AMS-JSPS-AMED Joint Symposium on Data-Driven Health:
Data strategies to predict risk, prevent and manage disease in individuals and populations / 26 February 2020 / Academy of Medical Sciences, London, UK

Session 1: The health data landscape and resources in the UK and Japan

The Advanced Research Center for Innovations in Next-Generation Medicine (INGEM) and Personalized Medicine

—Introduction of the next-generation medical development in Tohoku University—

Chikashi Ishioka, MD

COI Disclosure Information

Chikashi Ishioka

I have the following financial relationships to disclose.

- ☐ **Leadership position/advisory role for:** none
- ☐ **Stockholder in:** none
- ☐ **Patents and royalties from:** none
- ☐ **Honoraria（lecture fee) from:** Chugai, Taiho
- ☐ **Honoraria(manuscript fee) from:** none
- ☐ **Grant/Research funding from:** Hitachi, Riken, Chugai, Taiho, Merck-Serono, Yakurt, Daiichi-Sankyo, Novartis, Takeda, Asahi-Kasei, Eisai, Ono,
- ☐ **Other remuneration from:** none

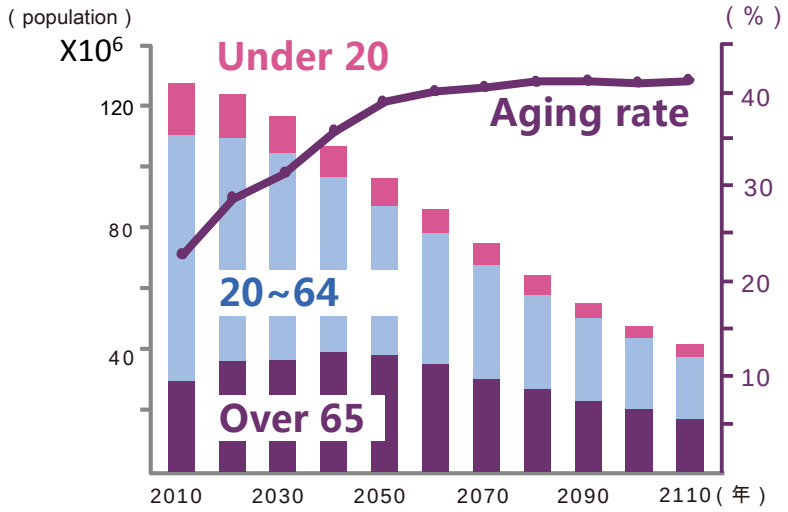
- According to the COI Guideline of Japan Medical Society
- Since Jan 2017~ Dec 2019

Today's topics

1. Direction of health and medical care development
2. Activities in the Tohoku Medical Megabank Organization (ToMMo)
3. Personalized cancer medicine in Tohoku University Hospital
4. Utility of big-data in health and medical care, and its current problems

Tohoku University Hospital, Sendai City, Japan

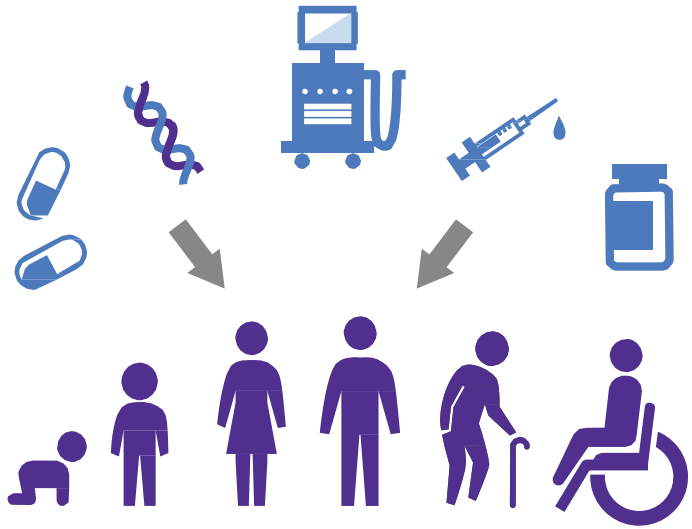
Japan reaches ‘super’ -aged society



参照 | 国立社会保障・人口問題研究所『日本の将来人口推計(平成24年1月推計)』2012年

Japan as a aged society

Japan reaches rapid aging ahead of the world, and two of five people of the nation become the elderly in 2050



Need highly-advanced precise medical care

Precise medical care is demanded to reach old age while the people maintains health as much as possible securing rich life.

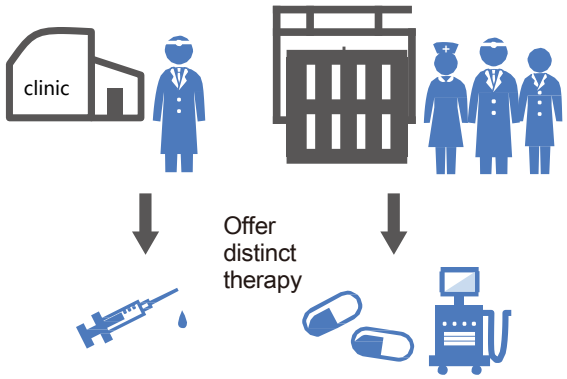
Need the development and spread of highly-advanced precise medical care

Social problem

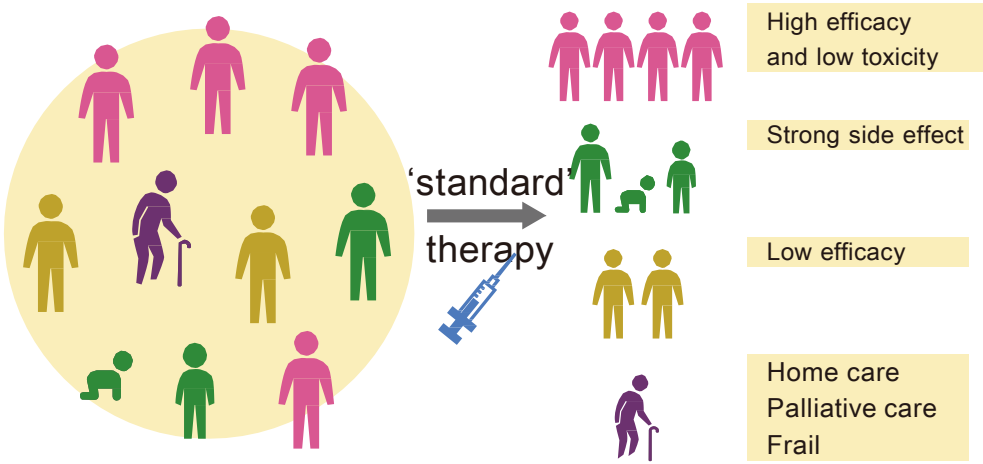
Difference in medical treatment (care) offer and acceptance

TOHOKU UNIVERSITY

Local clinic **Center hospital** **various patients**



Efficacy and side effect that vary among individuals



Difference by medical institutions and healthcare workers

Treatment varies according to and the specialty of healthcare workers and their experience.
Regional disparity in a medical institution

Difference by personal needs and life stage

There is an individual difference in an effect of treatment and care by a gene, a lifestyle and a health condition.

Differences by medical institutions and the healthcare workers, and by the personal needs and life stage

Purpose of project

TOHOKU UNIVERSITY

The medical care that is optimal for an individual

Desirable medical care is suggested to the background and life stage of the individual patient.

The medical care for the social minority

A therapy is developed for rare disease that a clinical study was hard to plan so far.

The medical care that the patients can choose

by an area, a lifestyle and sense of personal values

The final aim

Healthy longevity society by personalized medicine without medical care difference

Development of personalized medicine in Tohoku University

Creation of next-generation medical system and medical difference correction by both development and spread of personalized medicine easy for an individual

- FEB 2018
  Core Hospital for Cancer Genomic Medicine
- SEP 2017
  The Advanced Research Center for Innovations in Next-Generation Medicine (INGEM)
- JUN 2017
  the Designated National University
- APR 2017
  Personalized MEdicine Center (P-MEC)
- FEB 2015
  Ms. Shigeo Yoshimura's Fund
- FEB2012
  Tohoku Medical Megabank Organization (ToMMo)

INGEM
東北大学 未来型医療創成センター

東北大学病院
みんなのみらい基金

P-MEC

TUH
Tohoku University Hospital

東北メディカル・メガバンク機構
TOHOKU MEDICAL MEGABANK ORGANIZATION

Personalized Medicine and Personalized Healthcare

Endeavor for “Society of Health and Longevity"

Personalized Medicine

Onset of a disase

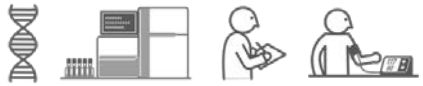
Analysis of DNA

Precise diagnosis and selection of treatment

Personalized Healthcare

Healthy people

Analysis of DNA and lifestyle info



Return of results

Prevention by adequate healthcare

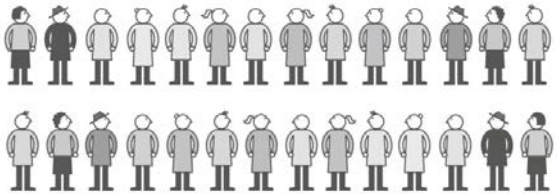
By (Iressa®) is a silver bullet for EGFR gene mutated cases.
Cold medicine (granule)：PL granule causes 2-day long strong sleepiness for specific type of CYP2D6 .

By now：Onset probability of breast cancer and ovarian cancer is estimated to 50-80% by BRCA1 mutation

ToMMo's Residential Cohort and Birth and Three-Generation Cohort

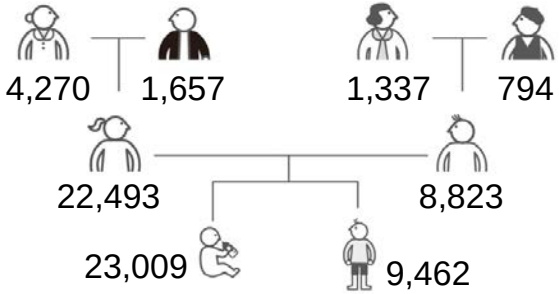
Community-Based Cohort

Recruit **80,000 residents** from coastal areas in Miyagi and Iwate prefectures through joint session with health check by local government, and through seven regional support centers in each area



Birth and Three-Generation Cohort

Recruit **70,000** people including offspring, parental and grandparental generations
Request expectant mothers for cooperation in maternity hospitals



At March 31, 2016, we have finished recruit of **84,000** participants for Community-Based Cohort and,
at March 31, 2017, we have finished recruit of more than **73,000** for the Birth and Three-Generation Cohort .

We recruited more than **150,000** participants in total.

ToMMo Is an Integrated Biobank

Blood & Urine

Whole blood, serum, WBCs are stored
→ **metabolome and proteome**

Genomic DNA

DNA extracted from blood is also stored
→ **genomics and transcriptome**

Questionnaire

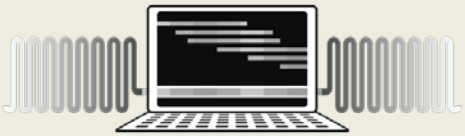
Main part is for life style (including food), psychological condition, experiences of the disaster

+ **MRI** &

More than 10 physiological examinations, and cognitive and psychological assessment

Integrated biobank

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

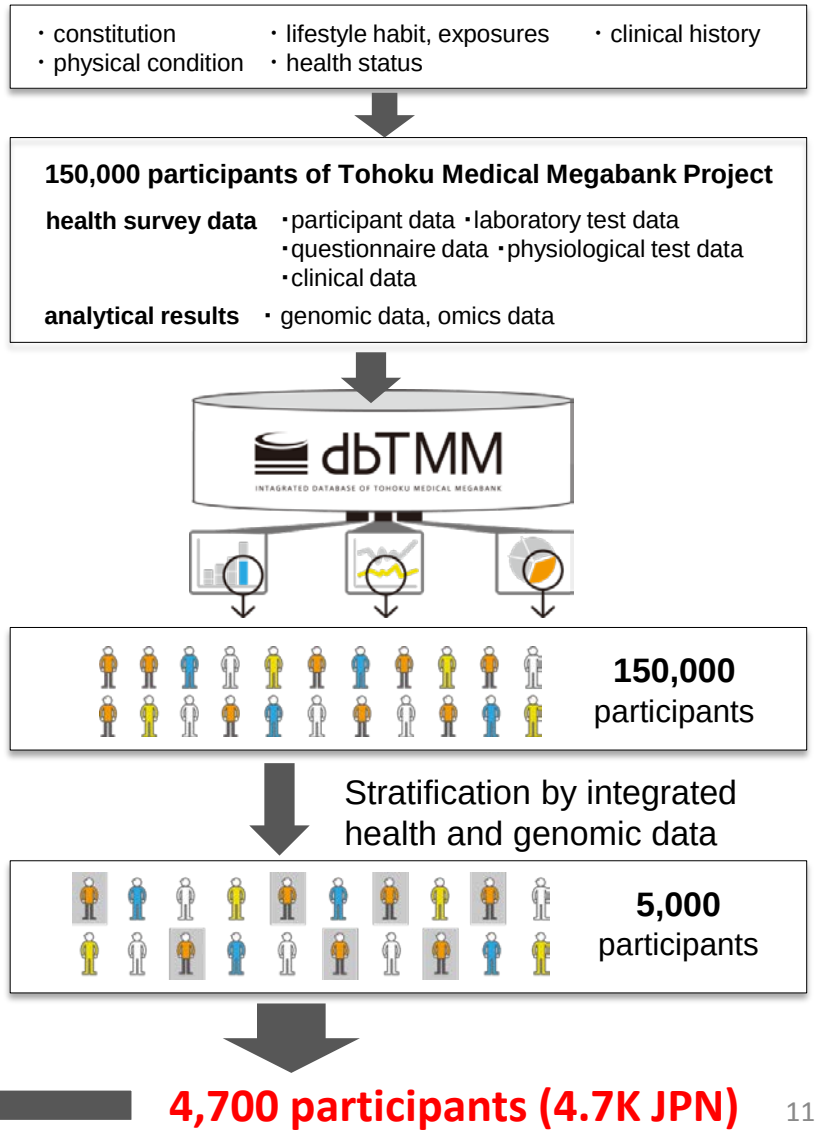


Integrated Database “dbTMM”

“dbTMM” integrates both health data and genomic/omics data concomitantly toward development of genome medicine

Search

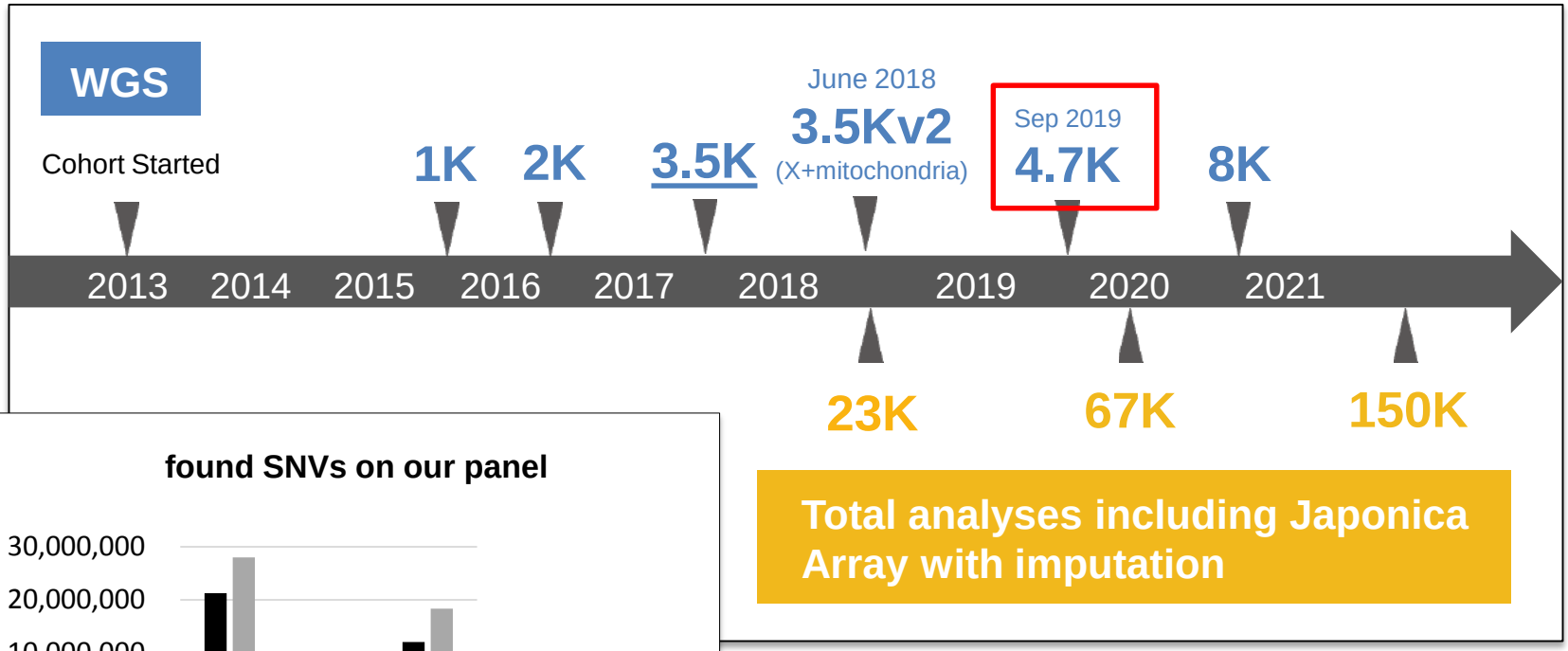
Constitution (Genomic data)
Chromosome 8 41519462 (rs515071) = TT
&
Health status (Lab test data) : HbA1c > 6.2
&
Lifestyle (QA) : Alcohol Drinking = Yes
&
Disease History (QA) : Type II Diabetes = Yes

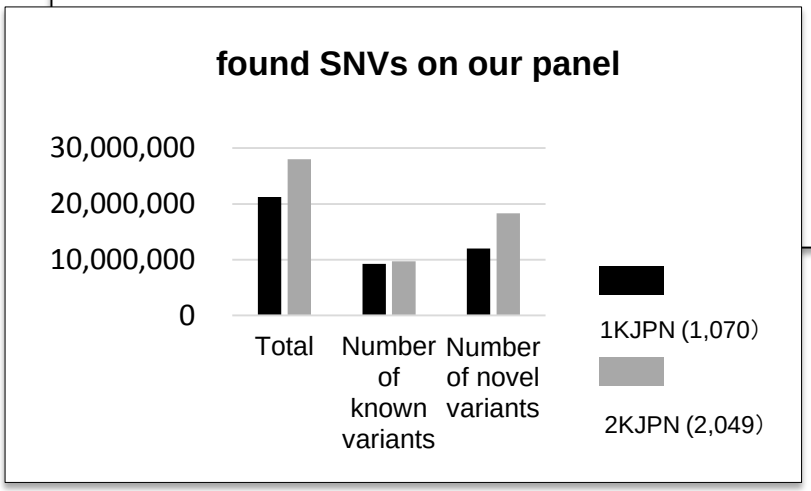


Familial hypercholesterolemia
Hereditary cancer syndromes
e.g. HBOC syndrome, Lynch syndrome

TMM Genome Analyses Roadmap

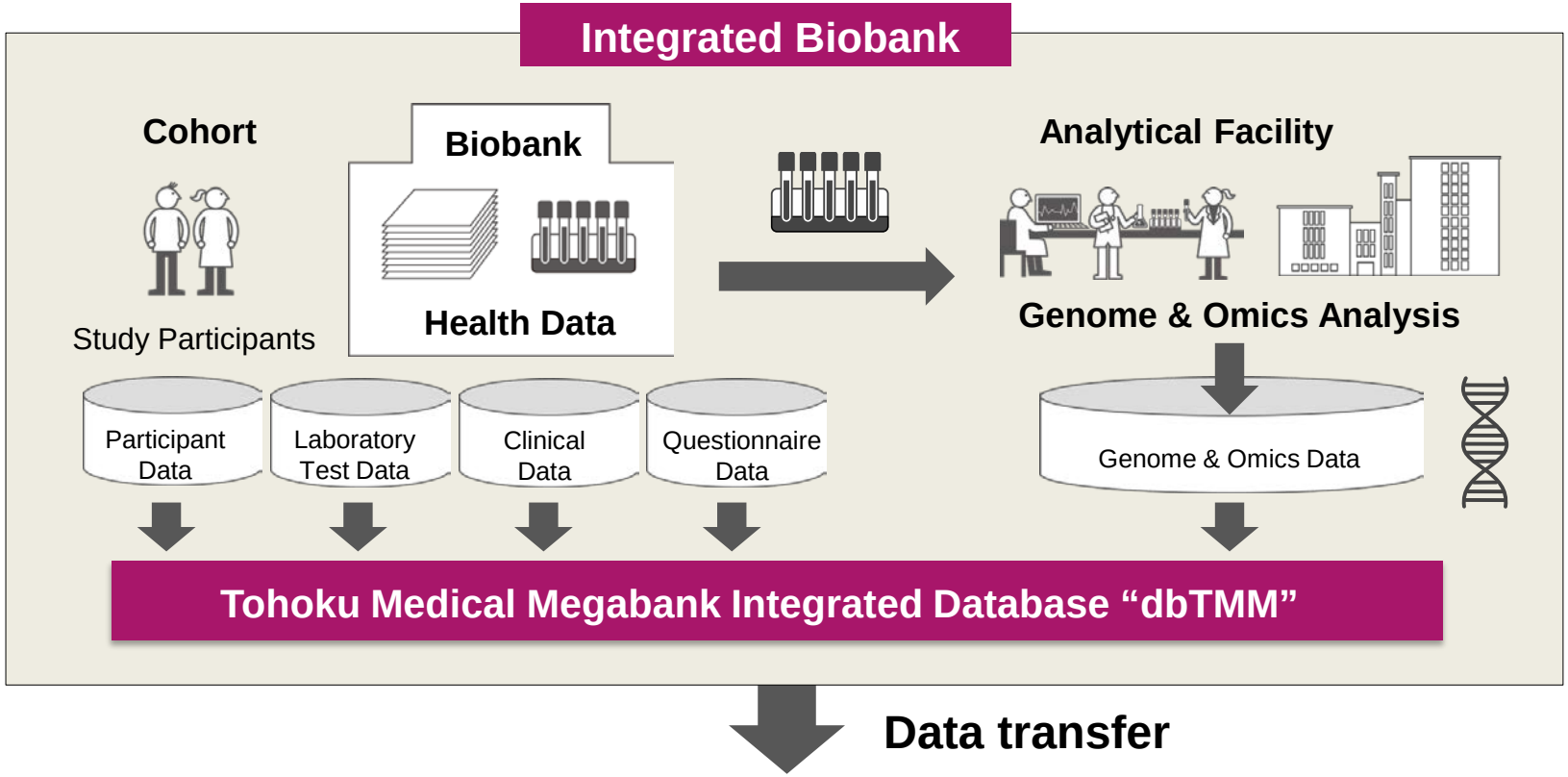
Genome analyses：All SNV frequency data can be downloaded openly





Integrated Biobank and Database

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



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TOHOKU MEDICAL MEGABANK ORGANIZATION

Strength of the Tohoku University
Use of the accumulated information in ToMMo

Tohoku University Hospital (TUH)

P-MEC

Comparability

A part of the disease cohort comes from the healthy subject cohort of the Tohoku district.
→Analysis of the specimen and management of the information in the same institute

Tohoku Medical Megabank Organization (ToMMo)

INGEM

Disease cohort
（Cancer, Rare diseases, Life-style related diseases）

Contribute to more precise R&D

Healthy cohort prospective cohort

The research organization only in the country having the biobank of the large-scale healthy cohort and disease cohort.

INGEM is one of the four core research centers in Tohoku University as the Designated National University

- Advanced Institute for Materials Research
- Advanced Research Center for Spintronics
- Advanced Research Center for Disaster Science
- Advanced Research Center for Innovations in Next-Generation Medicine (INGEM)　未来型医療創成センター

8 Research Groups

• Gene Mutation Verification	←	**VUS, animal model etc.**
• Genome Information Science	←	**Genome DB**
• Genome Drug Discovery	←	**New target agents**
• Clinical Biobank	←	**Cancer tissue, blood, etc.**
• Clinical Sequence	←	**Genome and RNA sequencing,**
• Clinical Phenome	←	**Metabolome, proteome etc.**
• Clinical Genome Diagnosis	←	**Clinical interpretation**
• Clinical Database	←	**Patient registration & Clinical DB**

Personalized Medicine Center (P-MEC)

Tohoku University Hospital (TUH)

Tohoku Medical Megabank (ToMMo)

P-MEC

INGEM

- Clinical Biobank
- Clinical Sequence

Pathologist

Sample preparation

Patient

Doctor

IC Explanation

Propose therapy

Research purpose

- exome
- RNA sequence

Outsourcing

- NCC Oncopanel, Foundation One CDx (reimbursed)
- MSK IMPACT etc.

Report

- C-CAT
- Hitachi Inc.

Secondary Findings

Genetic couselling for Hereditary cancer

Division of Genetic Diagnosis

Clinical Geneticist
Genetic Counsellor

Cancer genetic diagnosis conference (Expert panel)

Medical Oncologist, Surgical Oncologist, Pathologist, Periatrician, Biologist, Bioinformatician, Clinical Geneticist etc.

Data science /AI

Big-data Medicine Center

llaboratolies

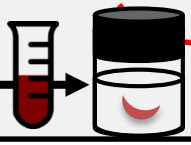
DNA extraction

Bioinformatics

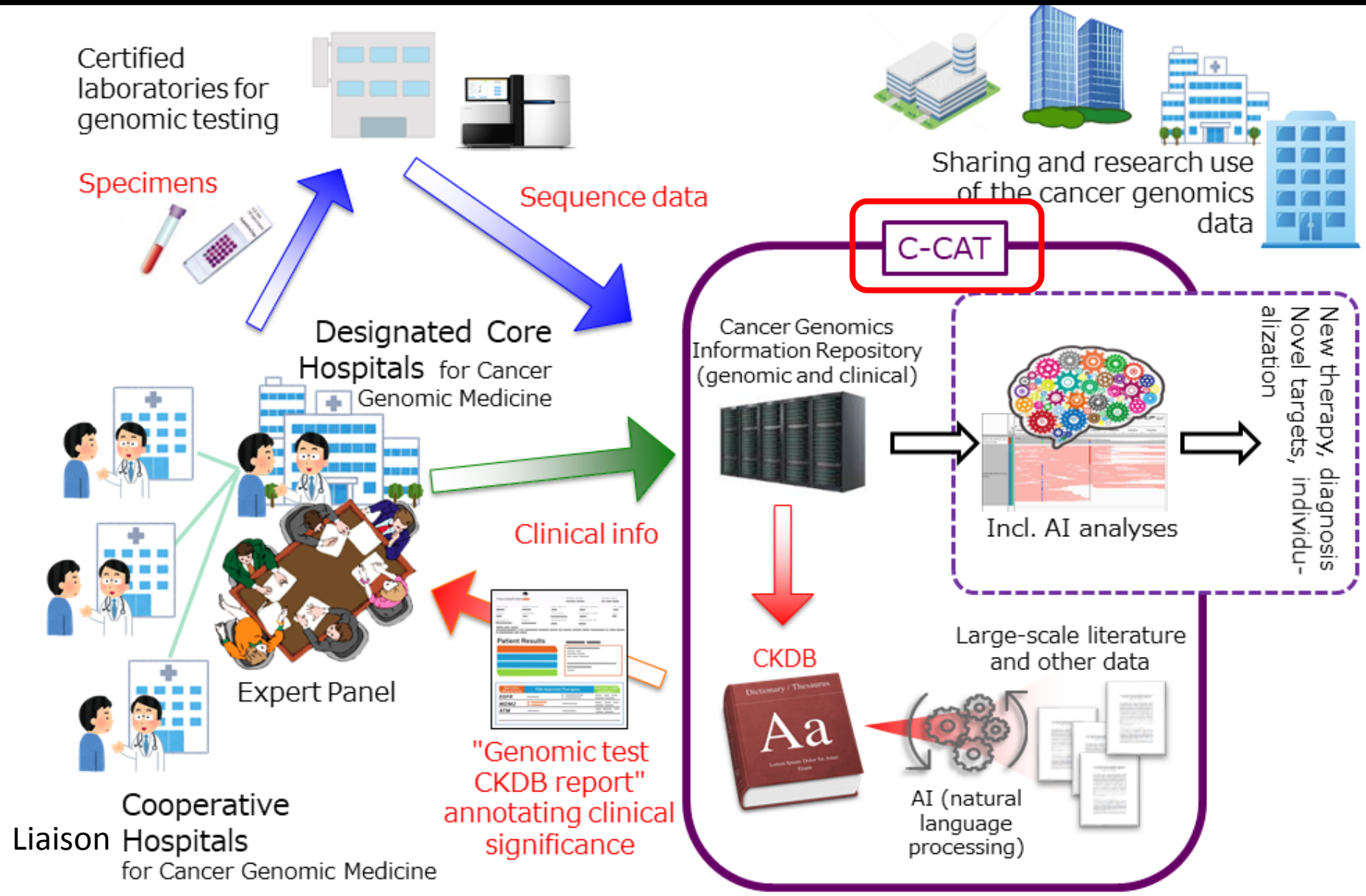
Clinical bio-bank

Dispensing

Biological specimens



Action for the cancer genomic medicine promotion (Ministry of Health, Labour and Welfare (MHLW)



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

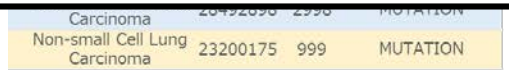
October, 2019
More than 3.7 million sample storage in total

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

The report system kind to a physician and the patients

- 2017: a comprehensive agreement on the joint development with Hitachi, Ltd.
- 2018: a collaborative investigation section supported by Hitachi, Ltd. in Tohoku Univ. Hosp.

1. Evaluation of variants
   - ClinVar
   - COSMIC (Catalogue of Somatic Mutations in Cancer)
   - ToMMo 4.7KJPN
   - *in silico* prediction tools (SIFT, Polyphen2, MutationTaster, FATHMM)
2. Proposal of therapies
   - CIViC
   - Onco KB
   - Clinical practice guidance for next-generation sequencing in cancer sdiagnosis and treatment (Edition 1.0)/JSMO-JSCO-JCA Collaboration
3. Clinical Trials
   - Japic CTI (Japic Clinical Trials Information)
   - UMIN-CTR (UMIN Clinical Trial Registration System)



Clinical Decision Supporting Tool

Issue of variant unknown significance (VUS)

- Genome DB is indispensable to next-generation medical development.
- We have already used reference genome DB (4.7K JPN) in the cancer genomic medicine.
- VUS is a major problem as ever.
- Curator of the data of the past articles is insufficient.
- Healthy cohorts of the ToMMo may answer pathogenic significance of some of VUSs, *but we have to wait for a long time*.

ToMMo's Residential Cohort and Birth and Three-Generation Cohort → Follow-up → cancer onset?

- Functional analyses of the protein by the site-directed mutagenesis are urgent, *but great efforts are necessary*.

J Hum Genet (2004) 49:391–395
DOI 10.1007/s10038-004-0160-5

SHORT COMMUNICATION

The problem 16 years ago is not settled at all!

**Masanori Kawahara · Masato Sakayori
Kazuko Shiraishi · Tadashi Nomizu · Motohiro Takeda
Rikiya Abe · Noriaki Ohuchi · Seiichi Takenoshita
Chikashi Ishioka**

Identification and evaluation of 55 genetic variations in the *BRCA1* and the *BRCA2* genes of patients from 50 Japanese breast cancer families

Table 1 Sequence variations detected in the *BRCA1* and the *BRCA2* genes

SNP ID[a]	Location	Variation[b]	Flanking sequence (5′ to 3′)	dbSNP ID[c]	BIC[d]	Volunteers[e]
*BRCA1*gene						
BRCA1-1	Intron 1	IVS1-115C > T	tggtttgtat C/T attctaaaac	rs3765640		+
BRCA1-2	Exon 3	K38 (silent) (114G > A)	tctccacaaa G/A tgtgaccaca	rs8176099	+	+
BRCA1-3	Intron 8	IVS8-58delT	tacatttttt T/– aaccettta		+	+
BRCA1-4#	Exon 11	G275D (824G > A)	gagccatgtg G/A cacaaatact			
BRCA1-5	Exon 11	S694 (silent) (2082C > T)	gacatgacag C/T gatactttcc	rs1799949	+	+
BRCA1-6	Exon 11	L771 (silent) (2311T > C)	cagtatttca T/C tggtacctgg	rs16940	+	+
BRCA1-7#	Exon 11	2389–2390delGA*	ggcaaaaaca GA/– accaaataaa			
BRCA1-8	Exon 11	P871L (2612C > T)	tcatttgctc C/T gttttcaaat	rs799917	+	+
BRCA1-9	Exon 11	E1038G (3113A > G)	gtttttaaag A/G agccagctca	rs16941	+	+
BRCA1-10	Exon 11	K1183R (3548A > G)	agcgtccaga A/G aggagagctt	rs16942	+	+
BRCA1-11#	Exon 12	C1372X (4116T > A)*	catctgggtg T/A gagagtgaaa			
BRCA1-12	Exon 13	S1436 (silent) (4308T > C)	taagtgactc T/C tctgcccttg	rs1060915	+	+
BRCA1-13#	Intron 14	IVS14 + 14A > G	agaaacatca A/G tgtaaagatg		+	
BRCA1-14	Exon 16	S1613G (4837A > G)	atctgcccag A/G gtccagctgc	rs1799966	+	+
BRCA1-15#	Exon 16	M1628T (4883T > C)	tataatgcaa T/C ggaagaaagt	rs4986854	+	
BRCA1-16	Intron 18	IVS18 + 66G > A	tacacctaac G/A tttaacacct	rs3092994	+	+
BRCA1-17#	Intron 22	IVS22 + 33A > T	gagagggagg A/T cacaatattc			
BRCA1-18#	Intron 23	IVS23 + 8G > T	atggtaaggt G/T cctgcatgta		+	
BRCA1-19	Exon 5	L63X (188T > A)*	cagtgtcctt T/A atgtaagaat		+	
BRCA1-20	Exon 3	H41R (122A > G)	aagtgtgacc A/G catattttgcaaa			
BRCA1-21	Exon 8	470–471delCT*	tccaactct CT/– aaccttggaa		+	
*BRCA2*gene						
BRCA2-1	Exon 2	5′UTR-26G > A	tatttaccaa G/A cattggagga	rs1799943	+	+
BRCA2-2#	Intron 2	IVS2-16T > A	taaggtggga T/A ttttttttta			
BRCA2-3#	Intron 2	IVS2-9T > G	ggatttttttt T/G ttaaatagat			
BRCA2-4	Intron 4	IVS4 + 67A > C	tgttctataa A/C gatgaatctg			+
BRCA2-5	Intron 4	IVS4-89T > C	acaatttata T/C gaatgagaat		+	+
BRCA2-6	Intron 7	IVS7 + 183T > A	caaatacatt T/A agtggtagtc			+
BRCA2-7	Intron 8	IVS8 + 56C > T	tttggaatgc C/T ttgttaaatt		+	+
BRCA2-8#	Exon 10	F266 (silent) (798T > C)	gtcatggatt T/C ggaaaaacat			
BRCA2-9	Exon 10	N289H (865A > C)	gtcaatgcca A/C atgtcctaga	rs766173	+	+
BRCA2-10	Exon 10	H372 N (1114C > A)	aaatgtagca C/A atcagaagcc	rs144848	+	+
BRCA2-11	Exon 10	S455 (silent) (1365A > G)	taccaaaatc A/G gagaagccat	rs1801439	+	+
BRCA2-12#	Exon 10	T582P (1744A > C)	tttaatatcc A/C ctttgaaaaa		+	
BRCA2-13	Exon 11	H743 (silent) (2229T > C)	cagtacaaca T/C tcaaaagtgg		+	+
BRCA2-14	Exon 11	M784V (2350A > G)	aaacctagtc A/G tgattctag		+	+
BRCA2-15	Exon 11	N991D (2971A > G)	tgattacatg A/G acaaatgggc	rs1799944	+	+
BRCA2-16	Exon 11	K1132 (silent) (3396A > G)	agtttagaaa A/G ccaagctaca	rs1801406	+	+
BRCA2-17#	Exon 11	S1140 (silent) (3420T > C)	tgcagaagag T/C acatttgaag			
BRCA2-18#	Exon 11	3830delA*	aagatagaaa A/– tcataatgat			
BRCA2-19#	Exon 11	L1522F (4566G > T)	ctactctgtt G/T ggttttcata			
BRCA2-20#	Exon 11	G2044V (6131G > T)	tcccaaaaag G/T cttttcatat		+	+
BRCA2-21	Exon 14	S2414 (silent) (7242A > G)	aaactaaatc A/G cattttcaca	Rs1799955	+	+
BRCA2-22#	Exon 11	6491–6495delAGTTG*	gacaaacaac AGTTG/– gtattaggaa			
BRCA2-23	Intron 16	IVS16 + 47A > G	gtattccctc A/G tccctcttte			
BRCA2-24	Intron 16	IVS16-14T > C	aatattctac T/C tttatttgtt		+	+
BRCA2-25	Exon 11	V2109I (6325G > A)	acttcctcgt G/A ttgataagag		+	
BRCA2-26#	Exon 20	S2835X (8504C > A)*	gagaagacat C/A atctggatta			
BRCA2-27	Intron22	IVS22-147A > G	cagataaagt A/G taaagttagt			
BRCA2-28	Exon 25	R3128X (9382C > T)*	Aacctccagtgg C/Tgaccagaatcc		+	
BRCA2-29	Exon 10	1278delA*	ttcagaaaaa A/– gacctattag			
BRCA2-30	Exon 10	K322Q (964A > C)	aaatctacaa A/C aagtaagaactagc		+	
BRCA2-31	Exon 10	E425 (silent) (1275A > G)	aaatatttcaga A/G aaagacct			
BRCA2-32	Exon 11	V1269 (silent) (3807T > C)	catgatttctgt T/C gtttcaatgt		+	
BRCA2-33	Exon 11	E1455 (silent) (4365A > G)	cagaaaccaga A/G gaattgcata			
BRCA2-34	Exon 18	K2729N (8187G > T)	tatgctgttaa G/T gcccagttagatcct		+	

[a]The SNP ID that have been found in this study. #Published previously (Sakayori et al. 2003)
[b]The nucleotide number in the coding region indicates the position downstream of the first nucleotide of ATG (initiation codon) in the *BRCA1* gene or the *BRCA2* gene. *: Nonsense or frame-shift mutation
[c]National Center for Biotechnology Information (NCBI) dbSNP database
[d]Breast Cancer Information Core (BIC) database, +: listed in BIC
[e]28 Japanese healthy volunteers, +: found at least one individual

Table 2 Allele frequencies of SNPs in the *BRCA1* and the *BRCA2* genes

SNP ID[a]	Allele frequency		
	Breast cancer patients[b]	Volunteers[c]	dbSNP[d]
*BRCA1*gene			
BRCA1-1	$C = 0.43$, $T = 0.57$	$C = 0.52$, $T = 0.48$	$C = 0.343$, $T = 0.657$
BRCA1-2	$G = 0.93$, $A = 0.07$	$G = 0.98$, $A = 0.02$	$G = 0.994$, $A = 0.006$
BRCA1-3	$T7 = 0.65$, $T6 = 0.35$*	$T7 = 0.50$, $T6 = 0.50$	
BRCA1-4	$G = 0.98$, $A = 0.02$	$G = 1.00$, $A = 0.00$	
BRCA1-5	$C = 0.62$, $T = 0.38$	$C = 0.56$, $T = 0.44$	$C = 0.657$, $T = 0.343$
BRCA1-6	$T = 0.62$, $C = 0.38$	$T = 0.54$, $C = 0.46$	$T = 0.678$, $C = 0.322$
BRCA1-8	$C = 0.62$, $T = 0.38$	$C = 0.54$, $T = 0.46$	$C = 0.619$, $T = 0.381$
BRCA1-9	$A = 0.62$, $G = 0.38$	$A = 0.54$, $G = 0.46$	$A = 0.725$, $G = 0.275$
BRCA1-10	$A = 0.62$, $G = 0.38$	$A = 0.54$, $G = 0.46$	$A = 0.703$, $G = 0.297$
BRCA1-12	$T = 0.62$, $C = 0.38$	$T = 0.54$, $C = 0.46$	$T = 0.747$, $C = 0.253$
BRCA1-13	$A = 0.98$, $G = 0.02$*	$A = 1.00$, $G = 0.00$	
BRCA1-14	$A = 0.62$, $G = 0.38$	$A = 0.54$, $G = 0.46$	$A = 0.696$, $G = 0.304$
BRCA1-15	$T = 0.98$, $C = 0.02$	$T = 1.00$, $C = 0.00$	$T = 0.995$, $C = 0.005$
BRCA1-16	$G = 0.63$, $A = 0.37$	$G = 0.54$, $A = 0.46$	$G = 0.693$, $A = 0.307$
BRCA1-17	$A = 0.98$, $G = 0.02$*	$A = 1.00$, $G = 0.00$	
BRCA1-18	$G = 0.99$, $T = 0.01$	$G = 1.00$, $T = 0.00$	
BRCA1-20	$A = 0.99$, $G = 0.01$	ND	
*BRCA2*gene			
BRCA2-1	$G = 0.55$, $A = 0.45$	$G = 0.49$, $A = 0.51$	$G = 0.762$, $A = 0.238$
BRCA2-2	$T = 0.97$, $C = 0.03$*	$T = 1.00$, $C = 0.00$	
BRCA2-3	$T = 0.98$, $G = 0.02$*	$T = 1.00$, $C = 0.00$	
BRCA2-4	$A = 0.84$, $C = 0.16$*	$A = 0.84$, $C = 0.16$	
BRCA2-5	$T = 0.84$, $C = 0.16$*	$T = 0.84$, $C = 0.16$	
BRCA2-6	$T = 0.32$, $A = 0.68$*	$T = 0.58$, $A = 0.42$	
BRCA2-7	$C = 0.96$, $T = 0.04$*	$C = 0.96$, $T = 0.04$	
BRCA2-8	$T = 0.98$, $C = 0.02$	$T = 1.00$, $C = 0.00$	
BRCA2-9	$A = 0.86$, $C = 0.14$	$A = 0.84$, $C = 0.16$	$A = 0.838$, $C = 0.024$, $G = 0.009$, $T = 0.129$
BRCA2-10	$A = 0.80$, $C = 0.20$	$A = 0.82$, $C = 0.18$	$A = 0.607$, $C = 0.281$, $G = 0.026$, $T = 0.085$
BRCA2-11	$A = 0.86$, $G = 0.14$	$A = 0.84$, $G = 0.16$	$A = 0.875$, $G = 0.125$
BRCA2-12	$A = 0.99$, $C = 0.01$	$A = 1.00$, $C = 0.00$	
BRCA2-13	$T = 0.86$, $C = 0.14$	$T = 0.84$, $C = 0.16$	
BRCA2-14	$A = 0.93$, $G = 0.07$	$A = 0.95$, $G = 0.05$	
BRCA2-15	$A = 0.85$, $G = 0.15$	$A = 0.84$, $G = 0.16$	$A = 0.970$, $G = 0.030$
BRCA2-16	$A = 0.47$, $G = 0.53$	$A = 0.50$, $G = 0.50$	$A = 0.705$, $G = 0.295$
BRCA2-17	$T = 0.99$, $C = 0.01$	$T = 1.00$, $C = 0.00$	
BRCA2-19	$G = 0.98$, $T = 0.02$	$G = 1.00$, $T = 0.00$	
BRCA2-20	$G = 0.97$, $T = 0.03$	$G = 0.98$, $T = 0.02$	
BRCA2-21	$A = 0.58$, $G = 0.42$	$A = 0.50$, $G = 0.50$	$A = 0.758$, $G = 0.242$
BRCA2-23	$A = 0.96$, $G = 0.04$*	$A = 1.00$, $G = 0.00$	
BRCA2-24	$T = 0.36$, $C = 0.64$	$T = 0.27$, $C = 0.73$	
BRCA2-25#	$G = 0.99$, $A = 0.01$	$G = 1.00$, $A = 0.00$	
BRCA2-27#	$A = 0.98$, $G = 0.02$*	$A = 1.00$, $G = 0.00$	
BRCA2-30	$A = 0.97$, $C = 0.03$	ND	
BRCA2-31	$A = 0.97$, $C = 0.03$	ND	
BRCA2-32	$T = 0.86$, $C = 0.14$	ND	
BRCA2-33	$A = 0.98$, $G = 0.02$*	ND	
BRCA2-34	$G = 0.98$, $T = 0.02$	ND	

[a]Identical to the SNP ID listed in Table 1, #: found in a relative but not in the proband
[b]110 alleles from 55 patients, *: data derived from 68 alleles (34 patients)
[c]56 alleles from 28 healthy volunteers, ND: not determined
[d]National Center for Biotechnology Information (NCBI) dbSNP database

Good afternoon Dr. Ishioka, Chikashi, e-mail/ January 31, 2020
I hope all is well.

Recently, I engaged in a genetic testing program with Color Genomics and my test identified a **"VUS" within the TP53 gene. The "VUS" c.998G>A (p.Arg333His)** was my variation. I have attached those findings. Immediately, **I became very anxious** and went online to research it. Through those efforts, I found that you have studied and researched the TP53 gene through several published journals and continue to be a prominent researcher in this field. At this point, **it is listed as a "VUS", but my concern is that I am a carrier of LFS**. It appears this **is a rare variation with 12 other folks listed in the database**. If you don't mind, could you please provide

color

Hereditary Cancer Test

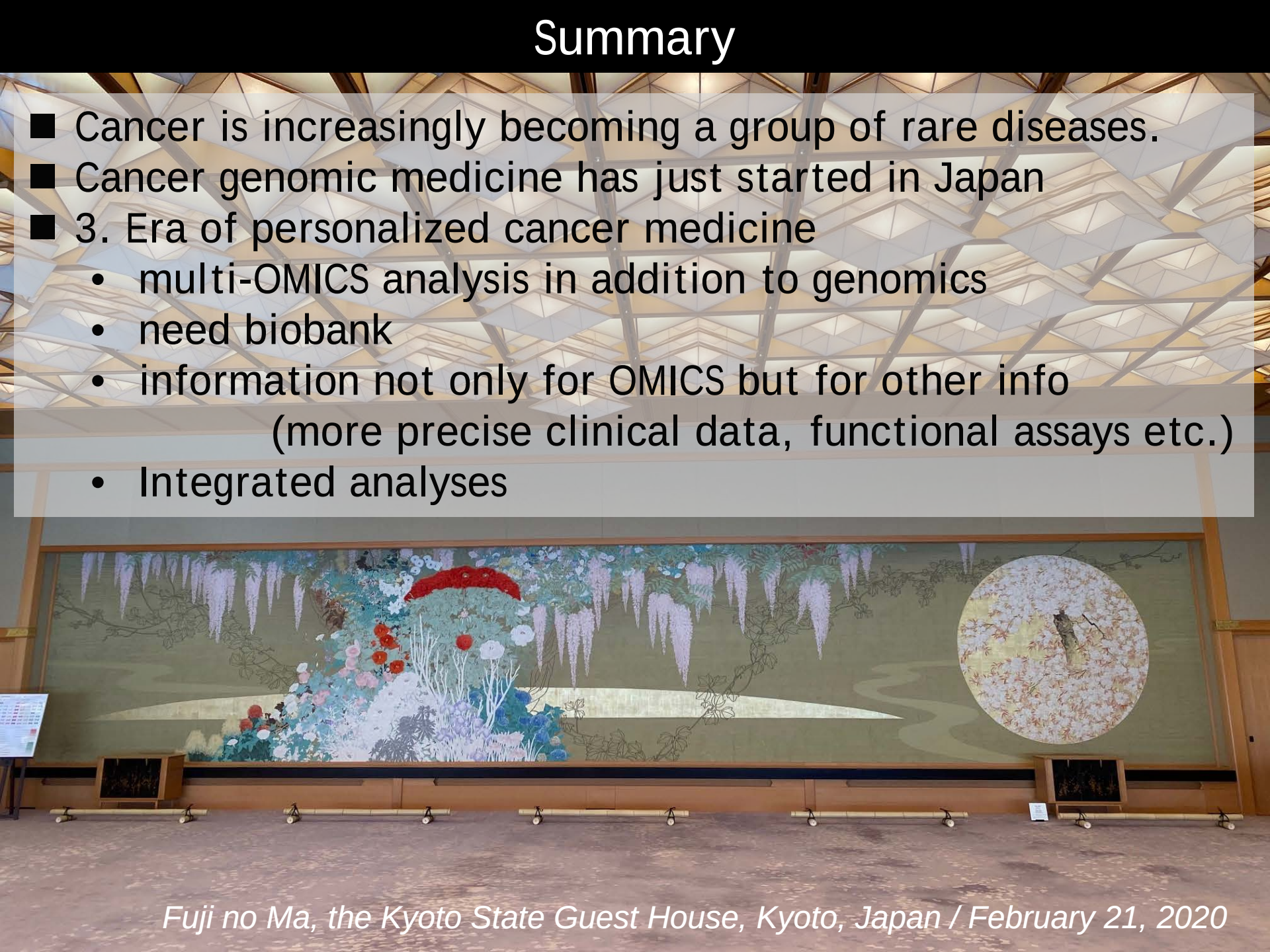
GENE	VARIANT	CLASSIFICATION
TP53	c.998G>A (p.Arg333His) *Alternate name(s): g.7574029C>T* *Transcript: ENST00000269305* *Zygosity: Heterozygous*	Variant of Uncertain Significance

SUPPORTING EVIDENCE

This missense variant replaces arginine with histidine at codon 333 of the TP53 protein. Computational prediction is inconclusive regarding the impact of this variant on protein structure and function (internally defined REVEL score threshold 0.5 < inconclusive < 0.7, PMID: 27666373). Splice site prediction tools suggest that this variant may not impact RNA splicing. Functional studies have shown that this variant does not impact transcription transactivation activity in a yeast assay (PMID: 12826609). To our knowledge, this variant has not been reported in individuals affected with hereditary cancer in the literature. This variant has been identified in 12/281972 chromosomes in the general population by the Genome Aggregation Database (gnomAD). The available evidence is insufficient to determine the role of this variant in disease conclusively. Therefore, this variant is classified as a Variant of Uncertain Significance.

Summary

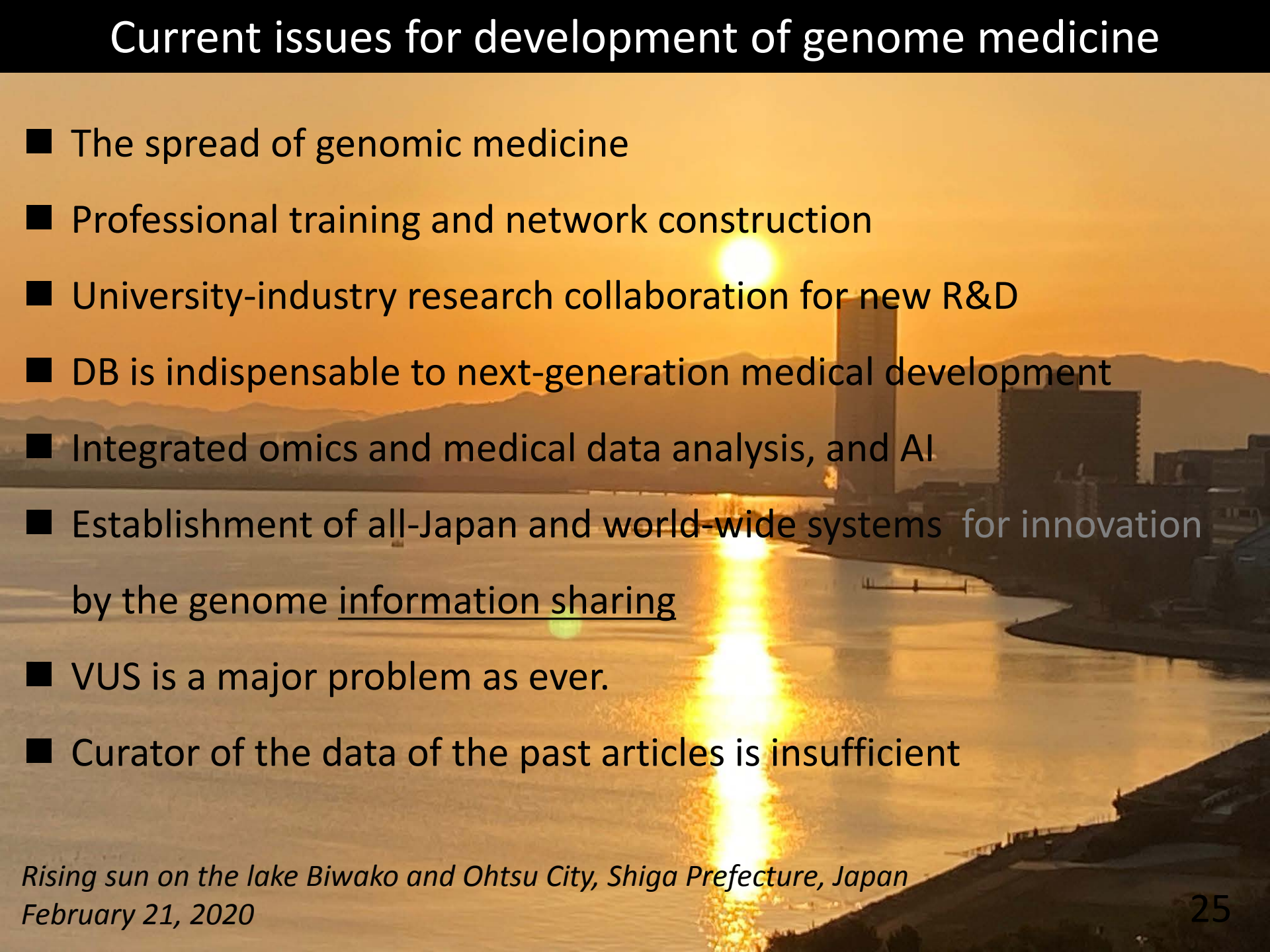
- Cancer is increasingly becoming a group of rare diseases.
- Cancer genomic medicine has just started in Japan
- 3. Era of personalized cancer medicine
  - multi-OMICS analysis in addition to genomics
  - need biobank
  - information not only for OMICS but for other info
    (more precise clinical data, functional assays etc.)
  - Integrated analyses



Fuji no Ma, the Kyoto State Guest House, Kyoto, Japan / February 21, 2020

Current issues for development of genome medicine

- The spread of genomic medicine
- Professional training and network construction
- University-industry research collaboration for new R&D
- DB is indispensable to next-generation medical development
- Integrated omics and medical data analysis, and AI
- Establishment of all-Japan and world-wide systems for innovation by the genome information sharing
- VUS is a major problem as ever.
- Curator of the data of the past articles is insufficient



Rising sun on the lake Biwako and Ohtsu City, Shiga Prefecture, Japan
February 21, 2020

Future issues in data strategies to predict risk, prevent and manage disease

- Reciprocal utility for daily updated data: metadata accessibility
- Data management

  Electric medical record for a total hospital management and solution e.g. Tasy by Phillips with Tohoku University
- Seamless total optimization and networks

  e.g. Flexible and intensive data availability for cost-benefit effect
- Solution to the local healthcare problems

  e.g. Healthcare mobility such as a 'mobile hospital to your town'

Rising sun on the Matsushima Islands near Sendai City, Miyagi Prefecture, Japan

Thank you!

Japanese Garden, the Kyoto State Guest House, Kyoto, Japan / February