ELSI issues of Precision Medicine

- Comparison of US, South Korea, China and Mongolia focusing on informed consent and privacy

Norov Tumendemberel

Graduate School of Public Health
Yonsei University
Department of Global Health
Division of Global Health

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This certifies that the Master's Thesis
of Norov Tumendemberel is approved.

_____
Thesis Supervisor: So Yoon Kim

_____
Thesis Committee Member: Ilhak Lee

_____
Thesis Committee Member: Hannah Kim

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Yonsei University
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List of Abbreviation

AURP	All of Us Research Program
BSA	Bioethics and Safety Act
CDC	Center for Disease Control and Prevention
CDR	Chronic Disease Registries
DTC	Direct-to-consumer
EHR	Electronic Health Record
ELSA	Ethical, legal and social aspects
ELSI	Ethical, legal, and social implications
EMR	Electronic Medical Record
EU	European Union
FDA	Food and Drug Administration
HGP	Human Genome Project
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HPO	Healthcare provider organization
IT	Information Technology
KCDA	Korea Disease Control and Prevention Agency
KUMC	Korea University Medical Center
MHI	Mongolian Health Initiative
MOHW	Ministry of Health and Welfare
NCCR	National Central Cancer Registry
NCI	National Cancer Institute
NDSS	National Death Surveillance System
NHS	National Health Service
NIH	National Institutes of Health
NIST	National Institute for Standards and Technology
NRC	National Research Council
ONC	Office for the National Coordinator
P-HIS	Precision Medicine Hospital Information System
PIPA	Personal Information Protection Act
PIPL	Personal Information Protection Law
PMI	Precision Medicine Initiative
RRI	Responsible Research and Innovation
UK	United Kingdom
US	United States

Abstract

ELSI issues of Precision Medicine
- Comparison of US, South Korea, China and Mongolia focusing on informed consent and privacy

This study aims to review current precision medicine, analyze ELSI issues and compare legal and regulatory framework of informed consent and privacy issues in countries, namely US, South Korea, China and Mongolia. This has been conducted through analysis of current situation and challenges that four countries are facing in terms of informed consent and privacy issues in precision medicine. The purpose of this study is to develop recommendation for Mongolia based on three countries experiences and pros during development of precision medicine regarding informed consent and privacy.

In order to carry out this study, mainly two study methods are applied. First, the literature review was performed with academic articles and reports on precision medicine and its ELSI research including informed consent and privacy issues, and officual documents from each government website. Secondly, the comparative analysis of the legal and regulatory frameworks that relate to informed consent and privacy on prevision medicine was conducted in four countries.

Through the analysis, it has clearly revealed that Mongolia need to improve regulation related to informed consent, including appropriate language and terms, evaluation questions and approval of electronic version. But in Mongolia, special contemplation

should be discussed in order to develop electronic informed consent due to nomadic life, lack of infrastructure, like internet, computer in remote areas, and low computer and health literacy, especially in non-capital areas. Since Mongolia is taking first step in privacy protection in context of personal information and sensitive information including genetic and biometric, several updates and recommendation could be proposed based on described approaches and solution ways from respective countries. This includes official implementation of PIPL, development of guideline for de-identification of personal information and building capacity for human resources and technology. Moreover, experience from developed countries can help improvement but approach need to be naturalized accordance with Mongolian background.

Even though Mongolian government is started to focus on biomedical researches and related issues to enhance quality of research field and open more gates to researchers, infrastructure preparedness has developed very slowly. Recommendations arise from this study, may provide some opinions in building better frameworks targeting informed consent and privacy issues in Mongolian situation. Furthermore, detailed analysis from expert's perspective will need to be conducted for achieving successful results with improvement from international experts' experiences and support.

Keywords: Precision medicine, ELSI, informed consent, privacy, legal and regulatory frameworks

Chapter 1 Introduction

1.1 Background

Across the globe, new generation of research, especially genome related, has been promoted in recent years due to development of advanced technologies and large-scale databases, like biobank, with big data. Particularly in biomedical science, these developments play big role as future of diagnosis and treatment of diseases. The task is that how we can use them effectively in healthcare fields to tackle the diseases, like cancer, diabetes, cardiovascular and so on in era of increased life expectancy.

Researchers have been going deeper into genome to discover mystery of diseases development with the rapid growth of scientific knowledge and analysis methods of data and genetics. This attempt has started with Human Genome Project (HGP) and now, it is "precision medicine to develop disease treatment and prevention that seeks to optimize effectiveness by considering individual characteristics in genes, lifestyle and environment". [1] In order to fulfill it, President Obama announced Precision Medicine Initiative (PMI) in United States (US) in 2015 [2] and following it, other countries, such as South Korea, United Kingdom (UK), Japan [3], China and France [4] initiated precision medicine research as one of their national strategic plans.

On the other hand, there are ethical and legal issues related to not only the precision medicine but also, human genome studies [3, 5]. The research for these issues such as privacy, genetic discrimination, genetic testing and so on is called ELSI program which first implemented during the HGP in US. [6] Since implementation of precision medicine, several challenges and concerns, related to ELSI, have been identified and discussed. [3, 7] Especially

concerns regarding genetic privacy, data protection, public awareness and informed consent are included. Based on the discussion and characteristics and limitation of the countries, it is required to improve current situation for national strategy because precision medicine requires more advanced approach comparing to traditional research. [8]

However, implementation of precision medicine has not initiated as national plan in Mongolia which requires experience-based learnings from countries, such as US, South Korea, China and many others. Also, there have been few studies that compares legal and regulatory frameworks in Asian countries and national strategy in developed countries. [3, 8, 9] Yoshizawa et al. (2014) showed the differences regarding regulatory frameworks in East Asian countries, and significance of ethical review and informed consent based on country's characteristics. [8] Minari et al. (2018) highlighted concern related to ethics and policy in implementing precision medicine, lessons from US, UK and Japan. [3] However, these studies showed limitations, i.e. concentrated on developing or developed countries that are not included Mongolia for comparison, and lack of detailed review of informed consent requirements in those countries.

1.2 Purpose

Based on the above background information, the aims of this study are determined as follows:

1. To review the concept and characteristics of precision medicine in US, South Korea and China.
2. To study ELSI challenges and practices and focusing on informed consent and privacy issues from ELSI research in precision medicine.
3. To conduct a comparative analysis for regulation, guidance and improvisation experiences corresponding informed consent and privacy issues and
4. To make recommendation or suggestion for the new direction in Mongolia

1.3 Methodology

This study is aimed to review current precision medicine and analyze ELSI issues and regulations relating to informed consent and privacy issues in countries, namely US, South Korea, China and Mongolia. Selection of these countries is due to influence of precision medicine to Mongolia, especially current initiation of collaboration between China and Mongolia in private sector. In addition, US is selected as original and well-achieved country for precision medicine initiative and South Korea as one of Asian country that implemented precision medicine and comparator to China.

In order to carry out this study, mainly two study methods are applied. First, the literature review was performed with academic articles and reports on precision medicine and its ELSI research including informed consent and privacy issues, and official documents from each government. Second, the comparative analysis of the legal and regulatory frameworks that relate to informed consent and privacy on precision medicine was conducted in four countries. The academic articles which are published between 2015-2021 have been collected through PubMed, Google Scholar and Medline databases. Official documents, including legal and regulatory frameworks and guidelines, were collected through government and project official websites which provided the latest and original documents. (Figure1) Few of official documents were translated into English using Google translate due to lack of official translation.

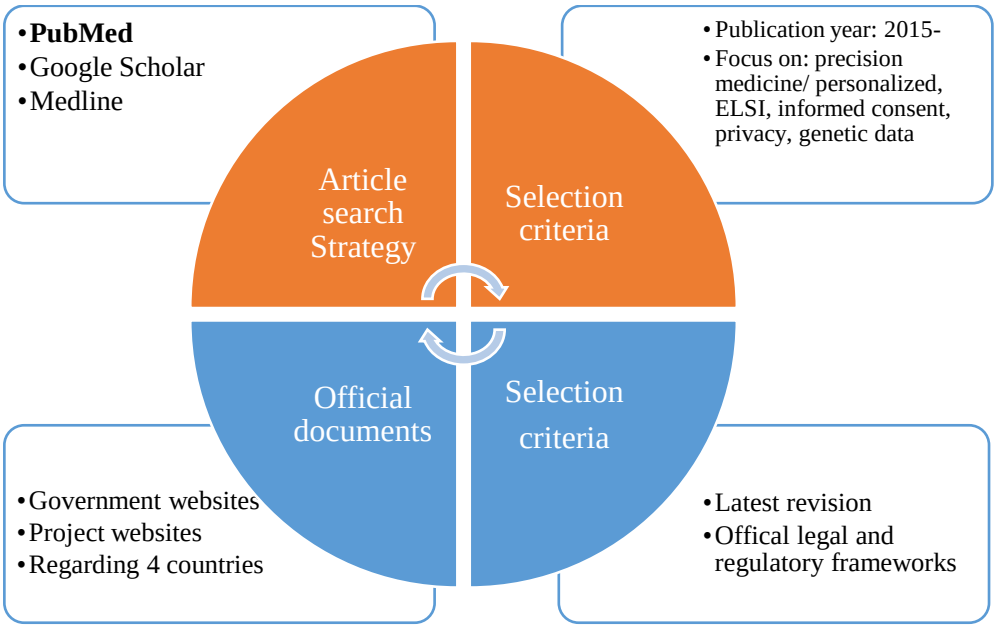

Figure 1. Research Methodology

Chapter 2 Precision medicine

2.1 Definition of precision medicine

The term “precision medicine” has been introduced more widely over recent years as scientific perspectives in many countries. It has first defined in the report called “Toward Precision Medicine” by National Research Council (NRC) in 2011 which refers to “the tailoring of medical treatment to the individual characteristics, like life style, genetic and environment, of each patient”. [10] As mentioned in the report, it does not mean that new drug or treatment will be created for each patient but it will classify population into subgroups based on disease characteristics, prognosis or their response to specific treatment. There are many similarities between the terms “precision medicine” and “personalized medicine”. According to the NRC, “precision medicine” is a new term with meaning similar to “personalized medicine”. However, some experts still debate that the two terms are different from each other. [11, 12] The differences may reflect perceptions of how research participants acknowledge and react to the terms.

As the Precision Medicine Initiative Cohort Program initiated in 2015, the PMI-Working Group had developed the report to the National Institutes of Health (NIH). According to the report, precision medicine is “an approach to disease treatment and prevention that seeks to maximize effectiveness by taking account individual variability in genes, environment and lifestyle”. And they believe that with help of more advanced technology and instruments, precision medicine tries to specify and understand about onset and development of disorders, treatment response and health outcomes. [13]

The National Health Service (NHS) defines precision medicine as a tailored approach that could better manages patients’ health and outcomes through the use of targeted therapies

with genome sequencing, personalized data and other technologies. [14] In South Korea, the Ministry of Health and Welfare formed the Precision Medical Research and Development Promotion Committee in 2016 to promote the industrialization of precision medicine. In this meeting, precision medicine is stated as a customized predictive medicine that integrates personalized medicine (genome medicine) that considers the genome and clinical information, and mobile healthcare based on health, life environment and habits information. [15]

However, there is no official definition that is determined by China yet, Chinese experts who are participated in Precision Medicine and Policy Summit in 2018 are defined precision medicine as “a new medical model that combines modern technologies and traditional medical techniques to improve the understanding of human mechanisms and diseases to achieve optimal outcomes for the health of individuals and the general public through care provided in a more efficient, safe and affordable manner”. [16] Although there is a little difference in definition of precision medicine in countries due to customization of local context, overall components that are applied in precision medicine research, such as cohort study, are same with each other. Along with definition, its translation and explanation need careful consideration to make it comprehensive not only for public, but also for professionals.

2.2 Components of precision medicine

There are several key components for implementation of precision medicine. One of those components is big data derived from participants and community to understand disease biology and pathogenesis, and providing better health both in individual and population. Over decade, reduction in the cost of data storage have enabled large scale data collection with advanced information technology (IT), digital health information systems, such as electronic health records (EHR), and mobile technologies. [13] Data derived from these sources are analyzed using advanced methods to discover new connection of disease factors. As much as data, data collection and its management are essential in successful precision medicine.

As IT is advancing rapidly these years, many countries have developed and now, are using national integrated health information system, electronic medical records (EMR) or EHR in the hospitals to collect patients' health data, such as medical history, laboratory or radiology results, and treatment, timely and safely as a source of big data. [1, 17] When conducting study to build data platform in precision medicine, survey and interview from participants and wide spread use of wearables are another source of data collection, with EHR/EMR. Since these collected data includes sensitive and personal information, data access control and maintenance of privacy should be managed accordance with study protocol and regulatory frameworks. [18]

The second component is genetic profiling of the individual with rapid DNA sequencing methods. [19] Due to limitation of characterized genes which are clinically applicable, there were many problems, such as cost and lack of advanced technology in gene sequence analysis of individuals. However, with advanced sequencing tools, current next sequencing technologies allows to include more comprehensive genetic analysis. [20, 21] Comparing to thirty years ago, genome sequencing time and cost of genetic information extraction have

been decreased dramatically which have led to expansion of genetic research and genetic testing. [22] But, developing countries, which are new to genome sequencing or lack of experts and infrastructure, need international collaboration to adapt tools with sufficient education as well as government support, especially in regulation and funding. [23]

The precision medicine connects patients, providers, clinical laboratories, researchers and policymakers which is the third component, to provide infrastructure for further co-operation and aim to set framework for health and disease management for everyone. For data collection, patients or participants provide health-related data with biospecimen which are the main source of data. Also, in recruitment of the participants, many studies are including rare disease or specific-diseases patients but there are several favors over healthy individual, such as early detection of disease risk and preventive health strategies. [3] Researchers and clinicians analyze these data using advanced technologies to understand mystery of diseases and develop new treatment. Since precision medicine is a new scientific approach to promote integration of research findings and evidence-based interventions into clinical practice, government support and decision-making from policymaker are very influential for building infrastructure and further regulation at national level. [24] Without relevant legal regulation, guidelines or strategy in precision medicine development, protection of data privacy, accessibility of valid genetic information and quality of tests and services cannot give assurance to patients and public in clinical practice to improve health outcomes. [25]

To create a research repository that is consisting of medical records, physical measurements and biospecimens with follow-ups over a period of time for precision medicine, national cohort study have been conducting as base of precision medicine in US, South Korea and China. [18] For instance, a cohort study of more than 1 million people was established in US, and general and specific-disease population cohort studies are ongoing in South Korea and China. All of these cohort studies are collecting participants' health data, such as medical

history, lifestyle, family history and so on, physical measurements and biospecimen samples for further DNA analysis.

2.3 Precision Medicine Initiatives in the selected countries

2.3.1 US

The precision medicine is a long-term research to understand how individual's genetics, environment and lifestyle can help determine the best approach to prevent or treat diseases by integrating with advanced technologies like biomedical big data and artificial intelligence. In 2015, the Precision Medicine Initiative was first made public by President Barack Obama. The President announced that $215 million investment in total will be provided to the NIH, the National Cancer Institute (NCI), the Food and Drug Administration (FDA) and the Office of the National Coordinator for Health Information Technology (ONC) for development of national research and database with privacy and security of personal information. [13]

Current medical treatments have been outlined for the "average patient" so that every patient have not shown same effectiveness from the treatment which is called "one-size-fits-all approach". [26] But with help of novel approach, precision medicine, each individual's variability in gene, environment and lifestyle will be considered for disease prevention, diagnosis and treatment. [2] According to objectives of the PMI, NIH has launched national cohort program called the *All of Us Research Program (AURP)* to enroll at least 1 million individuals. Participants will share their EHR data by giving a consent and answer prepared survey, provide biospecimens, such as blood and urine, for genomic and other laboratory assessments, and give physical measurements. The AURP initiated the enrollment in May 2018 and enlist participants who are 18 years of age or older from a network of more than 340 sites. [27]

The AURP has developed two methods for participant recruitment and enrollment. The first method is that healthcare provider organizations (HPO) enlist participants from their patients. The second one is volunteers who want to enroll the program apply by using website or smartphone. Those participants should firstly complete the electronic consent modules which include videos with explanation, health surveys and questions, and provide permission for access to their EHR. All question and surveys (Table 1) are prepared in English and Spanish with sample terminology so that, every participant can understand easily. [28]

Table 1. Types of data collection and it details in the All of Us Research Program

Type	Name	Details
Core*	The basics	- Nationality - Ethnicity - Gender - Education - Marital status - Health insurance and disability - Income and address - Contact number, address and person
	Lifestyle	- Smoking - Alcohol usage - Drug substances, including cocaine, gas and etc.
	Overall Health	- Health status including physical and mental - Quality of life - Questions for women - Transplantation and recent travel history
Additional*	Personal Medical History	- Heart and blood conditions - Lung conditions - Cancer conditions - Digestive conditions - Hormone/endocrine conditions - Kidney conditions - Bone, joint and muscle conditions - Hearing and eye conditions

Type	Name	Details
		- Infectious diseases - Brain and nervous system conditions - Mental health and substance use conditions - Others (obesity, vitamin deficiency, so on)
	Health care access and utilization	- Health insurance or coverage - Health care services from doctor, nurse, midwives or specialists - Accessibility and affordability to health care
	Family Health History	- Health problems in relatives - Mother's condition - Father's condition - Brothers and sisters' condition - Daughter's condition - Son's condition - Grandparents' condition

* National Institutes of Health - All of Us Research Program. https://allofus.nih.gov/

The program also collects health data from EHR which is a digital version of medical chart, under participants' permission. This record includes participants' health problems, received health care services such as medication, laboratory and radiology tests, and medical and surgical procedures. Since it includes sensitive and private data, the program provides explanation of what EHR is and how they are going to use with security and confidentiality to the all participants. The program will access to EHR data of participants, who are enrolled by HPO, though HPO whereas volunteers will share their EHR through health information exchange.

After completion of survey and sharing EHR data, all participants provide their physical measurements and biologic samples at HPO or contracted clinic. Physical measurements include blood pressure, height, weight, waist and hip circumference, and heart rate. Adult participants provide up to 50 ml of blood and 50 ml of urine, in case where it is not possible to obtain blood sample, a saliva sample can be collected instead for purposes of isolating DNA. Collected biospecimen will be shipped and stored in the Biobank at Mayo Clinic. [18]

All participants' EHR, health survey, physical measurements and sample data from biobank are added into the All of Us scientific database, a common cloud environment. In order to use the database, researchers have to be approved by the All of Us Resource Access Committee as passport-model and then, permission will be provided to the researchers to use web-based tools and cloud-based computing for inspect the collected data. Personal information, like name, social security number etc. is removed (de-identification) from the data which is available for the researchers. In addition, participants or public also can access to dataset using data browser tool (https://databrowser.researchallofus.org/) while approved researchers are available to data using Researchers Workbench, as private. The security of software platform (web-based) has been assessed in accordance with the Federal Information Security Management Act. Most result of research testing and participants' own physical measurements are open to participants in AURP. [27] Moreover, when there is a risky genetic variant which can cause serious diseases, participants will be informed about it. As the program continues and number of participants increases, they keep improving and developing advanced and secure technologies for the data privacy and others. [18]

2.3.2 South Korea

Following PMI in US, Korean National Institute of Health and U.S. counterpart signed a Letter of Intent (LOI) for collaboration on precision medicine research on October, 2015. [29] Through this, efforts for international cooperation in the field of precision medicine were started, such as initiating joint research program, solving funding issues and strengthening human resources and training. In 2016, precision medicine was selected as one of the nine field of national science and technology strategy project. In this meeting, it is planned to establish precision medicine cohort that collects genetic, medical, lifestyle and environment information of at least 10,000 individual, and develop data integrated-system of genomes, medical and health status for easy accessing from hospitals and related

healthcare or pharmaceutical companies. [30] In addition, genomic information of 100,000 Koreans' three major cancers, including lung cancer, stomach cancer and colon cancer, is planned to secure for personalized anti-cancer diagnosis and treatment development and further to initiate chronic disease management programs with advanced mobile technologies. [30]

At the same time, Korean government announced new 2 national strategic projects to integrate precision medicine with healthcare more accurately in 2017. The first one is the Precision Medicine Hospital Information System (P-HIS) and other one is The Precision Medicine-Based Cancer Diagnosis and Treatment development (K-Master). The both projects are led by Korea University Medical Center (KUMC) under supervision of the Ministry of Science and ICT and MOHW. The project is anticipated to highlight new paradigm in the national medical system by developing new cancer treatments based on precision medicine and establishing cloud-based hospital information system with support of fund from the government. [31]

The K-Master project team was launched in June 2017 with the goal of expanding customized medical care through establishment and activation of a cancer diagnosis and treatment platform based on precision medicine in order to improve the national health and quality of life along precision medicine. With the project, genome analysis of 10,000 Korean who are recurrent and metastatic cancer patients, is planned to be conducted for 5 years to develop nationwide genome screening protocol. The cancer genome analysis program started with Korea University Anam Hospital in October 2017 and as of April 2019, a total of 52 institutions nationwide are participating. [32] By January, 2021, The K-Master project group had registered a total of 8,695 cancer patients, of whom 8,271 had undergone genome profiling and 7,902 had obtained reports of genome analysis findings. It is anticipated that the genome analysis of 10,000 cancer patients will be completed. [33]

Moreover, in 2019, the Ministry of Health and Welfare announced the 2020 R&D Project Integrated Implementation Plan that contains the National Project of Bio Big Data Construction as one of the seven key directions. This is a research program that collects and analyzes genetic information data of one million people. [34] Through the study of the genetic characteristics of Koreans, diseases that are vulnerable to Koreans can be predicted in advance and used in medical treatment and treatment development research. [35] This project aims to build a system in which Koreans' health information and genetic information are collected through voluntary participation of the people, managed in safe platform and analyzed by qualified researchers. Because personal genetic information is very sensitive, the data must be managed and protected at the public and governmental levels. The project is in cooperation with four governmental departments, four government-funded research institutes and sixteen national hospitals. As the first step in the national bio big data construction project, Korean government plan to build clinical information and genomic data through recruitment of rare disease patients first. [36]

During the project, clinical information, including basic information, disease information, health status information, and disease-related information are collected through interview and medical records at other institutions' data (EMR). In addition, for genomic data, blood and urine, (alternatively saliva) are collected less than 40 ml and 25 ml (2ml), respectively from the adult participants. All this information will be stored in the National Integrated Bio Big Data Platform. The resident registration number is only used for the purpose of linking with the health-related information of the participant stored in public data sources and medical institutions holding medical records. Those are "Death data from Statistics Korea", "National Health Insurance Service's medical and examination data", "Health Insurance Review and Assessment Service's data" and "Cancer registration data from National Cancer Center". [36] From the National Integrated Bio Big data Platform, general population or participants and researchers will access to their own information and research results.

2.3.3 China

Precision Medicine Initiative was introduced into China's 13th five-year plan in 2016 by the government, with an estimated $9 billion which is the largest comparing to other countries spent on research and development. [37] As the development of precision medicine in China entered a period of acceleration, the Ministry of Science and Technology released a national key development plan, and "Precision Medicine Research" was announced as one of the priority project to be launched in 2016. In this plan, four-research directions of precision medicine were included. The first direction is research and development of new generation of clinical technology for future precision medicine. The second one is large-scale population cohort study which divides into two subgroups, general population and disease-specific population. In general population cohort study, especially two main regions are selected, conducing 100,000 population each. 50,000 participants each for rare, cardiovascular and metabolic diseases, and esophageal and breast cancers are planned to be recruited for disease-specific cohort study. The third is construction of platform for resource integration, storage, utilization and sharing of precision medicine big data. And the last one is precision research on disease prevention, diagnosis and treatment plan which will be the key result and integration of all study. [38]

Moreover, accordance with the plan, the Ministry of Science and Technology's "Precision Medicine Research" invested in 61 cohort studies for period of five-year with various types of disease-specific, especially rare disease, and general population from the most part of the country. During these cohort studies, 30-79 years of participation enrolled voluntarily by providing questionnaire surveys, medical examination, and bio samples for laboratory test and biobank (genetic variants). As strongly supported by every level of government, and CDCs, cohort database is linked with National Death Surveillance System (NDSS), Chronic Disease Registries (CDR) and National Central Canter Registry (NCCR) to allow credible and timely check of the participants' health condition as well as five-year follow-up. [39], [40]

On the other hand, china is at the forefront of data collection and analysis methods for studying human genetics and biology. The Beijing Genome Institute is the world's largest sequencer and archive of genetic material – the DNA code that distinguishes everyone. Besides, as early of 2017, the Beijing Genome Institute's China National GeneBank in Shenzhen had over 500 million genetic sequences from over 8,000 species deposited in more than 40 databases. [37] It is believed that the advancement of computational power and artificial intelligence systems to discover new medicines and therapies, and bring them to the right patients is another power of China in precision medicine.

In company with the government, there are private big organizations, such as iCarbonX, WuXi NextCODE, CloudHealth Genomics and so on, which are taking a big part in data collection and AI data mining, cloud-based platform of massive amount of data, database, and precision medicine solutions. In particular, with over 20,000 Chinese individuals, CloudHealth Genomics has one of the biggest Chinese population whole genome sequencing database in China. [41]

2.3.5 Mongolia

In Mongolia, precision medicine related cohort study like in US, South Korea or China has not initiated officially yet at national level. However, Shanghai-based CloudHealth Genomics and the Mongolian Health Initiative (MHI) signed collaboration in advance precision medicine research for nutrition deficiencies and nutrition-related diseases during the Central Eurasian Nutrition Forum which was held in Ulaanbaatar, Mongolia. (The launch of CloudHealth Genomics-8) The MHI is a non-governmental research organization focusing on health issues such as tuberculosis and vitamin D deficiency. [42] The CloudHealth Genomics, Ltd., is the one of leading company in China focused on whole genome tests and providing genomics-based precision medicine and scientific well

solutions. This collaboration is aimed to create new diagnostics and therapeutics by identifying biomarkers for nutrition-related diseases with innovation of biomedical research. [43] It was confirmed that data and results would be made public in the future. Additional information accordance with research were not disclosed. This initiative is only project of private organization which is collaborating with CloudHealth genomics.

Table 2. Comparison of precision medicine programs in US, South Korea, China and Mongolia.

	US*	South Korea**	China***	Mongolia
Initiation of Precision Medicine	2015 PMI – All of Us Program	2017 – 2021 The K-master project	2016 – 2030 Chinese Precision Medicine Initiative	-
Cohort study population	1,000,000	10,000	1,000,000	-
Focus	Cancer	Cancer (stomach, lung and colon)	Cancer, rare diseases, cardiovascular, metabolic …	-
Budget	$215 million	$55.7 million	$9 billion	-
Data collection	Health survey, EHR, physical measurements	EMR	-	
Biospecimens	Blood and urine, alternatively salvia	Blood and urine	Blood, urine and saliva	-

*National Institutes of Health – All of Us Research Program. https://allofus.nih.gov/

**K-MASTER Cancer Precision Medicine Diagnosis and Treatment Enterprise. http://k-master.org

***Ministry of Science and Technology. The People's Republic of China – Precision Medicine Initiatives in China. http://most.gov.cn

Chapter 3. Informed consent and privacy as issues of genomic study

3.1 Ethical, legal and social implications (ELSI)

3.1.1 Initiation of ELSI research

In the mid-1980s, the Human Genome Initiative started to highlight the development of resources and technologies for genome mapping and sequencing that would lead to the entire human genome map in the worldwide. During planning stages of the HGP in 1990s, it was accepted that the ethical, legal and social aspects of genomics research are influential to successful development and progress of the project. This acknowledgement led to formation of ELSI Program which has supported and funded many projects related to ELSI research at NIH. [44] It was believed that ELSI will give support on solutions to the potential problems raised from HGP prior to integration of genetic information and modern health practices. [45]

Francis Collins et al. (1998) outlined focus points for the ELSI research Program in the HGP strategic plan for 1998-2003. These goals are (1) to look at the issues surrounding the human genome's completion and the analysist of genetic variation; (2) to examine the challenges posed by the integration of genetic technologies and knowledge into healthcare and public health activities; (3) to examine the problems posed in non-clinical settings by the integration of genomics and gene-environment interactions expertise; (4) to investigate how modern genetic understanding interacts with various philosophical, religious and ethical viewpoints; and (5) to study how racial, cultural and socioeconomic factors influence the usage perception, and understanding of genetic knowledge, as well as the use of genetic services and policy creation. [46]

As it was mentioned before, ELSI provides a new approach to scientific study by discovering, assessing and discussing the ethical, legal and social implications of human genetics research while the fundamental science is being studied according to the HGP until 2003. [6] Even though HGP completed in 2003, it did not conclude the ELSI Research Program. On the contrary, as the ELSI Program showed good influences and results in HGP, many other areas of research, such as biology, neuroscience, nanotechnology, big data and precision medicine are applying into ELSI research, not only in human genomics and genetics. [47] The countries which launched Precision Medicine, has anticipated some potential ELSI, as demonstrated by its attention to cohort diversity, privacy and security, [48] genetic discrimination [49], participant engagement and data sharing and accessibility. Along with ELSI program in U.S., European countries, Canada and South Korea have also initiated ELSI program in not only genomics although their acronyms are varying from each other. [50]

In European Countries, ELSI program was called as ELSA which is an acronym for ethical, legal and social aspects of emerging sciences and technologies and it was implemented two decades ago, in the form of the 4th EU Framework Program (launched in 1994), to frame problems and to fund research, stakeholder dialogue, education, and other activities to resolve them. Since then, other initiatives, especially in European partner countries, have adopted the ELSA research, such as the ELSA program for the Research Council of Norway and ELSAGEN to fund research on ELSA issues of genomics and other associated sciences (a partnership of research funding agencies in Germany, Austria and Finland). [50] Throughout Europe, ELSA programs were not only gaining interest and integration with other fields, but also, faced challenges and arguments from researchers. Recently, the concept of ELSA started to change into Responsible Research and Innovation (RRI), especially in the light of recent EU funding initiatives (notably Horizon 2020). RRI is a science policy paradigm that aims to expand innovation process and support collaboration for innovation with other fields. [51] There are five European Commission RRI keys,

including ethics, societal engagement, gender equality, open access/science and science education. [52]

The Ministry of Science and Technology of South Korea initiated ELSI Program in 2001 as the Frontier Project, including studies in the humanities and social sciences, following the ELSI Research Program of United States. ELSI Program of human genome project in Korea focused on development of ethical guidelines in human genome research, suitable informed consent form [53], ELSIKOREA database and research infrastructure. [54] During this time, the ELSI concept was expanded to include ELSI of Nano [55] and neurotechnology, in addition to ethical, legal and social implications of biotechnology, especially in genomic and precision medicine. This expansion represented an expansion of the broader collection of research areas that were now given priority, which are sometimes referred to as "emerging technologies". It shows the importance of ELSI in scientific researches in various types of fields.

3.1.2 ELSI challenges in Precision Medicine

Since inception of ELSI Program in HGP, the program set goals to address major issues of the HGP and develop initial policy options. These issues are fairness, privacy and confidentiality of genetic information, genetic counselling, genetic information on medical practice, and uses and misuses of genetics. [6] As a result, ELSI research has showed many impacts, produced policy outcomes, and accomplished improvements in genomic research and genetics. [44] One of the accomplishments of ELSI research can be shown in upgraded informed consent form for genomic research. With understanding of harms and benefits related to genetic research during ELSI Program, ethical review, the drafting and trends in consent forms has changed to protect participants and research subjects as well as gain public trust. Even issues that are addressed in the research shows importance, it is difficult that all of the research results can arise impact on policy outcomes.

Due to novel technology approaches and increased use of personal health related information, such as medical history and genetic information from various sources in new era of precision medicine, ELSI associated issues have becoming more challenging for researchers and policymakers, and it requires new approach and analysis of situation and in context of these issues. Many researchers from various countries that has implemented precision medicine have been conducting ELSI research and addressing ELSI issues based on experiences and outcomes from the HGP-ELSI Program. Brothers et al. (2015) addressed issues related ELSI in personalized medicine, similar to precision medicine approach. According to their analysis, two broad issues are reviewed as significant, these are health information related concerns - privacy, discrimination, and healthcare disparities related concerns. [49]

Moreover, Adams et al. (2016) highlighted a number of ethical, legal, and social issues related to precision medicine in order to improve and upgrade existing principles and regulations that can be helpful to promote trust between patients and researchers/health professionals and achieve goal of precision medicine in healthcare. As stated by them, patient privacy and informed consent have been chosen and known as common issues in many researches which collect a large amount of medical and health related information from participants or patients, so those cannot be excluded from ELSI issues in precision medicine. [56]

In addition, advancements in next-generation sequencing technology have made it possible to large-scale sequencing with many opportunities in analysis of human genomes from biospecimens. Although it has helped the diagnosis and treatments in many undiagnosed rare disorders, and the identification of disease risks and cancer treatments, some consideration of practical and ethical implications are continuously drawing attention from researchers and clinicians. [57] To manage them, informed consent process need to be revised for well understanding of risks and benefits associated with research, as well as privacy

issues of their health information. Several studies in population survey regarding precision medicine cohort study found that participants' the most concern is privacy about their health information and genetic information. [58, 59] Thus, consideration of ethical, legal and social issues in precision medicine will great help on conducting national cohort study for data collection and analysis, and achieving precision medicine goals in healthcare by understanding developments of diseases and discovering new diagnostic and treatments.

3.1.3 Focused issues of ELSI

Most countries started considering and analyzing ethical, legal and social issues along with the development plan of Precision Medicine. As Precision Medicine Initiative started in US, ELSI issues associated with PMI-AURP were addressed by organizer although PMI-AURP have not initiated ELSI research independently. But funding announcement of the program showed main issues that are arising in context of ELSI. [48] In 2015, international conference titled "the Translation in Healthcare" held at the University of Oxford to discuss the ethical, legal and social challenges raised by novel healthcare technologies, and informed consent and privacy are themed as some of fundamental issues of ELSI according to studies [60, 61] focused on translation research of genomics, not only in US but also in UK. [62] There are many debates about suitable paradigm to the traditional informed consent in terms of precision medicine. [5], [63] Moreover, in large and international networks, informed consent should be either universal or easily adaptable while still accommodating ethical, legal, social and cultural differences. [64]

At the same time, Finland have been conducting precision (personalized) medicine researches regarding concerns in traditional ethical issues and regulation due to new technology, Big data activities. This led to attention of developing innovation-friendly regulatory approaches and practices, which including revision of informed consent, and privacy and autonomy rights in Finland. [65] In China, Pang et al. (2020) pointed out key

ethical issues in field of precision medicine research as informed consent, returning of results and data use and sharing due to complex technology, large-scale sequencing, accidental or unexpected findings and uniqueness of genetic information. [66] Even though, update and adjustment to relevant law, policies and regulations need to be carried out in response to these challenges, there are some obstacles from the cultural side of China to proceed solution based on other countries experiences and principles, and it requires different solution way, i.e. genetic counselling.

By analyzing articles and researches in many countries, informed consent and privacy are the most commonly addressed issues from ELSI and a lot of deliberation and debates have been labelled in order to cover scope of emerging technologies with upgradation of policy and regulation frameworks, even from lower level. Moreover, Based on ELSI discussion regarding precision medicine, revision of the act is proposed in some countries for solution of ethical challenges and achieve goals of precision medicine without risks and harms to the participations or public. With demand from ELSI research, policymaker and government officer are getting to understand importance of precision medicine and its effectiveness in legal and regulatory frameworks.

3.2 Informed consent

3.2.1 Background and key pillars

Informed consent is a key component of conducting human research ethically. The biggest turning point in history with regard to human subject research is the Nuremberg Code (1947) that articulates the requirements of fully informed voluntary consent of the human subject or study participants. [67] The aim of informed consent, which is based on the ethical concept of respect for individuals, is to ensure that participants are aware of the risks and possible benefits of engaging in research as well as rights and make a voluntary decision. Even

Nuremberg Code was integrated into numerous human rights legislations, it had an indirect impact on the research community and there were still problematic or unethical studies, which contributed to be the creation of its own guidelines for human-subject research was approved by the World Medical Association in 1964 with title of Ethical Principles for Medical Research Involving Human Subjects and since then, there were several times of revision. [68] Following these regulations, every country has enacted their legal acts and guidelines related to ethical points of human-subject research, such as the Belmont Report, the Common Rule, and Bioethics and Safety Act. [69]

Most of official documents about informed consent define three main pillars or elements of informed consent as disclosure information, subject's comprehension and understanding, and voluntary participation. [70] Disclosing all information about the study to the participants such as research procedures, the purpose of the research, risks and benefits, and any other information for subject need to know is crucial regardless the effect of the study. [71] In addition, comprehension of informed consent allows subjects or participants to understand all disclosed information before giving consent on participation. However, there are several factors that limits comprehension including illness, poverty, illiteracy or low level of education, especially health education, and unfamiliarity with conduct of medical research. [72] To enhancing comprehension of informed consent, provision of information at the education level of the individual participant, comprehensibility of language and design regarding consent forms, and use of aids to easier understanding, such as pictures, animations, audiovisuals etc. are commonly used in biomedical research. [73] Another key pillar of informed consent is voluntariness which requires free of constraint and improper influence in participation as well as withdrawal. The voluntary withdrawal from research is rather recent in many countries with inclusion in the regulation, such as the Common Rule, the Declaration of Helsinki.

3.2.2 Types of informed consent and challenges

As innovations in technology advance at such a rapid speed, it is difficult to predict future risks related to research using biospecimens and data. Therefore, ethical standards of informed consent need to be reconsidered and finding a solution associated with these future problems in precision medicine is required. [74] For instance, various types of consent is being used in biomedical research field to overcome the limitations. One of the commonly used consents is broad consent that approves researchers to use data and biospecimens for future studies without additional consent but when it is within the scope of the consent. Recently, the use of broad consent is included in the Common Rule officially as alternative. [75]

While dynamic consent, new approach to consent, has been started to be implemented in several projects due to its integration with modern IT, others are blanket, tiered, and open consent that each has own advantages and limitations. [74] Such dynamic consent model enables alerting individuals of new research opportunities and processing consent documents in real-time by communication between researchers and participants. Blanket consent refers to a process by which subject donate their samples without any restriction in future studies but it may conflict with individual's fundamental values and requires donors to be contacted constantly over time. However, it opens door for researchers to study biological materials in future studies without restriction, research participants' protection is valued more precisely for ethical research. Tiered consent allows participants to choose general research areas they wish to participant in and exclude others. Moreover, participants can ask for re-consent when there is a use of their data.

However, traditional conceptions of informed consent have been challenged by innovative developments in biomedical research, especially the increasing advent of large-scale

population studies and DNA databases in era of precision medicine, there are a number of summons related to informed consent. Firstly, research participants often do not comprehend the contents of the study's information sheet or the consent form for the study, particularly if the consent form is containing advanced terminology. [76] Also, many of consent forms are 15 to 20 pages in average which requires some time to read and understand. Due to its length and time, it is possible that participants are not reading the whole form, or not paying attention to researcher's explanation and miss out critical information needed to make an informed decision. [77] Secondly, determining consent approach arises because traditional informed consent is designed one specific study during pre-arranged timespan but in the era of precision medicine research, collected data and biospecimens can be used for future studies and it is difficult to foresee all future uses and application of the data in the beginning of data collection. For instance, re-contacting participants to obtain additional consent for new usage can be one of solution, however this method may show impact on research participants as discouragement to participation and misunderstanding. [74] Depending on requirement of country and types of research, the process of informed consent requires updates in regulatory framework and ethical standards.

3.3 Privacy

3.3.1 Background

Privacy defined as a condition restricting access to an individual or information about an individual. However, due to its complexity, there is no globally agreed definition of the term, and there is still debate about meaning, value and scope of the concept of privacy. [78] In reaction to a wide range of privacy-invading technologies underlying applications in everyday use by government agencies and businesses alike, people's expectation and understanding of privacy are rapidly changing, especially in recent years. To reduce

possibility of information privacy risks, a variety of technical protections have been implemented but still it does not prevent fully in various types of information. Furthermore, the notion of privacy mirrored in these technologies is changing over time, partially as a result of new vulnerabilities being discovered, a process that has increased dramatically in the last two decades. [79]

Recent advances in medicine, particularly the tendency toward precision medicine and learning health systems have resulted in substantial privacy protection. Especially in genetic and personal health-related data, the sensitivity, nature and future advantages, threats and uses of the data should all be considered every time by policymakers, researchers and legal scholars. [80] This is difficult task in an era where sensitive personal data is collected and processed on a large scale for determining and innovating precise diagnosis and treatment. In addition, reasons to importance of privacy protection are to prevent from stigma and discrimination in case of revealing of sensitive information, to improve quality of health care and to protect public from any health risks. As arise in collection, usage and analysis of health data from various sources for precision medicine research, public selects privacy as a top concern in everywhere, including US, South Korea and Australia. [58, 59, 81] Moreover, governments are also paying attention about privacy of health data, including personal and genetic information by developing policies and legislation as well as technical approaches to privacy protection.

3.3.2 Data protection and challenges

When it comes to health (health data) privacy policy and legislation, the principal is whether the information is personally identifiable. Such data flow freely if it is not personally identifiable, and it is not subject to the obligations imposed by the applicable privacy legislation. To protect privacy of data, privacy preserving methods have been used in stages of data collection, storage and processing. [82] In particular, there are some

techniques such as de-identification or anonymization for privacy protection in data processing and it is stated in the legislation of the countries. De-identification could be defined as the process to remove both direct and indirect identifiers of the data while pseudonymization is to replace identifiers in a set of data with artificial identifiers or pseudonyms. Pseudonymized data can be re-identified with integration of additional data. Anonymization refers to apply technical safeguards to de-identified data which has zero re-identification risk. [81] However, procedures and use of these techniques are varying in countries, especially in legal and regulatory frameworks. Therefore, the difficulties of generalizing and scaling de-identification and anonymization techniques, as well as the lack of widely accepted metrics to measure effectiveness of results, are frequently highlighted problems in several studies. [83], [84]

However, concerns about re-identification risks are rising due to the emergence of personal health data as well as genetic data which it cannot be confidently guaranteed that the data cannot be traced back to a person, and advanced technologies. [85] Due to the inability of totally de-identifying genetic information, genetic data and biological samples containing genetic material are often regarded to differ from other types of health data. The basic notion is that even though the individual's name and other identifying details are removed, genetic data, itself, may still be connected back to the relevant individual and families. [86] For instance, matching and connecting genetic data to non-genetic database, and profiling from genetic data to determine age, gender and even face figure are available due to advanced development of technologies, and have being used in some fields, like criminals to identify and determine the person from the genetic data. In order that, researchers should inform potential research participants about the risk of re-identification of genetic information that their identity could be discovered by anyone who obtains access to the data for their genetic sample. [87]

Chapter 4. Comparison of legal and regulatory framework focusing on informed consent and privacy

4.1 Informed consent

4.1.1 United states

4.1.1.1 Regulatory framework

In 1979, the National Commission for the Protection of Human Subjects Biomedical and Behavioral Research issued the Belmont Report, entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research that provides three principles, including respect for persons, beneficence and justice for ethical research with human beings. Following this report, the Department of Health and Human Services (HHS) Common Rule (45 CFR Part 46) and the US FDA regulation (21 CFR part 50) were established as human subject protection regulation of all research involving human subjects by any federal department or agency, and of all clinical investigations regulated by the FDA, respectively. Both regulations define the requirement that are for legally valid informed consent, including electronic version with activities related to research policy in protection of human subjects. Recently in 2017, HHS revised the Common Rule which is officially effective from 2019 January. Accordance with the revised Common Rule, FDA updated requirements of informed consent to avoid the need for two separate information consent forms, [88] even though regulation related to clinical trials, as FDA regulation is independent from all research involving human subjects. Moreover, the informed consent form to represent the expansion of precision medicine and genomic analysis has started updating in the Protection of Human Subjects known as the Common Rule. [77]

4.1.1.2 Requirements of informed consent

Both HHS and FDA regulations require that certain basic and additional elements/information be given to each subject when obtaining informed consent. [89] According to the regulations, there are 8 basic elements, including description of clinical investigation, risks and discomforts, benefits, alternative procedures or treatments, confidentiality, compensation and medical treatment in event of injury, contacts and voluntary participations. Additional elements of informed consent are unforeseeable risks, involuntary termination of subject's participation, additional costs to subject, consequences of subject's decision to withdraw, providing significant new findings to subjects and number of subjects. [90]

In the revised Common Rule, general requirement for informed consent are changed into new standards and requirements regarding comprehension and length of the form. According to the revision, key information about the study must be provided at the beginning of the informed consent form in order to provide subjects with information needed to make an informed decision about whether to participate. This information includes the purpose of the study, the risks and benefits, and others. Moreover, one new element, has been added to the basic elements of informed consent, is to notify about either information and biospecimens collected as part of the current research might be removed identifiers and used for other research in the future. There are three new additional elements of informed consent that are a notice about commercial profits, returning of research results and whole genome sequencing for research involving biospecimens. [91]

Regarding type of consent in the Common Rule, secondary use of identifiable information or biospecimen allowed through study-specific consent by obtaining an IRB waiver of consent, or by removal of identifier. In the revision, new type of consent, "broad consent" is provided as alternative consent for use only for the storage, maintenance and secondary

use of identifiable private information or identifiable biospecimens for future unspecified research. In broad consent, some of the basic and additional elements from standard informed consent should be included. [91]

4.1.1.3 Example of informed consent process

Accordance with regulation of informed consent, the All of Us Research Program have developed informed consent which has several advantages comparing to other research and studies. First one is electronical informed consent that is accessible through a web browser or application, in addition to the long-form consent. The program's ethics review board have supported introducing an eConsent [92] process to ensure that potential participants have a clear informed consent experience regardless of their geographic location or affiliation. Secondly, informed consent materials of the program were written at a fifth-grade reading level in the United States, with animated video clips to illustrate relevant information for easier understanding about the research. Thirdly, a four-question formative evaluation is provided to participants during informed consent process for reinforcing understanding of the core concepts about the program and challenging misconceptions. The concept of formative evaluation in primary consent includes purpose of study, voluntary participation, ability to withdraw and risk to privacy. After evaluating participants understanding, signature should be obtained in the informed consent. [18] , [92]

To develop the most suitable consent form for the program, special team were set up. Before the program could began to recruit and enroll participants, the All of Us Institutional Review Board (IRB) had to approve All of Us protocols, informed consent and materials. For all studies, the IRB follows the Office for Human Research Protections' regulations and guidelines, ensuring that the rights and health of research subjects are consistently monitored and secured. [93]

4.1.2 South Korea

4.1.2.1 Regulatory Framework

Following the Belmont Report and Declaration of Helsinki, guidelines and legislation for clinical trials, especially in pharmaceutical field, have been developed and implemented in South Korea since 1995. [94] For protection of human subject in all research, the Bioethics and Safety Act was officially enforced in 2013 with wide coverage of not only research involving human subjects but also human subject materials and banking. Before this, this act was enacted only for regulation of embryo research, and gene banks and therapy in 2005. [95] The Bioethics and Safety Act defines the standards for informed consent and other ethics and safety assurance steps as well as a framework for registering institutes that perform medical technology on humans, and the National and Institutional Bioethics Committees in South Korea.

4.1.2.2 Requirements of informed consent

According to Article 16 in the Bioethics and Safety Act, [96] written consent, including electronic version, should be obtained from human subjects of research before the research. This includes objectives of the research on human subject research, duration, procedure for and methods of participation, foreseen risks and benefits, protection personal information, provisions of personal information, withdrawal of consent and others. In case of subject who cannot give consent, informed consent should be obtained from legal representative. As such, every information that are included in the fully informed consent should be explained to everyone before obtaining the consent. Moreover, regarding research on human materials and human material bank, written consent should also be obtained from the donor of human materials. [96] In this kind of consent, key requirement is to include information about preservation and discards of the collected human materials.

4.1.2.3 Example of informed consent process

During K-MASTER project, participants who want to participate the clinical study, must agree and provide fully-informed consent. In this consent, purpose of research, course of study, possible profit and risks, the rights of participants, voluntary choice of participation, withdrawal information, and additional relevant information are included and participants are given enough time for discussion with family. When participants finalize to participate in the study, signature will be taken on the informed consent. [97] In order to participate in the National Project of Bio Big Data, participant who have indicated their intention to participate in the project voluntarily, will provide a consent to participate and a donation agreement for human materials. Since personal sensitive clinical and genetic information must be provided, detailed explanation of the project is given with informed consent. [35] Along with paper based informed consent form, short video and brochures about explanation of consent form and its importance are provided in the website as well as in social networking services, like Facebook and Instagram that are commonly used by people, to improve public awareness and their participation.

4.1.3 China

4.1.3.1 Regulatory Framework

Introduction of research ethical review concept has started in 1990s in China with establishment of committees at big university hospitals. To protect the rights and interests of human subject of clinical trials, the State Food and Drug Administration and National Health and Family Planning Commission issued Good Clinical Practice in 1999 [98] which

recognizes the Declaration of Helsinki as the basis for research involving humans. Moreover, for strengthening the protection of human research participants and the regulation of biomedical activities, the Ministry of Health released Interim Measures for the Ethical Review of Biomedical research Involving Humans in 2007 and the National Health and Family Planning Commission officially releases Measures for the Ethical Review of Biomedical Research involving Humans in 2016 which require the obtaining of the subject's informed consent. [99], [100] Besides, this explained the roles and responsibilities of medical ethics committees, substantiated the content regarding the principles, guidelines and tracking of ethical review, and established the basic scope of informed consent. National regulations on management of human genetic resources was adopted by the State Council and came into force on July 1, 2019 in China. According to the Regulation on Management of Human Genetic Resources in the People's Republic of China, participant's genetic data cannot be collected or used without informed consent in order to respect their privacy. [101] However, since the main focus of the Regulation is to secure and use human genetic data in China, it does not provide specific standards and requirement for informed consent. [101, 102]

4.1.3.2 Requirements of informed consent

As stated in the Measures for the Ethical Review, the current main regulation on biomedical research, the Project investigator should obtain an informed consent form voluntarily signed by the subject and in case of subject or participant cannot give consent in writing, oral informed consent should be obtained. The contents that should be included in the informed consent are (1) research purpose, basic research content, process, methods and time limit; (2) basic information of the researcher and qualifications of the research institution; (3) benefits and risks associated with the research; (4) protective measures for the subjects; (5) security and confidentiality of research data; (6) subjects' rights (regarding voluntary, withdrawal, compensation, treatment and new version of informed consent) and

(7) precautions for the subject. During the process of informed consent, the contents of the informed consent form should be explained to subject item by item according to the contents with subject's understandable language and participants should be given sufficient time to understand and make decision. [100] When there are changes in research scope, program and content or to use identifiable information and biological samples in new research, informed consent have to be obtained from subjects again.

4.1.3.3 Example of informed consent process

The Cohort study involving northwest and southwest region have obtained written informed consent from all participants or legal representatives before collecting information and biospecimens for the study. Written informed consent was approved by the Ethics Committee for research involving human subjects in Xi'an Jiao tong University Health Science Center and Sichuan University.

4.1.4 Mongolia

4.1.4.1 Regulatory framework

Following footsteps of other countries, international ethical principles and guidelines for research, especially in human subject research, such as Nuremberg Code, Belmont Report and so on, have been reflected in Mongolia to develop and implement universal ethical principles and regulatory frameworks. In 2002, Medical Ethics Review Committee was established under Ministry of Health to regulate projects, clinical trials in treatment and other researchers in Mongolia. Besides, international ethical guidelines for biomedical research including "Operational guidelines for ethics committee that review biomedical

research" (WHO, Geneva, 2000), "Ethical Guidelines for Biomedical Research Involving Human Subjects" (CIOMS 2002) and "Declaration of Helsinki" have been translated and implemented in biomedical research fields with detailed informed consent process. Afterward, in 2007, Ministry of Health established official order named "Guideline and principles for Medical Ethical Review Committee" to manage process related to researches.

In 2018, new codes and principles regarding Medical Ethical Review Committee (Order No. A/217) was renewed by Minister of Health, Mongolia to coordinate the activities of the Ethical Review Committee that are to protect human rights, to conduct research involving human subjects with ethical standards, especially in biomedicine, epidemiology, observational and experimental research. [103] Under this order, Ethical Review Committee should follow all related legal acts and ethical guidelines, such as Declaration of Helsinki (2014) and Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2002) to evaluate informed consent and approve it. Besides, there is a separate Regulatory Order for collecting and using human blood, blood products, biological fluids, tissues and organs for the purpose of clinical trials and research that was established in 2018 by the Order of the Health Minister, No. A/526. To collect biospecimens for clinical trials and research, informed consent has to be taken from participant and Ethical Review Committee must give approval for the research including the informed consent process and contents. [104]

4.1.4.2 Requirements of informed consent

As stated by this order and Ethical guidelines for Biomedical Research Involving Human Subjects, written informed consent (can be orally) must be obtained voluntarily from subjects or legally authorized representative in case of individual who is not capable of giving informed consent. [103] Moreover, the investigator must explain the information in accordance with level of subject's understanding, answer all questions honestly to help

decision making of participation, and give enough time to discuss with family before signing the consent form. The information that should be provided in the informed consent are (1) purpose of research, procedures, research design, and duration, (2) research findings and accessibility to data, (3) foreseeable risks, pain or discomfort, and benefits, (4) privacy and confidentiality, especially in genetic information, (5) direct or secondary use of medical records and biological samples for research, (6) compensation, and (7) affiliation of researchers and sponsors. Depending on types of research and target groups, special principles and information in the informed consent are applied for the means of protecting subjects' rights and eligibility.

Table 3. Differences of regulation, contents and type for informed consent

	USA*	South Korea**	China***	Mongolia****
Law & Regulation	Regulation	Law	Ethical Review	Ethical guidelines
Contents of informed consent	Contact information	Provisions of personal information	Researchers and affiliation information	Research affiliation information
	Future use of records and biospecimens			Future use of records and biospecimens
Type of consent (additional)	Electronic Broad consent	Electronic	Oral	Oral

*Department of Health & Human Services and U.S. FDA http://fda.gov/ ; National Institutes of Health – All of Us Research Program. https://allofus.nih.gov/

**Korean Legislation Research Institute – BSA http://elaw.klri.re.kr/

***National Health Commission of the People's Republic of China - Measures of the Ethical Review of Biomedical Research involving Humans;

**** New codes and principles regarding Medical Ethical Review Committee (Order No. A/217), 2018 www.legalinfo.mn

4.1.5 Proposed recommendation to Mongolia

In context of informed consent, there are several similarity and difference in the regulation and requirements of US, South Korea, China and Mongolia. Firstly, some contents (elements) of information that are required to be included in informed consent are ideal in all countries, but other elements are varying by stating in one or 2 countries. Besides, considering development of precision medicine and genomic analysis, informed consent requirements and elements are updated in USA's Common Rule. But, it is difficult to criticize one from another, even Nuremburg Code, Belmont Report and Universal Declaration of Helsinki are being upgrading and revising based on situation of legislation and principles. Secondly, regarding subject's comprehension and understanding, South Korea and China's regulation stated that every information in the informed consent should be explained one by one, while US's recent revision applied new requirement to include key information in the beginning of the consent. But in Mongolia, it is stated that researcher should explain informed consent at the same level of participant's understanding and answer participant's all questions regarding the consent form. Thirdly, voluntary of informed consent is applied to all three countries according to the regulations. However, still, informed consent rises debate among researchers due to large-scale research project that collect, store, re-use and manage data, especially genetic information.

Table 4. Three pillars of informed consent in US, South Korea, China and Mongolia

	Disclosure of Information	Subject's comprehension	Voluntary
United States (Common rule)	- Basic elements (9), - Additional elements (9)	- key information in the beginning	√
South Korea (BSA)	- contents (8)	- explanation	√
China (Measures for Ethic Review)	- contents (7)	- explanation - sufficient time	√

	Disclosure of Information	Subject's comprehension	Voluntary
Mongolia (ethical guideline)	- contents (7)	- explanation - sufficient time	√

Through the analysis, it has clearly revealed that Mongolia need to improve regulation related to informed consent as followed. First, appropriate language and terms that participant can understand without problem should be used and explained in the informed consent. Since precision medicine is new term in Mongolia, general population as well as some of help professionals do not have any knowledge or information about it. As US and South Korea's project team developed animated videos with informed consent to make participant understand fully about the research. This kind of educational interventions or approach will help comprehension of research related information in informed consent and result in right decision for the participation. In addition, promoting all information about research through social network and television is another approach to improve public awareness and understanding.

Second, it is necessary to develop formal questions or quizzes to assess level of understanding of participants, especially in context of key information, including purpose of study, study methods, duration, rights and risk and benefits. The ethical guideline in Mongolia did not cover evaluation of understanding, only stated about asking questions from researchers regarding informed consent information. Moreover, several studies on informed consent showed that participants are not aware of rights to withdrawal or refusal to participation, even it is included in the consent form. So that, it is fundamental to educate or inform well about rights to withdrawal to public, including participants or patients.

Third, electronic informed consent needs to be carefully considered in Mongolia to open possibility for enrolling various ethnic population. It has started to be approved and used in many studies, like precision medicine cohort study involving various diversity of people

from many places, regardless location. Also, enhanced IT and digital technologies allows more opportunities to evolve informed consent to electronic version with numerous advantages. But in Mongolia, special contemplation should be discussed in order to develop electronic informed consent due to nomadic life, lack of infrastructure, like internet, computer in remote areas, and low computer and health literacy, especially in non-capital areas. For this reason, there are many preparations that need to be done by government as a national strategy, such as improving literacy amongst population, and infrastructure in remote areas. As another option, informed consent could be obtained from non-capital areas or nomadic population with traditional approach – like explaining informed consent by focus-group or face-face interview with comprehensive explanation.

4.2 Privacy

4.2.1 United States

4.2.1.1. Regulatory framework

To date, health-data and new legislation proposals in United States have appeared to emphasize privacy by restricting or regulating access health-relevant data rather than ensuring its availability for uses that might enhance person and population health. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH) of 2009 have extensive privacy, security and violation notification regulations but only for data inside the health care system.

The HIPAA Privacy Rule establishes adequate protections to protect the privacy of personal health information, as well as restrictions and limitations on the uses and disclosures of such information that are permitted without patient authorization. [105] All "individually identifiable health information" is protected by the Privacy Rule and it is called as Protected Health Information which includes one or more of the 18 identifiers (e.g., name, address, birth date, social security number) as stated in HIPAA. Regarding genetic information, there are no special protection in the Privacy Rule and it is placed under the ordinary protections. In case of removal of these identifiers, it is De-Identified Health Information that results no restriction on use or disclosure meaning not protected the HIPAA. [106]

4.2.1.2 Privacy protection method – De-identification

The standard and implementation specification for de-identification of protected health information is provided in the HIPAA Privacy Rule, Section 164.514. According to this rule, there are 2 de-identification methods, including Expert Determination and Safe Harbor. The Expert Determination method provides an expert to review personal information and establishes an appropriate de-identification method by applying statistical or scientific principles that minimizes the risk of re-identification. For example, k-anonymity technique which replace certain values of the attributes by an asterisk or with broader category, can be used in this method to de-identify. [82] The Safe Harbor method applies to remove 18 specific identifiers of the data. [107] Although, neither method is a safe de-identification method with no risk of re-identification, they enable processing and sharing of de-identified data while lowering the risk of re-identification. But, genetic information is not considered as one of 18 specific identifiers, even though it can be used to identify individual because genetic information, itself determine each person and differ from each other. [108]

4.2.1.3 Example of privacy protection

PMI-AURP have developed Data Security Policy Principles and Framework to guide decision-making in precision medicine activities. Data Security Principles intended to assist organizations in establishing and implementing a proper security plan in uses of the data. One of the frameworks to organize data security programs in PMI-AURP, is developed by the National Institute for Standards and Technology (NIST) which consists of five functions to assess cybersecurity and data security performance. [93] In addition, data that are accessible to researchers are de-identified by removing names and other identifying information with following all federal laws and regulations.

4.2.2 South Korea

4.2.2.1 Regulatory framework

Like many other countries, South Korea have implemented precision medicine, and developed legal and administrative frameworks for privacy of personal and health-related information. In 2011, Personal information Protection Act (PIPA) enacted with purpose to protect the freedom and rights of individuals, and further, to realize the dignity and value of the individuals by prescribing the processing and protection of personal information. According to PIPA, personal information defined as information applicable to any living person that makes it possible to identify such individual by name, registration number, address etc. but, DNA information and biometric information are clearly stated as "sensitive information" which is defined in Article 18 of Enforcement Decree of the PIPA with criminal record, and racial or ethnic origin information. [109]

Separately, the Bioethics and Safety Act is frequently applicable when it comes to the use of health and medical data. Biospecimen research, in particular, is only permitted under this Act if a research proposal has been approved by an IRB and biospecimen donors have given their written consent. On the other hand, the Bioethics and Safety Act describes genetic information as "information about an individual's genetic characteristics obtained through the analysis human body components or biospecimens" (Article 2). While this definition helps to distinguish genomics research and resolve concerns about discrimination, it also addresses privacy aspects. [110] All that personal information should not be provided to third party unless consent is taken from the participant or special occasions that is permitted by laws.

4.2.2.2 Privacy protection method

In 2020, amendment to the Personal Information Protection Act was passed by the National Assembly by introduction of the concept of pseudonymized information for statistical and research purposes. [111] According to the amendment, pseudonymization refers to process of removing or replacing identifiers of personal information that requires additional information for identification and personal information controller can process pseudonymized information without the consent of the data subject only for purposes of statistic, scientific research and public data preservation. However, anonymous information that cannot be identified even if it is combined with additional information is not part of personal information [109] and can be use more freely.

The Guidelines for De-Identification of Personal Data was published under joint leadership of the Korean government including ministries and commission in 2016 in order to safely utilize the information with standards of de-identification, measures and scope of use. In accordance with the guidelines, there are 5 methods and 17 detailed techniques for de-identification. 5 methods are pseudonymization, aggregation, data reduction, data suppression and data masking. For pseudonymization method, heuristic pseudonymization, encryption and swapping techniques can be used as explained in the guidelines. [112] However, privacy protection methods that are included in this guideline are not suitable enough for biomedical data due to its difference from other industries. [113]

4.2.2.3 Example of privacy protection

The National Project of Bio Big Data complies five principles, including principle of minimum collection, principle of prohibition of use for other purposes, principle of data quality assurance, principle of transparency, and principle of data safety management in order to protect the personal information of participants. The information provided by the participant and human biospecimens such as blood and saliva are safely stored at the National Central Human Resources Bank of Korea Disease Control and Prevention Agency (KDCA). Individual clinical information and genetic information collected for research are provided to researchers through de-identification processing at KDCA so that it is never known who provided the information. Researchers who want to use the provided data can use the information only when they submit a research proposal and pass the deliberation of the Research Ethics Committee. All research processes conducted by researchers are conducted only within a closed research platform that can be monitored by the state and data is never allowed to be exported. [36]

4.2.3 China

4.2.3.1 Regulatory framework

In terms of privacy and personal data protection, China lacks special legislation at the national level to protect personal data- including genetic data – and privacy. However, in context of Direct-to-consumer (DTC) genetic testing services, related laws and standards apply to protect customers' personal information including genetic data. The SCNPCC promulgated the Cybersecurity Law of the People's Republic of China in 2017, which states that DTC genetic testing providers must not steal or use other illegal means to obtain consumers' personal information, including biometric information, nor sell or provide consumers' personal information to others. [114] In addition, China's National Information

Security Standardization Technology Committee published the Personal Information Security Specification in 2017, revision in 2020, a national standard that governs the collection, storage, use, transfer and disclosure of personal data. Personal genetic information is classified as personal sensitive information and is specifically identified as a type of biometric information. [115]

In October 21, 2020, a draft of China's Personal Information Protection Law was published for a month-long public comment period. Once it is implemented, the Personal Information Protection Law (PIPL) will be a central and universal governing law for protecting personal information in China. According to Article 4 of the Draft, personal information applies to "all kinds of information" about identified or identifiable natural persons that is registered electronically or otherwise, but does not include information that has been anonymized. Sensitive personal information is defined as personal information about ethics, race, religious beliefs, personal biometrics, medical health, financial accounts and personal whereabouts that, if leaked or improperly used, may lead to discrimination or seriously endanger personal or property protection. [116] Under the Draft PIPL, individual consent should be obtained voluntarily for personal information processing, such as collection, storage, use, processing, transmission, provision and disclosure of personal information. Anonymized information is no longer considered as personal information (Article 4). [116]

4.2.3.2 Privacy protection method

In the revision of the Personal Information Security Specification, [117] the principles and security requirements are stated as term of anonymization and de-identification with definition, technical methods and application in the process of regulating personal information. For technical methods, k-anonymity from anonymization, and pseudonymization, encryption and hash functions from de-identification were mentioned. In addition, the National Information Security Standardization Technical Committee of

China implemented a national standard entitled Information Security Technology – Guidelines for De-Identifying Personal Information to describe the goals and principles of de-identification of personal information, and proposed the process of de-identification and management measures. Common de-identification techniques (statistical tools, cryptographic tools, suppression, pseudonymization, generalization and randomization) and models (k-anonymity and differential privacy), and their characteristics and selection method are specified in the guidelines. [118]

4.2.4 Mongolia

4.2.4.1 Regulatory framework

The State Great Hural (the Parliament) of Mongolia adopted the Law on Personal Privacy in 1995 in accordance with the Constitution of Mongolia, which applies for the protection of personal secrets. The Law on Personal Secrecy (Privacy Law) specified the right in detail, classifying it into five categories, such as health information secrecy. The government should protect citizens' secrets in compliance with procedures and on legal grounds, according to the Privacy Law. Only officials of designated state agencies have access to citizens' personal data, which is kept according to procedures and on ground determined by law. Furthermore, the law forbids the disclosure of a person's private information obtained by legal processes and on legal grounds. An individual who violates the law and exposes a person's private data in an unauthorized manner will be punished by the court. [119] However, this law wasn't sufficient for regulating results of rapidly evolving technology.

In 2021, the Ministry of Justice and Internal Affairs proposed Draft of "Personal Information Protection Law" [120] to the Parliament for approval. The draft of law has total of 8 chapters and 29 articles and is aimed to regulate collection, processing, use and privacy of personal information. Along with personal information, biometric and genetic

information are specifically defined and considered as “personal sensitive information”. All information, in particular sensitive information should be collected, processed and used with written consent (or electronically) of the owner. It is allowed to process or use information in case of removal of personal identifier. But, de-identification terms, methods and techniques are not stated in detail under the draft.

Table 5. Privacy regulation, guidelines for de-identification and methods in US, South Korea, China and Mongolia

	US*	South Korea**	China ***	Mongolia****
Law & Regulation	Privacy Rule	PIPA	Personal Information Security Specification,	The Law on Personal Secrecy,
			Draft of PIPL (2021)	Draft of PIPL (2021)
Guidelines for de-identification	De-identification Standard	Guidelines for De-identification of Personal data	Guide for De-Identifying Personal Information	X
De-identification methods	- Experimental determination - Safe Harbor	- 5 methods - 17 techniques	- 2 models - 6 techniques	X

*Department of Health & Human Services – HIPAA Privacy Rule http://hhs.gov/ ;

**Korean Legislation Research Institute – PIPA http://elaw.klri.re.kr/ ; Guidelines for De-identification of Personal data (http://privacy.go.kr/)

***The Draft of Personal Information Protection Law and Personal Information Security Specification (2020); Information security technology - Guide for De-Identifying Personal Information (http://chinesestandard.net/)

****Integrated Legal information System - The Law on Personal Secrecy (Privacy Law), www.legalinfo.mn
Draft of Personal Information Protection Law (http://mojha.gov.mn)

4.2.5 Proposed recommendation to Mongolia

Regarding privacy, main legal regulatory framework for health data protection had officially applied in US and South Korea as Privacy Rule and PIPA, respectively. However, there is no special legislation for privacy at the national level in China yet, instead personal information protection is governed by the Personal Information Security Specification as national standard in data collection, use, transfer, storage and disclosure, and the Cybersecurity Law, related to direct-to-consumer. Recently, Draft of Personal Information Protection Law introduced in 2020 to public for feedback but has not officially implemented in China. At the same time, Mongolia also developed Personal Information Protection Law in 2021 which is under approval process by Great Khural. When those legislations are enacted in China and Mongolia, Personal Information Protection Act will be key regulatory law in privacy issues of personal information, including genetic information and biometric information.

All countries, except Mongolia applied a statement about de-identification of personal information in the legislation accordingly. Related to this, guidelines for de-identification of personal information is published in South Korea and China, separately as the national standards. But, Privacy Rule of US includes guidance of de-identification standards and implementation specifications as whole regulation. Guidelines for de-identification in each country explained techniques and methods with detailed instructions. From de-identification methods, pseudonymization is articled in the PIPA of South Korea and Draft of PIPL of China. As technology expands, de-identification methods are being newly developed based on characteristics of data and purpose of the researches. So that, it is impossible to define the most effective method just by comparing, but the most concerning thing is risks of re-identification in every country.

Since Mongolia is taking first step in privacy protection in context of personal information and sensitive information including genetic and biometric, several updates and

recommendation could be proposed based on described approaches and solution ways from respective countries.

First, although new privacy law is under progress of approval in Mongolia, it needs to be implemented officially to provide privacy protection since there is no official legislation or standard for privacy until now. In addition, de-identification definition and process need to be enacted in the Personal Information Protection Law. Identifiers need to be defined and listed in the law to avoid hesitation for personal information. For instance, US defined the 18 identifiers that need to be removed for de-identification so, it makes easier for researchers and experts.

Second, it needs to develop a guideline for de-identification of personal information to improve data protection with advanced techniques, especially in processing of a huge amount data which arises privacy issues. Except from Mongolia, each country has guideline or guidance for de-identification methods based on type of data and process of data. This kind of guideline helps better protection of personal information, especially sensitive information, even though re-identification problem is another obstacle that come out from experiences in these countries and also due to advanced technologies.

Lastly, with above recommendations, building capacity for human resources and technology is essential in improvement of privacy protection. Professional experts can determine and define suitable methods or technique to use in privacy protection based on countries and research characteristics, and ability of technology. So, enhancing them will bring many advantageous changes in personal and health information protection, especially in future of biomedical research in Mongolia. Moreover, experience from developed countries can help improvement but approach need to be naturalized accordance with Mongolian background.

Chapter 5. Discussion

Current status of precision medicine in countries were determined through literature review and actual examples of program. In addition, along with precision medicine studies, its informed consent and privacy issues were identified with other countries experiences. By comparison, countries current regulation and legislation in context of informed consent and privacy were determined and made background for improvement recommendation to Mongolia.

Informed consent, as pre-stage of Precision Medicine in Mongolia, there are many changes and improvement that should be delivered to researchers and policy-makers in preparation based on US, South Korea and China's experiences. Many recent studies in these countries are showing that written informed consent is converting into electronic version with additional multimedia approaches. This approach includes short-length videos with graphics and icons to improve understanding of information in informed consent more comprehensively. In addition, developing evaluation questions for research participants before signing the consent is another approach to assess understanding level and further improvement in consent form. But it needs to be careful consideration and preparation in evaluation questions because some participants may think it as kind of tests and results burden to participants. Depending on health literacy, there are some difficulties in terminology to understand that requires understandable translation and education using medias to general population. Even tough, electronic informed consent shows good impact comparing to paper-based consent form, printed consent should be provided to participants as well. For this reason, US, Korea and China allows both written and electronic informed consent in their legislation. Because of Mongolian nomadic life, less development of infrastructure and low computer literacy, it may result obstacles in obtaining electronic informed consent, especially in remote areas. For this reason, process of informed consent

in Mongolia need to be various depending on living condition to enroll large diversity of participants for development of Precision Medicine.

Privacy issues are still complicated in many countries due to advanced technologies in very short time. But, as shown in US, South Korea and China, law on personal information protection is very required, especially in era of precision medicine from prospective of ELSI researchers. Personal information protection law will provide detailed regulation regarding privacy issues that arose in many countries as reflection of future medicine. Along with this act, de-identification term and methods need to be developed in Mongolia to assure privacy into next level. Until now, several types of methods and techniques are developed around the world but every country select or develop suitable methods based on the countries needs and requirements. Therefore, professionals should develop guidance to manage large-amount of data. Along with it, human resource training and infrastructure preparation in Mongolia are required as well as awareness of privacy importance to public with education. It will result in more familiarities in privacy concerns of public side.

This study contained several limitations as followed. Firstly, precision medicine development as well as its infrastructure in US, South Korea and China is not comparable to current Mongolian situation. There are many barriers in Mongolia. Secondly, the reports or guidelines have been studied may have possibility of updating issue which is a risk that may not be included in this research. The study was conducted only the literature review from academic journals, national and international guidelines and legislation. So, it lacks experts' viewpoints from law and guidelines. In addition, examples of precision medicine research in the countries are not completed and well-introduced due to scarcity of official information through literature review. Especially in China, there are several cohort studies that are conducted and now in follow-up stage but detailed information regarding informed consent and privacy are not provided.

Chapter 6. Conclusion

Precision medicine has been showing many good results and improvements in the countries, especially in the diagnosis and treatment of cancer and rare diseases. Along with innovation, there are challenges that follows and rises due to new discovery and advancement. So that, countries keep upgrading their policy and regulation according to level of expansion of medicine which can protect and prevent population from any kinds of risks and harms. In particular, informed consent and privacy issues are the most common issues that get many attention and concerns from population and researcher as well as policy-makers in the field of modern research. Finding ways to ease problems and issues with legal and regulatory frameworks is possible way to avoid the complications and disillusionment experienced with precision medicine- ELSI issues from countries.

This study's recommendations will help on policy development of the precision medicine and further improvement regarding ELSI issues in Mongolia. I found that legal and regulatory frameworks of informed consent and privacy in Mongolia has been slowly following international steps to prepare for future development of precision medicine. However, there are still many barriers that need to be removed to build strong ethical, legal and social protection to human subjects especially in cases of informed consent and privacy in Mongolia comparing to US, South Korea and China. Furthermore, detailed analysis from expert's perspective will need to be conducted in the future for achieving successful improvement from international experts' experiences and support. To conclude, this study expect to Mongolia may need to be well prepared in implementation of precision medicine, regarding informed consent and privacy issues.

References

1. Group PMIW. *Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21st Century Medicine* 2015.
2. Secretary Of. The White House President Barack Obama. 2015. https://obamawhitehouse.archives.gov/precision-medicine. Accessed March 10, 2021.
3. Minari J, Brothers KB, Morrison M. Tensions in ethics and policy created by National Precision Medicine Programs. *Human Genomics*. 2018;12(1):22.
4. Lévy Y. Genomic medicine 2025: France in the race for precision medicine. *Lancet*. 2016;388(10062):2872.
5. Korngiebel DM, Thummel KE, Burke W. Implementing Precision Medicine: The Ethical Challenges. *Trends Pharmacology Science*. 2017;38(1):8-14.
6. Institute NHGR. Human Genome Project. Available at: https://www.genome.gov/leadership-initiatives/History-of-Genomics-Program.
7. Goetz LH, Shork NJ. Personalized medicine: motivation, challenges, progress. *Fetil Steril*. 2018;109(6):952-963.
8. Yoshizawa G, Ho CWL, Zhu W, et al. ELSI practices in genomic research in East Asia: implications for research collaboration and public participation. *Genome Medicine*. May 2014;6(39).
9. Chong HY, Allotey PA, Chaiyakunapruk N. Current landscape of personalized medicine adoption and implementation in Southeast Asia. *BMC Medical Genomics*. October 2018;11(94).
10. Committee on A Framework for Developing a New Taxonomy of Disease; Board on Life Sciences; Division on Earth adn Life Studies. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a Taxonomy of Disease*. Washington, D.C: The National Academies Press; 2011.
11. Ashley EA. The precision medicine initiative: a new national effort. *JAMA*. June 2015;313(21):2119-20.
12. Juengst ET, McGowan ML. Why Does the Shift from "Personalized Medicine" to "Precision Health" and "Wellness Genomics" Matter". *AMA J Ethics*. September 2018;20(9):E881-890.
13. Precision Medicine Initiative Working group. *Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21st Century Medicine*: National Institutes of Health; 2015.
14. National Health Service. Personalized medicine. *Genomics Education*. May 30, 2019. Available at: https://www.genomicseducation.hee.nhs.uk/glossary/personalised-medicine/. Accessed March 12, 2021.
15. Ministry of Health and Welfare. *Accelerating "Precision medicine R&D" for the industrialization of precision medicine such as future-oriented personalized treatment*. Seoul: Ministry of Health and Welfare; 2016.

16. Precision Medicine and Policy Summit. *School of Pharmaceutical Sciences Tsinghua University*. September 21, 2019. http://www.sps.tsinghua.edu.cn/uploadfile/2018/1211/PrecisionMedicinePolicySummitReport.PDF. Accessed March 12, 2021.
17. Porche DJ. Precision Medicine Initiative. *Americal Journal of Men's Health*. 2015;9(3):177.
18. *All of US Research Program - Operational Protocol*: National Institutes of Health; 2018. AURP.
19. Gameiro GR, Sinkunas V, Liguori GR, Auler-Júnior JOC. Precision Medicine: Changing the way we think about healthcare. *Clinics (Sao Paulo)*. Dec 2018;73:e723.
20. Durmaz AA, Karaca E, Demkow U, Toruner G, Schoumans J, Cogulu O. Evolution of Genetic Techniques: Past, Present, and Beyond. *BioMed Research International*. 2015;2015:7.
21. Chen C, He M, Zhu Y, Shi L, Wang X. Five critical elements to ensure the precision medicine. *Cancer and Metastasis Reviews*. April 2015;34:313-318.
22. Andrew A. Will genome sequencing bring precision medicine for all? *The Guardian*. Sep 28, 2019. Available at: https://www.theguardian.com/science/2019/sep/28/genome-sequencing-precision-medicine-bespoke-healthcare-nhs. Accessed March 13, 2021.
23. Davis AA, McKee AE, Kibbe WA, Villaflor VM. Complexity of Delivering Precision Medicine: Opportunities and Challenges. *Am Soc Clin Oncol Edu Book*. May 2018;38:998-1007.
24. Khoury MJ. Precision Medicine, Implementation Science and Public Health: How do we scale up from 1 million to 300 million? *Centers for Disease and Control Prevention*. August 24, 2015. Available at: https://blogs.cdc.gov/genomics/2015/08/24/precision-2/. Accessed March 13, 2021.
25. Hulsen T, Jamuar SS, Moody A, et al. From Big data to Precision Medicine. *Frontiers in Medicine*. March 2019;6:34.
26. Kohler S. Precision Medicine - moving away from one-size-fits-all. *Science for South Africa*. Vol 14: Academy of Sciences of South Africa; 2018.
27. The All of Us Research Program Investigators. "The All of Us" Research Program. *New England Journal of Medicine*. 2019;381:668-676.
28. All of Us Research Program. *National Institutes of Health, All of Us Research Program*. https://allofus.nih.gov/. Accessed March 13, 2021.
29. Ministry of Health and Welfare. *Korea-US precision medicine/MERS vaccine/therapeutic development cooperation*. Seoul: Health and Medical Technology Development Division; 2015.
30. Nine National Strategical projects for the future of Korea. *Ministry of Health and Welfare*. August 9, 2016. http://www.mohw.go.kr/upload/viewer/skin/doc.html?fn=1470796910058_201

60810114150.hwp&rs=/upload/viewer/result/202106/. Accessed March 21, 2021.
31. The Ministry of Science, ICT and Future Planning. Ministry of Science, ICT and Future Planning. *Precision medicine project for patient-tailored medical services*. June 29, 2017. Available at: https://www.khidi.or.kr/board/view?pageNum=1&rowCnt=20&menuId=MENU01501&maxIndex=00487142859998&minIndex=00002073179998&schType=0&schText=&categoryId=&continent=&country=&upDown=0&boardStyle=&no1=95&linkId=218047. Accessed April 13, 2021.
32. Choi YJ, Kim YH. The Cancer Precision Medicine Diagnosis and Treatment (K-MASTER) Enterprise. *Korean Journal of Medicine*. 2019;94(3):246-251.
33. Bae Jy. Doctors Times. *Korea Universeity's K-MASTER Project Group, Genome Analysis of 8,000 Cancer Patients*. February 18, 2021. Available at: http://www.doctorstimes.com/news/articleView.html?idxno=214028. Accessed May 29, 2021.
34. Confirmation of investment and implementation plan - 2020 Ministry of Health and Welfare R&D 527.8 billion won support. *Ministry of Health and Welfare*. December 16, 2019. http://www.mohw.go.kr/react/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&page=1&CONT_SEQ=351899. Accessed May 25, 2021.
35. Korean National Institutes of Health. *National Pilot Project of Bio Big Data Construction*. 2021. http://www.nih.go.kr/contents.es?mid=a40510010100. Accessed May 22, 2021.
36. The National Project of Bio Big Data. *Korean Disease Control and Prevention Agency*. 2021. Available at: https://bighug.kdca.go.kr/bigdata/bb0010.do. Accessed May 27, 2021.
37. Schenker JL. China Leaps Ahead in Precision Medicine. *The Innovator*. August 7, 2019. Available at: https://innovator.news/china-leaps-ahead-in-precision-medicine-72cfc469df3d. Accessed April 16, 2021.
38. 2016 Annual project application guidelines for precision medicine research in the national key research and development plan. *Ministry of Science and Technology*. 2016. http://en.most.gov.cn/. Accessed April 22, 2021.
39. Li C, Liu Y, Shi G, et al. Cohort Profile: The China Northwest Cohort Study. *Research Square*. January 2021.
40. Zhao X, Hong F, Yin J, et al. Cohort Profile: the China Multi-Ethinic cohort (CMEC) study. *International Journal of Epidemiology*. November 2020(dyaa185).
41. Gryphon scientific. *China's Biotechnology Development: The Role of US and other Foreign Engagement*: Rhodium Group; 2019.
42. Mongolian Health Initiative. Official Subconstractor of Harvard School of Public Health. Available at: https://mhi.mn/.

43. Staff Reporter. CloudHealth, Mongolian Health Initiative Form Precision Medicine Alliance. *GenomeWeb*. June 9, 2017. Available at: https://www.genomeweb.com/business-news/cloudhealth-mongolian-health-initiative-form-precision-medicine-alliance#.YMx-wDYzaRs. Accessed March 24, 2021.
44. McEwen JE, Boyer JT, Sun KY, Rothenberg KH, Lockhart NC, Guyer MS. The Ethical, Legal, and Social Implications Program of the National Human Genome Research Institute: reflections on an ongoing experiment. *Annual Review of Genomics and Human Genetics*. April 2014;15:481-505.
45. Boehm D. Applications and Issues of the Human Genome Project. *North DAkota State University*. 1999. Available at: https://www.ndsu.edu/pubweb/~mcclean/plsc431/students99/boehm.htm. Accessed March 26, 2021.
46. Collins F, Galas D. A new five-year plan for the U.S. Human Genome Project. *Science*. October 1993;262:43-46.
47. Parker LS, Sankar PL, Boyer J, McEwen JDJ, Kaufman D. Normative and conceptual ELSI research: what it is, and why it's important. *Genetics in Medicine*. February 2019;21(2):505-509.
48. Sankar PL, Parker LS. The Precision Medicine Initiative's All of Us Research Program: an agenda for research on its ethicall, legal, and social issues. *Genetics in Medicine*. Jul 2017;19(7):743-750.
49. Brothers KB, Rothstein MA. Ethical, legal and social implications of incorporating personalized medicine into healthcare. *Personalized Medicine*. January 2015;12(1):43-51.
50. Chadwick R, Zwart H. From ELSA to responsible research and Promisomics. *Life Sciences, Society and Policy*. December 2013;9:3.
51. Hilgartner S, Hurlbut B. Ethics as Governance in Genomics and Beyond. In: Felt U, Fouche R, Miller CA, Smith-Doerr L, eds. *Handbook of Science and Technology Studies*. 4th ed. Cambridge, MA: MIT Press; 2016.
52. Responsible research and Innovation. *European Commission*. 2020. https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation. Accessed April 13, 2021.
53. Yoon JR, Cho SK, Jung KW. The Challenges of Governing Biotechnology in Korea. *East Asian Science, Technology and Society*. June 2010;4(2):335-348.
54. Yoon JR. Human Genome Research and ELSI Program. *Journal of Science and Technology Studies*. 2003;1(2):423-438.
55. Lee Jw. Ethical, legal, and social implications (ELSI) in Nanotechnology. *Global Issue paper*. 2016;16(20):5.
56. Adams SA, Petersen C. Precision Medicine: opportunities, possibilities, and challenges for patients and providers. *Journal of the American Medical Informatics Association*. July 2016;23(4):787-790.

57. Tanjo T, Kawai Y, Tokunaga K, Ogasawara O, Nagasaki M. Practical guide for managing large-scale human genome data in research. *Human Genetics*. October 2020;66:39-52.
58. Kim H, Kim HR, Kim S, Kim E, Kim SY, Park HY. Public Attitude Toward Precision Medicine: A Nationwide Survey on Developing a National Cohort Program for Citizen Participation in the Republic of Korea. *Frontiers in Genetics*. May 2020;11:283.
59. Kaufman DJ, Baker R, Milner LC, Devaney S, Hudson KL. A Survey of U.S Adults' Opinion about Conduct of a Nationwide Precision Medicine Initiative Cohort Study of Genes and Environment. *PLoS One*. August 2016;11(8):e0160461.
60. Garrison NA, Sathe NA, Antommaria AHM, Smith ME, McPheeters ML, Clayton EW. A systematic literature review of individuals' perspectives on broad consent and data sharing in the United States. *Genetics in Medicine*. July 2016;18(7):663-71.
61. Chalmers D, Nicol D, Kaye J, et al. Has the biobank bubble burst? Withstanding the challenges for sustainable biobanking in the digital era. *BMC Medical Ethics*. July 2016;17(39).
62. Michael M, Dickenson D, Lee SSj. Introduction to the article collection 'Translation in healthcare: ethical, legal, and social implications'. *BMC Medical Ethics*. November 2016;17(74).
63. Fiore RN, Goodman KW. Precision medicine ethics: selected issues and developments in next-generation sequencing, clinical oncology, and ethics. *Curr Opin Oncol*. January 2016;28(1):83-7.
64. Ong S, Ling J, Ballantyne A, Lysaght T, Xafis V. Perceptions of 'Precision' and 'Personalized' Medicine in Singapore and Associated Ethical Issues. *Asian Bioethics Review*. March 2021;13:179-194.
65. Mansnerus J, Lahti R, Blick AA. Personalized Medicine: Legal and Ethical Challenges. Helsinki: University of Helsinki, Faculty of Law; 2020.
66. Pang C, Chen H, Wang Y, Yin J. Ethical Challenges of Precision Medicine in China. *Chinese Journal of Evidence-Based Medicine*. October 2020;20(12):1367-1372.
67. Moreno JD, Joffe S. The Nuremberg Code 70 Years Later. *JAMA*. September 2017;318(9):795-796.
68. World Medical Association. *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*. July 9, 2018. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed May 1, 2021.
69. Lee IJ. Ethics in Human Participants Research. *Korean Journal of Aesthetics and Cosmotelolgy*. April 2014;12(2):141-146.

70. Shah P, Thornton I, Turrin D, Hipskind JE. Informed Consent. *StatPearls*: StatPearls Publishing LLC; 2020.
71. Dankar FK, Gergely M, Dankar SK. Informed Consent in Biomedical Research. *Comput Struct Biotechnol J*. March 2019;17:463-474.
72. Richardson V. Patient comprehension of information consent. *J Perioper Pract*. Feb 2018;23(1):26-30.
73. Sutter ED, Zaçe D, Boccia S, et al. Implementation of Electronic Informed Consent in Biomedical Research and Stakeholders' Perspectives: Systematic Review. *Journal of Medical Internet Research*. April 2020;22(10):19129.
74. McGuire AL, Beskow LM. Informed Consent in Genomics and Genetic Research. *Annu Rev Genomics Hum Genet*. September 2010;11:361-381.
75. Maloy JW, Bass PF. Understanding Broad Consent. *Ochsner Journal*. Spring 2020;20(1):81-86.
76. Budin-Ljøsne I, Bentzen HB, Solbakk JH, Myklebost O. Genome sequencing in research requires a new approach to consent. *Tidsskr Nor Laegeforen*. December 2015;135(22):2031-2.
77. Matrana MR, Campbell B. Precision Medicien and the Institutional Review Board: Ethics and the Genome. *The Ochsner Journal*. 2020;20(1):98-103.
78. Ferguson AH. The Role of History in Debates Regarding the Boundaries of Medical Confidentiality and Privacy. *J Med Law Ethics*. August 2015;3(1-2):65-81.
79. Milligan DK, Koopman C, Doty N. Privacy is an essentially contested concept: a multi-dimensional analytic for mapping privacy. *Philos Trans A Math Phys Eng Sci*. December 2016;374(2083):20160118.
80. Ginsburg GS, Phillips KA. Precision Medicine: From Science to Value. *Health Aff (Millwood)*. May 2018;37(5):694-701.
81. Thapa C, Camtepe S. Precision health data: Requirements, challenges and existing techniques for data security and privacy. *Computers in Biology and Medicine*. February 2021;129.
82. Jain P, Gyanchandani M, Khare N. Big data privacy: a technological perspectives and review. *Journal of Big Data*. November 2016;3(25).
83. Sariyar M, Schlünder I. Reconsidering Anonymization-Related Concepts and the Term "Identification" Against the Backdrop of the European Legal Framework. *Biopreservation and Biobanking*. October 2016;14(5):367-374.
84. Prasser F, Kohlmayer F, Kuhn KA. Effecient and effective pruning strategies for health data de-identification. *BMC Medical Informatics and Decision Making*. April 2016;16:49.
85. Beauvais M, Knoppers BM. When information is the treatment? Precision Medicine in healthcare. *Healthcare Management Forum*. May 2020;33(3):120-125.

86. Hansson MG, Lochmüller H, Riess O, et al. The risk of re-idenification versus the need to identify individuals in rare dusease research. *European Journal of Huam Genetics*. May 2016;24:1553-1558.
87. Schwab AP, Luu HS, Wang J, Park JY. Genomic Privacy. *Clinical Chemistry*. December 2018;64(12):1696-1703.
88. Food and Drug Administration. *Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations*. October 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/impact-certain-provisions-revised-common-rule-fda-regulated-clinical-investigations. Accessed May 21, 2021.
89. Lipkin S. The Regulation of Research with Human Subjects. *Research Compliance Professional's Handbook*. 3rd ed; 2019.
90. Food and Drug Administration. *Informed Consent - Guidance for IRBs, Clinical Investigators and Sponsors*. July 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent. Accessed May 22, 2021.
91. U.S. Department of Health & Human Services. *CFR 46.116 Revised Common Rule*. 2018. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html. Accessed May 22, 2021.
92. Doerr M, Moore S, Barone V, et al. Assessment of the All of Us research program's informed consent process. *AJOB Empirical Bioethics*. December 2020;12(2):72-83.
93. National Institutes of Health. *All of Us Research Program*. 2020. https://allofus.nih.gov/. Accessed May 22, 2021.
94. Choi IS, Choi EY, Lee IH. Challenges in informed consent decision-making in Korean clinical research: A participant perspective. *PLoS One*. May 2019;14(5):e0216889.
95. Park H. Effect of Bioethics and Safety Act in medical research. *J Korean Med Assoc*. August 2013;56(8):665-675.
96. Korea Legislation Research Institute. *Bioethics and Safety Act*. 2013. https://elaw.klri.re.kr/eng_mobile/viewer.do?hseq=33442&type=part&key=36. Accessed May 12, 2021.
97. K-MASTER. *Cancer Precision Medicine Diagnosis and Treatment Enterprise*. 2020. http://k-master.org/eng.php. Accessed May 12, 2021.
98. Yu X, Li W. Informed Consent and Ethical Review in Chinese Human Experimentation: Reflections on the "Golden Rice Event". *Biotechnology Law Report*. August 2014;33(4):155-160.
99. Xinqing Z, Wenxia Z, Yandong Z. *The Chinese Ethical Review System and its Compliance Mechanisms*: TRUST - Equitable Research Partnerships; 2014.
100. National Health and Family Commission. *Measures for the Ethical Review of Biomedical Research Involving Human*. October 16, 2016.

http://www.nhc.gov.cn/fzs/s3576/201610/84b33b81d8e747eaaf048f68b174f829.shtml. Accessed May 22, 2021.
101. State Council. *Regulation on Management of Human Genetic Resources*. May 28, 2019. http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm. Accessed May 22, 2021.
102. Du L, Wang M. Genetic Privacy and Data Protection: A Review of Chinese Direct-to-Consumer Genetic Test Services. *Frontiers in Genetics*. April 2020;11(416).
103. Ministry of Health. *Rules of Medical Ethical Review Committee and Branch Committee - Order No. A/217*. May 30, 2018. https://moh.gov.mn/uploads/files/1d38a68476126f6360f76bcd66994b11a103e107.pdf. Accessed May 12, 2021.
104. Ministry of Health. *Regulation for collecting and using human blood, blood products, biological fluids, tissues and organs for the purpose of clinical trials and research - ORder No. A/526*. December 14, 2018. https://moh.gov.mn/uploads/files/f54a6c5d58ed9644b960e8526ea4dfeccab8e04e.pdf. Accessed March 22, 2021.
105. U.S. Department of Health & Human Services. *HIPAA Privacy Rule - 45 CFR Part 160*. 2019. https://www.hhs.gov/hipaa/for-professionals/privacy/index.html. Accessed May 22, 2021.
106. Chen C. Privacy in Precision Medicne - Cyber Security in Healthcare, with a Concentration in Electronic Health Record adn Genome Sequencing Data Management. *Journal of Advances in Health*. March 2019;01(01):38-43.
107. Services USDoH&H. U.S. Department of Health & Human Services. *Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the HIPAA Privacy Rule*. 2019. https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html. Accessed May 24, 2021.
108. Martinez C, Jonker E. A Practical Path Toward Genetic Privacy in the United States. Vol April: Future of Privacy Forum; 2020.
109. Korea Legislation Research Institute. *Personal Information Protection Act*. February 4, 2020. https://elaw.klri.re.kr/eng_service/lawView.do?hseq=53044&lang=ENG. Accessed April 12, 2021.
110. Lee D, Park M, Chang S, Ko H. Protecting and Utilizing Health and Medical Big Data: Policy Perspectives from Korea. *Healthcare Informatics Research*. October 2019;25(4):239-247.
111. Kwon Js. 'Personal Information de-identification' rises with three Acts regarding data. *Computer world*. February 29, 2020. Available at: https://www.comworld.co.kr/news/articleView.html?idxno=49812. Accessed May 29, 2021.

112. Office for Government Policy Coordination, Ministry of Interior Korea Communications Commission, Financial Services Commission, Ministry of Science, ICT and Future Planning, Ministry of Health and Welfare. *Guidelines for De-identification of Personal Data*. Seoul; 2016, June 30.
113. Shin SY. Issues and Solutions of Healthcare Data De-identification: the Case of South Korea. *Journal of Korean Medical Science*. January 2018;33(5):e41.
114. Cybersecurity Law of the People's Republic of China. June 1, 2017. https://www.newamerica.org/cybersecurity-initiative/digichina/blog/translation-cybersecurity-law-peoples-republic-china/. Accessed April 28, 2021.
115. Information Security Technology - Personal Information Security Specification. *National Information Security Standardization Technology Committee*. 2017. https://www.chinesestandard.net/PDF.aspx/GBT35273-2017. Accessed May 13, 2021.
116. Qi G, Li Q, Abernethy D. *China Releases Draft Personal Information Protection Law*: National Law Review; 2021.
117. The revision of the Personal Information Security Specification. *China's National Information Security Standardization Technical Committee*. June 17, 2020. https://www.tc260.org.cn/front/postDetail.html?id=20200617154145. Accessed May 15, 2021.
118. Information Security Technology - Guidelines for De-Identifying Personal Information. *National Information Security Standardization Technical Committee*. March 2020. https://www.chinesestandard.net/. Accessed May 22, 2021.
119. The Law on Personal Secrecy (Privacy Law). *Law of Mongolia*. April 21, 1995. https://www.legalinfo.mn/law/details/537. Accessed March 27 2021.
120. Draft of Personal Information Protection Law. *Ministry of Justice and Internal Affairs*. February 16, 2021. https://mojha.gov.mn/newmojha/. Accessed April 16, 2021.