of genetic tests as medical devices under the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act.²⁹ The agency has historically practiced enforcement discretion for laboratory-developed tests (LDTs), a class of *in vitro* diagnostics that is manufactured by and used within a single laboratory.³⁰ Since 2010, the FDA has expanded its scope to deliberate on how it develops its regulation for LDTs, including DTC genetic tests. In the regulatory action on 23andMe of November 2013, the FDA ruled that the test was a medical device that needed to be regulated, despite 23andMe providing health reports saying it was considered an educational product.⁵ The FDA highlighted potential adverse health consequences of the testing offered, such as having unnecessary surgery to prevent cancer because of the results. The FDA authorized 23andMe to market DTC genetic carrier testing

Table 1. Legal regulations for genetic testing and affect to health-related DTC genetic testing services

DTC genetic testing services	Country	Provision of genetic testing		
		Involvement of health professionals	Genetic counseling	Informed consent
Prohibition	Austria	+	+	+
	France	+	+	+
	Germany	+	+	+
	Portugal	+	+	+
	Switzerland	+	+	+
Limitation	USA*	+**		+**
	South Korea***	+		+
No direct application	UK			+
	Belgium			
	Canada Japan			

DTC, direct-to-consumer

+The country has enacted legislation in the indicated circumstance.

*The USA limits certain genetic testing regarding requiring a premarket review.

**No federal regulation but state law

***South Korea limits conducting certain genetic tests.

for autosomal recessive diseases in February 2015,³¹ and authorized genetic health risk tests for 10 conditions including Parkinson's disease and late-onset Alzheimer's disease in April 2017.³² Recently, the US FDA established “special controls” for genetic carrier testing for autosomal recessive disease and testing for Genetic Health Risk testing. The controls permit companies to sell certain DTC genetic tests as long as they meet specific requirements, such as analytical performance, clinical validity, and obtaining access to genetic counseling services.³³⁻³⁵

In South Korea, Article 50 of the Bioethics and Biosafety Act sets limits for conducting certain genetic tests, such as to predict physical characteristics or personality traits; these tests may mislead subjects due to a lack of scientific evidence. Also, certain tests are forbidden by Presidential Decree after being reviewed by the National Committee.

The last pattern is regarding legislation stipulations in the medical field, such as those in the UK, Belgium, Canada, and Japan. From the legal perspective for 23andMe in the UK and Canada, DTC genetic testing kits themselves may fall within their respective jurisdictions in both countries but actual service does not.¹⁴ Belgium and Japan do not have a specific legislative framework to cover appropriately the provision of genetic testing outside of medical practice. Japan especially is lacking any concrete standards or basic oversight of genetic services. The only legal guidance applying to DTC genetic tests may be found in Article 2 of the Law on the practice of healthcare professionals³⁶ in Belgium and in Article 17 of the Medical Practitioners' Act³⁷ in Japan, each stipulating that medical practice may only be provided by a certified medical practitioner. The acts would not apply because most DTC companies cite, in their terms of services, that they are not practicing medicine but only serving informational or educational purposes.

The current efforts of 4 countries

Four of 11 countries, the UK, Belgium, Canada, and Japan, did not have legal regulations applicable to DTC genetic testing services. In the clinical setting, medical supervision and genetic counseling is available in Belgium and the UK, and DTC genetic testing is currently not prohibited in these countries. The Belgian Superior Health Council stated in 2012 that DTC health-related genetic testing should be considered as a practice of medicine.³⁶ In 2010, the UK Human Genetics Commission, a government advisory body, published a common framework of principles for DTC genetic testing services to promote standards and consistency to

safeguard the interests of consumers; it addressed counseling and continuing support, consent, laboratory processes, and the provision and interpretation of the results.³⁸ In Canada, there are legal regulations of genetic testing for diagnosis purposes, but Health Canada determined that 23andMe's testing service is not recognized as a medical device beyond the scope of the regulation.³⁹ Japan has a voluntary set of guidelines drawn up by the Ministry of Economy, Trade and Industry (METI) and an industry organization, but this is not legally binding.³⁵ The Ministry of Health, Labor and Welfare announced in 2016 that it would develop a framework for overseeing genetic tests but since then has not yet responded with any attempts to regulate DTC genetic testing.²¹ Therefore, the METI has allowed the provision of DTC genetic testing, although regulations and standards are as yet in need of further development.

Discussion

This study reviewed the general legal and policy landscapes in 11 countries and found several different legal approaches for genetic testing which also affects the current status of DTC genetic testing services. The findings showed that more than half of these countries have legal frameworks that apply fully or in part to strict DTC genetic testing services (Table 1).

In countries without specific legislation on genetic testing, such as the UK, Belgium, Canada, and Japan, the question of whether DTC genetic testing should be defined as a health service or as an informational service have an important impact on the way such tests may be regulated. Most DTC genetic testing services explicitly state in their terms of services that they are not practicing medicine, and that their tests should not be considered medical information, but only serve informational purposes. Along these same lines, the Department of Health in the UK and Health Canada have determined that 23andMe's test is not a medical device³⁹; however, the services offered by 23andMe purports to be medical testing with important potential healthcare benefits.⁴⁰ In contrast, the US FDA has treated its testing service as a medical device, regulated to ensure the safety and effectiveness of the test. It is evident that there will need to be further discussions to define the types of services offered by DTC genetic testing companies, and whether or not these are relevant in legal terms.

Among the 4 countries mentioned above, Japan has the least regulatory legal frameworks for laboratory accreditation, regulations of genetic testing, and provisions of genetic testing, e.g., appropriate consent

procedures with the involvement of health professionals; this has negatively affected the current status of DTC genetic testing services. The present genetic testing services in Japan, including DTC sales, have several problems, the first of which being that there is no legal regulatory system to assess genetic testing. To assess the benefits and risks of genetic testing, it is important to examine the analytical and clinical validity, clinical utility, and ethical social issues.⁴¹ Although the definition of clinical utility may differ between countries, it is important to make sustained efforts to ensure that clinically useful tests are promoted and less useful tests are discouraged.⁴² Indeed, a consumer help center received from Japanese members of the public who had purchased DTC tests; they reported inappropriate responses from the DTC companies, such as insufficient information to interpret their test results.⁴³ In Japan, in particular, it is essential that an appropriate system for the evaluation and provision of genetic testing be constructed with the involvement of medical societies and federal regulatory bodies.

Furthermore, a number of companies have changed their business model so that consumers need to contact a physician before being able to consider the test from the company. These companies may formally hire a health care professional in order to circumvent legal issues.² The current regulations on genetic testing services in Japan allow advertising of DTC genetic testing in a clinical setting, so that individuals may access testing from DTC companies through a doctor in general hospital or health care center. Thus, a potential consequence of the provision of DTC genetic testing services is a downstream impact on clinical settings and the health care system. The previous study has shown that many consumers seek counseling and medical follow-up after having purchased such a test.⁴⁴ This has the potential to place an extra burden on the healthcare system as consumers look for support that the DTC testing companies are not equipped to provide; in addition to this, not every physician has been trained sufficiently in interpreting the test results and, therefore, may not be confident in supporting a patient to manage genetic risk information.⁴⁵

There has been new movement recently to regulate DTC genetic testing in the USA. The FDA has established special controls for carrier testing of autosomal recessive diseases and certain health related genetic testing to ensure access to genetic counseling in the genetic testing process. The involvement of physicians and genetic counselors ensures clinical validity and utility and ensures the sharing of results in an understandable and actionable manner.⁴⁶ Most DTC companies also refer consumers to the

healthcare system for interpretation of their test results. There is still a need for education of the general public and healthcare professionals about the limitations and concerns regarding DTC genetic testing.

The limitations of this study are that it provides only partial parameters regarding health-related genetic testing in each country. An additional concern, that requires further exploration, is that of developing regulations to protect an individual's genetic information in DTC companies. E.g., there needs to be specific, clear, and enforceable guidelines for how such information is handled by its owners, especially if DTC companies may cease providing their testing services, at some future time, or if they are taken over by a third party (e.g., due to bankruptcy or other factors). This study has examined various legal parameters and issues surrounding DTC genetic testing services, and the results clearly indicate that future research is warranted to expand on these findings.

In conclusion, it will be necessary to develop assessment procedures addressing the usefulness of various genetic testing in Japan. Irrespective of whether genetic testing is offered DTC or provided in a clinical setting, there should be overall standards for genetic testing ensuring that they benefit individual patients and consumers. Proper oversight will be vital to synthesizing the available evidence on the clinical validity and utility of emerging genetic tests, as well as identifying current gaps in knowledge along with the studies and measures needed to resolve them. Further debates and discussion are most certainly needed to determine the appropriate response to DTC genetic testing in Japan. Along with greater opportunities for the general public to gain individual genetic information, consumers should not have difficulty accessing appropriate genetic testing or health information about themselves and their results.

Acknowledgments

This work was supported in part by a Grant-in-aid for Special Research from the Ministry of Health, Labor and Welfare in Japan (H26 special designation 049). The authors thank Yoshimitsu Fukushima, MD, PhD, and staff who helped with this project.

References

1. Hogarth S, Javitt G, Melzer D. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. *Annu Rev Genomics Hum Genet* 2008; 9: 161-82.

2. Howard HC, Borry P. Is there a doctor in the house? : The presence of physicians in the direct-to-consumer genetic testing context. *J Community Genet* 2012; 3: 105-12.
3. Niemiec E, Borry P, Pinxten W, et al. Content analysis of informed consent for whole genome sequencing offered by direct-to-consumer genetic testing companies. *Hum Mutat* 2016; 37: 1248-56.
4. U.S. Food and Drug Administration. 23andMe, Inc. 11/22/13. Warning Letter. 2013. Available at: <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm>. Accessed December 19, 2017.
5. Picard A. Controversial genetic self-testing kits coming to Canada. *The Globe and Mail*. 2014. Available at: <http://www.theglobeandmail.com/life/health-and-fitness/health/genetic-self-testing-kits-to-come-to-canada/article20885678/>. Accessed December 19, 2017.
6. Burton A. Are we ready for direct-to-consumer genetic testing? *Lancet Neurol* 2015; 14: 138-9.
7. Borry P, van Hellemond RE, Sprumont D, et al. Legislation on direct-to-consumer genetic testing in seven European countries. *Eur J Hum Genet* 2012; 20: 715-21.
8. Kalokairinou L, Howard HC, Slokenberga S, et al. Legislation of direct-to-consumer genetic testing in Europe: a fragmented regulatory landscape. *J Community Genet* 2017. doi: 10.1007/s12687-017-0344-2 [Epub ahead of print].
9. Bioethics and Safety Act. Available at: <http://www.law.go.kr/%EB%B2%95%EB%A0%B9/%EC%83%9D%EB%AA%85%EC%9C%A4%EB%A6%AC%EB%B0%8F%EC%95%88%EC%A0%84%EC%97%90%EA%B4%80%ED%95%9C%EB%B2%95%EB%A5%A0>. Accessed December 19, 2017 (in Korean).
10. Austrian Gene Technology Act-Provision on Genetic Testing. Available at: https://www.eshg.org/fileadmin/www.eshg.org/documents/Europe/LegalWS/AustrianGeneTechnologyAct_English.pdf. Accessed December 19, 2017.
11. Law n.º12/2005 of 26 January 2005. Available at: https://www.eshg.org/fileadmin/www.eshg.org/documents/Europe/LegalWS/Portugal_Law-UnofficialEnglishTranslation.pdf. Accessed December 19, 2017.
12. Federal Act on Human Genetic Testing. Available at: <http://www.admin.ch/ch/e/rs/8/810.12.en.pdf>. Accessed December 19, 2017.
13. Human Genetic Diagnosis Act. Available at: https://www.eshg.org/fileadmin/www.eshg.org/documents/Europe/LegalWS/Germany_GenDG_Law_German_English.pdf. Accessed December 19, 2017.
14. Howe E. Medicines and Healthcare Products regulatory Agency: Written Question HL3347. Available at: <http://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Lords/2014-12-02/HL3347>. Accessed December 19, 2017.
15. Official response of the EuroGentest Network of Excellence in Genetic Testing. Available at: http://www.eurogentest.org/fileadmin/templates/eugt/pdf/EuroGentest_Response_to_IVDD_Revision_Consultation.pdf. Accessed December 19, 2017.
16. World Health Organization. A risk based approach for the assessment of *in vitro* diagnostics (IVDs). 2014. Available at: http://www.who.int/diagnostics_laboratory/evaluations/140513_risk_based_assessment_approach_buffet.pdf. Accessed December 19, 2017.
17. Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA). Available at: <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=clia/>. Accessed December 19, 2017.
18. Hens K, Nys H, Cassiman JJ, et al. The use of diagnostic collections of DNA for research: Interviews at the 8 Belgian centers for human genetics. *Euro J Med Genet* 2010; 53: 274-9.
19. Department of Health. Our Inheritance, Our Future: Realising the Potential of Genetics in the NHS. 2003. Available at: <http://www.nhshistory.net/genetics.pdf>. Accessed December 19, 2017.
20. Petit É Tassé AM, Godard B. An Empirical Analysis of the Legal Frameworks Governing Genetic Services Labs in Canadian Provinces. *Health Law Review* 2008; 16: 65-72.
21. Ministry of Labor and Welfare. Task Force Report on Genome Medicine. Available at: <http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000140440.pdf>. Accessed December 19, 2017 (in Japanese).
22. Kim N. Legislation on Genetic Diagnosis: Comparison of South Korea and Germany. *Dev Reprod* 2015; 19: 111-8.
23. The European Union Committee of Experts on Rare Diseases. 2012 report on the state of the art of rare disease activities in Europe of the European Union Committee of Experts on Rare Diseases. State of the art of rare disease activities in Belgium. Available at: http://www.eucerd.eu/?post_type=document&p=1419. Accessed December 19, 2017.
24. Farndon F. Quality Issues in Genetics Services in the United Kingdom. In: Kristoffersson U, Schmidtke J, Cassiman JJ, editors. In: *Quality Issues in Clinical Genetic Services*. Dordrecht, Heidelberg, London, New York: Springer; 2010; 63-74.

25. Human Tissue Authority. Human Tissue Act 2004. Available at: <https://www.hta.gov.uk/policies/human-tissue-act-2004>. Accessed December 19, 2017.
26. Anderson EE. Direct-to-consumer personal genome services: need for more oversight. *Virtual Mentor* 2009; 11: 701-8.
27. The Japanese Association of Medical Sciences. Guidelines for Genetic Tests and Diagnoses in Medical Practice. Available at: http://jams.med.or.jp/guideline/genetics-diagnosis_e.pdf. Accessed December 19, 2017 (in Japanese).
28. Somerville MJ, Allingham-Hawkins D. Regulation of Genetic Testing/Service in Canada. In: Kristoffersson U, Schmidtke J, Cassiman JJ, editors. *Quality Issues in Clinical Genetic Services*. Dordrecht, Heidelberg, London, New York: Springer; 2010; 83-90.
29. Sarata AK, Johnson J. Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests. Available at: <https://fas.org/sgp/crs/misc/R43438.pdf>. Accessed December 19, 2017.
30. U.S. Food and Drug Administration. Laboratory Developed Tests. Available at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm>. Accessed December 19, 2017.
31. U.S. Food and Drug Administration. FDA permits marketing of first direct-to-consumer genetic carrier test for Bloom syndrome. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435003.htm>. Accessed December 19, 2017.
32. U.S. Food and Drug Administration. FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm>. Accessed December 19, 2017.
33. Electronic Code of Federal regulations. §866.5940 Autosomal recessive carrier screening gene mutation detection system. Available at: http://www.ecfr.gov/cgi-bin/text-idx?SID=1828e8fb074984a9289ad9ea99a8a899&mc=true&node=pt21.8.866&rgn=div5#se21.8.866_15940. Accessed December 19, 2017.
34. Electronic Code of Federal regulations. §866.5950 Genetic health risk assessment system. Available at: https://www.ecfr.gov/cgi-bin/text-idx?SID=1828e8fb074984a9289ad9ea99a8a899&mc=true&node=tpt21.8.866&rgn=div5#se21.8.866_15950. Accessed December 19, 2017.
35. Fukuda R, Fumio T. Current international efforts and issue of regulating direct to consumer genetic testing. *Jpn J Gent Counsel* 2017; 38: 1-11 (in Japanese).
36. Superior Health Council. Publication of the Superior Health Council No. 8714. Direct-to-consumer genetic testing service. Available at: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/19080855/Direct-to-consumer%20genetic%20testing%20services%20%28April%202012%29%20%28SHC%208714%29.pdf. Accessed December 19, 2017.
37. Medical Practitioners' Act. Available at: <http://www.japaneselawtranslation.go.jp/law/detail/?id=2074&vm=04&re=02>. Accessed December 19, 2017.
38. Human Genetics Commission. A Common Framework of Principles for direct-to-consumer genetic testing services. Available at: <http://www.cellmark.co.uk/pdfs/HGCprinciples.pdf>. Accessed December 19, 2017.
39. Cussins J. Direct-to-consumer genetic tests should come with a health warning. Available at: <https://www.pharmaceutical-journal.com/opinion/comment/direct-to-consumer-genetic-tests-should-come-with-a-health-warning/20067564.article>. Accessed December 19, 2017.
40. Canadian College of Medical Geneticists. Direct-to-consumer (DTC) genetic testing in this country. Available at: https://www.ccmg-ccgm.org/images/pdf/DTC-letter-Final-April-15-2015_V6.pdf. Accessed December 19, 2017.
41. Grimaldi GA, Markus LP, Scioli GA, et al. Personal genetics: regulatory framework in Europe from a service provider's perspective. *Euro J Hum Genet* 2011; 19: 382-8.
42. Borry P. Direct-to-consumer genetic testing: from ethical concerns to policy answers. *Bioethics Forum* 2013; 6: 114-7.
43. Ministry of Economy, Trade and Industry. Reports on the commercialization of genetic testing. Available at: http://www.meti.go.jp/policy/mono_info_service/mono/bio/pdf/140428idenshikensa-houkokusyo2.pdf. Accessed January 04, 2018 (in Japanese).
44. Van der Wouden CH, Carere DA, Matland-van AH, et al. Consumer perceptions of interactions with primary care providers after direct-to-consumer personal genomic testing. *Ann Intern Med* 2016; 164: 513-22.
45. McGowan ML, Fishman JR, Settersten RA, et al. Gatekeepers or intermediaries? The role of clinicians in commercial genomic testing. *PLoS One* 2014; 9: 1-7.
46. Borry P, Cornel MC, Howard HC. Where are you going, where have you been: a recent history of the direct-to-consumer genetic testing market. *J Community Genet* 2010; 1: 101-6.