

Commentary

## Direct-to-Consumer Genotyping in Pre-Disease Field in Japan and the United States

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### Summary

DNA testing technology has made remarkable progress, including advanced personal genomics and improved accuracy of genetic diagnosis. The market for genetic testing for personal and chromosomal disorder screening has remained limited, with genetic tests being conducted less than 10 percent of laboratory tests for diagnosis of infectious diseases. Human genetic testing performed without medical facilities has been increasing in a business category known as direct-to-consumer (DTC), in which companies, not hospitals, sell genetic testing services directly to consumers. The most important feature of the service is that a DNA sample collected at home in contrast to conventional collection and laboratory testing performed at a hospital laboratory or a commercial reference laboratory. Accordingly, some health care professionals have raised concerns about the accuracy and reliability of DTC genetic test results. It is considered very important to improve the prevention of chronic disease in pre-disease stage by helping to maintain good health because of soaring medical expenses associated with aging population. Under such circumstances, the current situation and problems of DTC testing, including genetic medicine are discussed.

### DTC Testing in Pre-Disease Stage

Ninety percent or more of the clinical specimens collected at hospitals have been tested through outsourcing to commercial reference laboratories in Japan. Japan's clinical testing market is estimated to be about 6 billion USD, and the global market is estimated at between 60 to 70 billion USD in 2017. The annual growth rate is expected to be on average 2 to 3 percent. The ratio of the number of genetic tests to the entire number is expected to be higher in the major commercial clinical reference laboratories rather than individual hospitals. More than 90% of all nucleic acid tests in hospitals are derived from the testing for infectious disease. The global market for these genetic testing except infectious disease is estimated at 6 to 7 billion USD in 2017. Currently, chromosome DNA and genetic testing have mostly been outsourced except for certain research uses in Japan. On the other hand, the DTC test has allowed detecting personal predispositions, not through hospital, but by taking advantage of self-obtained samples. The Japanese DTC market is estimated to be about 50 million USD in 2017. In recent years, there has been an explosive growth in this market because of the major capital investments. One of the reasons behind this has been the improved convenience via non-invasive

sampling without drawing peripheral blood. Therefore, the DTC market can meet consumer demand for its convenience at a lower cost than that of genetic testing in hospitals. In the meantime, the entry into the DTC market of America's private companies facilitated collection and analysis of human DNA from all over the world. Personal genetic information from all over the world, have been accumulated for the purpose of providing regional disease development data and genetic databases for drug discovery. In Japan, the most frequently used DTC genetic test is a personal predisposition to certain diseases including lifestyle-related diseases as compared to serious genetic disorders. The reasons are as follows:

- 1) The incidence rate of severe genetic disorders per population is very low, and thus the test cannot be expected to make a profit.
- 2) The genetic tests associated with lifestyle-related diseases can help improve a person's lifestyle by following a proper exercise or diet.
- 3) Dietary supplement businesses have less demanding regulatory obligations compared to pharmaceutical medicines.
- 4) There is a possibility of widespread use of the DTC genetic tests as it is used at beauty salon, fitness clubs, and gyms.

At the same time, there has been some movement in the government's regulation of DTC genetic testing. The genetic tests for child geniuses in fields such as music and art often provide questionable interpretations. In particular, DTC genetic testing is called direct-to-consumer-genotyping. Genetic testing was done with samples shipped by regular mail, but more recently it has adapted to e-commerce systems. Yahoo and DeNA, Japan's largest internet companies have entered into the market, and it has drawn

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considerable attention.

### Genetic Testing in Pre-Disease Stage

Genetic testing has been shown to be an important marker in predicting the current and future risks of significant diseases in pre-disease stages. Pre-natal and pre-implantation testing are part of the present trend and may be reliable enough to become widely used. Recently, there has been an increasing interest in the development of a concept of personal care based on personal genomics, through a lifestyle that matches an individual constitution to prevent the onset of disease. It is possible to capture the early signs of disease or state of health and symptoms. It can be an effective means to help avoid the disease on the basis of the DTC test results. This is more likely to provide the key to success as DTC testing is considered complementary to hospital testing. A complementary relationship will be created as long as credibility can be ensured with the tests. DTC testing can also be a clue to effective health management along with the test via mail. Such tests enable early and accurate assessment of disease risk in the future. Commercially available testing that is personally deployed along with a person's environment and the DTC testing so far is called Personal Genome Service (PGS). The number of births is decreasing every year and the older generations are expanding in numbers in almost all other advanced countries. The reduction in the number or duration of hospital visits, medical cost due to the spread of generic medicines, the number of hospital beds and testing fee on clinical specimens will make a positive contribution to the health care economy. The personalized medicine may play an important role in the early detection and management of pre-disease states. The DTC test is often indirectly related to the disease or correlated disease symptoms for which it is meant to test, such as the case of obesity, anti-aging, immune response, tendency toward dementia, and hair-loss susceptibility. Some of the genetic tests have been performed in European testing service companies, but the results are quite different from those in Japan. Especially in the case of extremely rare genetic diseases, only a few institutions have conducted the tests. Also, some of the genetic disorders common in Europe do not occur or are of lower frequencies in Japan. Among a number of genetic diseases, a race-specific incidence has been reported. In particular, the frequencies of occurrence of single nucleotide polymorphism (SNP) in subjects from European and those from Japanese are often different from each other. With regard to SNP tests from lifestyle-related diseases that are currently being conducted, there seems not to be a significant difference in P-value between the two. A statistical significance of association between disease and genetic predisposition testing is evaluated using an index of odds ratio. Odd ratios cannot indicate that a person is affected by a particular disease, but it can give evidence on the risks associated with the possibility of onset of diseases. The P-value is the most commonly used statistical method in clinical research. SNPs with  $p < 0.01$  should be highly recognized as rare diseases. The Illumina chips are commonly used for the efficient implementation of high-throughput SNP genotyping in 23andMe which has strong managerial assistance from Google, and deCode Genetics acquired by Amgen Inc. in 2012. Some of

the testing companies are probably using the similar chip to those from Agilent Technologies, Inc., or in-house(self-manufactured) products, including real-time PCR or DNA sequencing.

### Future Trends

There are pros and cons to the DTC genetic test in the social reaction perspective and divergent views cannot be expected to converge. The expert opinion of Cervinski, et al. was shown to relevant parties [1]. The Japan Society of Human Genetics has a guideline in 2008 [2] (Table 1). From these discussions, comprehensive evaluation of DTC testing is a little confusing and needs more time to achieve a reliable consensus among users. The National Institutes of Health (NIH) guidelines addresses a number of issues [3]. It is important to ensure that the test is properly validated to produce accurate and precise results, thereby; enabling it to proceed to be used as clinically as a genetic test. The clinical validity and utility of genetic tests in addition to validated analytical methods need to be appropriately applied. The DTC companies in the US and Japan will build a better business plan in close conjunction with hospitals and medical universities. Incorporating medical doctors and other healthcare professionals like genetic counselors into their business will be an essential requirement for future PGS business strategy and development. In the US, the testing laboratories are proceeding with business plans for obtaining College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) certificates to ensure the accuracy and reliability of the test results. The DTC companies have promoted the acquisition of regulatory qualifications. In Japan, the registered private clinical laboratories will be required to respond to the improvement of quality management by receiving ISO15189 or CAP certificates. The DTC companies have not necessarily been successful in growing their businesses[4]. Many of the companies that attracted a lot of attention in the last decade, deCode genetics, Navigenics, Pathway Genomics and Gene Essence are not major factors today. Meanwhile 23andMe has continued to be factor in influencing market direction. As an example, the clinical reference laboratories in the 1970s were founded independent from the hospital, but have since evolved to bear a significant portion of the specimen testing business of modern medicine. We are wondering whether the same scenario is possible with respect to the DTC business. There seems to be some challenging problems that need to be resolved before the DTC market can expand into the future.

**Table 1. Comments from Japan Society of Human Genetics for DTC Genetic Testing**

1. In DTC genetic testing, clinical experts, who have professional knowledge in the fields of medical genetics, should be involved in the process from receiving an order for laboratory test through proper interpretation of the results.
2. Relevant guidelines should be complied with when carrying out DTC genetic testing.
3. Public institutions should urgently consider how to supervise DTC genetic testing.
4. Professional persons concerned, taking every possible opportunity shall educate and enlighten the public about the basics of genetics and the DTC genetic testing.

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