

Precision Medicine: Legal and Ethical Challenges

# Precision Medicine Ethics: Prospects on Clinical Application and Ethical Issues

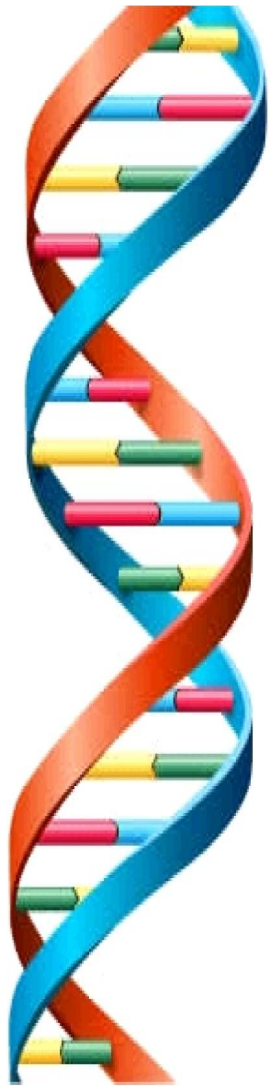
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# PART 1. PRECISION MEDICINE IN KOREA

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# Precision Medicine in Korea

- In South Korea, discussion on the possibility of personalized medicine became active since 2010, including forums and grants supported by Ministry of Health and Welfare.
- Korea has several strengths in the infrastructure toward the development of precision medicine.
- Since 2015 October, Precision Medicine became a focus of a concerted effort from the various stakeholders driven by the government initiative.

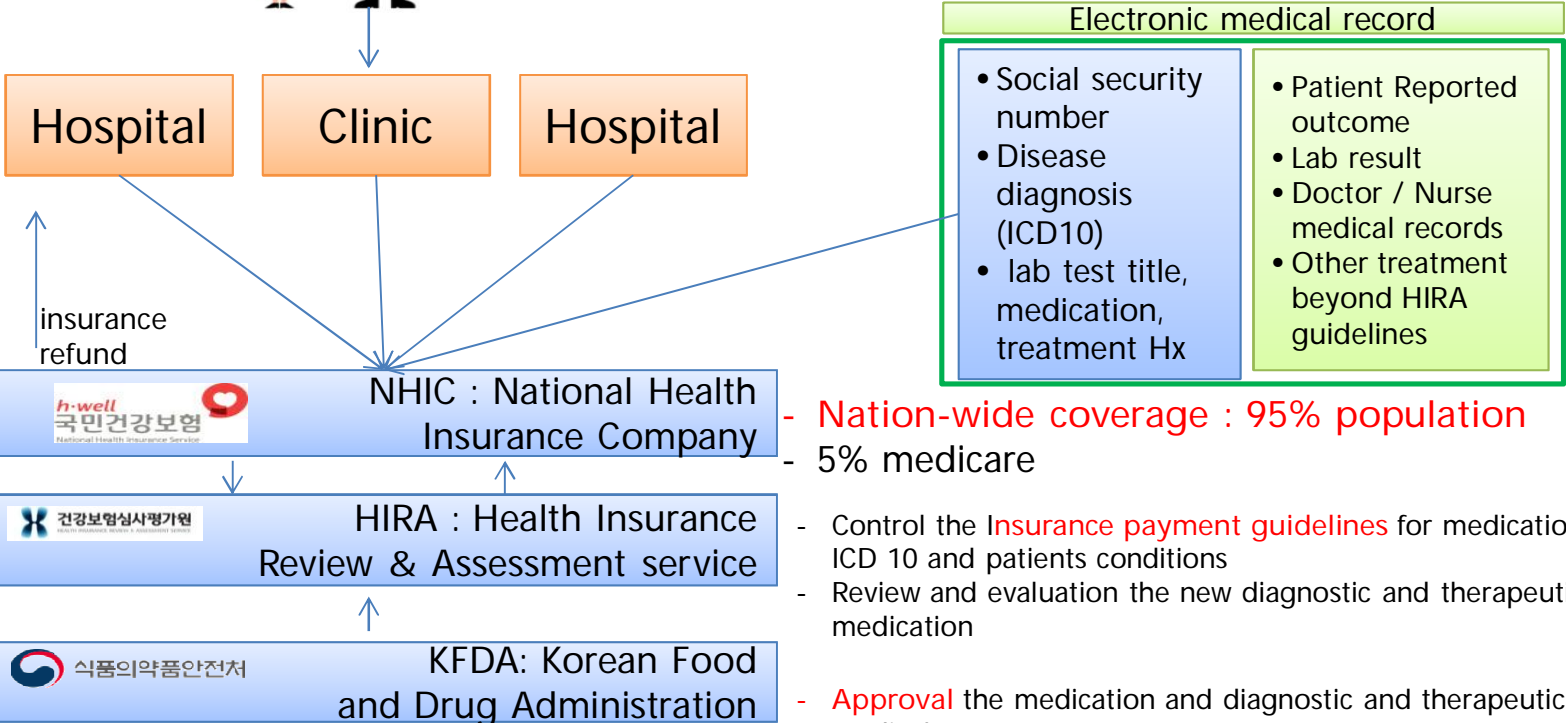
# Precision Medicine in Korea: Current Status and Strengths

- **National Biobanks in KOREA**
  - Korea Center for Disease Control has established large biobanks for population based cohorts and patient cohorts.
  - National Biobanks infrastructure retaining **biospecimen of 670,000 people**
  - **Cohort study on 250,000 people**, genomic information of 100,000 Koreans scheduled for completion in 2018

# Health Care System in Korea



- co-payment system within HIRA guidelines  
 : in general 20%, 0%(TB), 5% (cancer, heart dx,..) ~ 40% (URI)

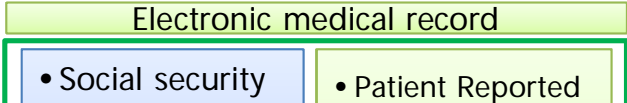


- Nation-wide coverage : 95% population
- 5% medicare
- Control the Insurance payment guidelines for medication, test, practice by ICD 10 and patients conditions
- Review and evaluation the new diagnostic and therapeutic technology and medication
- Approval the medication and diagnostic and therapeutic technology for medical use

# Health Care System in Korea



- co-payment system within HIRA guidelines  
 : in general 20%, 0%(TB), 5% (cancer, heart dx,..) ~ 40% (URI)



- NHIS coverage : 95% population  
 - 5% medicare

Korean National Health Insurance Service maintains health care data of all Koreans that can be used for research.

by  
and

식품의약품안전처  
 KFDA: Korean Food and Drug Administration

medication  
 - Approval the medication and diagnostic and therapeutic technology for medical use

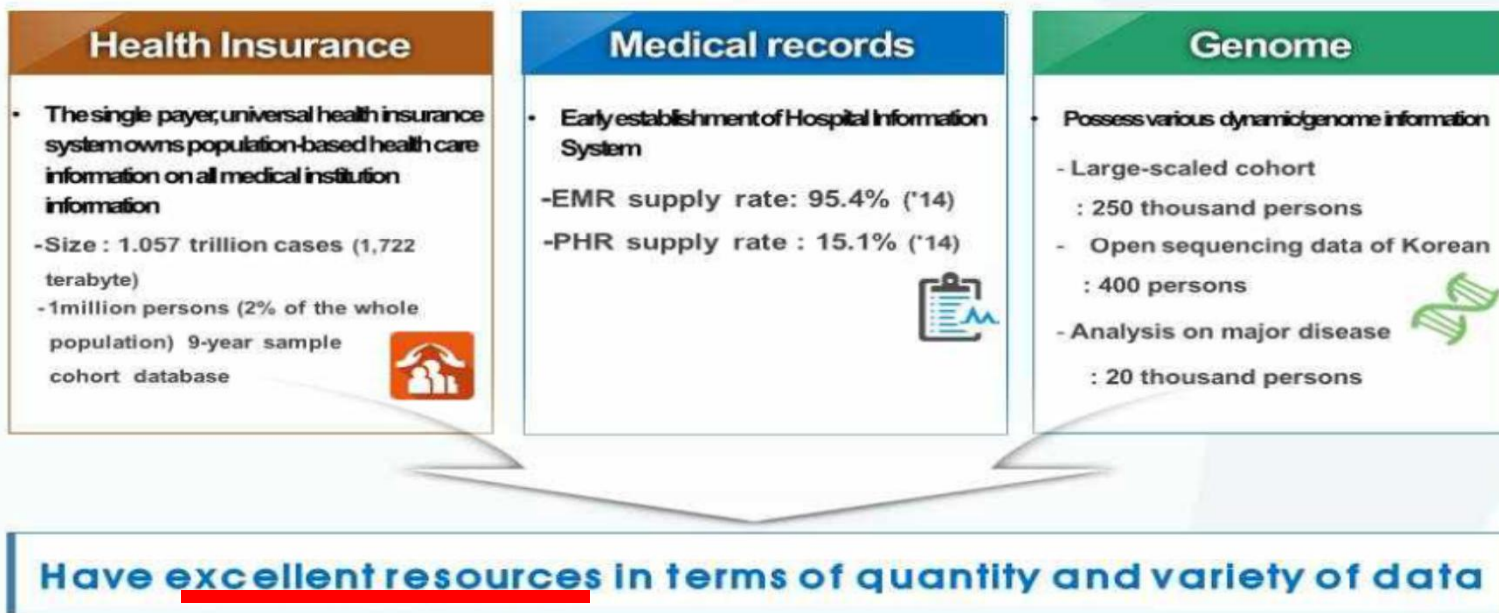
# Institutes having Health Big Data in Korea

Institute	Database	Resources
<b>NHIC</b> National Health Insurance Corporation	<ul style="list-style-type: none"> <li>National Health Information DB</li> <li>Sample cohort DB</li> </ul>	<ul style="list-style-type: none"> <li>92.4 Billion Cases as Medical Treatment/Checkup Results, Patient Registration Information</li> <li>A million cases for sample cohort</li> </ul>
<b>HIRA</b> National Health Insurance Review and Assessment Service	<ul style="list-style-type: none"> <li>Medical Information Center DB</li> </ul>	<ul style="list-style-type: none"> <li>204 Billion Cases per year including Medical Care benefit Claiming, Prescription, Dispensation DB, Patient Treatment, etc</li> </ul>
<b>CDC</b> Center for Disease Control, National Institute of Health	<ul style="list-style-type: none"> <li>Pathogen Recourses DB management system</li> <li>Korea National Biobank Network</li> </ul>	<ul style="list-style-type: none"> <li>pathogen Recourses DB</li> <li>23,000 Genome Sample Data of 250,000 people.</li> <li>Cohort, Disease-based human bioresources</li> </ul>
<b>NCC</b> National Cancer Center	<ul style="list-style-type: none"> <li>National Cancer Early Detection Program system</li> <li>Cancer patient medical expenses support information system</li> </ul>	<ul style="list-style-type: none"> <li>Health Checkup Target Information</li> <li>Cancer Checkup Result Data (2.5million people)</li> <li>Cancer patient medical expenses support Specification Data</li> </ul>
Hospitals	<ul style="list-style-type: none"> <li>Electronic Medical Recording DB of each hospital</li> </ul>	<ul style="list-style-type: none"> <li>Patients visit, hospitalization Treatment records</li> </ul>
Health care related Institutes	<ul style="list-style-type: none"> <li>Personal Health Records DB of each Institutes</li> </ul>	<ul style="list-style-type: none"> <li>Life log Data including biological information of each person</li> </ul>



# Health Big Data Resources in Korea

**Possess resources such as the National Health Insurance, clinical, genetic, and biospecimen data**



# Acceleration of precision medicine after ..



- 2015 Oct 14-16
- Visit of President Park Geun-hye of South Korea to meet President Obama United State

# LOI for Collaboration on Precision Medicine research between Korea and USA



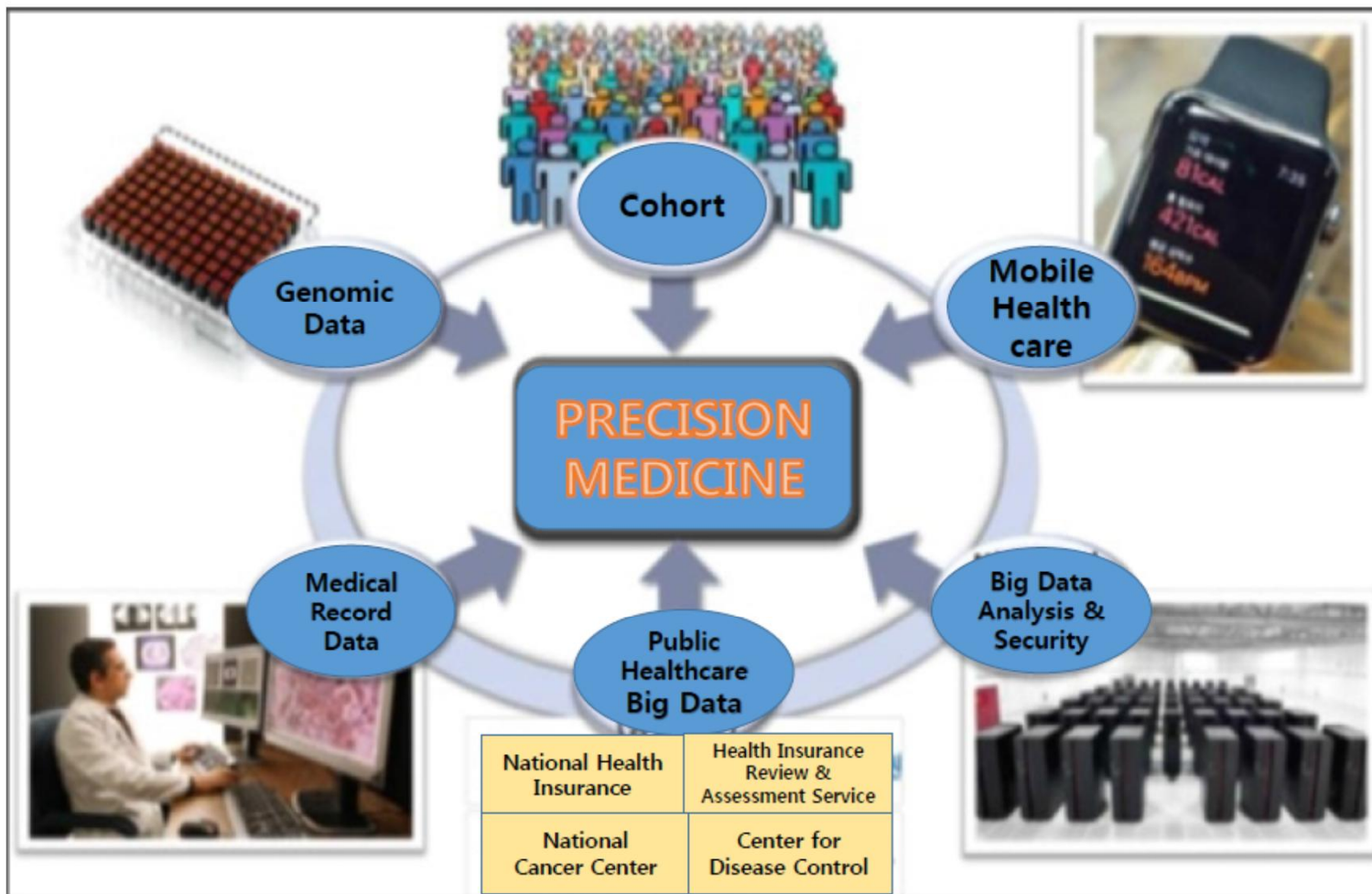
- Lee Joo-shil, left, the director-general of the Korea National Institute of Health, and her U.S. counterpart
- Francis S. Collins sign a letter of intent on collaborative research in precision medicine and MERS-CoV between the two countries on Oct. 2016 at Bethesda, Md.

- Courtesy of Ministry of Health and Welfare Korea

[http://www.koreatimes.co.kr/www/news/culture/2016/02/319\\_189785.html](http://www.koreatimes.co.kr/www/news/culture/2016/02/319_189785.html)

## “Precision medicine as a typical case of Creative Economy” (2015. 11)

- Korea President Park Geun-hye (2016. 1. 18)  
“Bio-health industry should lead for creation of a new source for national wealth in the future. For this, we need to establish Government-Civil Collaboration model, regulatory reform, Research and Development, and manpower training.”
- “Precision medicine as a typical case of Creative Economy” (Korea Ministry of Health, 2015. 11)
  - President Park Geun-hye defined the creative economy as:  
*“A creative economy is defined by the convergence of science and technology with industry, the fusion of culture with industry, and the blossoming of creativity in the very borders that were once permeated by barriers. It is about going beyond the rudimentary expansion of existing markets, and creating new markets and new jobs by building on the bedrock of convergence. At the very heart of a creative economy lie science technology and the IT industry, areas that I have earmarked as key priorities.”*  
-During her 2013 inaugural address

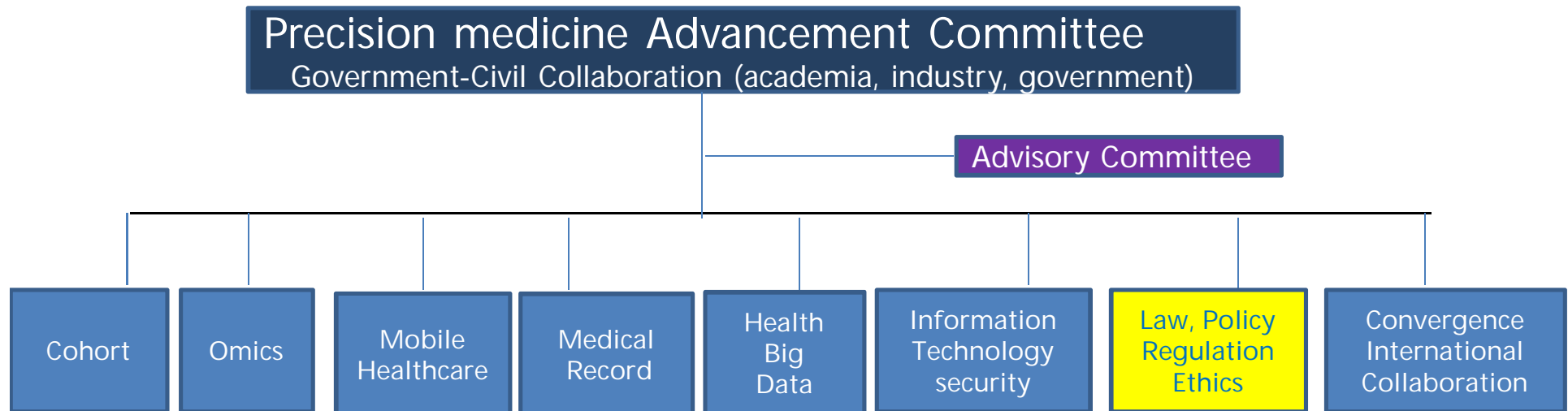


[http://hmnews.co.kr/bbs/board.php?bo\\_table=B01&wr\\_id=220](http://hmnews.co.kr/bbs/board.php?bo_table=B01&wr_id=220)

# Korean Government initiatives for PM

## 2016. March

### Precision Medicine Advancement Committee and Task Forces



## Korean Government: Three Domains and Seven Key Initiatives in Precision Medicine (2016. March 23)

	Domain	Key Initiatives
1	Building Precision Medicine Cohorts	Building New Precision Medicine Cohorts
		Utilization and Linking Plans of Preexisting Cohorts and Biobanks
2	Building Platform for Precision Medicine Big Data and Its Association with Industries	Standardization and Linking Plans of Medical Information and Genomic Data
		Building Open Portals For Precision Medicine Information
		Development of Artificial intelligence-based alpha-MED
3	Improving Law, Regulation, and Policy related to Precision Medicine	<b>Improvement of Law, Regulation, and Policy</b>
		Professional Workforce Development for Bioinformatics and Precision Medicine

## Laws related to Precision Medicine, Korea

- Bioethics and Safety Act, Korea (Law No. 13651)
  - Genetic test, Biobank, Human material research, Human subject research
- Personal Information Protection Law (Privacy Law)
- Pharmaceutical Affairs Law
- Medical Device Law
- National Health Act
- Medical Affairs Law
- Resident Registration Act

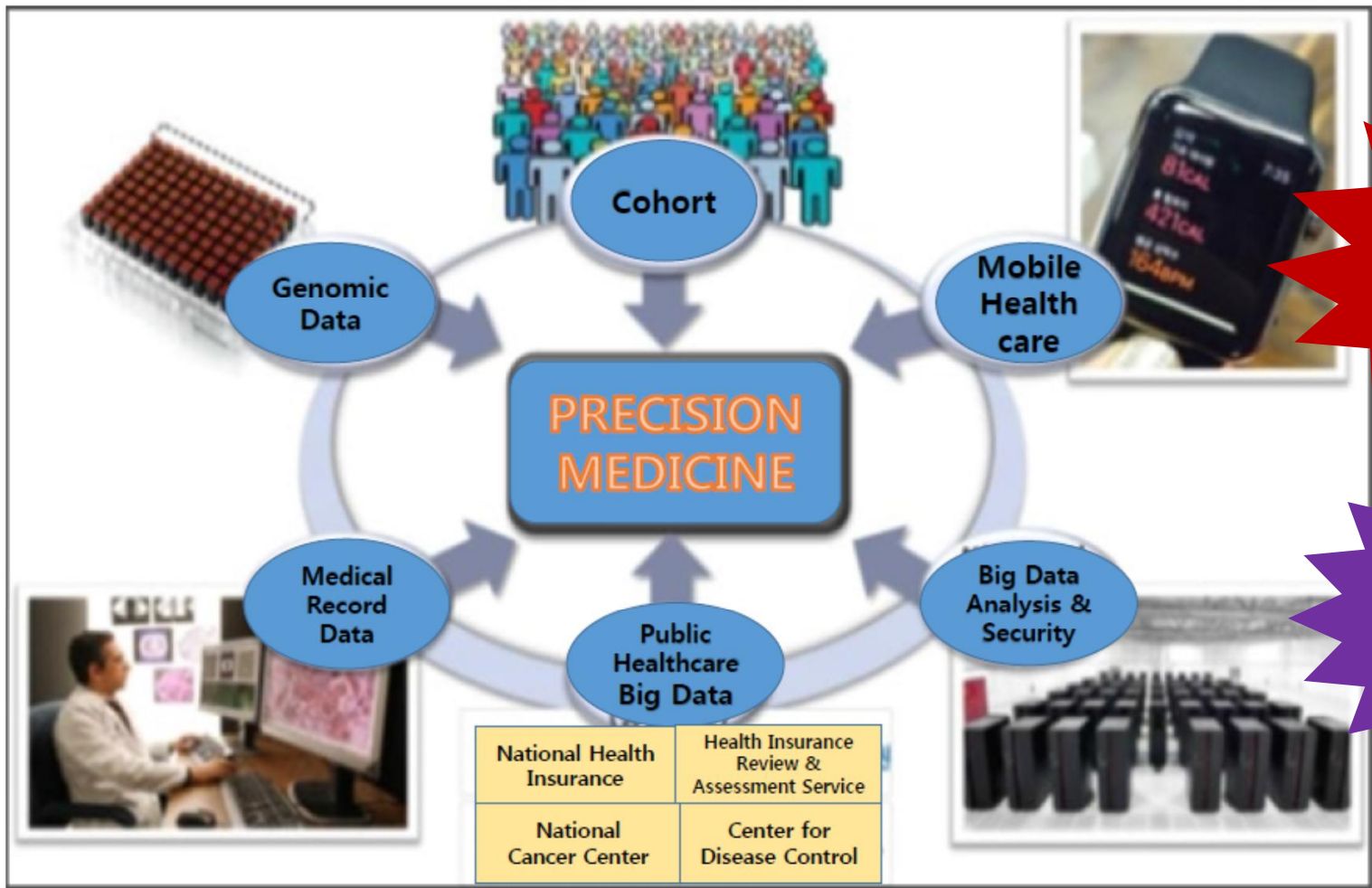


## Bioethics and Safety Act, Korea (Law No. 13651)

- Article 46 (Prohibitions on Discrimination Based on Genetic Information)
  - ① **No one shall be discriminated** against in educational opportunities, in **employment** or promotion, or in eligibility for **insurance coverage** on the basis of his or her genetic information.
  - ② Unless specifically stated otherwise in a different law, **no one shall force others to take genetic tests** or to submit genetic test results.
  - ③ No medical institution render genetic information involved in **medical records or a chart** provided to other people than the patient under article 21-② of the Medical Act. However, disclosure of a patient's genetic information is allowed when it is requested by another medical institution seeking to diagnose and cure the same disease as the patient's and when appropriate measures are taken to protect the patient's personal information.

## Issues related to the linking identifier: Resident Registration Number 住民登録番號 in Korea

- **Resident Registration Number, RRN**(住民登録番號,) is the national identification number written on the ID card system, which is issued to all citizens residing in the Republic of Korea in the Republic of Korea, is granted by the social security law.
- RRN is **a unprecedented powerful personal identification number** "that gives collectively to all citizens without any specific purpose, such as "social security number "of South Korea.
- The leakage of personal information of almost all citizens of Korea through RRN became a serious social problem
- In 2014 **Privacy Act** was revised **to prohibit the collection** of RRN and only permitted in exceptional cases based upon law.



Linking Identifier?

Who/what will be control tower?

## A bill for promotion of personalized medicine using genome, Korea

- 遺傳體を活用したカスタム医療技術開発の促進法案
- 遺傳體活用 定做医療技術開発促進法案
  
- Bill No. 5136
- The bill number 5136
- Submission date: 2013. 5. 27.
- Current status: **Pending** on 19<sup>th</sup> National Congress
- After the election of the 20<sup>th</sup> National Congress on 2016 April 13, the bill needs to be submitted again as a new bill.

## Reasons of proposing the bill on genomic PM

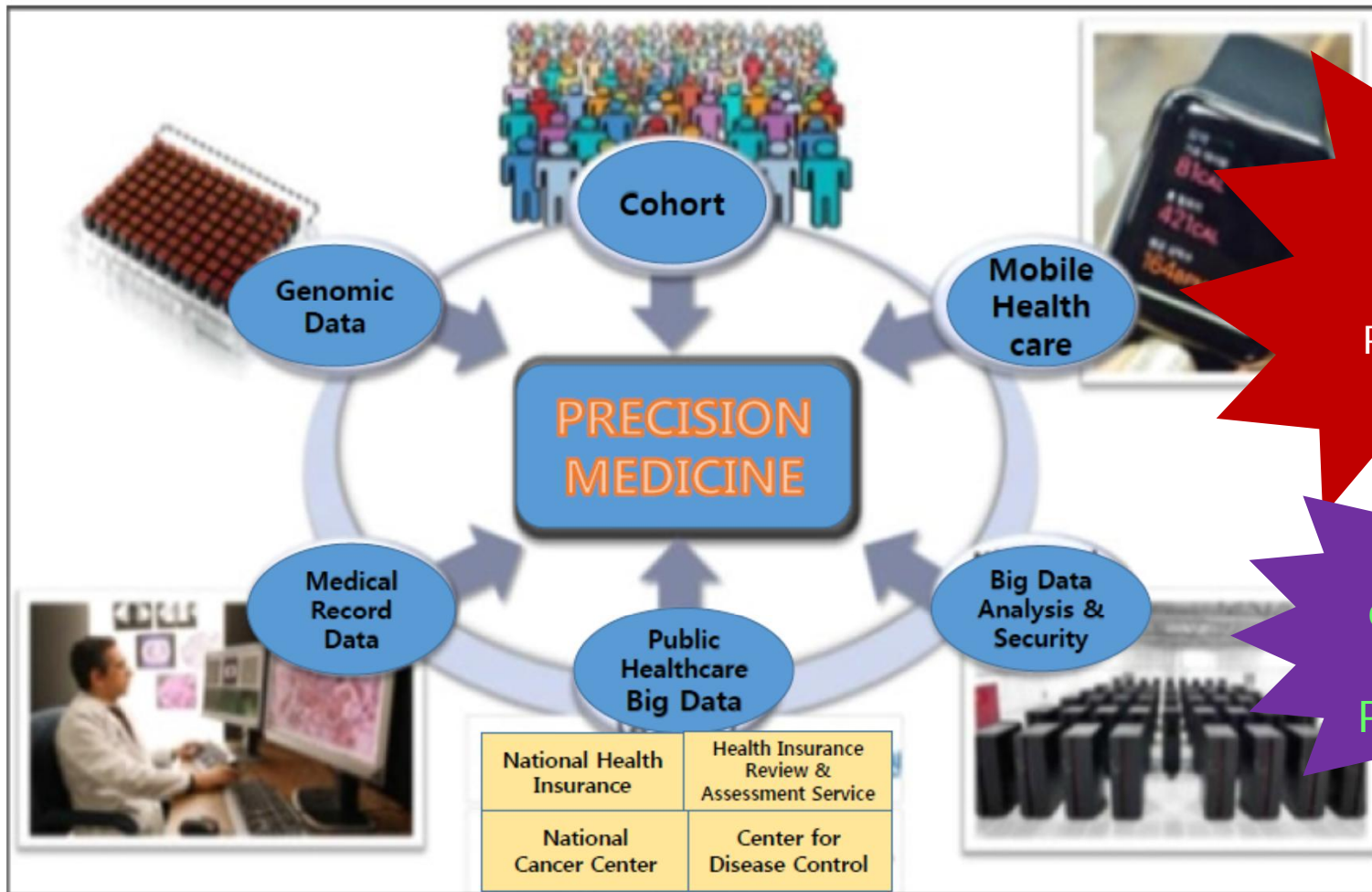
- Personalized medicine using genome (“genomic PM”, hereafter) is an urgent field of **development and investment** by fierce international competition for patents and intellectual property rights technology touted as promising areas.
- In particular, because genomic PM enables treatment suitable to individual genetic characteristics, it has the effect of protecting the citizens’ the right to health, and reduce medical costs through increasing the therapeutic effect, and reducing the side effects of drugs and unnecessary treatment.
- Therefore, we propose this bill for systematically laying **the legal foundation** to continue to foster the development of health technologies of genomic PM as a **key driver for development of the future medical industry**, and to **eliminate regulatory barriers** when we apply genomic PM.

# Contents of the bill on genomic PM (1)

- The Minister of Health and Welfare (Minister of Health, hereafter) shall set up mid-term and long-term plans to develop and promote genomic PM every five years to establish a **pan-Ministry Development Plan and Annual Implementation Plan** (Article 5).
- The Minister of Health has also installed **a customized integrated genomic PM information resource center (“genomic PM Center”)** for the collection, management, analysis, and provision of genome resources.
- The genomic PM Center may *handle and manage* **personal identifier and sensitive personal information** within the scope that is not against the subject of the information **despite the Personal Information Protection Law (“privacy law”)**.
- The Minister of Health shall establish personal information protection measures for the genomic PM Center.

## Contents of the bill on genomic PM (2)

- Article 8 (genomic resource utilization) Minister of Health can *provide* the genomic resources **despite the Personal Information Protection Law ("privacy law")** if the parties to study the genome to develop PM, research and development objectives require the provision of a genomic resources.
- Article 15 (collection of information) ① Minister of Health, in order to promote the genomic PM and *collect* the genomic information resources, may request information from the **NHIS** (National Health Insurance Service) and **HIRA** (National Health Insurance Review and Assessment Service), and other related authorities. **Requested authorities shall provide information to the Minister of Health, despite the Personal Information Protection Law ("privacy law").**
- Article 16 Minister of Health **may request the data submission** to researchers, research institutions, businesses, and organizations when they are necessary to analyze · investigate. The researchers, research institutions, businesses, and organizations are asked to submit data shall cooperate in this case if there is no special reason for this.



Linking identifier issues: Override Privacy Law

Ministry of Health, Genomic PM Center?



# Changes of concepts in Precision Medicine

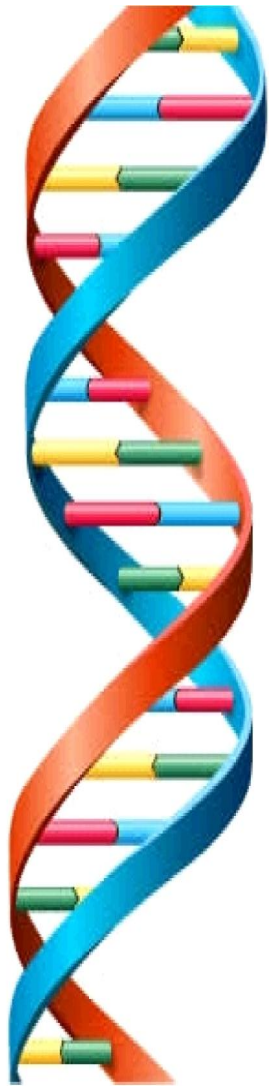
Domain	Health Care	Precision Medicine	Research
Legal & social status	Patient	Currently health individual with potential (predictive) risk factors	Research subject/ Participant
Primary Relationship (Right vs. Duty)	Patient - Doctor Relationship	Client/Customer - PM Service Providers (genetic counselor, etc.) multiple Relationship?	Subject-Researcher Relationship
Legal framework	Medical Law	multiple laws involved? Or A new law needed?	Research Law on human subject protection
Ethical, social, implications	Usually confined to individuals	Usually beyond individual realm: family, relatives, groups	Usually confined to individuals
Ethical issues	Autonomy, Beneficence, non maleficence	Protection from Discriminations in Insurability, employability , etc	Autonomy, Beneficence, non maleficence <sup>25</sup>

# Ethical and Social Issues in PM in Korea (1)

- Precision Medicine; Predictive, Personalized, Preventive, Participatory (P4) medicine
- **Lack of Participatory perspectives in Korea:** Lack of public participation and social engagement (lack of patients groups, civil right or privacy groups)
- **Economic rationale may override considerations for patients or participants** in the discourse in the policy documents of precision medicine in Korea
  - Framed as an exemplary initiative of Creative Economy of President Park Geun-hye
  - Legacy to characterize science and technology as one of the most important driving forces to develop the nation's economy in the Park Jung Hee's Regime ("the Militarized Modernity")
- **Data security by IT group,** and personal data protection are emphasized to to get public trust and promote individual participation to the PM program
- **Public communication and education** have **not** been emphasized
- Lack of consideration of **marginal or disadvantageous groups** for participation

## Ethical and Social Issues in PM in Korea (2)

- **Citizens' participation & public engagement** are necessary to get public trust
- Ethical issues such as informed consent, return of results, privacy issues, data sharing, and governance have not been addressed fully and openly
- Public understanding, awareness, and provision of information on uncertainties, risks and limitations, as well as potential benefits
- Legislation for a new legal framework also needs to seek wide public consultation and participation



## PART II: PRECISION MEDICINE AND HEALTH CARE SYSTEM IN KOREA

### NATIONAL CANCER CENTER EXPERIENCES

Yoon-Jung CHANG

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and Policy, National Cancer Center, South Korea

# Clinical use of PM in cancer care

Drug of choice for treatment	<ul style="list-style-type: none"><li>• EGFR mutation for NSCLC</li><li>• CYP17AI for prostate cancer</li><li>• HER2 positive for breast cancer</li></ul>	<ul style="list-style-type: none"><li>• Target matched treatment choice</li></ul>
Prognosis prediction	AML <ul style="list-style-type: none"><li>• T(8:21) : good prognosis</li><li>• T(9:11) : medium prognosis</li><li>• -5, -7, inv(3), t(3;3): poor prognosis</li></ul>	<ul style="list-style-type: none"><li>• Same Treatment</li><li>• Consider the 2<sup>nd</sup> line treatment</li></ul>
Disease prediction	<ul style="list-style-type: none"><li>• BRCA mutation : breast ca. ovary ca.</li><li>• Pathologic variant / <b>Unclassified variant</b> / benign variant</li></ul>	<ul style="list-style-type: none"><li>• Preventive surgery</li><li>• High risk group screening for early detection</li><li>• Risk life style modification</li></ul>



Original Article

## The Role of Gefitinib Treatment for Korean Never-Smokers with Advanced or Metastatic Adenocarcinoma of the Lung: A Prospective Study

Dae Ho Lee, MD\*, Ji-Youn Han, MD, PhD\*, Sun Young Yu, BS\*, Hyaе Young Kim, MD, PhD\*, Byung-Ho Nam, PhD†, Eun Kyung Hong, MD, PhD\*, Heung Tae Kim, MD, PhD\*, Jin Soo Lee, MD, MPH\*  

[Show more](#)

### **First-SIGNAL: First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never Smokers With Adenocarcinoma of the Lung**

Ji-Youn Han, Keunchil Park, Sang-We Kim, Dae Ho Lee, Hyaе Young Kim, Heung Tae Kim, Myung Ju Ahn, Tak Yun, Jin Seok Ahn, Cheolwon Suh, Jung-Shin Lee, Sung Jin Yoon, Jong Hee Han, Jae Won Lee, Sook Jung Jo and Jin Soo Lee 

[+ Author Affiliations](#)

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#### **Abstract**

Genetic test  
+ life style  
+ race

EGFR mutation in  
NSCLC  
+  
Non-smoker  
+  
Asian

# Genetic Counselling Clinic at NCC

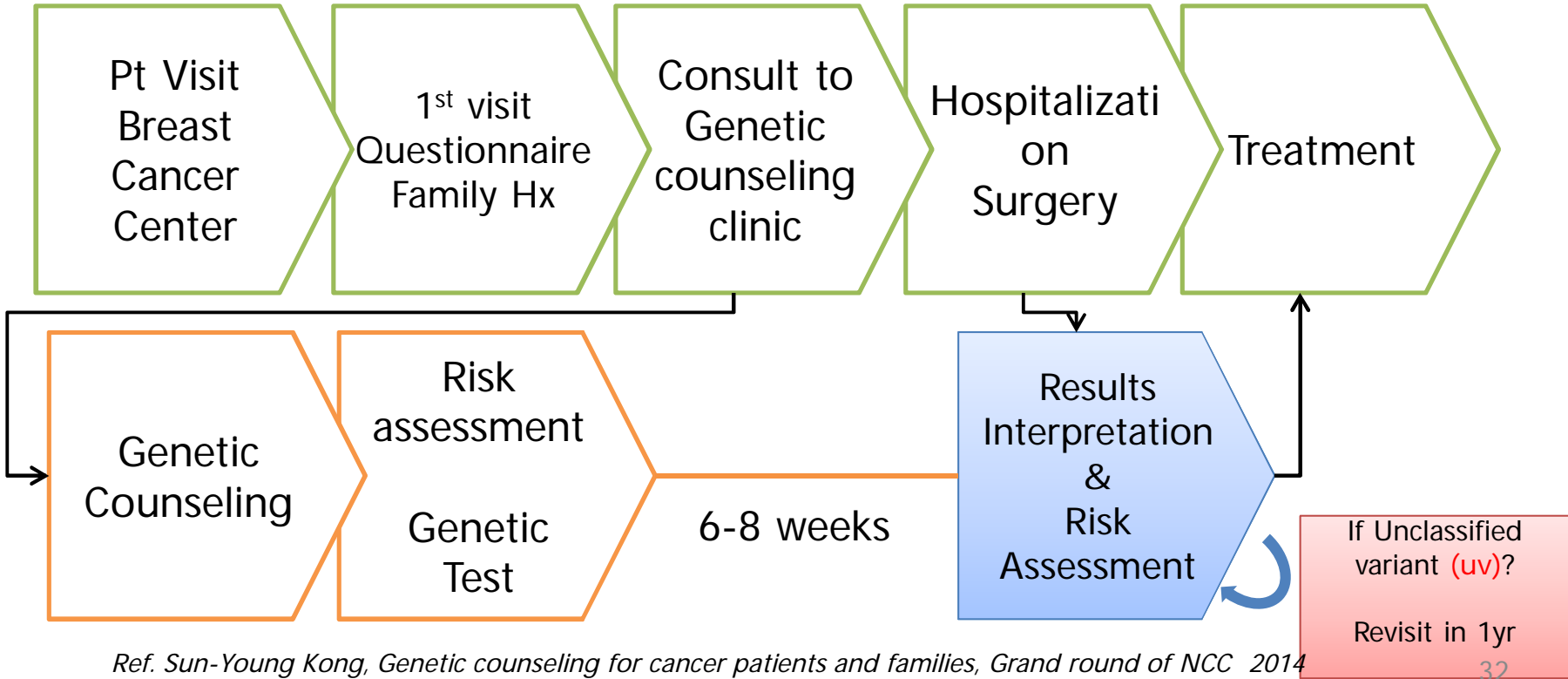
Multidisciplinary team clinic covered by NHIS from Aug 2014

- 4 medical specialists
- One assistant nurse for family tree
- Laboratory medicine
  - Interpretation of genetic test result
- Breast surgeon
  - Tx plan for breast ca or residual breast
- Gynecologist
  - Tx plan for ovary
  - Iatrogenic menopause management
  - Infertility after oophorectomy
- Family medicine
  - Life style management (obesity...)
  - Screening test
  - Co-morbid NCD management (HTN, DM...)



# Flow of Genetic Counseling at NCC

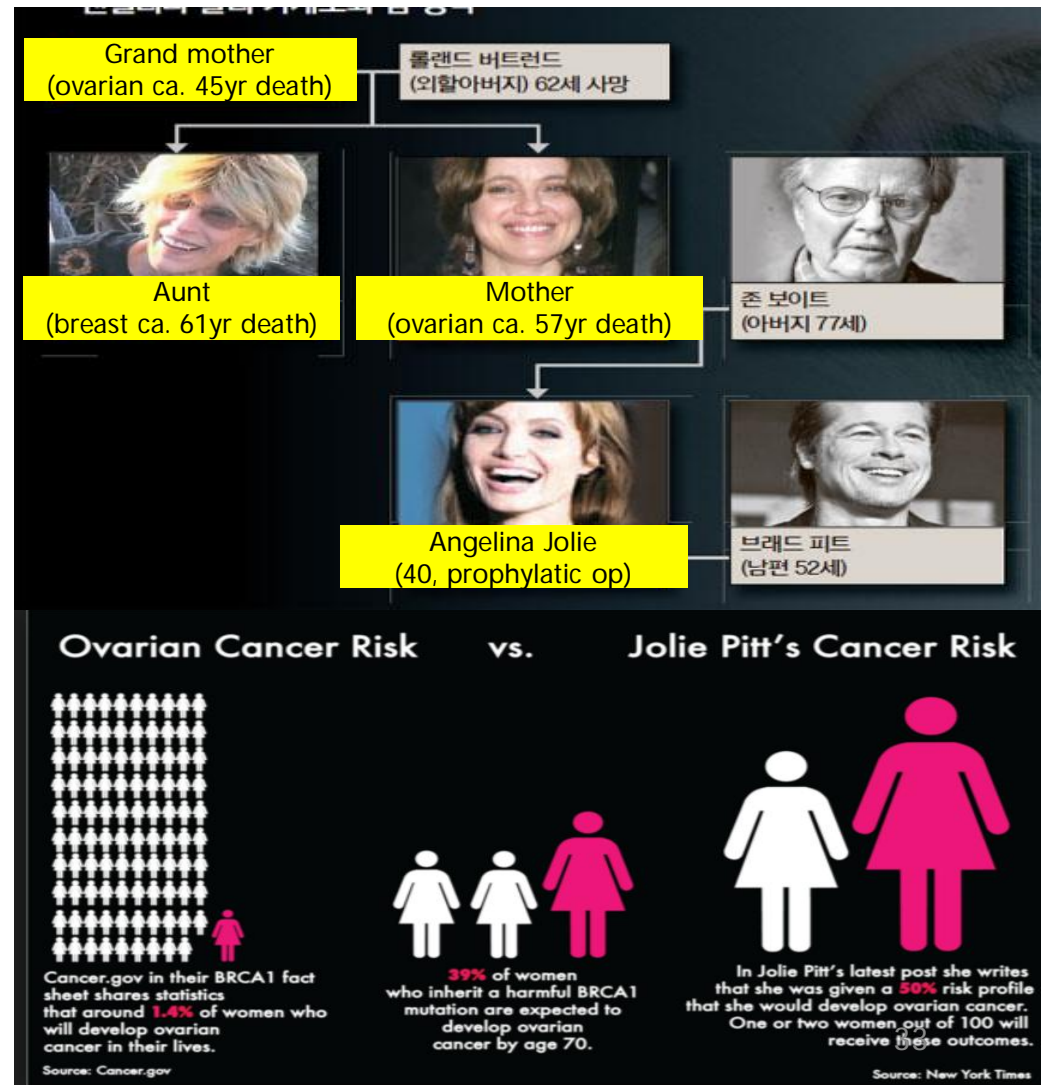
- Breast Ca. Patient with Family history-



Ref. Sun-Young Kong, Genetic counseling for cancer patients and families, Grand round of NCC 2014

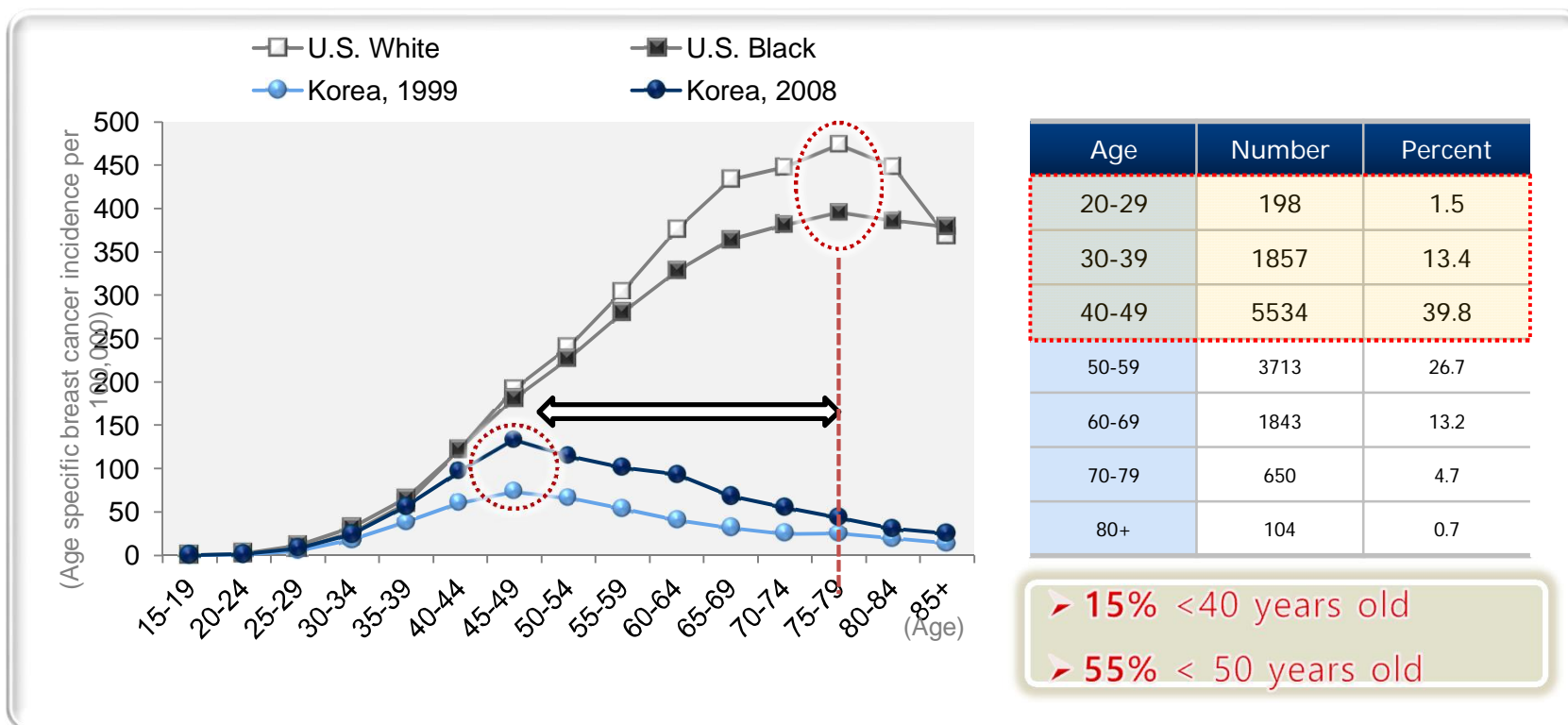


# BRCA mutation family



# Differences in Onset age of breast ca.

**ONSET AGE** US White US Black Korea 1999 Korea 2008



# BRCA1/BRCA2 Gene test indication in Korea

-Health insurance review & assessment service-

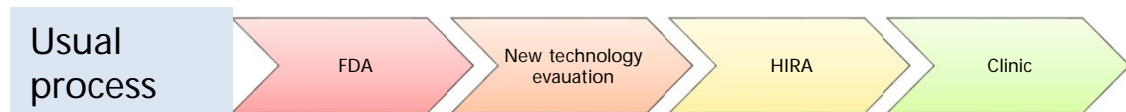


- Breast ca. or Ovarian ca. with  
     $\geq 1$  close relatives in 2<sup>nd</sup> degree with breast ca. or ovarian ca.
- Patient with both Breast ca. and Ovarian ca.
- Patient with Breast ca. **diagnosed <40 y** (NCCN guideline of US <45y)
- Bilateral Breast ca.
- Multiple ca. including breast ca.
- Male breast ca.
- Epithelial ovarian ca.

2012.4.30. 진료심사평가위원회

# Regulatory reform for Precision Medicine

- November 2015: proposal for regulatory reform to promote Precision Medicine (Ministry of Health)
- **Introduction of Laboratory Developed Tests (LDTs) – 2016. March-June**
- LDT - manufactured and used by a healthcare facility laboratory accredited by Korean MFDS
- **(K-FDA) – exempted from approval process as Medical Device**, being diagnosed and/or treated at that same **certified health care facility or within that certified laboratory.**
- Purpose:
  - **Facilitate introduction of genetic test** based upon Next-Generation Sequencing **(NGS) to clinical care of Precision Medicine**
- **National Health Insurance service (NHIS) will cover** the payment for cancer panel from August 2016
- **Goals:**
  1. reduce the healthcare cost **(5% co-payment)**
  2. Promotes **Diagnostics industries regulatory reform.**



# Genetic test will open to general clinic

## Till now

- **Single genetic test** was available in Clinic with strict indication for **NHIS guideline**
- **Gene panel** was allowed for basic & clinical research

## To be

- **K-FDA** will treat the **NGS without evaluation** as a clinical diagnostic tool.
- **In August 2016, NHIS guideline for cancer panel** will be built soon

**Cancer Gene Panel Includes:**

ABL1	ERBB4	JAK2	PIK3CA
AKT1	FBXW7	JAK3	PTEN
ALK	FGFR1	KDR	PTPN11
APC	FGFR2	KIT	RB1
ATM	FGFR3	KRAS	RET
BRAF	FLT3	MET	SMAD4
CDH1	GNA11	MLH1	SMARCB1
CDKN2A	GNAQ	MPL	SMO
CSF1R	GNAS	NOTCH1	SRC
CTNNB1	HNF1A	NPM1	STK11
EGFR	HRAS	NRAS	TP53

**National Health Insurance cover Aug 2016**

# Ethical consideration

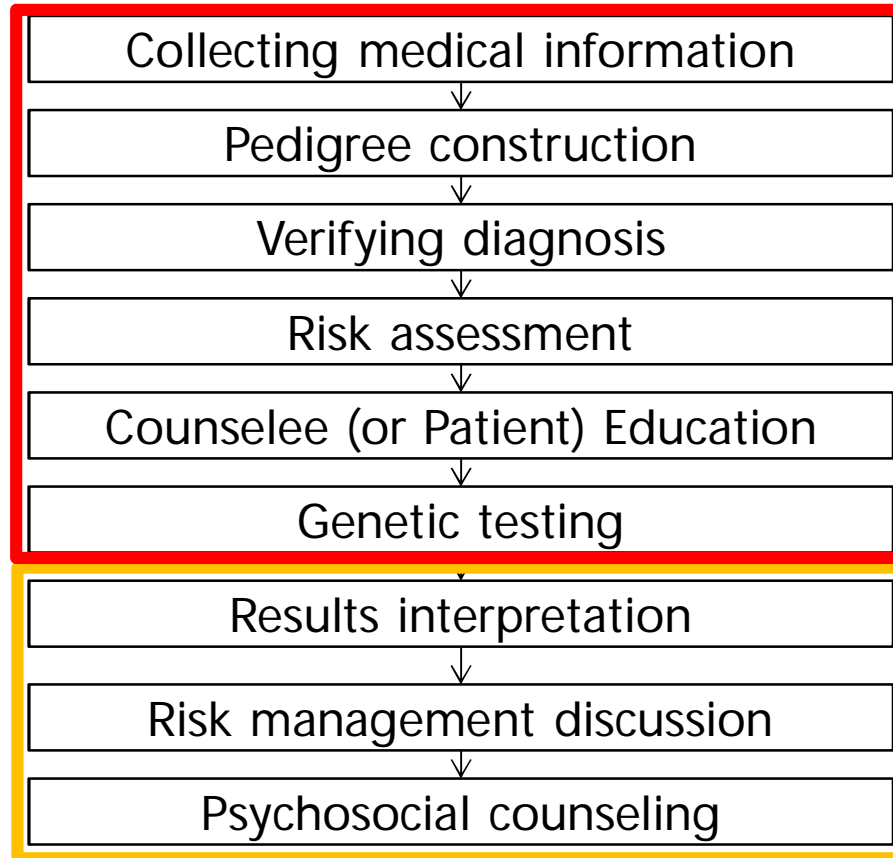
No genetic counselor  
education or certification

Few clinical guideline  
for genetic high risk patient  
or carrier

Affordability & Accessibility

Stigma

# No genetic counselor education or certification



<Step for genetic counseling>



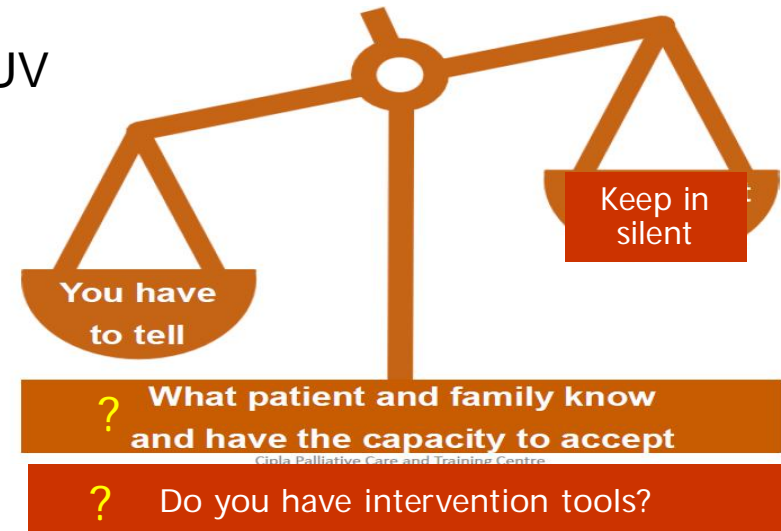
Well-trained GC:  
Risk communication  
With medical knowledge

# Few clinical guidelines for genetic results

- Few **available intervention** for disease prevention
  - NHIC indication : Preventive oophorectomy for BRCA mutation carrier
  - Else?
- **Unclassified variant (UV)** management (**pathologic var. vs normal var.**)
  - BRCA : In 2014, **30%** UV → in 2015, **20%** UV
- **Incidental finding** management



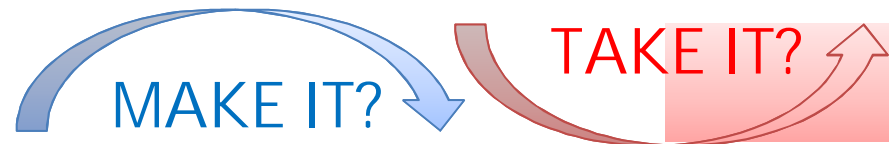
Uncertainty vs. **genetic determinism**





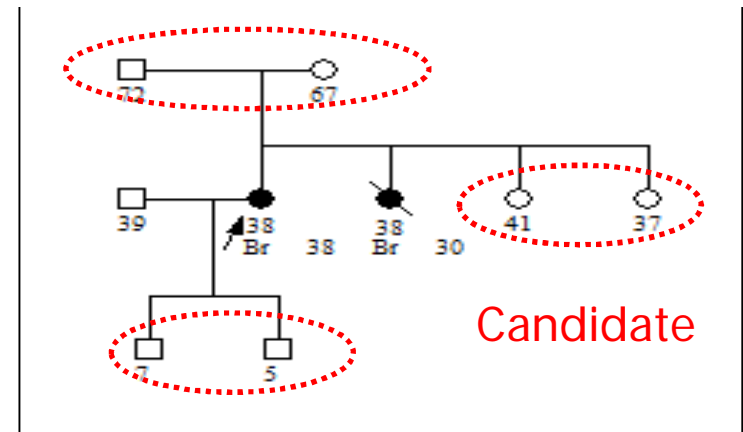
# Affordability & accessibility

- Strict indication for genetic test (only cancer?)
- Few available target Treatment
- Few patients gets benefit with high-cost test and target treatment by national insurance
- Lots of health information & bio-materials was needed for research..... for long term goals



# stigma

- Psychological burden
  - Anxiety, depression
  - Suicide attempt
- Uncertainty vs. genetic determinism
- Invite to get genetic test to their relatives
  - Guilty feeling
- Genetic information discrimination
  - Health insurance payment?
  - Marriage, employment?





Special thanks to Sun-Young Gong, MD