Science and Technology Trends
Strategy for Convergence of ICT and Biohealth and their Implications

Current Trends and Development Plans of Genome Sequencing in Korea

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1. Introduction

Genome sequencing, which emerged as an innovative healthcare technology, has been popularized with reduced turnaround time and costs and higher accuracy of analysis. The whole world is focusing on genome sequencing, as data generated therefrom play a pivotal role in future healthcare, which would ultimately enable personalized medicine and health management.

As genome sequencing attracted people's attention as an innovative technology in the 2000s and thereon, many startups and enterprises all over the world have entered this field, and the global genome sequencing market passed the introduction stages and is marching towards the growth stages. However, this is not the case in the genome sequencing market in Korea, which remains stagnant, even considering the small local market size, and the direct-to-consumer genetic testing market is becoming a red ocean. This study aims to identify causes behind the different landscapes between the local and global markets and present orientations to develop the local market by looking into: ① current status of the global genome sequencing industry; ② current status of the Korean genome sequencing industry and obstacles to industrial development; and ③ policy support required for the development of the local industry.

In Chapter 2, the author looks into the evolution of the genome sequencing technology as a background to understand what genome sequencing is. Chapter 3 focuses on the comparison of genome sequencing between local and global industries by looking into sequencing analysis equipment, clinical diagnosis, and healthcare management and convergent applications. The sequencing analysis equipment market is mono- or oligopolistic and convergent applications still remain in the early stages. In this sense, Chapters 4 and 5 are dedicated to implications and policy recommendations related to clinical diagnosis and health management, respectively, for the development of the genome sequencing industry in Korea. In Chapter 4, the author discusses the status of local and global industries and identifies key institutional issues with a particular focus on next generation sequencing (NGS)-based gene tests and analyses in medical institutions. Chapter 5 gives an in-depth analysis of direct-to-consumer genetic testing services for health management and discusses the case study of 23andMe and the FDA's regulatory orientations. In Chapter 6, based on the insights and discussions in the aforementioned chapters, the author presents

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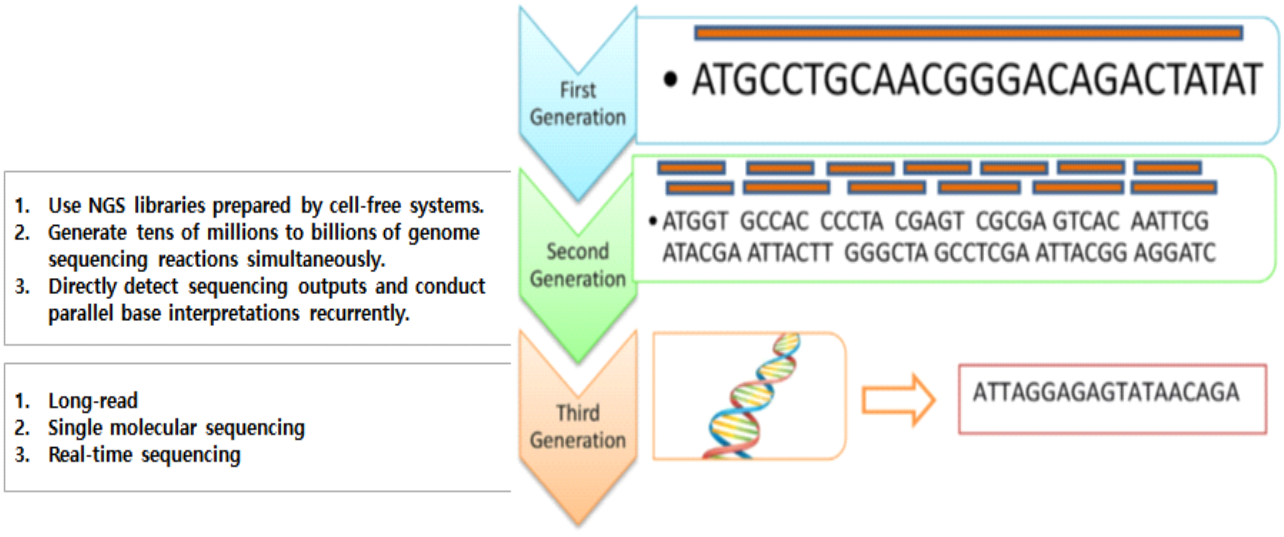
orientations and policy recommendations for the development of genome sequencing in Korea.

2. Evolution of genome sequencing

Finished in 2003, the Human Genome Project (HGP) demonstrated the doability of the sequencing of all human genes (Gullapalli, R. R. et al, 2012). The HGP used Sanger sequencing developed in the 1970s. This first generation sequencing method developed by Sanger and colleagues became popular and was commonly used for almost three decades. As a significant milestone accomplished by cooperation among many institutes across the globe, the HGP costed 2.7 billion dollars for 13 years (National Human Genome Research Institute, n.d.). As Sanger sequencing was shown to be too time-, cost- and labor-intensive, they started looking for a faster and cheaper sequencing technique. Underpinned by knowledge and experience earned from the success of the HGP, the National Human Genome Research Institute (NHGRI) set a goal to lower the cost of whole-genome sequencing to 1,000 dollars in 10 years, which triggered the swift evolution of the DNA sequencing technology in 2004 (Schloss, J.A.,2008). The post-HGP sequencing technology was named next generation sequencing, commonly known as NGS (Goodwin et al., 2016). NGS features three significant improvements compared to the first generation Sanger sequencing technology. First, NGS does not require bacterial DNA replication but uses NGS libraries prepared in a cell-free system. Second, it involves tens of millions to billions of gene sequencing reactions happening simultaneously. Third, sequencing outputs are immediately detected and parallel base interpretations are conducted recurrently. It takes significantly less time and costs compared to Sanger sequencing (Gullapalli, R. R. et al, 2012). Indeed, these developments have made NGS a key technique in basic, translational and clinical studies and be incorporated in clinical practice as a diagnostic tool.

Figure 1. Generational improvement of sequencing techniques



[Source] Wadapurkar and Vyas (2018), Figure 1. Reproduced by the author.

Table 1. Post-HGP development of genome sequencing

Area	2003	2015
Genome sequencing		
Cost to generate a human genome sequence (excluding cost of analysis)	$54M	$1,000
Time to generate a human genome sequence	105 days	1-2 days
Number of human genomes sequenced annually	1	228,000
Human genetics		
Number of genes with known phenotype/ disease-causing mutation	1,474	2,937
Genetic medicine		
Drugs labeled with biomarker information	46	132
Genetic testing products on market	2000-3000	65,839
Basic EHR use by office-based physicians	17%	83%

[Source] The Personalized Medicine Report (2017), p. 47

NGS has limitations, too, one of which being relatively short read sequences. The third generation sequencing, TGS, is also known as long-read sequencing, which generates longer read sequences. TGS features single molecular sequencing and real-time sequencing (whereas sequencing is paused after each bas introduction in NGS). While TGS is primarily used in laboratory settings, it is bringing a revolution in genetic research by enabling genome sequencing with unprecedented precision (Nekrutenko, A., & Taylor, J., 2012).

3. Local and global genome sequencing industries

To take an overview of local and global genome sequencing industries, Chapter 3 focuses on the major applications of genome sequencing, which are divided into sequencing analysis equipment (analysis platforms), clinical diagnosis, and healthcare management and convergent applications. In reality, it is very challenging to classify major applications into four precise categories, as most companies keep expanding their business domain.

Figure 2. Major applications of genome sequencing

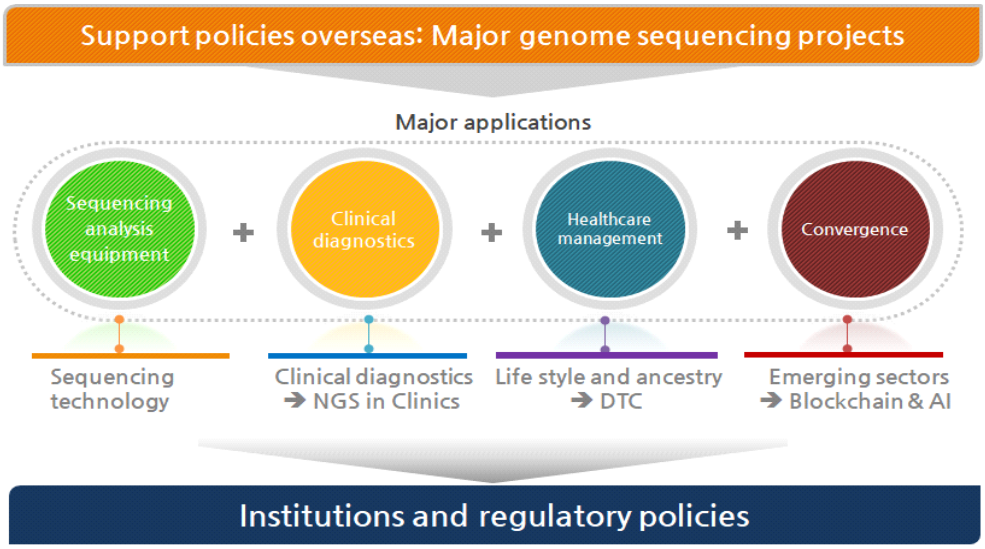
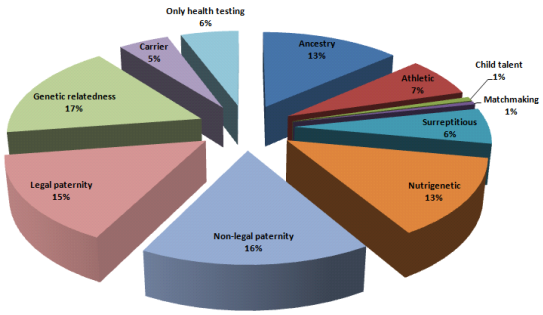


Table 2. Services offered by DTC-GT companies

Service	No. of companies	% share
Ancestry	74	30%
Athletic	38	15%
Child talent	4	2%
Matchmaking	3	1%
Surreptitious	34	14%
Nutrigenetic	74	30%
Non-legal paternity	88	36%
Legal paternity	83	34%
Genetic relatedness	92	37%
Carrier	27	11%
Only health testing	31	13%
Total	246	100%



[Source] Andelka (2016), p.17. Reproduced by the author.

3.1. Overseas genome sequencing industry

For sequencing analysis equipment, Illumina, Thermo Fisher Scientific and BGI Genomics occupy more than 80% of the market (Statista, 2018). As these three companies have dominion over analysis platforms and equipment, there is no significant market dynamics, but relevant companies are actively developing their own business models. Illumina, the market leader in sequencing analysis equipment, offers an analysis platform (BaseSpace) for efficient genome data analysis. Aiming at miniaturization and popularization, the company unveiled its small NGS testing device iSeq100 at the JP Morgan Healthcare Conference held in San Francisco, the USA on January 9 2018 (Biospectator, January 10 2018). It is also expanding its business model by finding and investing in businesses with technical competitiveness. GRAIL was founded in January 2016 to develop blood tests for early cancer detection, and Helix was founded in 2015 as a direct-to-consumer genetic testing and service provider (Illumina, 2017). Given the leading companies' technical and financial abilities and mono/oligopoly in the sequencing analysis equipment market, it does not seem rosy for Korean companies to make strategic move into this area to take some market share.

The field of clinical diagnostics has embraced NGS-based genome sequencing. According to BIS Research (2017), the global NGS market size was estimated to be approximately USD 3.4 billion in 2016 and is expected to reach USD 10 billion in 2024. Foundation Medicine and Myriad Genetics, which are among the leaders in the clinical diagnostics market, are actively launching products and expanding business models.

The market for direct-to-consumer genetic testing (DTC-GT) is surging recently. According to a DTC-GT market insight by Credence Research in 2016, the market was estimated to be USD 125 million in 2018 and expected to grow at an annual growth rate of 25%, reaching USD 290 million in 2022 (Credence Research, 2017). The US company 23andMe is one of the innovative business models in the DTC-GT market. Not only do they provide genetic testings for healthcare, they have had many different disease risk prediction products FDA-approved, further diversifying the overall offerings on the market. According to Andelka

(2016), the company's key services include ancestry, nutrigenetics, and paternity tests, without the need to go through medical institutions, can purchase genetic tests online and receive test results by themselves. Lastly, a new business landscape is developing in convergent genome sequencing applications, combining existing genome sequencing with new technologies such as artificial intelligence and blockchain.

3.2. Local genome sequencing industry

Major Korean companies that offer genome sequencing services include Macrogen, Theragen, DNALink, Medizen Humancare, EDGC, and LabGenomics. Macrogen has world-class sequencing skills and plays leading roles in the global market by, for example, pursuing the Asian Genome project (building a genome database of 100,000 Asian people). Theragen was involved in the human genome mapping project, and recently the company is developing new markets by launching the personal genome sequencing service "HelloGene," which is available at major hospitals.

Looking into these companies' major businesses and revenues reveals that revenues from genome sequencing still account for a minor portion. Taking Theragen's business portfolio as an example, revenues from generic drugs account for 80% of its total revenues, and revenues from genome sequencing services account for 14% (retrieved from the Financial Supervisory Board's Data Analysis, Retrieval and Transfer System). In addition, financial statements from major NGS service providers unveil operating losses most of them are experiencing in relation to continued investment in R&D.

The local genome sequencing market remains stagnant in contrast to the global market, partly due to insufficient demands compared to the number of products and services on the market and regulatory issues that fundamentally block the marketing of certain products and services. For example, a 2007 Presidential Decree banned the testing of 22 genes related to 14 diseases, which was subsequently amended in 2017 to unban four of them: hyperlipidemia associated with the LPL gene, hypertension linked with angiotensinogen, alcohol decomposition associated with the ALDH2 gene, and asthma associated with the IL-4 or beta2-AR gene. However, the testing of the PPAR-gamma (linked with obesity), BRACA (breast cancer), and APOE (dementia) genes is still prohibited (Korea Law Information Center, 2018). Among them, there have been significant progress globally in the study of the BRACA gene known to be associated with breast cancer, and the US DTC-GT provider 23andMe already launched a product therefor (Kim, K., 2018). Regulations on this type of genetic test have not been lifted yet, which would lead to the lack of local genetic analysis data collection in the long run and relevant medical studies, which in turn would hinder the development of treatments.

4. NGS in clinics

4.1. Clinical genome sequencing in the USA

As of March 2018, there are five clinical NGS products that are FDA-approved (CMS, 2018). Initially, three products were approved as companion diagnostics (CDx), which are essential to identify targets of targeted therapies. CDx and therapeutic agents may be matched one-to-one, or one-to-many (Kim, G., 2018).

Foundation Medicine's FoundationFocus™ CDxBRCA was the first to be approved. It is an NGS-based in vitro diagnostic medical device that quantifies BRCA1 and BRCA2 mutations in ovarian tumor tissues. The US FDA approved this NGS-based device, FoundationFocus CDxBRCA, as a CDx to be used with Rubraca. The NGS test identifies the presence of malignant BRCA gene mutations in ovarian cancer patients' tumor tissues, and if one

or more mutations are identified, the patient may be treated with Rubraca. BRCA mutations were observed in 96% of the subjects in the FoundationFocus CDxBRCA trial, and 44% of the patients treated with Rubraca experienced complete or partial tumor reduction with an average duration of 9.2 months (FDA, December 19 2016).

The second was Thermo Fisher Scientific's Oncomine ™ Dx Target Test, which is used to detect BRAF, ROS1, and EGFR mutations in non-small cell lung cancer patients' tumor tissues. This test is used in combination with dabrafenib and trametinib to identify non-small cell lung cancer patients with BRAF V600E mutations. In 2015, the FDA designated it as a Breakthrough Therapy, to be used with dabrafenib and trametinib, for the treatment of progressive and metastatic non-small cell lung cancer patients with BRAF V600E mutation. It was also designated as an Orphan Drug (FDA, June 22 2017).

Illumina's Praxis ™ Extended RAS Panel was the third to be approved as a CDx. On June 29 2017, the FDA approved the use of Praxis Extended RAS Panel, an NGS test to detect RAS mutations in patients' tumor samples, for metastatic colorectal cancer (mCRC). This was the first FDA-approved NGS test to detect a number of RAS mutations for mCRC. The Praxis Extended RAS Panel helps identify the presence of 56 types of RAS gene mutations in mCRC patients' tumor tissues and find appropriate treatments (FDA, June 29 2017).

The fourth was MSK-IMPACT, an NGS-based cancer panel developed by Memorial Sloan Kettering Cancer Center (MSK) in November 2017. This test is widely available, rather than being individually conducted at CLIA-certified labs. The IMPACT obtained FDA approval through the de novo premarket review process, which is applicable to low-to-medium risk submissions for which there is no legally marketed predicate device. Before being FDA-approved, the IMPACT underwent independent review by the New York State Department of Health (NYSDOH), which allowed them to use patient samples in the State of New York. The FDA considered the NYSDOH as an accredited third party reviewer, and MSK included in its FDA submission for the IMPACT information and data filed with the NYSDOH, which streamlined the approval process. The FDA also gave Class II designations to other NGS-based CDx for patients diagnosed with cancer, thereby allowing this type of diagnostic tests to pursue the FDA 510(k) approval process, under which applications are allowed to submit data directly to the FDA or have their data pre-reviewed by accredited third party reviewers such as the NYSDOH.

The FDA Commissioner Scott Gottlieb said "The goal of allowing NGS-based tumor profiling tests to undergo review by accredited third parties is to reduce the burden on test developers and streamline the regulatory assessment of these types of innovative products. As this field advances, we are modernizing the FDA's approach to the efficient authorization of laboratory tests from developers that voluntarily seek 510(k) clearance" (FDA, November 15 2017).

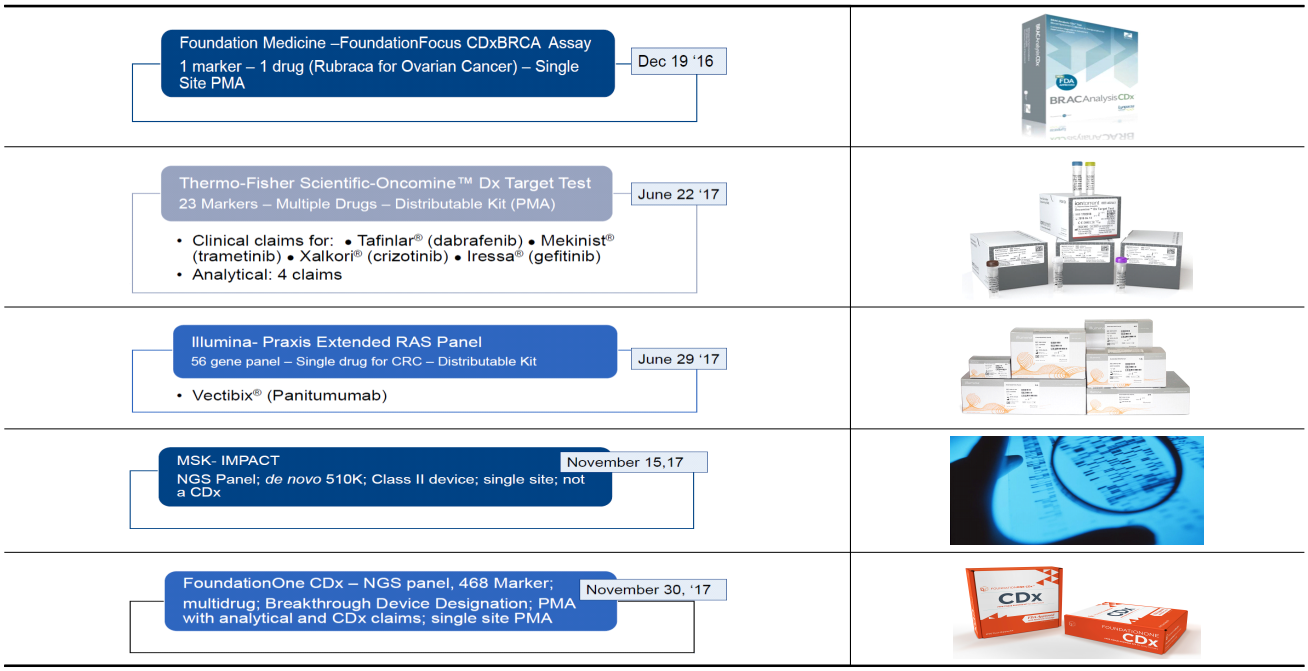
Lastly, the US FDA approved the use of Foundation Medicine's FoundationOne CDx (F1CDx), the first Breakthrough-Designated NGS-based IVD used to detect mutations of 324 genes for all types of solid tumors on November 30 2017. At the same time, the Center for Medicare and Medicaid Services (CMS) approved the payment of benefits for the F1CDx. This was the second IVD reviewed and approved by the FDA and the CMS under the Parallel Review Program. The FDA and CMS approval was granted in six months after the FDA received the application for this novel IVD through the Breakthrough Device Program and the Parallel Review Program (FDA, November 30 2017). The F1CDx obtained its medical device approval and insurance benefit listing at the same time, and the CMS' final decision on the insurance benefit applied to much wider applications than in the preliminary assessment. The simultaneous approval by the FDA

and CMS matters, since being included in the public insurance benefit list would usually mean being included in most private insurance companies' benefit lists. In addition, coverage by the public insurance means higher test accuracy and treatmentability, hence driving many clinics to accept the test.

Regulations related to NGS include both direct regulations by 'approval' processes applicable to NGS-related drugs and medical devices under relevant laws and subsidiary regulations by FDA instructions. In the USA, a New Drug Application (NDA) means the initiation of an official assessment process for FDA approval.

Diagnostics using NGS primarily targets cancer and rare diseases, and in many cases CDx approval is granted to be used with certain drugs, meaning GT products are highly likely to benefit from eased regulations along with relevant drugs, and the five approved products indeed took advantage of deregulation. The FDA offers four deregulation pathways, i.e., the Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review (APEC Harmonization Center, 2016:40). These four processes share the common goal of swift approval for novel drugs but differ in eligibilities and time factors. To be marketed in the USA, a medical device should be approved by the FDA, of which procedures and time frames depend on the product classification. All medical devices to be sold in the US market are classified into Class I, II, or III, and different regulations apply to different classes. Class III devices are ones that are essential for life supporting or have significant impact on health, hence subject to Premarket Approval (PMA), whereas Classes I and II devices are subject to 510(k) (Premarket Notification) (Park J., 2017). The US FDA's eased regulatory programs applicable to medical devices are: the Breakthrough Devices Program; 510(k) (Pre-market Notification 510K); Third Party Review; and De Novo Program (FDA, October 25 2017; FDA, September 27 2018(a); FDA, September 13 2018; FDA, September 27 2018(b)).

Figure 3. FDA-approved NGS products for clinical diagnostics



[Source] Celgene (2017), reproduced by the author.

In addition to these regulations, the FDA also reveals its orientations through its guidelines. In relation to NGS, the FDA announced two guidelines in 2018. The first is the Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics, which provides guides for clinical developers to use FDA-approved public databases to support their clinical claims (FDA, April 13 2018(a)). The second is the Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases (FDA, April 13 2018(b)), which is related to elements required to design and develop NGS-based GTs and demonstrate their analytical validity. Not being an official FDA guideline, these considerations unveil where the FDA's policy is oriented towards.

4.2. Clinical genome sequencing in Korea

To introduce NGS-based genome sequencing techniques, the Korean Ministry of Health and Welfare established the Details on Medical Care Benefit Application Standards and Methods in 2017, thereby initiating insurance benefits for NGS-based genetic panels (Ministry of Health and Welfare Announcement, 2017). NGS tests may be used for cancer patients, patients with hereditary diseases and suspected patients, and insurance benefits are applied to 10 solid tumors including gastric, colorectal, lung, breast, ovarian cancer and melanoma, six types of blood cancer (acute myeloid and lymphocytic leukemia, etc.), and other diseases including three hereditary disorders (congenital deafness, retinitis pigmentosa, etc.). In Korea, 52 institutions are approved to conduct NGS-based gene panels, which are subject to annual re-assessment. To vitalize NGS genome sequencing, the Korean Ministry of Food and Drug Safety established the NGS Clinical Laboratory Accreditation System in August 2016, which aimed to ease the regulations at a reasonable level to ensure the timely use of new technologies such as NGS tests in the local market. Previously NGS medical devices were subject to individual approval processes for their safety and effectiveness, but under the new system they may pursue approval as individual medical devices, or NGS laboratories may be accredited and genome sequencing devices used therein are deemed approved.

Table 3. NGS Clinical Laboratory Accreditation System

Rules on Medical Device Approval, Reporting and Assessment, Etc.
Article 20-2 (Production and Import Permits, Etc.) Genome sequencing devices (A22530.01, Class 2) used for next generation sequencing in clinical laboratories of which quality management systems and testing performances are evaluated and deemed appropriate by the Minister of Food and Drug Safety shall be deemed approved, certified or reported under Article 6 of the Act.

[Source] Korea Law Information Center (retrieved on June 25 2018).

Despite the swift introduction of NGS services to the Korean market, there have been many issues raided so far. First, NGS-based genetic panels may only be conducted in medical institutions reported as genetic testing institutions. The diagnostics industry in Korea is calling for the removal of the provision that prevents diagnostic testing businesses from being approved as genetic testing institutions so that more institutions can offer NGS tests. Second, as there are no approved agents and programs available, there may be possible analytical errors and results differing by laboratory. This is thought to be associated with the fact that individual devices, agents and programs do not need to be approved separately as long as the institution itself is accredited as an NGS laboratory. Third, as clearly shown in the Ministry of Health and Welfare's notification, NGS testing fees are calculated based on the number or length of genes tested, which may lead to genes with little clinical significance being added to the

test or the tester elongating the length of genes on purpose. Lastly, these tests are yet to be recognized as standard tests, hence limitations in treatment applications and limited clinical applications.

5. Genome sequencing for healthcare management: DTC-GT

Recently the DTC-GT market in the USA is surging. Market analytics shows that the number of customers started rapidly increasing in the second half of 2016, reaching 12 million globally in February 2018. Most of the DTC-GT customers are in the USA, and it is estimated that one out of 25 adults in the USA has his/her genome data obtained from DTC-GT. In terms of the number of customers, Ancestry leads the market, serving seven million customers, followed by 23andMe, MyHeritage, and Family Tree DNA (Antonio Regalado, 2017).

Two of the market leaders, Ancestry and 23andMe, offer the following genome sequencing and testing services. Ancestry, as the name says it all, offers genome sequencing and testing services with a particular focus on ancestry. These include information on clients' ethnicity, as well as their ancestors' location results, temporal changes and expected migration routes. In addition, the company offers DNA Matches to Living Relatives and allows its users to build and maintain family trees and share them with other Ancestry users online (Ancestry website). 23andMe offers the most number of genome sequencing and testing services, which are divided into the following five categories: ancestry, wellness, traits, carrier tests, and genetic health risk tests. 23andMe is the only provider of FDA-approved carrier and genetic health risk tests. Carrier tests are applicable to more than 40 hereditary diseases including cystic fibrosis, Bloom syndrome, and Gaucher disease, and genetic health risk tests are designed to detect genetic variants for the following diseases.

Table 4. 23andMe's disease risk tests

Hereditary disease	Genetic variant
BRCA1/BRCA2 (Selected Variants) breast, ovarian and other cancers	3 variants in BRCA1 and BRCA2 genes (relevant for Ashkenazi Jewish descent)
Age-Related Macular Degeneration form of adult-onset vision loss	2 variants in ARMS2 and CFH genes (relevant for European descent)
Alpha-1 Antitrypsin Deficiency lung and liver disease	2 variants in SERPINA1 gene (relevant for European descent)
Celiac Disease gluten-related auto immune disorder	2 variants near HLA-DQB1 and HLA-DQA1 genes (relevant for European descent)
G6PD Deficiency anemia	1 variant in G6PD gene (relevant for African descent)
Hereditary Hemochromatosis iron overload	2 variants in the HFE gene (relevant for European descent)
Hereditary Thrombophilia harmful blood clots	2 variants in F2 and F5 genes (relevant for European descent)
Late-Onset Alzheimer's Disease	1 variant in APOE gene
Parkinson's Disease	2 variants in LRRK2 and GBA genes

[Source] 23andMe website, https://www.23andme.com/dna-reports-list/ (retrieved on October 10 2018).

As mentioned earlier, 23andMe is the only DTC-GT provider that is approved by the US FDA to offer certain genetic tests. Indeed, regulations on 23andMe represent the FDA's regulatory history in the DTC-GT market. In 2013, the FDA placed sanction against 23andMe for conducting carrier, disease risk and drug response tests without FDA approval, which drove the company to face the risk of closure (FDA, November 22 2013). However, the FDA started granting approval for 23andMe's genetic tests in 2015 in favor of DTC-GT. In 2015, the FDA gave 23andMe the first approval for the Bloom syndrome carrier test (Department of Health & Human Services, October 1 2015), followed by approval for genetic health risk (GHR) tests for 10 diseases in April 2017 (FDA, April 6 2017). More recently, the FDA approved three BRCA1/2 genetic variants tests for the diagnosis of breast and ovarian cancer in March 2018, confirming its positive stance to the DTC-GT market (FDA, March 6 2018).

Alongside approval for genetic tests offered by 23andMe, the FDA announced a general policy for DTC-GTs. In its announcement in November 2017, the FDA made it clear that the agency gives priority to consumer safety while coordinating its roles to ensure efficient approval for novel, innovative technologies (FDA, November 6 2017). Accordingly, it unveiled the plan to allow DTC genetic health/disease risk tests to undergo approval processes similar with that applicable to digital healthcare products (FDA, October 3 2018). Given the currently announced and/or approved DTC-GTs, applications for carrier and genetic health/disease risk tests seem to be processed under the De Novo Program. This program is for novel medical devices with low-to-moderate risk levels that have no pre-marketed products, hence no need for clinical trials to demonstrate new devices' equivalency or superiority to conventional treatments or devices. The DTC carrier test undergoes the same approval process as the De Novo Program through the Autosomal Recessive Carrier Screening Gene Mutation Detection System, and recently 23andMe had its BRCA1/2 genetic health/disease risk tests approved through the De Novo Program (FDA, March 6 2018). This implies that approval for disease risk-related DTC-GTs is increasing in line with the FDA's intention to keep up with this new healthcare paradigm.

In the Korean market, DTC-GTs are available for 46 genes related to 12 test items designated by the Ministry of Health and Welfare in June 2016 (Ministry of Health and Welfare press release, 2016), but most of them are not available for end customers to purchase for their healthcare management. Major providers of DTC-GT products available on the market include DNALink, Theragen, Medizen Humancare, EDGC, LabGenomics, and Bionia, but the Korean genetic test market does not seem to have strong growth potential yet (Maeil Economy, July 13 2016; Biospectator, August 20 2018).

6. Conclusion and policy recommendations

6.1. Expert Delphi to develop policy recommendations for genome sequencing

To develop policy recommendations for genome sequencing, the author conducted an expert Delphi survey. The questions were divided into ① policy measures to secure genetic data and expand the base, and ② policy measures for genome sequencing for clinical diagnostics and healthcare management, which were further sub-divided into detailed question areas. All multiple choice questions were based on the 5-point Likert scale, and the questionnaire was semi-structured with response questions designed to collect different opinions from experts. The expert Delphi to develop policy recommendations for genetic data collection had nine respondents from academia and medicine and 17 from industry, who all answered by email.

Table 5. Expert Delphi questions

Area	Key questions
Genetic data collection and base expansion	• Overall evaluation of genetic data collection and base expansion policy - Policy to build and use genetic databases - Medical school education policy to expand the base for genomics - Policy to foster professional human resources to expand the base for genomics. • Measures to improve genetic data collection and base expansion policy
Genome sequencing for clinical diagnostics and healthcare management	• Overall evaluation of policy for genome sequencing for clinical diagnostics and healthcare management - Evaluation of policy for genome sequencing for clinical diagnostics - Evaluation of policy for genome sequencing for healthcare management • Dilemma in policy for genome sequencing for clinical diagnostics and healthcare management - Presence of dilemmatic situations in policy for genome sequencing for clinical diagnostics and healthcare management - Approval-based regulations for product safety - Permission-based regulations for market vitalization • Orientations and improvement of genome sequencing for clinical diagnostics and healthcare management

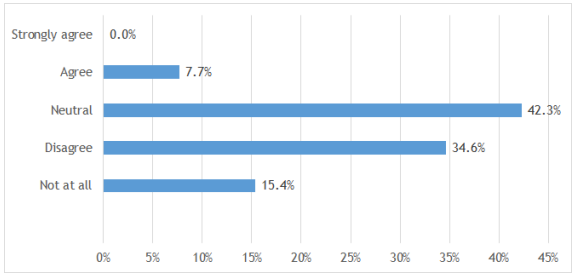
[Source] Prepared by the author.

6.1.1. Genetic data collection and base expansion

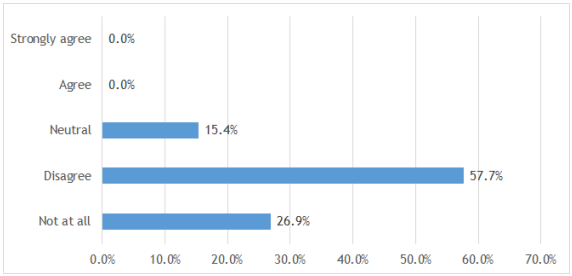
Respondents to the expert Delphi on genetic data collection found the nation's policy to build and use genetic databases unsuccessful: 84.6% of them answered that the data use policy was not successfully implemented. There were no dividing opinions between academia/medicine and industry, urgently calling for improvements in the data use policy. As to the implementation of policies for medical school education and professional human resource fosterage to expand the base for genomics, 69.2% and 84.6% of the experts saw these policies negative, respectively. For policy measures to collect genetic data and expand the base, 81% of experts from both academia/medicine and industry answered that large-scale genome projects are the most urgently needed (multiple choices allowed). Sixty-five percent of the respondents found that the sharing of profits from the use of genetic information between individuals and institutions is needed, 62% were in favor of R&D investment in genetic data analysis and interpretation capacity building, and 62% had a positive view to legal and institutional development for genetic information protection. These results show that local experts share the common view to database building, use, protection and profit sharing regardless of their affiliation.

Figure 4. Overall evaluation of genetic data collection and base expansion policy

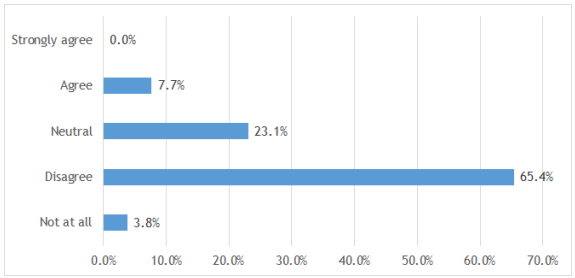
Successful implementation of policy to build and use genetic databases



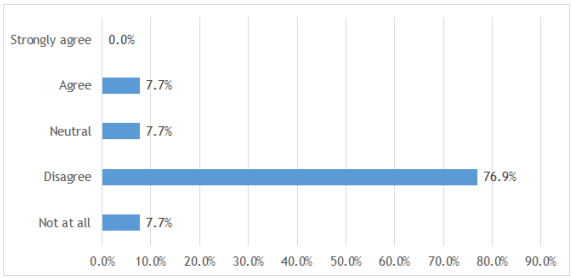
Successful implementation of genetic data use policy



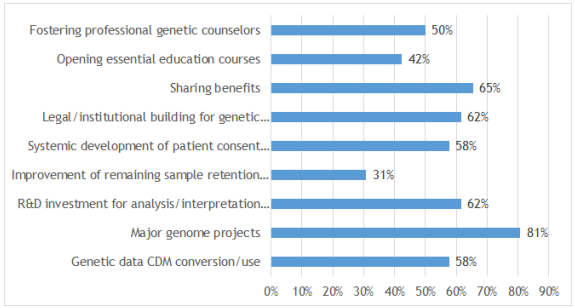
Successful implementation of medical school education policy to expand the base for genomics

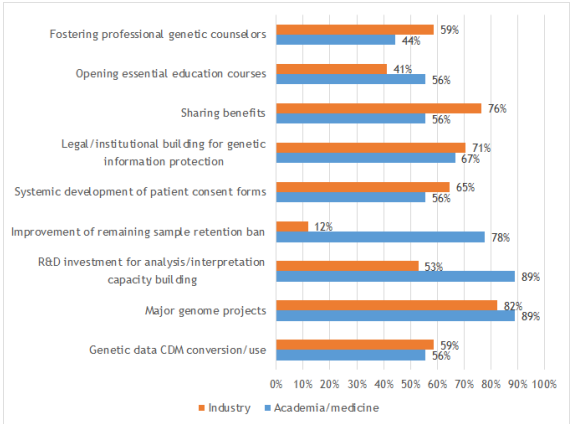


Successful implementation of policy to foster professional human resources to expand the base for genomics.



Measures to improve genetic data collection and base expansion policy (overall/by affiliation)





[Source] Prepared by the author (results from the expert Delphi)

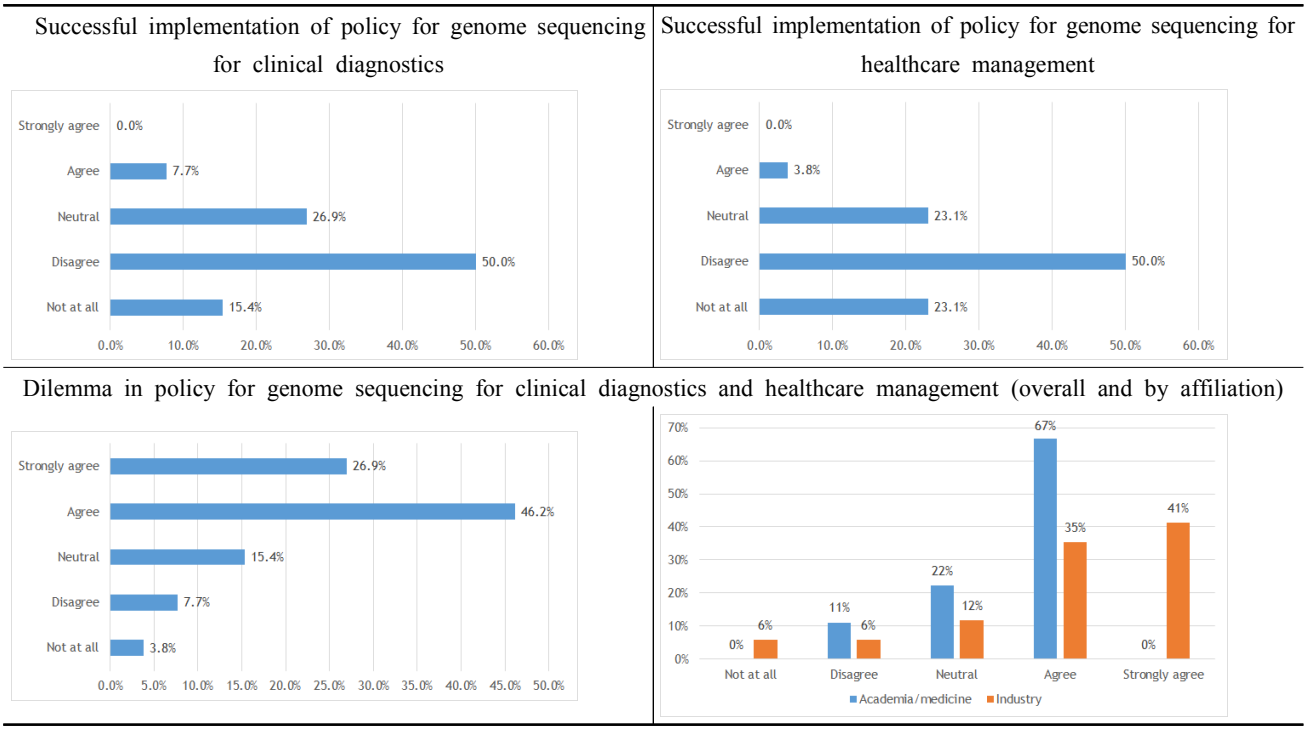
6.1.2. Policy measures for genome sequencing for clinical diagnostics and healthcare management

Among the respondents to the exert Delphi on the nation's policy for genome sequencing for clinical diagnostics and healthcare management, 65.4% and 73.1% found them unsuccessful, respectively. They were particularly negative to the policy for genome sequencing for healthcare management, which is thought to be associated with the limited number of items available for genetic tests. As for the dilemma in the genetic test policy for clinical diagnostics and healthcare management, i.e., the situation that makes it difficult to determine the policy orientation towards eased or tightened regulations, 73.1% of the experts said there is a dilemmatic situation.

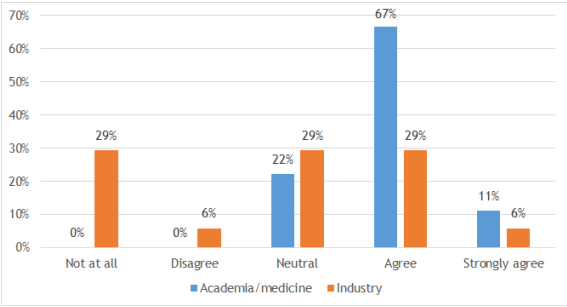
Their response shows that the dilemmatic situation the nation's genetic test policy is facing, which is further confirmed by their answers to the following questions. If there were no dilemmatic situations in the nation's genetic test policy, academia/medicine and industry would have answered differently to two contrasting questions, i.e., "do you think it is necessary to consider product approval-based regulations to ensure the safety of genetic tests?" and "do you think it is necessary to the current permission-based regulation system for the vitalization of genetic tests?," or shared the same view to strengthening or easing the regulations. However, their actual answers showed that industry would be in favor of eased regulations for market vitalization but at the same time would see product approval worth considering for safety, and academia/medicine would not only value safety but would agree on the need to expand the list of item permissions for market vitalization.

Concerning the genetic test policy orientations and improvements for clinical diagnostics and healthcare management in Korea, answers varied by affiliation. In academia/medicine 78% of the respondents said that increasing NGS-based genetic tests applicable for clinical diagnostics to increase insurance benefits for and vitalize NGS-based genetic tests and strengthening regulations on NGS genetic test institutions are both needed. Scholars and practitioners found the need to increase genetic tests in the field of clinical diagnostics but also said that regulations on genetic testers should be stricter for safety's sake. In industry, 76% of the respondents were in favor of increasing NGS genetic test items for clinical diagnostics for market vitalization, and 65% in favor of expanding the list of DTC-GT items subject to permission to increase insurance benefits for NGS-based genetic tests and vitalize the market. These results showed that the industry saw it necessary to increase test items in both clinical diagnostics and healthcare management for market vitalization.

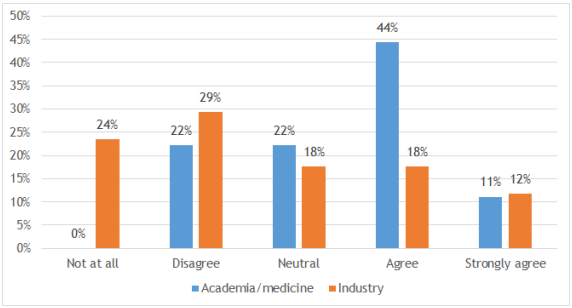
Figure 5. Evaluation of policy for genome sequencing for clinical diagnostics and healthcare management



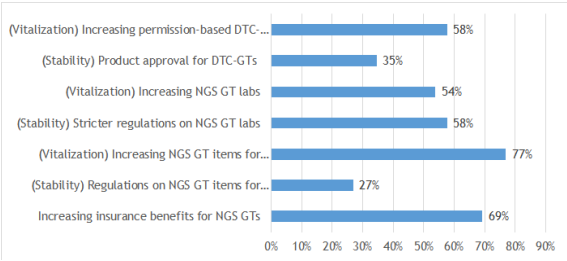
Need for approval-based regulations for product safety

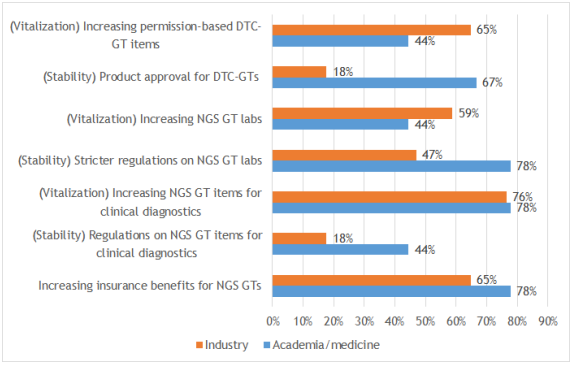


Need for retaining and expanding permission-based regulations for market vitalization



Orientations and improvement of genome sequencing for clinical diagnostics and healthcare management (overall and by affiliation)





[Source] Prepared by the author (results from the expert Delphi)

6.2. Policy recommendations for the development of genome sequencing

In the field of genome sequencing, Korea should adopt a strategy to support overall technical and service improvements, rather than narrowing the targets and promoting specific areas. Genome sequencing has big intra-disciplinary ripple effects and scalability. Although the local market remains insignificant compared to the global market, genome sequencing has the potential to serve as foundations for precision medicine and bring changes in lifestyles and the way people live in the future, which highlights the need to support the development of all steps of genome sequencing ranging from data generation to variant detection, interpretation and diagnosis. For that purpose, the author presents the following policy recommendations.

6.2.1. Conduct major genome projects stably in the long run

As of 2018, there have been no major human genome database building projects pursued in Korea. The state recognizing the importance and pursuing major genome projects would allow for generating big genome databases and help participating researchers and institutions obtain knowledge on genetic data generation, analysis and interpretation. As shown in the HGP, universities and institutes from the USA, the UK, France, Germany, Japan, and China took part in the project, and subsequently the USA and the UK conducted their own major genome projects, and the Beijing Genomics Institute (BGI) China established to participate in the HGP has grown remarkably, positioning itself as one of the top three players in the sequencing analysis equipment market. In addition to data collection,

major projects have advantages including participating institutions' capacity building, private business promotion, and surrounding environment building. In Korea, the Cohort Building Project for Precision Medicine was pursued in 2017, but the preliminary feasibility assessment recognized its necessity by found relevant grounds and plans insufficient, hence failing to advance into the final stages (Korea Institute of Science & Technology Evaluation and Planning, 2017). Genome project would not normally yield short-term outcomes and need stable planning and implementation in the long run if wishing to ensure findings for precision medicine, private businesses' research capacity building, and relevant environment creation. Without a far-sighted view to genome projects, major projects could not be anticipated in Korea, hence unable to collect genome data and medical research and industrial development based thereon.

6.2.2. Invest in R&D on data analysis and interpretation

Efforts to retain genetic databases and develop new genetic data should be accompanied by continued investment in R&D on variant interpretation. Both public and private sectors all over the world are aggressively working to generate and acquire genetic data. In particular, private global pharmaceutical companies are making massive joint investment to acquire databases from genome sequencing companies. In April 2016, the global pharmaceutical major AstraZeneca commissioned Human Longevity Inc. to initiate a genome sequencing project with two million subjects and provided funds therefor. In 2018, GlaxoSmithKline paid 23andMe three million dollars to obtain exclusive access to a genetic database of approximately five million people (GSK website). A large amount of public and private funds are invested in generating and collecting data, but what is more challenging and matters more is to detect variants from sequenced genetic data, interpret them and make diagnosis, which is the core capability in genome sequencing in the future (Biospectator, July 27 2018). However, most of the research funds have been invested in generating sequencing data. For continued development of genetics, research funds should go to demonstrating the clinical validity and effectiveness of the results and interpreting variants found from databases.

6.2.3. Make a fundamental shift in regulatory approaches and diversify review processes

The FDA plays the pivotal role in drug and medical device regulations in the USA. In particular, the FDA is making efforts to ensure that relevant regulations are enforced in a transparent and reasonable manner under the Federal Food, Drug and Cosmetic Act and FDA Guidances as practical enforcement measures.

For drugs, the USA enacted the Orphan Drug Act, under which eased regulations are applied to new drugs for the treatment of rare diseases. Detailed process-wise, the agency offers procedural easement through the Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review Programs.

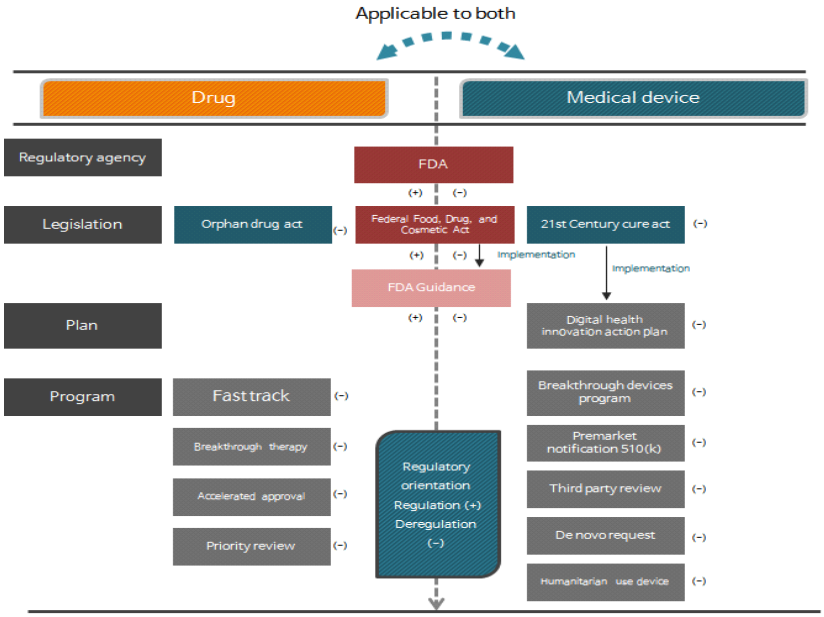
For medical devices, the nation enacted the 21st Century Cure Act as a legal ground for eased regulations for medical devices. In doing so, the USA established the Digital healthcare Innovation Plan to present action plans to make actual regulatory easement happen. The newly introduced Breakthrough Device Program, along with the existing deregulation pathways before the 21st Century Cure Act, i.e., the 510K Pre-market Notification, Third Party Review, and De Novo Request, is the pioneer in the nation's efforts for deregulation for medical devices.

Regulations on NGS-related medical devices are facing two-faced legitimacy: having control to ensure the safety of new medical devices and minimize relevant risks and deregulation in a humanitarian

perspective to facilitate the treatment of rare or stubborn diseases. In addition, there is justification for deregulation from the economic perspective to ensure the development of relevant industries. The recent US drug and medical device regulations have fidelity in many different legal and policy measures to pursue regulatory and de-regulatory actions, which are largely categorized into the following three.

The first is duality in regulations. The FDA's policy aims to build a dualism regulatory system that embraces both strict and eased regulatory review processes in order to accomplish two policy goals of ensuring the safety of drugs and medical devices and meeting unsatisfied medical demands. In particular, the agency offers a range of detailed programs designed to reduce processing time to meet urgent needs, under which eligible products can benefit from simplified review processes. The second is a fundamental change in the regulatory approach. Taking its legal ground from the 21st Century Cure Act and the Digital Healthcare Innovation Action Plan, the Breakthrough Device Program ensures bilateral communications between the developer and the regulatory body as early as in the development stages, whereby helping the developer enter the market with new medical devices. It is notable that the regulatory body assists the developer in the review process, rather than keeping the high profile as it used to do. The third is the establishment of organized, swift systems of laws, plans, guidances and policy programs. As the regulatory body, the FDA keeps updating its regulatory standards and levels in line with the development of new medical technologies and is particularly agile in easing regulations for low-risk products and cases where swift development is required, for example, for the treatment of rare diseases. The agency seems to be well-organized in improving regulations based on the organic connections between laws, action plans and detailed policies. Regulations are always one step behind products and services launched on the market, but the point should be how much we can reduce the time gap between them. In this sense, the Korean MFDS should consider diversifying and advancing its approaches and review processes, along with expanding the list of items available for genome sequencing.

Figure 6. Drug and medical device regulations in the USA



[Source] Prepared by the author

6.2.4. Develop essential medical school courses to improve genetics education

As genome sequencing develops, we pay less for genome sequencing services and receive results in a shorter period of time, hence the explosive increase of genetic data. Medical professionals are responsible for the understanding and use of the data, but many studies show that they are not yet ready for it (Carroll J.C. et al, 2016; Delaney S.K. and Christman M.F., 2016). And it is thought that additional education programs are needed for medical professionals to understand and interpret genetic data that are significantly bigger that data sets they used to read in their daily practice. Although they seem to recognize the importance and growth potential of genome sequencing and acknowledge the lack of relevant education programs, medical schools do not seem to have made sufficient improvements in their curricula. Plunkett-Eondeau et. al. (2015) investigated genetics education programs offered by American and Canadian medical schools in 2013 and 2014. Most medical schools had genetics courses in the first two years (before clinical practice), and only 26% reported that they had official genetics education programs for years 3 and 4, and most of the respondents answered that they found that medical school curricula lacked genetics studies. The most commonly offered genetics course topics included Mendel's disease (90%), cancer genetics (89%), and inheritance patterns (89%), and common recent additions included precision medicine (21%) and DTC-GT (18%). Common recent deletions included eugenics (17%), combination analysis (16%), and evolutionary genetics (15%). These recently added topics suggest that the medical schools in the USA and Canada are changing themselves to keep the pace with the recent healthcare paradigm. In Korea, too, universities and public institutes are opening genetics expert courses with the aim to expand education in the field of genome sequencing. As one would not expect a medical school course to be open in a short period of time, offering expert courses has its own significance. However, such courses would last for only three to four months, hence the focus is on analyzing a large amount of genetic data, rather than having in-depth understanding on genetics. To ensure long-term growth of genetic medicine and foster professionals, medical schools in Korea should consider opening essential genetics courses and making new attempts, in consideration of new courses and programs in American and Canadian medical schools.

6.2.5. Develop substantially effective patient consent form for genome sequencing and develop systems for genetic information protection

Advancement in genome sequencing is followed by the popularization of WGS(Whole genome sequencing). More people will tap into genome sequencing services in the future, and in doing so it is needed to develop a consent form that clearly states individuals' rights. A study by Carmen Ayuso et. al. (2013) presented ten essential elements for a WGS patient consent, which range from general elements such as the scope of the test, the test procedures and expected benefits to alternative test methods, measures to ensure confidentiality and privacy of the result, incidental findings (IFs) that may be generated from the use and study of bio samples, and the patient's right not to know. As a characteristic of genetic information, IFs refer to information that is incidentally found in the course of analysis and interpretation other than the original purpose of the test. As interpretation techniques keep developing, IFs may be continuously generated from pre-analyzed genetic information, and on the contrary to what the term 'incidental' implies, such information might lead to a material result for the patient. Therefore, a patient consent form should cleary state whether to retain such information, and

if doing so, how long.

In addition to developing a consent form in consideration of the characteristics of genetic information, also needed are in-depth studies on personal genetic information protection and privacy. Given the aforementioned nature of genetic information, the management of genetic information requires more considerations than any other types of health information. In traditional personal information protection and use, de-identification played an important role. But some point out the ultimate unavailability of de-identification measures for genetic information that contains all information on a certain individual, which is underpinned by recent studies. A paper published in Science in 2013 created a big stir by reporting that part of personal identity might be retrieved from de-identified public databases for research or non-research purposes, and another paper showed that individuals' face may be inferred by looking at genetic information (Melissa Gymreck et al., 2013). In the era of big data, more personal information is accessible to a general run of people, and the development of data processing technologies has made re-identification easy, which used to be technically impractical. In addition, more and more health information is stored in digital formats, like most types of personal information, it is easier to access such information and combine with genetic information.

While the USA has no comprehensive privacy laws, the HIPAA Privacy Rule serves as the federal-level protection for health information in traditional healthcare services, and the Genetic Information Nondiscrimination Act of 2008 prohibits discrimination based on genetic information. However, many have expressed criticism and concerns on that there are no laws or institutions that control re-identification based on genetic information (Kulynych, J., & Greely, H. T., 2017). In the EU, Article 26 of the newly effective GDPR clearly provides that the use of pseudonymized data reasonably likely to be used for re-identification is restricted, but it gives no explanations on how to determine the reasonable likelihood of re-identification and contains no articles to clearly regulate or ban re-identification. On the other hand, the Australian government proposed the Re-identification Offence Bill in October 2016, under which re-identification of personal information would be considered a criminal offence, but has faced strong objections from academia. In this regard, discussions are needed as to the sufficiency of the existing privacy and life ethics laws in Korea for the protection of genetic information and the necessity for new legislations or regulations, along with efforts to pursue state-level genome projects and promote relevant industries.

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