



Introduction of Tohoku Medical Megabank Project

Feb 12th, 2020

Masayuki Yamamoto

Tohoku University

Tohoku Medical Megabank Organization

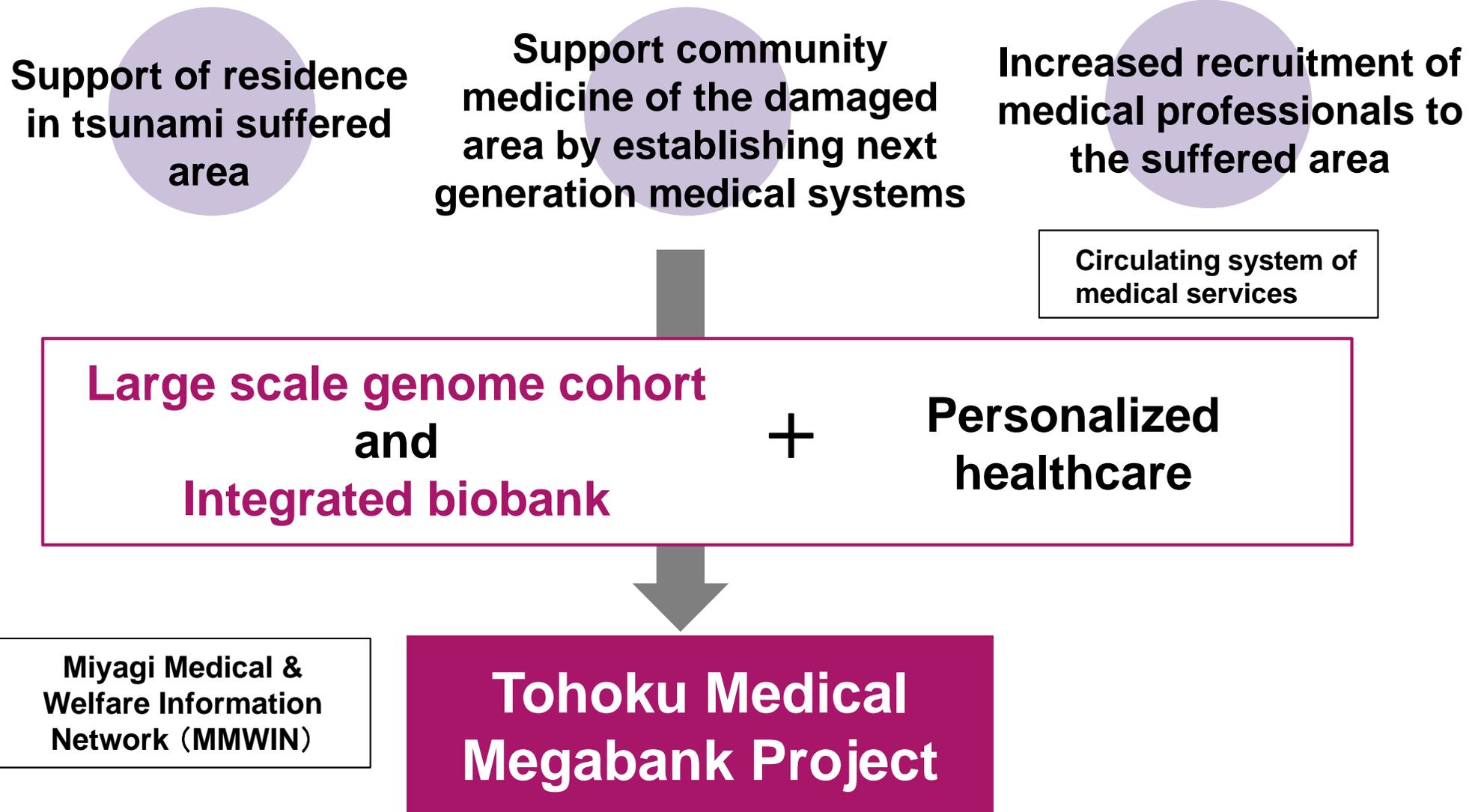


TOHOKU
UNIVERSITY



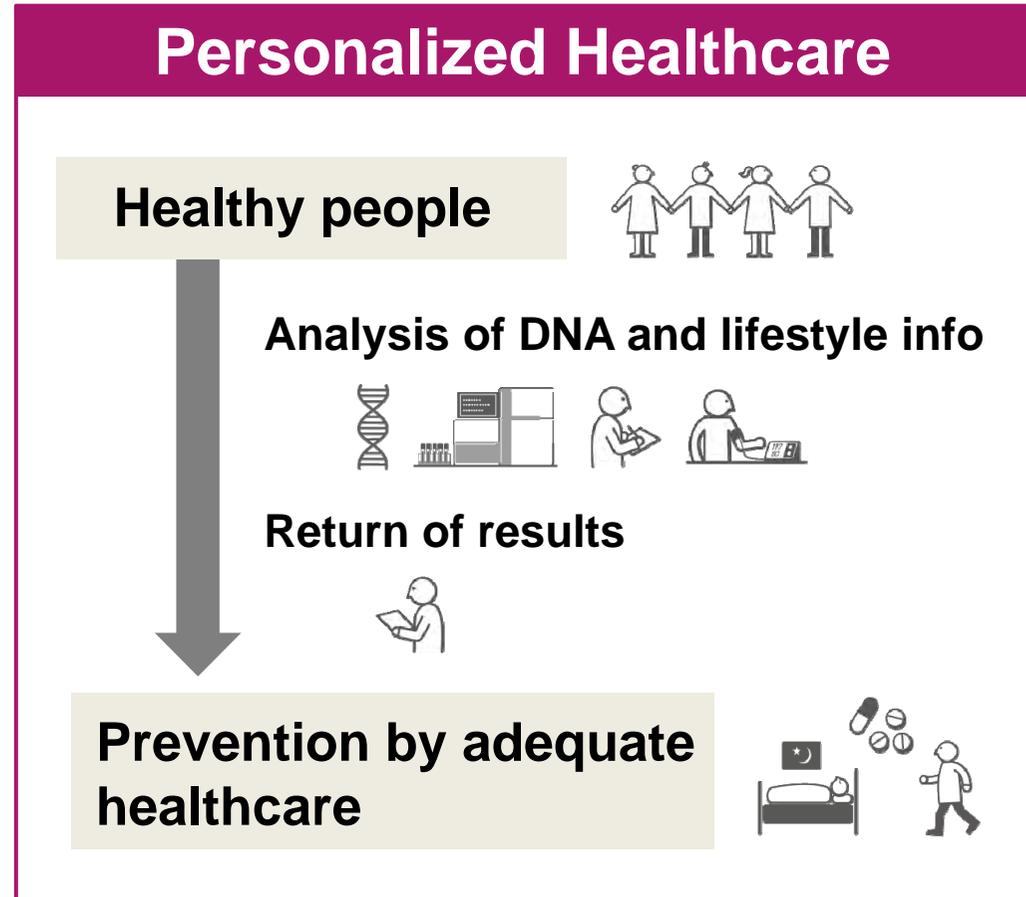
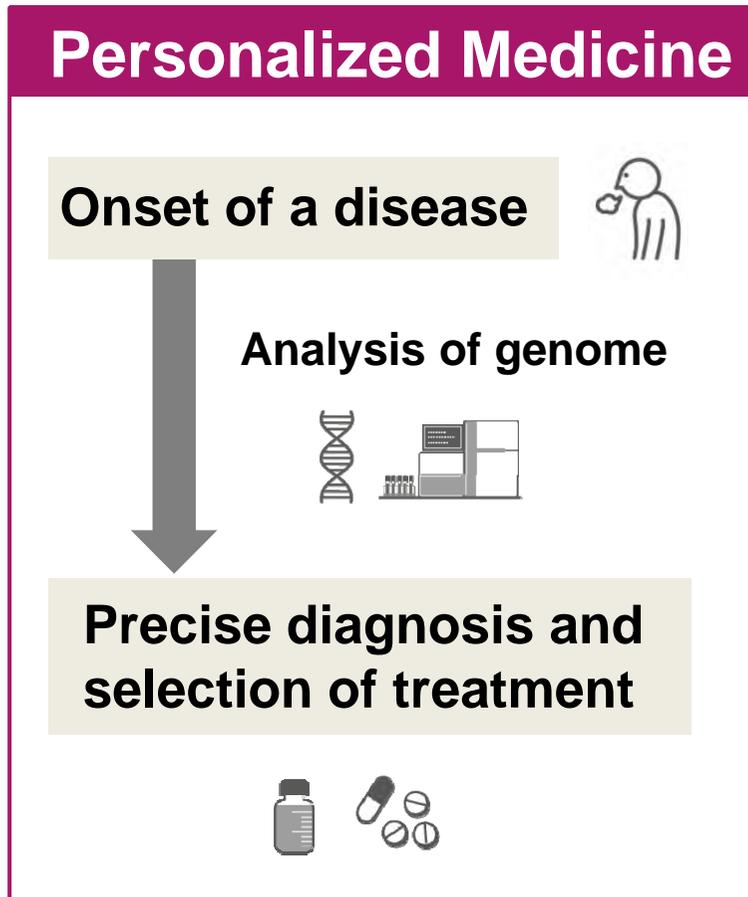
Tohoku Medical Megabank Project

Towards Creative Reconstruction of Tohoku Region



Personalized Medicine and Personalized Healthcare

Endeavor for “Society of Health and Longevity”



Toward Realization of Personalized Healthcare

ToMMo Have Established Strategically Two Types of Cohort Studies

Residents Cohort and Birth & Three Generation Cohort

■ Community / Residents Cohort (in Miyagi and Iwate)

Recruit **80,000 residents** from coastal areas in Miyagi and Iwate provinces

■ Birth & Three Generation Cohort (in Miyagi)

Recruit **70,000** people including offspring, parental and grandparental

- TMM established two types of cohort to strategically achieve our goal
- TMM genome cohorts are in a cutting edge design

We have finished recruit of

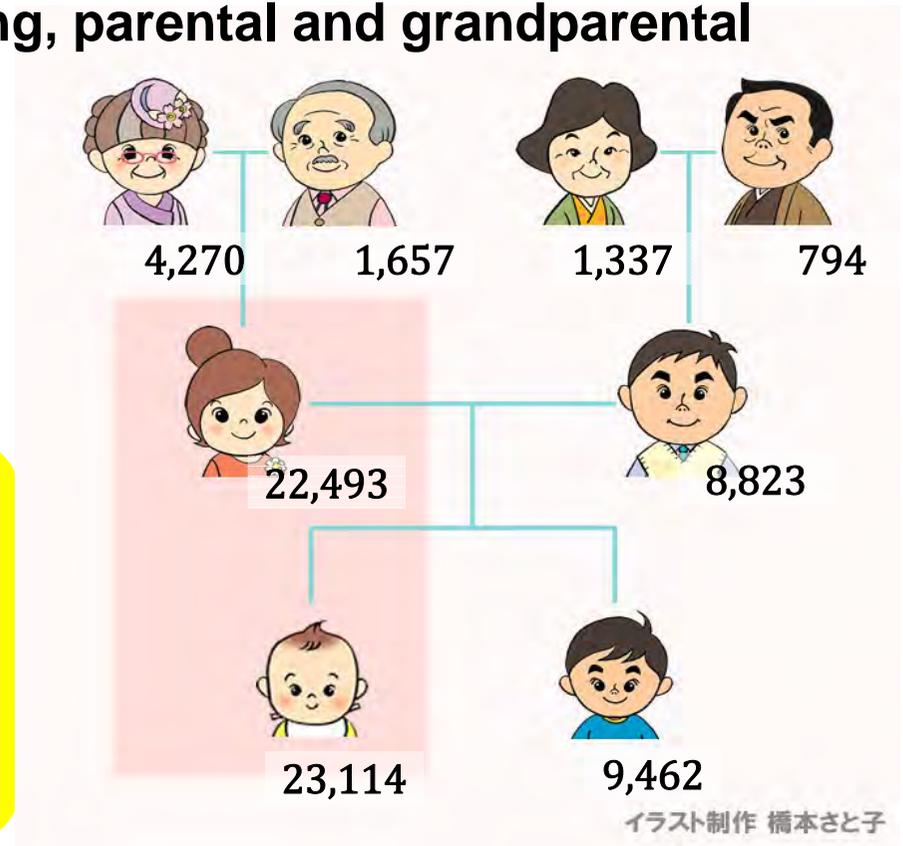
84,073 participants for Resident

Cohort and

73,500 for Birth & Three Generation

Cohort

Total of 15,573



ToMMo Community Support Center (CSC)

- Center for ToMMo Cohort Studies
- Center for GMRC activity

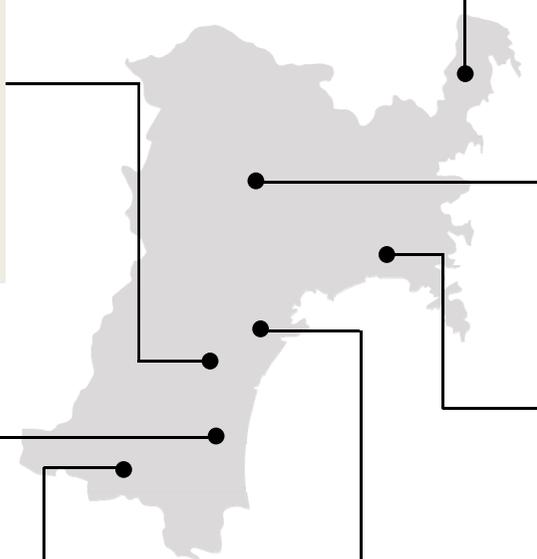
Sendai CSC
Sendai Child Health Square/
Headquarter of ToMMo
Nobuo Fuse



Iwanuma CSC
Akira Uruno



Shiroishi CSC
Eiichi N.Kodama



Kesennuma CSC
Yohei Hamanaka



Osaki CSC
Kichiya Suzuki



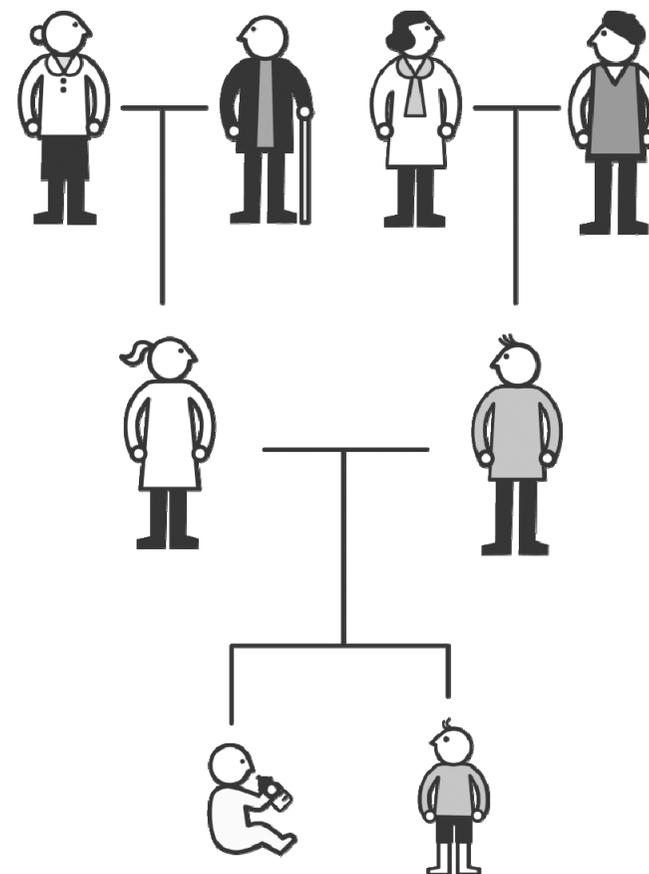
Ishinomaki CSC
Junichi Sugawara



Tagajo CSC
Naho Tsuchiya

Birth and Three Generation Cohort Study

- **Target area :**
Whole Miyagi Prefecture
- **Target subjects :**
20,000 pairs of pregnant women and their fetus, siblings, fathers grandparents and other family members (20,000 family, 70,000 participants)
- **Place for the recruitment :**
 - Obstetric clinics or hospitals and 7 Community Support Centers
 - We recruit pregnant women who are diagnosed pregnancy
 - After their participation, we ask their family to participate
 - Individually obtained informed consent is required



Scenes of Our Cohort Recruits

Community Cohort Recruits

- Join annual health surveys of local governments and recruit participants at the sites
- Recruit participants at the Community Support Centers



Birth and Three Generation Cohort

- Recruit pregnant mothers at OB hospitals by our GMRC*



*GMRC: Genome Medical Research Coordinator

Samples and Data from One Participants

Blood 34 ml (21ml for Storage) + Urine

13 ml	Regular Blood Test + HbA1c, Blood Glucose, Cholesterol, AST, ALT, BUN, Cr, IgE, Helicobacter pylori
7 ml (EDTA)	Plasma / Buffy Coat (DNA Extraction)
9 ml (Plain)	Serum
5 ml (Heparin)	Mononuclear Cells
Urine	

Physiological Examinations

Cardio-Vascular, Respiratory, Ocular, Bone Density, Dental etc.

MRI (10, 000 Participants, Test on Cognition and Depression)

Questionnaire (Japanese-Cohort Standard)

Age, Sex, Area, Job, Diet, Sleep, Exercise, Alcohol, Smoking History,
Prescription, Gynecologic Problems, Mental Health, Psychosocial Factors

Disaster-Related Questions

Damage, Life-Style Change



MRI in Tohoku University

Aims

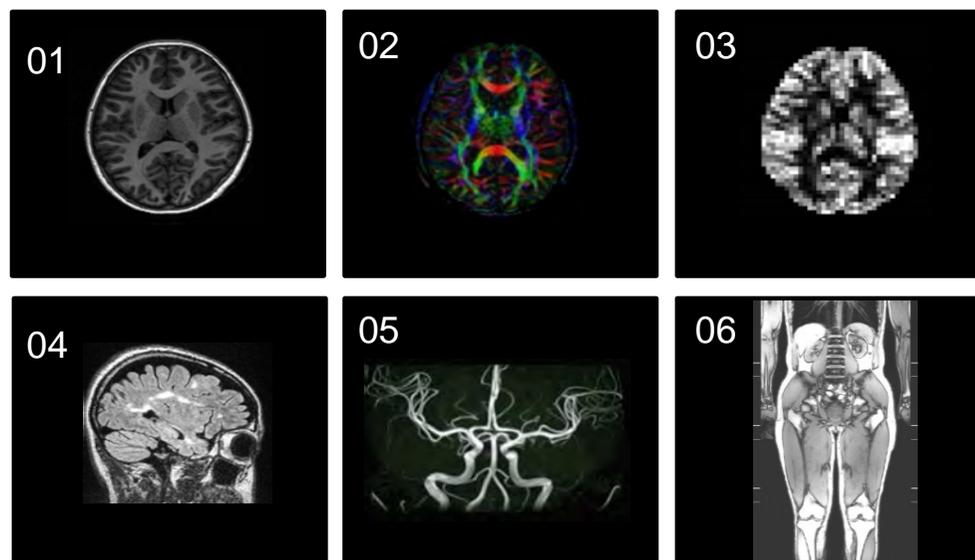
- Early diagnosis of Dementia and Alzheimer diseases
- Evaluate relationship of tsunami stress and brain structure changes
- Detection of biomarkers for disease prevention



Philips Ingenua 3.0T
(Two machines)

Volunteer basis

Relatively rigorous exclusion criteria



Around **12,000** imagings have been done

TMM Biobank

A system that collects, stores, and distributes biological specimens and related information for the advancements of medicine and science

Biobank is beneficial for the society

Large size biobank is good for

- Efficient use of resources
- Good quality control
- Reasonable use of resources



February, 2020

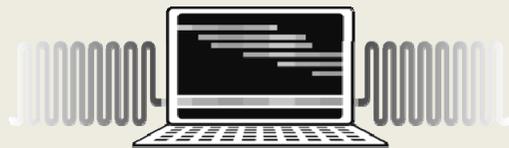
More than 3.8 million sample storage in total

From August 25th, 2015, ToMMo has started distribution of samples and information to research scientists

TMM Biobank Is an Integrated Biobank

Integrated Biobank

- TMM sets up an analytical center that executes standard analyses of samples
- To avoid rapid depletion of samples, TMM distributes analysis information first, and then bio-samples



Blood & Urine



Whole blood, serum, WBCs are stored

→ **metabolome and proteome**

Genomic DNA



DNA extracted from blood is also stored

→ **genome and transcriptome**

Questionnaire



Main part is for life style (including food), psychological condition, experiences of the disaster

+ **MRI** &

More than 10 physiological examinations, and cognitive and psychological assessment

Whole Genome Sequencing in TMM

Finished 4,773 whole genome sequencing

WGS in single laboratory, single protocol, and single facility with **high coverage** is first in the world

Catalogue more than 61 million SNVs and 26 million are new SNVs

Of the new SNVs, more than 99% are rare variants

August, 2014

Parts of the SNV information was open from ToMMo and NBDC.

June, 2016

All SNV information was open from ToMMo.

June, 2018

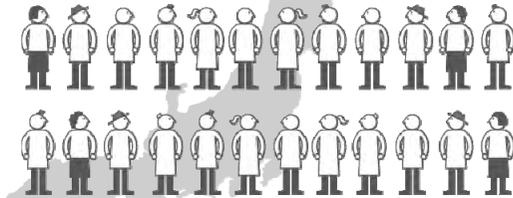
SNV information on X Chromosome and mitochondria were released (3,552 people).

Sep, 2019

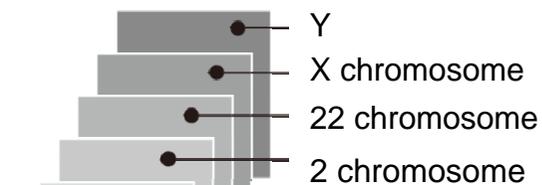
4,773 people SNV, INDEL, X Chromosome and mitochondria were released.

4.7KJPN

Residential cohort
4,773 people



4,773 people **WGS analysis**



1 chromosome

Position **Sequence Variation and Frequency**

.
3458697 **C: 70%** **T: 30%**

8768942 **A: 99.9%** **G: 0.1%**

⋮

TMM Whole Genome Variation Database

Position and frequency of sequence variation



- Characteristics of Japanese genome structure are getting clear
- TMM whole characteristics of genome database will facilitate clinical sequence studies

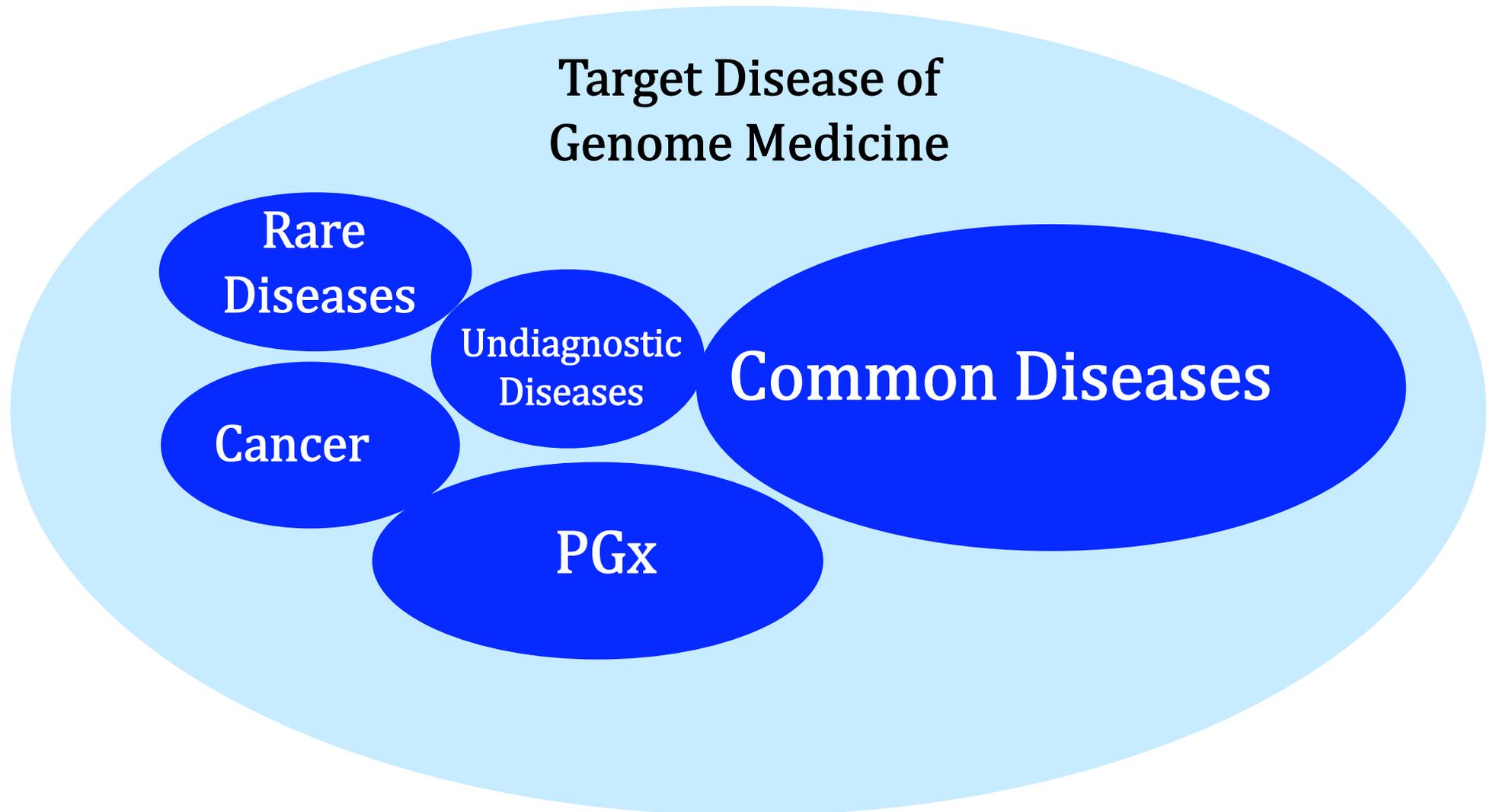
Segmented drug development

TMM integrated data will be of important for **new drug development for specific group of people**

Personalized healthcare and ethnic array

Generate a special array that enable efficient imputation of Japanese genome

Risk Assessment of Common Diseases Is Important for Personalized Healthcare



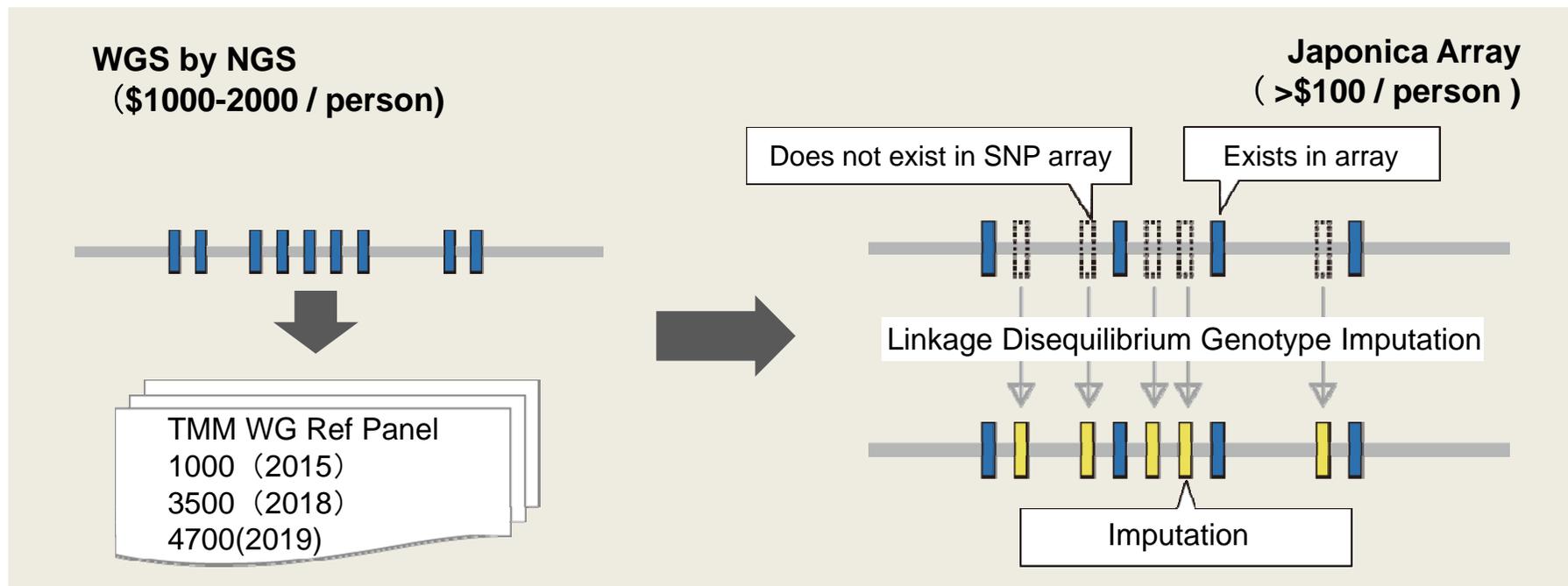
DNA Array Highly Adopted for Japanese Population

Japonica Array[®] is designed for various cohort studies in Japan, and will contribute to personalized healthcare and medicine

- Based on Japanese WGS data (3.5KJPNv2)
- Japonica Array is designed to minimize the number of probes but to maximize capacity of genotype imputation for Japanese
- **Inexpensive: providing the low cost WGS information will realize mega-size survey of genes responsible for common diseases**



Japonica Array[®] was started marketing ver.1 in 2014, ver2. in 2017, and NEO in 2019.



Japanese Multi_omics reference panel : jMorp

Phenome
To be provided

Metabolome

Proteome

Transcriptome
Iwate Medical Megabank Organization; iMethyl

Methylome
Iwate Medical Megabank Organization; iMethyl

Genome Variation

Genome Sequence

Welcome to Japanese Multi Omics Reference Panel.

jMorp release 201909

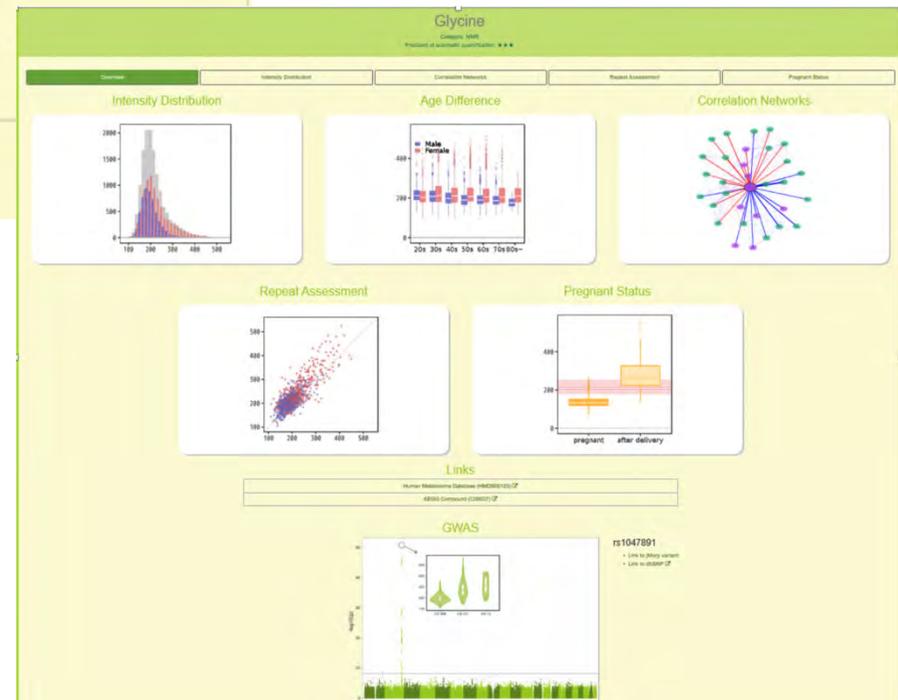
September 2nd, 2019
2019 Major Update
(Metabolome) The released distributions of concentrations of 43 metabolites identified by NMR detected in 13,423 individuals, distributions of peak intensities of 162 characteristic metabolites by GC-MS in 2,379 individuals.
We also released the qualified metabolomics data from 1,463 individuals by Shimadzu LC-MS analysis. (Genome) Information of metabolomics data obtained from individuals in repeat assessment survey and influence of metabolomics during pregnancy in tandem assessment survey is fully released.
(Genome Variation) 4,763,976 sites and genotype frequency panel from 4,763 Japanese individuals is released.

jMorp Publication

Takata S, Sugiura H, Mizushima M, Sasaki J, Aoki Y, Shirata M, Kusuda S, Yamashita M, Mizushima K: "jMorp Japanese Multi Omics Reference Panel". *Bioinformatics Research*. 2019; Aug. 4:462(1):0851-0907. [DOI](#)

Takata S, Katsuhira F, et al.: "iMethyl: An allele frequency panel of 3,552 Japanese individuals including the 3 chromosome". *Human Genome Variation*. 2019; Aug. 18:18(20):214328-476-0000-9. [DOI](#)

Sugiura H, Mizushima M, Takata S, Mizushima K, Kusuda S: "Metabolome Analysis of Human Plasma by GC-MS/MS in a Large-scale Cohort". *Proteome Letters*. 2019; Volume 1 Issue 1 Pages 11-45. [DOI](#) 10.1007/s12016-019-0011-7



Metabolomics and proteomics reference database from 15,000 cohort participants

<https://jmorp.megabank.tohoku.ac.jp/>

From Data Sharing to Data Visiting

Supercomputer is essential for biobank activities

Supercomputer is divided into Unit A through Unit C

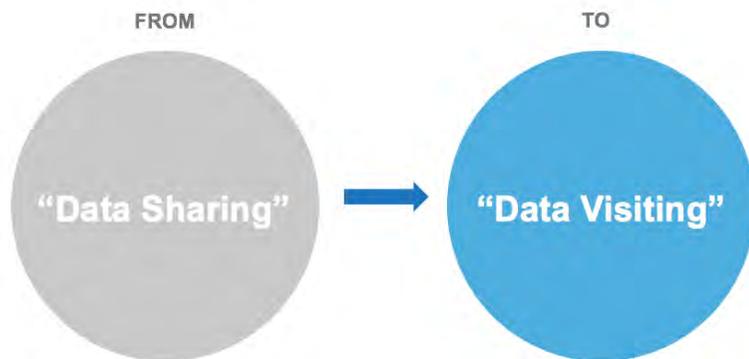
- Unit A is for open database
- Unit B is for data sharing / visiting
- Unit C is for informatics and data processing



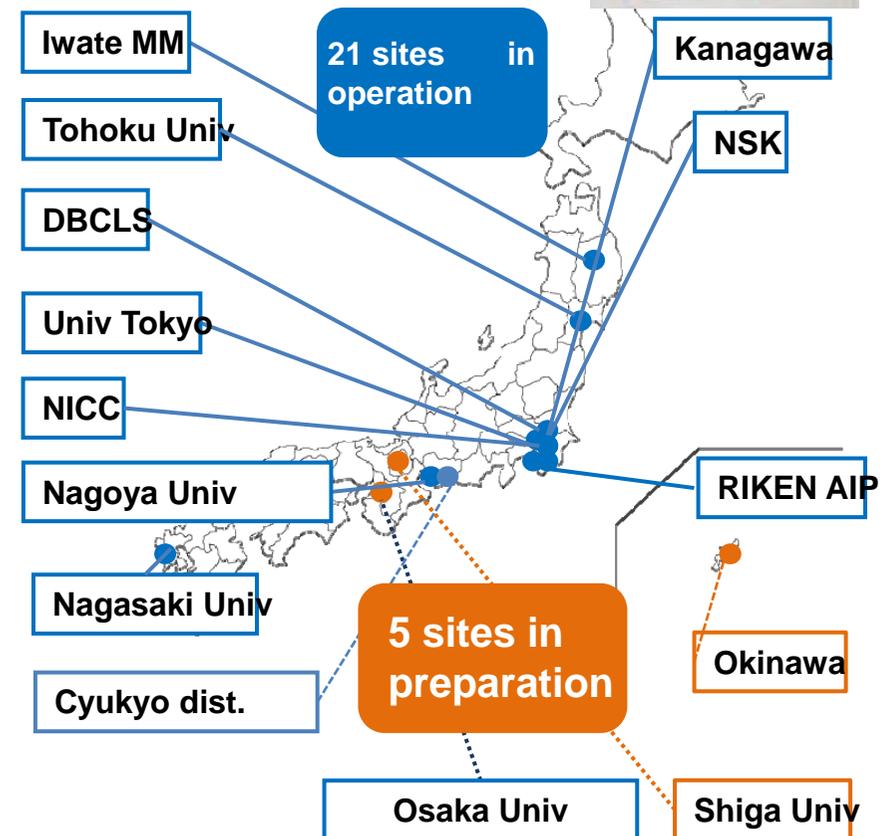
AMED Supercomputer
by ToMMo



A New Paradigm

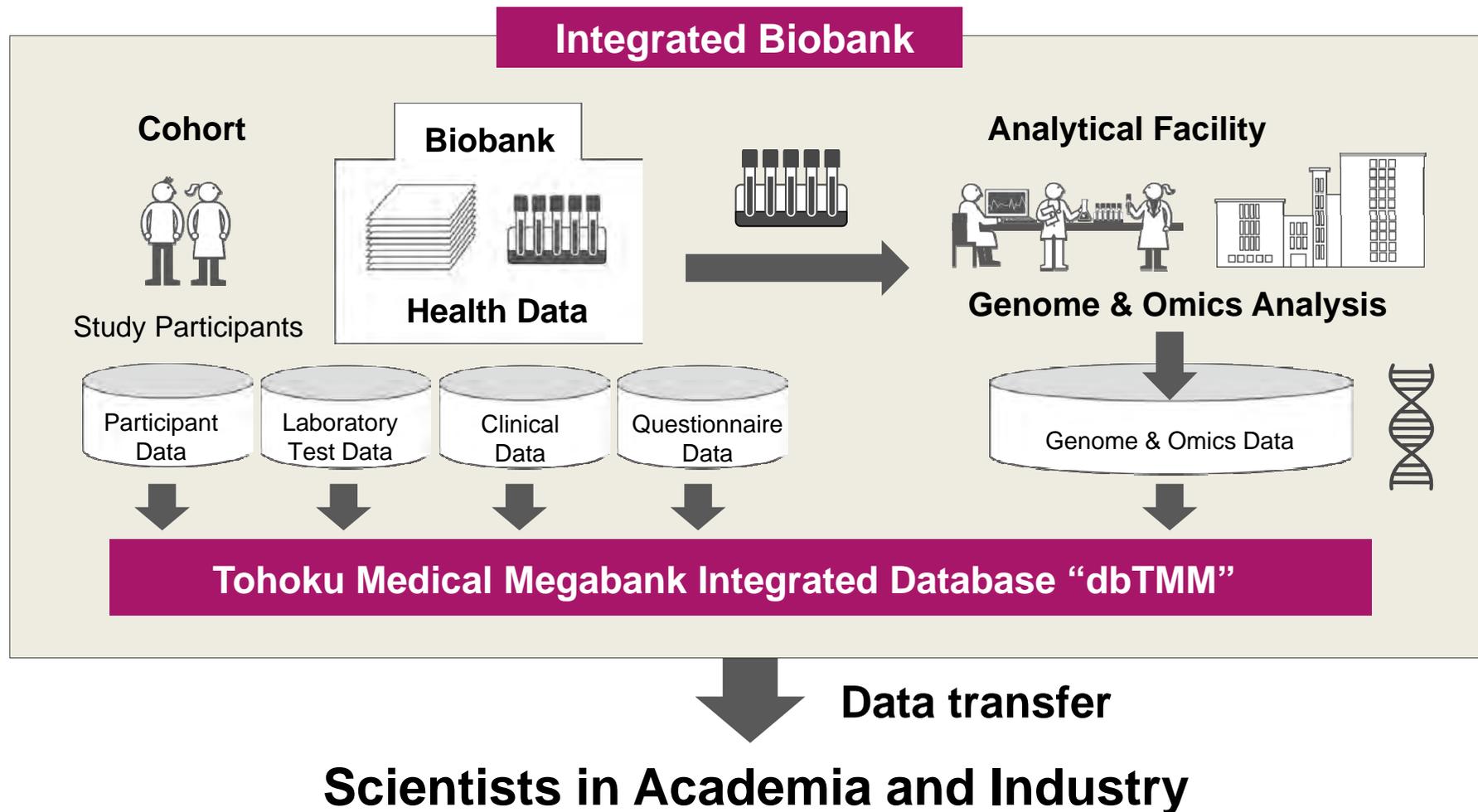


- Users can access AMED super computer and dbTMM from remote security rooms set up in distantly located area in Japan
- This system contributes to the wide ranging data visiting of TMM



Integrated Biobank and Database

Tohoku Medical Megabank (TMM) is an integrated biobank retaining both biobank and genome / omics analytical facilities



Toward Overcoming Problems Surrounding Biobank

- Budgets for secured managements
- Return of data / intellectual properties
- Technical issues on long term sample storage
- Ethical issues (Incidental findings, etc.)



International collaborations are essential to overcome these issues

Merits of collaborations

- Enable elaborate and large scale meta-analyses
- Standardization of sample collection, preparation and storage
- International standardization of questionnaire
- Approach to ethnic difference / similarity of genomes
- Large scale collaboration²¹





- We have established Tohoku Medical Megabank to realize personalized healthcare (PHC) and personalized medicine
- In the Tohoku Medical Megabank Project, we have designed and are operating of two types of cohorts; community cohort and birth-and-three-generation cohort, which in collaboration will realize cutting edge accomplishments in Longitudinal Population Studies
- We have established an integrated biobank and are conducting genome-omics analyses for genome medicine

<http://www.megabank.tohoku.ac.jp/index.php>

Directors / Professors

Masayuki Yamamoto

--

Shigeo Kure

Kengo Kinoshita

Nobuo Fuse

--

Inaho Danjo

Hiroaki Hasizume

Atsushi Hozawa

Hiroshi Kawame

Shinichi Kuriyama

Fumiki Katsuoka

Seizo Koshihara

Eiichi Kodama

Naoko Minegishi

Fuji Nagami

Tomohiro Nakamura

Soichi Ogishima

Kinuko Ohneda

Mika Sakurai

Ritsuko Shimizu

Junichi Sugawara

Kichiya Suzuki

Takako Takai

Yasuyuki Taki

Gen Tamiya

Hiroaki Tomita

Akito Tsuboi

Jun Yasuda

--

Nobuo Yaegashi

Sadayoshi Ito

Hiroshi Tanaka

Tadao Kobayashi

Yoshiyuki Sato

People in ToMMo



ToMMo has more than 380 members including GMRC / TCF

GMRC: genome medical research coordinators

TCF: ToMMo clinical fellows



Thank you for your help and cooperation !