New initiative for the implementation of Genomic Medicine in Japan

1) Office of Healthcare Policy, Cabinet Secretariat
2) Center for Integrative Medical Science, RIKEN
3) The Institute of Medical Science, The University of Tokyo

Naoko Okamura 1), Michiaki Kubo 2), Satoru Miyano 3)
Structure of the Headquarters of Healthcare Policy

**Headquarters of Healthcare Policy (HHP)**
- **Director-General of HHP**: Prime Minister
- **Vice Director-General of HHP**: Chief Cabinet Secretary
- **Members of HHP**: Ministers of State other than Prime Minister and Chief Cabinet Secretary

**<functions>**
- Promotion of the implementation of the Health and Medical Strategy
- The headquarters of medical R&D ("Japanese version of NIH")
  - The HHP shall
    - develop a comprehensive plan for promotion of medical R&D.
    - integrate medical R&D budget requests of relevant ministries.

**Promotion Council for Health and Medical Strategy**
- **Chairperson**: Chief Cabinet Secretary
- **Acting Chairpersons**: Deputy Chief Cabinet Secretaries (belonging to the House of Representatives and the House of Councilors)
- **Deputy Chairperson**: Director-General of the Office of Healthcare Policy
- **Members**: Director-Generals of relevant ministries

**Task Force for Global Reach of Japanese-style Medical Technology and Services**
- **Chairperson**: Director-General of the Office of Healthcare Policy
- **Members**: Director-Generals of relevant ministries, Officer of Organization concerned

**Committee of the Academia-Industry-Government Network for Drug Discovery Research**
- **Chairperson**: Director-General of the Office of Healthcare Policy
- **Members**: Director-Generals of relevant ministries, Officer of Organization concerned

**Special Committee on Medical Research and Development**
- consists of superior researchers in a medical field.
- advises the HHP on scientific matters required for development of a comprehensive plan for promotion of medical R&D.

**Advisors on Health and Medical Strategy**
- consist of superior expertise belonging to pharmaceutical and medical equipment industry, and medical institution, etc.
- advise the HHP on: Promotion of implementation of the Health and Medical Strategy, Promotion of industrialization, etc.

**Office of Healthcare Policy, Cabinet Secretariat**
- **Chairperson**: Director-General of HHP
- **Members**: Director-Generals of relevant ministries

**Technical Advice**
- Office of Healthcare Policy, Cabinet Secretariat
1. Functions of Headquarters (HQ) of Healthcare Policy

- Strategically integrating medical R&D budget requests of the government to allocate the budget upon priority projects, and developing a comprehensive plan for promotion of medical R&D early next year, the HQ shall determine prioritizing research fields and targets.
- The HQ shall establish two panels for the above purposes:
  - The panel of advisors, superior researchers in a medical field, to the HQ
  - The panel of advisors, eminent persons from industry, government, and academia, to the HQ

2. The HQ’s integration of medical R&D budget requests of the government

- The HQ shall integrate medical R&D budget requests in order strategically to concentrate the budget upon priority projects under a strong leadership of State Ministers from each ministry’s budget demand forward.
- The following measures shall be taken to integrate medical R&D budget requests of relevant ministries prior to budget demands:
  - The HQ shall formulate a basic policy for the medical R&D budget demands.
  - Each ministry shall submit total rough estimate of their medical R&D budget to the cabinet secretariat in accordance with the basic policy.
  - Each ministry shall obtain consent of the cabinet secretariat to their rough estimate
- Specifically:
  - The cabinet secretariat shall adjust each ministry’s estimate to a comprehensive plan for promotion of medical R&D and if necessary require each ministry to make an amendment to their estimate.
  - Each ministry shall make an amendment to their estimate in accordance with a requirement of the cabinet secretariat and report details of amendment to the cabinet secretariat.
  - Each ministry shall submit their budget demands obtained cabinet secretariat’s consent to the ministry of finance in collaboration with the cabinet secretariat.

3. The new independent administrative agency’s functions; Grants and funding for medical R&D in an integrated fashion

- Instead each ministry implements, the new independent administrative agency shall centrally allocate grants to researchers/institutions in order to continue nation’s R&D projects that cover phases from basic research to development of practical use without an interval.
- Promoting medical R&D more efficiently and effectively, the agency shall also implement the budget for infrastructure development (ex. a subsidiary for development of core hospital for clinical research/trial) in an integrated fashion.

4. Allocation on Special Coordination funds for the promotion of Medical R&D

- The HQ shall allocate on special coordination funds for the promotion of medical R&D across the ministries in order flexibly and efficiently to respond to advance in medical R&D projects and adoption of application for medical R&D subsidies etc.
- Special Coordination funds shall be appropriated from a part of scientific and technological innovation promotion funds (tentative name) entered in the budget of the Cabinet Office.
The new system of implementation of the Health and Medical Strategy

Headquarters of Healthcare Policy (HHP)

- develop a comprehensive plan for promotion of medical R&D.
- integrate medical R&D budget requests of relevant ministries.
- strategically and intensively decide allocating promotional adjustment funds.

Integration of medical R&D budget requests

Funds for individual Research

Nation's top-down scientific/clinical R&D
- The government will allocate about ¥100 billion for grant and funding into a new agency.
- management nation's top-down projects by Program Directors and Program Officers belonging the new agency

Manage and integrate both allocated grants to researchers/scientists and institutions, and funding
※ Integrate the budget for infrastructure development into a new agency

Researchers’ bottom-up Scientific Research
Grant-in-Aid for Scientific Research (KAKENHI)

Steadily implement the clinical research/trial based on the extra-international standard
 ※ Universities, Institutions, Researchers/Scientists

Smoothly transit discovered seeds

Core hospital for clinical research/trial etc.

Manage and integrate both allocated grants to researchers/scientists and institutions, and funding
※ Integrate the budget for infrastructure development into a new agency

Integration of medical R&D budget requests

Intramural research
National Institutions

Steadily implement the clinical research/trial based on the extra-international standard

Measure on source of revenue for Institutions
※ National Center for Global Health and Medicine, RIKEN, National Institute of Advanced Industrial Science and Technology, National Institute of Infectious Diseases etc.
<table>
<thead>
<tr>
<th>Budget Bill for Medical Research in FY 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New Agency</strong></td>
</tr>
<tr>
<td>FY 2014</td>
</tr>
<tr>
<td>121.5 billion yen</td>
</tr>
<tr>
<td>(MEXT57.0, MHLW47.6, METI16.9)</td>
</tr>
<tr>
<td>FY 2013</td>
</tr>
<tr>
<td>101.2 billion yen</td>
</tr>
<tr>
<td>(MEXT44.7, MHLW40.2, METI16.3)</td>
</tr>
<tr>
<td><strong>Related Research Institutes</strong></td>
</tr>
<tr>
<td>FY 2014</td>
</tr>
<tr>
<td>74.0 billion yen</td>
</tr>
<tr>
<td>(MEXT20.0, MHLW45.5, METI8.5)</td>
</tr>
<tr>
<td>FY 2013</td>
</tr>
<tr>
<td>71.3 billion yen</td>
</tr>
<tr>
<td>(MEXT15.5, MHLW47.6, METI8.1)</td>
</tr>
</tbody>
</table>

**For Development of New Medicine and Medical Devices**

- Medicine: 25.4 billion yen
- Medical Devices: 11.2 billion yen

**For Specific Diseases**

- Cancer: 17.2 billion yen
- Mental Diseases and Neurologic Diseases: 7.1 billion yen
- Emerging and Re-emerging Infectious Diseases: 5.3 billion yen
- Rare Diseases: 9.3 billion yen

**For Novel Medical Technologies**

- Regenerative Medicine (iPS cells, ES cells etc..): 15.1 billion yen
- Genomic Medicine: 7.0 billion yen

**For Clinical Study and Clinical Trial**

- 12.1 billion yen
To improve medical care and health care for common diseases including cancer and lifestyle-related diseases, MEXT and MHLW cooperate for the implementation of Genomic Medicine project. Based on the “Health and Medical Strategy” by Japanese government in June 2013, this project promotes clinical application of genomic research findings for aiming at the return to the public quickly, in parallel with the strengthening of genomic research infrastructure.

**Goals to be achieved by 2015**
- Construct biobank network
- Establish Central Genome Center (CGC) and Medical Genome Center (MGC)
- Construct Japanese reference genome sequence (Japanese RefSeq)
- Build comprehensive genomic variation DB linked to clinical phenotypes

**Goals to be achieved by 2020–30**
- Improvements for the medical and health care of lifestyle diseases
- Establish predictive diagnostics for cancer incidence and severe ADR
- Start clinical genomic research for depression and dementia
- Clarify the pathogenesis of neurological diseases, etc.

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**Development of research infrastructure**

- **BioBank Japan**
  - Disease-oriented biobank (200,000 patients)
  - RIKEN & IMSUT
- **National Center Biobank Network**
  - Budget intramural: ¥ 1,1 B
- **NCBN**
  - NCC, NCNP, NCGM, NCCHD, NCGG
  - Disease-oriented biobank cooperated with 6 national center
- **Tohoku Medical Megabank Project**
  - Tohoku Univ. & Iwate Med Univ.
  - Population-based biobank (150,000 local residents planned)

**Central Genome Center (CGC)**

- Large-scale genomic research
- Strengthening of Genomic Research infrastructure

**Medical Genome Center installation**

- Clinical application of genomic information
- Strengthening of clinical research by use of highly-specialized hospital functions

**Implementation of Genomic Medicine for all generations**

- **BioBank Japan**
  - Budget: ¥ 1,8 B
  - Supplementary budget: ¥ 3,0 B
- **Central Genome Center (CGC)**
  - RIKEN & IMSUT
  - Large-scale genomic research
  - Strengthening of Genomic Research infrastructure
- **Medical Genome Center (MGC)**
  - Based on high quality evidence from genomic research, MGC establish
  - Optimized treatment through prediction of drug responses
  - Predictive diagnostics
  - Optimized preventive health care for disease

**Coordinated Biobanks, CGC and MGC**

- Coordination secretariat
- Management and quality control of samples and information

**Universities**

- Studies for disease mechanisms

**Tohoku Medical Megabank Project**

- Population-based biobank (150,000 local residents planned)

**Long-term survey of disaster residents**

- Local-resident cohort (80,000 people)
- Three-generation cohort (70,000 people)

**Coordinate Biobanks**

- Disease-oriented biobank (200,000 patients)

**Budget**

- Nation’s top-down funds
  - FY2014 budget: ¥ 5,5 B
  - FY2013 supplementary budget: ¥ 3,0 B
- Intramural funds
  - FY2014 budget: ¥ 1,6 B
  - FY2013 supplementary budget: ¥ 0,8 B
Overview

- Taylor-made medical treatment program was started in 2003 as a Leading Project of MEXT for the implementation of personalized medicine.
- In the 1st period (2003-2007), this program constructed a large disease-oriented biobank (BioBank Japan) in collaboration with 66 hospitals in all areas of Japan.
- In the 2nd period (2008-2012), this program performed large-scale GWAS using the samples collected in the BioBank Japan and identified >260 novel susceptibility genes or loci for various diseases and drug responses.
- In the 3rd period (2013-2017), this program expands biobank infrastructure, further promote genomic research and move forward to apply findings into clinical research in collaboration with other national projects.

Research infrastructure of the BioBank Japan

- 1st cohort: 1st period (2003-2007), 47 diseases, 200,000 patients (DNA, serum, medical records)
- Follow-up survey
- 2nd cohort: 2nd period (2008-2012), 38 diseases, 100,000 patients (DNA, medical records)
- Follow-up survey

DNA & Serum bank

- Sample Providing Committee
- Steering Committee
- ELSI Committee
- Managing Committee
- Operating Committee
- Secretariat
- Representative meeting

Organization

BioBank Japan

- DNA bank
- Serum bank
- Clinical data bank

- IMSUT
- BioBank Japan
- 12 Affiliated Hospitals
- RIKEN IMS
- Core for Genomic Medicine (CGM)
- IMSUT Human Genome Center
- Research group for clinical data
- Research group for genomics

BioBank Japan samples in the 1st cohort

(199,998 patients, 340,298 cases)

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>Disease</th>
<th>N</th>
<th>Disease</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>53,863</td>
<td>Hay fever</td>
<td>6,282</td>
<td>Hepatitis B</td>
<td>1,508</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44,346</td>
<td>Glioma</td>
<td>6,135</td>
<td>Hematological cancer</td>
<td>1,478</td>
</tr>
<tr>
<td>Cataract</td>
<td>26,067</td>
<td>Prostate cancer</td>
<td>5,694</td>
<td>Esophageal cancer</td>
<td>1,453</td>
</tr>
<tr>
<td>Brain infarction</td>
<td>18,862</td>
<td>Unstable angina</td>
<td>5,286</td>
<td>Uterine cervical cancer</td>
<td>1,258</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>19,037</td>
<td>Rheumatoid arthritis</td>
<td>4,449</td>
<td>Nephritic synd.</td>
<td>1,180</td>
</tr>
<tr>
<td>Stable angina</td>
<td>17,655</td>
<td>Lung cancer</td>
<td>4,396</td>
<td>ILD</td>
<td>1,158</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13,988</td>
<td>Periodontis</td>
<td>3,958</td>
<td>Uterine corpus cancer</td>
<td>1,087</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10,063</td>
<td>ASO</td>
<td>3,824</td>
<td>Pulmonary tbc</td>
<td>1,011</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>9,561</td>
<td>COPD</td>
<td>3,504</td>
<td>Ovarian cancer</td>
<td>928</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>8,376</td>
<td>Liver cirrhosis</td>
<td>3,348</td>
<td>Keloid</td>
<td>896</td>
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<tr>
<td>Colorectal cancer</td>
<td>7,638</td>
<td>Atopic dermatitis</td>
<td>3,002</td>
<td>AIL</td>
<td>785</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>7,166</td>
<td>Brain aneurysm</td>
<td>2,999</td>
<td>Drug eruption</td>
<td>740</td>
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<tr>
<td>Urolithiasis</td>
<td>7,028</td>
<td>Epilepsy</td>
<td>2,727</td>
<td>Pancreas cancer</td>
<td>569</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>6,629</td>
<td>Basedow disease</td>
<td>2,494</td>
<td>Gallbladder cancer</td>
<td>504</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>6,392</td>
<td>Liver cancer</td>
<td>2,509</td>
<td>Febrile seizure</td>
<td>341</td>
</tr>
<tr>
<td>Uterine fibroid</td>
<td>6,217</td>
<td>Endometriosis</td>
<td>1,907</td>
<td>(as of Oct. 2013)</td>
<td></td>
</tr>
</tbody>
</table>
RNA sequencing of lung cancer tissues

One recent example (cancer)

Novel driver mutation

RET kinase inhibitors

Multi-center IIT for rare subtypes

Catalog DB for One-stop access
Since Dec 2013

Drug development & personalized medicine

Germline DNA 13,429
Plasma/serum 21,112
Tissues 75,824 etc.

Geriatric diseases

Cerebral & cardiovascular dis.

Infectious dis.
Metabolic syndrome
Autoimmune dis.

Cancer

Neurology and psychiatry

Child health & development

Academia, industries

Drug R&D, etc.

NCVC

NCGM

NCC

NCNP

NCCHD

NCGG

NCBN: National Center Biobank Network by Integrated Research Institutes & Hospitals for Specific Diseases

(Kohno T, et al. Nat Med 2012)
**Objective:** Revitalization of medical care in disaster-hit area of massive quake and tsunami of March 11, 2011 (Great East Japan earthquake) and develop infrastructure for next-generation medicine through a large-scale cohort study in the disaster-hit areas.

- Revitalization of local medicine through health check-up and medical services to eliminate health concerns of the affected residents
- Construct biobank for next-generation medicine through a large cohort study with genomic information

**Concept:** To create new innovative industries such as drug discovery and genomic medicine, this plan conducts genomic research through construction of biobank of 150,000 residents by the health survey in Miyagi and Iwate prefecture where massive earthquake and tsunami suffered many people.

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**Organization**

Tohoku Medical Megabank Project

**Cooperation**

Collect medical records

Related projects

Related projects

**Roadmap**

2011-12

Health Survey

Preparation of system and equipment

Disaster-hit prefectures

Development of medical information communication network system

2013

Preparation of system and equipment

Collection and storage of cohort samples

Investigation of sample delivery

Genomic analysis

2014

Sample delivery

Analyze the effect of earthquake on health condition

Disaster-related genes and environment

2015

2016

Coordination

*Health survey*

*Planning to enroll 150,000 residents until 2016*

*follow-up*

**Biobank (150,000 residents)**
1000 people are working in this campus

Organization

Departments
- Department of Microbiology and Immunology
- Department of Cancer Biology
- Department of Basic Medical Sciences

Research Centers
- Human Genome Center
- Center for Experimental Medicine
- Advanced Clinical Research Center
- Center for Stem Cell and Regenerative Medicine
- International Research Center for Infectious Diseases

Research Hospital (135 beds)

Supercomputer System
- Budget: $10M/Year
- Performance: 225 TFLOPS
- Storage: 3 PB (Lustre) + 2 PB (Nearline)
Genomic Medicine @ IMSUT Research Hospital
Since 2001

GM Organization

Clinical Departments

Clinical Laboratory

Team Genomic Medicine (TGM)

Genetic Laboratory

Human Genome Center

Laboratory of DNA Information Analysis

Laboratory of Sequence Analysis

Advanced Clinical Research Center

Division of Clinical Genome Research

Division of Molecular Therapy

Japanese Association of Hospitals for Genetic Medicine

Tokyo Genetic Counseling Network

Staff Members
• Doctors and Nurses
• Genetic counselors
• Clinical psychologists
• Genome scientists

Patients and Clients
• Cancer
• Hereditary diseases
• Common diseases
• Genetic issues

Businesses and Studies
• Genetic test for neoplasms: ~ 400 /year
• Genetic counseling: 30-40 cases/year
• Genetic Dx of hereditary tumors: ~10 /year
• Development of personalized medicine
Extension to Whole Genome Sequencing, and More@IMSUT

Since 2013

Patient

Genetic Counseling

GCT@IMSUT
Yoichi Furukawa, MD, PhD

ELSI Team@IMSUT
Kaori Muto, PhD

Specimen

Whole Genome Sequence
Exome Analysis
Transcriptome Analysis
Epigenome Analysis (not yet)

Personal Genomes and Omics Data

Prediction of Medical Intervention

Decision Support System (not yet)

Leukemia
Lymphoma
Gastrointestinal Cancer

• Optimizing therapeutics
• Avoiding adverse reactions by anticancer drugs
• Personalized medical examination/ Surveillance

Sequencing and Data Analysis Facilities & Management

NGS Facility
Nanopore Sequencer (not yet)

Data Analysis and Interpretation

Personal Genomes and Omics Data

Patient

Genetic Counseling

Genetic counseling
Psychological support
Request of a genetic test
Discussion in the TGM meeting
Performance of the genetic test
Assessment and return of the result
Psychological support
Follow up and surveillance

Advanced Clinical Research Center
Research Hospital

Satoru Miyano, PhD

Yoichi Furukawa, MD, PhD
Arinobu Tojo, MD, PhD

Human Genome Center
Sequencing and Data Analysis Facilities & Management @ IMSUT

Highly Secured Supercomputer System for Clinical Sequence
- Computation nodes: 3,840 CPU cores
- Storage: Lustre file system (642TB)

All logs from input to output are automatically recorded with software versions, parameters, who did, etc.

Closed Network
- Being expanded
- Clinical Sequence Laboratory
- Laboratory Information Management System (LIMS)

Data Analysis Rooms
- Control Room
- VPN connected to Clinician’s office
- No USB socket
- All rooms are monitored

Separated from medical record

All rooms are monitored
- No USB socket
- Being expanded
U TOKYO is founding “Int’l Genomic Medicine Research Organization” (IMSUT, Graduate School of Medicine, RCAST, Graduate School of Frontier Science)

- Optimizing therapeutics
- Avoiding adverse reactions
- Personalized medical examination/Surveillance
- Personalized Prevention

Whole Genome
Transcriptome
Epigenome

Familial/lifestyle data
Diagnosis/therapy data
Progress after treatment

Biomedical Big Data
Supercomputer System with Large Storage

Implementing Genomic Medicine
U Tokyo Hospital (1500 beds) & IMSUT Research Hospital

Innovation for therapy and prevention

Medical Informatics for Genomic Medicine
NGS
EMR

Research Center for Advanced Science and Technology
U Tokyo Int’l Genomic Medicine Research Organization

Foster specialists in genomic medicine