Abstract

Gene-testing technology has dramatically advanced in recent years, and it now provides a simple and relatively affordable way to test the genetic makeup of individuals. In addition to genetic testing at medical institutions, companies now provide a DTCGT (Direct-to-Consumer Genetic Testing) system, which allows consumers to undertake a genetic test directly without visiting a medical institution, resulting in an expansion of the available services that predict potential diseases. Today, most DTCGT tests are not performed under the supervision of a registered physician or trained medical professional, which is both a medical and an ethical issue, and there is no suitable established regulation for DTCGT testing. Here we compare genetic testing rules and regulations in Japan, the U.S. and Europe (the UK, Germany, and France). We note that there are established laws and regulations governing the DTCGT system in most western countries, whereas in Japan there is guidance but no rules or regulations. To clarify the current situation in Japan, we surveyed the organizations that use the DTCGT system both in person and over the internet. We found that most of the 112 organizations using the system did so without supervision of a registered physician or trained medical professional supervision. We also identified genetic-testing results diagnosing disorders that actually needed suitable medical gene counseling. We conclude that the timely implementation of appropriate laws and regulations is necessary to solve these issues arising from the rapid expansion of DTCGT use in Japan.
DTCGT is the rapid progress in genetic testing technology has led to its active use for disease diagnosis and treatment choices at medical institutions. Direct to consumer genetic testing (DTCGT), which allows genetic testing to be conducted by anyone, has become widespread, providing services that can predict future diseases. Specialist physicians and geneticists carry out genetic examinations at medical institutions, whereas DTCGT can be done directly by the individual by providing oral mucosa, hair, nail clippings, etc., and the individual can receive the results from the company that provided the DTCGT product. The various DTCGT systems are not difficult to use. There is no requirement for the use of a needle and thus no pain risk, and the sampling can be performed with relative ease. Because DTCGT can easily be undertaken without the supervision of a physician or genetic expert, the numbers of businesses offering DTCGT worldwide are rapidly increasing.

Polymerase chain reaction (PCR), sequencing, and DNA chips are used for the gene analyses in DTCGT. Genome-wide association studies (GWASs) are performed to search for single-nucleotide polymorphisms (SNPs) that are frequently present in a particular disease, and they identify the genes around these SNPs. Gene analyses can therefore be used to identify a broad range of genes that are or may be associated with disease risk factors, and this identification contributes to the understanding of possible mechanisms of disease prevention and treatment, which itself contributes to the development of new therapies. These are the commendable benefits of the use of DTCGT for gene analyses.

The currently available genetic testing is roughly divided into three types: (1) genetic tests that examine inherited genetic information, (2) somatic cell genetic tests that examine genetic information that has changed after birth, and (3) pathogen gene tests that determine the presence/absence of exogenous pathogens. In the first test type (i.e., genetic tests), although cells in the blood are typically used, tests using any cell from the human body such as the oral mucosa, hair, nails, saliva, etc. are possible. Regarding the second and third types of tests, the Japan Medical Association requires that cancerous cells from a somatic cell genetic test or a pathogen test must pass through a registered medical institution (April 2016), and according to Article 17 of the Medical Practitioner's Act, only registered physicians are allowed to carry out these tests.

However, the companies that are offering DTCGT products say that they are not offering
medical services; rather, they are simply facilitating the results of the tests and providing the results to their clients. The businesses state that their DTCGT products are purely for predicting the possibility of disease and not a diagnosis. Few countries regulate DTCGT as loosely as Japan; most countries in Europe and the U.S. provide quite thorough regulations for DTCGT. Recent research suggests that several diseases may be identified directly from the results of DTCGT. Moreover, the use of DTCGT without the supervision of a doctor or trained medical professional can lead to the possibility of medical and ethical problems.

We examined the regulations concerning genetic testing in Japan, the U.S. and Europe. We then compared and examined the regulations related to DTCGT, analyzing the current situation and issues arising from DTCGT in Japan.

**Methods**

1. **Regulation of genetic testing in Japan, the U.S. and Europe (the UK, Germany and France)**

   We searched for laws and guidelines on genetic testing in Japan, the U.S. and Europe (UK, Germany and France) by searching websites of the respective country’s administrative organization that issue the laws and guidelines. We then did a comparative analysis.

2. **The business of DTCGT in Japan**

   To compile a list of the organizations and companies that offer DTCGT in Japan, we used the search engines Google, Yahoo and Bing searching the keyword “遺伝子検査” (“gene testing”). We then analyzed the DTCGT service of each organization or company from the information provided on their website.

**3. Evaluation of the DTCGT gene mutation judgement risk classification**

   We evaluated the gene mutation judgement risk classification used by DTCGT systems in Japan, the U.S. and Europe (UK, Germany and France). We classified the genetic mutations identified by DTCGT into three levels. Two groups were also identified: malignant disease and benign disease. We gave one point for data written in a thesis, another one point for data regarding Japanese nationals in the thesis, and another one point if the data involved 1,000 people or more.

**Results**

1. **Genetic testing regulations in the U.S. and Europe**

   Table 1 summarizes the genetic testing regulations in the U.S. and Europe (UK, Germany and France). Regulations concerning genetic testing were published by the European Union in 1997. The UK, Germany and France then followed suit. In the U.S., genetic testing is regulated by each state, and a draft guidance for businesses was issued in 2014. In some states, consumers are free to use a DTCGT product, but it is banned or restricted in 25 states. Among the 25 states that do allow DTCGT, each state has its own list of rules and regulations. In Japan, as of October 2017, no laws or regulations have been issued.

   Table 2 shows the comparison between regulations in the U.S. and Europe (UK, Germany and France). In the European Union, France and Germany, DTCGT is prohibited by law. If it is to be used, it must be under the supervision of a registered physician who is
using it for treatment or research. In the UK, there is no such law, but a law was issued that allowed institutions that specialize in genetic research to use a DTCGT system.

In our analysis, we found that DTCGT is conducted freely only in the UK and Japan. In Japan, there are no regulations concerning the use of DTCGT. It is clear that this system is not fully functional and that many faults remain\(^{26}\).

2. A review of the DTCGT businesses in Japan

In our research into businesses in Japan that provide DTCGT, we used the search engines Google, Yahoo and Bing. We found 112 organizations that provide a DTCGT service to the pub-

Table 1 Laws concerning genetic testing in Europe and the US

<table>
<thead>
<tr>
<th>Year</th>
<th>US</th>
<th>Germany</th>
<th>France</th>
<th>UK</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The Committee of Ministers’ Recommendation(^{18}) (1997)</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Additional Protocol on Genetic Testing(^{19}) (2008)</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
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<td></td>
<td>Human Genetic Diagnosis Act(^{10}) (2009)</td>
</tr>
<tr>
<td>2015</td>
<td></td>
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<td>NHS STANDARD CONTRACT(^{17}) (2014)</td>
</tr>
</tbody>
</table>

Table 2 The differences between European and the US laws and regulations of the genetic testing industry

<table>
<thead>
<tr>
<th>US</th>
<th>Germany</th>
<th>France</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 13 states, genetic testing is prohibited. In 12 states, genetic testing is permitted but there are limits(^{21,25}).</td>
<td>It is permitted as long as it is for medical or scientific research purposes.</td>
<td>Genetic testing is permitted in cases of disease and health related situations as long as it is administered by a doctor.</td>
<td>Only guidances found. Human Genetic Commission(^{23}).</td>
</tr>
</tbody>
</table>

2. A review of the DTCGT businesses in Japan

In our research into businesses in Japan that provide DTCGT, we used the search engines Google, Yahoo and Bing. We found 112 organizations that provide a DTCGT service to the pub-
In Japan, the Council for Protection of Individual Genetic Information (CPIGI) has established a system called 'Voluntary Standards on Individual Handling of Genetic Information' for companies that deal with personal genetic information. Companies that provide DTCGT must comply with the voluntary standards by providing effective and adequate testing services. Companies are allowed to use the CPIGI certification mark. At this time, only 11 of the 112 DTCGT companies in Japan are certified by CPIGI (Fig. 1). We estimated that after the use of the DTCGT system, there was a consultation with a registered physician in only 32% of the cases. There are many cases in which a physician was not consulted at all (Fig. 2).

In terms of the age range of the individuals who were accepted for genetic testing, only 29% of the companies had rules concerning age, and each company’s age limit differed. In almost half of the organizations, no rules or restrictions regarding age could be identified; nor could we identify any consent form or a similar approval.
form (Fig. 3). The physical constitution analysis provided by the current DTCGT products examines alcoholism, obesity, lipid metabolism, nicotine or caffeine resistant disorders (Fig. 4). In Japan, DTCGT is used most often for testing for obesity and alcoholism (Fig. 4). Its use for predicting disease and for predicting a child's capability is increasing, and cases analyzing obesity or alcohol metabolism independently of other factors are very common. The number of genes examined for obesity and alcoholism is 2–3; many genes related to various diseases have been identified, and the numbers of examined genes are increasing steadily (Fig. 5).

Fig. 4 and 5 are arranged as shown because the companies providing DTCGT services use these factors. However, there are no fixed criteria for evaluating the selection of test genes and the interpretation of results by each company. We also observed that only parts of the results of each genetic test examination (which may be directly linked to the diagnosis of the disease) are included.

As shown in Table 3, the SNP mutations are very useful for predicting disease both epidemiologically and statistically. It is clear that some gene mutations cause disease, and it is likely that the SNP mutation results from DTCGT will lead to diagnoses of such diseases.
3. Evaluation of the DTCGT gene mutation judgement risk classification

Fig. 6 presents common non-malignant diseases, and Fig. 7 shows common malignant diseases. Each gene that is tested is considered to be related to each disease in the figures, and their risk is evaluated in three different ways. Our method for evaluating this was as follows: we gave one point for data written in a thesis, one point for data about Japanese nationals in a thesis, and one point if the data were drawn from ≥1,000 people. It has been shown that the mutation of a test gene classified as 3 on the risk scale has a higher certainty of influencing the disease than a gene mutation at 0 to 1 on the risk scale. Naturally, in this gene mutation risk assessment system, it is conceivable that a large difference may be observed in the type of mutation of each gene and the degree of influence on the disease. When test results of DTCGT are reported to the consumer, it is important to provide information that is sufficient and clear both medically and scientifically. Additionally, as research on genetic testing has advanced rapidly, it is important to update information on how the test results affect the disease and to provide the information to consumers in a manner that is easy to understand.

Discussion

Advances in genetic testing have increased rapidly worldwide. Japanese consumers in particular are increasingly using DTCGT. Compared to the U.S. and Europe, the rules and regulations surrounding gene testing and DTCGT are not adequate in Japan, and the implementation of DTCGT is insufficient.

DTCGT was first offered to the public in the U.S. in 2000, and 10 years later there were almost 400 companies providing DTCGT services. This has continued to grow exponentially, with one of the biggest companies being 23andMe. However, in November 2013, the U.S.
Fig. 6 (Non malignancy) Disease-specific Risk Classification

- **Risk 1**: 1 point (18 genes)
- **Risk 2**: 2 points (52 genes)
- **Risk 3**: 3 points (46 genes)

Additional Method
- Published study: 1 point
- Data from Japanese population: 1 point
- Data including ≥1000 people: 1 point

Fig. 7 (Malignancy) Disease-specific Risk Classification

- **Risk 1**: 1 point (18 genes)
- **Risk 2**: 2 points (52 genes)
- **Risk 3**: 3 points (46 genes)
Food and Drug Administration (FDA) issued a statement questioning the accuracy of the saliva collection kit (a DNA collection tool) used by 23andMe. The FDA sent a letter to 23andMe to suspend their testing because of the risks involved with the testing kit. The DTCGT service in the U.S. was subsequently banned; however, ancestral examinations and the provision of raw data continue. The problem of DTCGT was brought into the limelight when a consumer received his test results and unilaterally stopped his medical treatment.

In 2015, the FDA gave approval for the genetic testing of Bloom syndrome, and in April 2017, the FDA issued their approval for the testing of 10 more diseases: Parkinson’s disease, Alzheimer’s disease, celiac disease, α1-antitrypsin deficiency, primary dystonia, factor IX deficiency, Gaucher disease type 1, glucose-6-phosphate dehydrogenase deficiency, hereditary hemochromatosis, and congenital thrombophilia.

The U.S. government also clarified its intention to globalize personal medicine as a business. Former President Barack Obama said in 2015 that the U.S. would invest 215 million in US dollars in Precision Medicine (personalized medicine). The goals of this investment are to reduce medical expenses in the U.S. by collecting genetic information on 1 million American volunteers and to discover the genetic predisposition of diseases. This also includes DTCGT. However, standing in the way of personalized medicine in the U.S. are ethical, legal and social issues such as the need for genetic counseling, genetic information discrimination laws, the privacy of genetic information protection, and the ownership of genetic information.

The use of personalized medicine in Japan’s medical institutions has recently increased. A genomic analysis can be performed for individual patients by using a next-generation sequencer, and the results are then used for diagnosis. The clinical sequencing method is being used more and more often.

The Japan Society of Clinical Oncology, the Japanese Cancer Association, and the Japanese Society of Medical Oncology banded together to create ‘Guidance for cancer diagnosis based on genetic testing using the next-generation sequencer (ver. 1.0)’.” They released classifications including diagnostic procedure, therapeutic effects, and prognostic procedure, describing four stages:

1. Genetic abnormality shown in the guidelines
2. Sufficient genetic abnormality indicated in clinical trials of scale and consensus among experts
3. Genetic abnormality shown in multiple small clinical trials
4. Single or in combination with markers, indicated in multiple small clinical trials or case reports of genetic abnormalities

A law that applies to the appropriate evaluation method for DTCGT needs to be created. As advances in genomic medicine are made, it is hoped that systems including DTCGT are improved and revolutionized as well.

The number of DTCGT operators in Japan is increasing, due in part to the lack of clear legal regulations. In many cases the results of DTCGT are not clear medically and/or scientifically. Nevertheless, disease diagnoses are still being made based on DTCGT results. This will cause medical and ethical issues in the DTCGT business. Gene samples that are not taken directly at the study site can result in possible mistakes regarding the identity of a tested indi-
individual, although they are very few in number. The quality of gene analyses that are based on hair samples is low, and DTCGT cannot use hair samples. DTCGTs are usually undertaken with cell DNA from the saliva or mucosal epithelium from inside the mouth.

DTCGT recognize many problems, and it can be difficult to distinguish serious diseases from other possible problems. Non-medically trained staff may not be familiar with the differences between the different potential risk factors. If a DTCGT consumer finds out that he or she has some type of disease (e.g., if a causative genetic abnormality is recognized), he or she will need to consult with a registered physician or trained medical professional. It is also possible that an identified disease could lead to related hereditary genetic problems.

There are many ethical and social issues regarding the results of a DTCGT test. Examples of this are discrimination, employment problems, and insurance coverage. As illustrated in Table 3, a DTCGT analysis of gene abnormalities can be used in the diagnosis of a broad range of diseases. Although companies providing DTCGT state that the results of their test products cannot be used to diagnose diseases, these companies are still using DTCGT for the diagnosis of diseases by identifying specific genes. It is important that we assess the risks caused by DTCGT results even if they are not confirmed as genetic mutations that cause disease. In order to fully understand DTCGT test results, it is necessary to classify each risk of disease by accumulating information on a large number of gene tests.

At the present, only 10% of the DTCGT providers in Japan meet the voluntary standards of the CPIGI. It would be better to develop a more standardized system to guarantee the quality of genetic testing. In addition, when companies acquire a certification like that from the CPIGI, it can be expected that consumers will be able to receive accurate and useful genetic testing. The usefulness of developing a consumer genetic databank to help clarify the relationships between disease and genetic mutations is still unclear.

We conducted the risk classification using three factors in the evaluation procedure for genetic testing. This method is expected to have the merit of formatting the DTCGT results in a figure that the general population can easily understand. However, the suitability of this method is still not confirmed, and because the information regarding the permeability of each gene mutation is limited, an incidence rate evaluation within the actual disease or symptom may be required. In addition, rather than limiting the analysis to single gene mutations, combined analyses of multiple gene mutations may be required.

The redress of these limitations and additional information for further research are thus important for confirmations of the suitability of this genetic testing. In the future, with the expanding use of DTCGT, there should be government regulations as well as public debate about the problems concerning genetic testing. It is also necessary to focus on educating the public regarding the advantages and disadvantages of DTCGT. Further prospective or retrospective studies are needed to follow up and analyze the relationships between positive-risk factors and negative-risk factors in order to confirm the validity of the data described herein.
Conflicts of interest

Mariko Sugiura and Atsushi Aruga have no conflicts of interest to disclose.

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