The Institute of Medical Science
The University of Tokyo

Cancer Clinical Whole Genome Sequencing

Satoru Miyano, Ph.D.

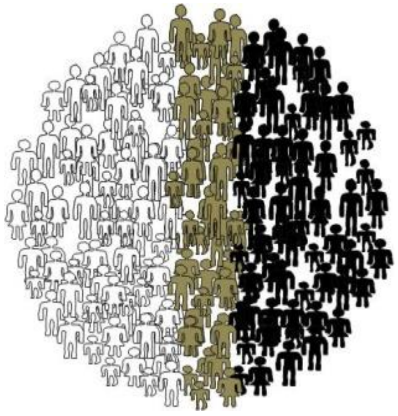
Abbreviated to IMSUT

Director, Human Genome Center

The Institute of Medical Science, The University of Tokyo, Japan

“The Only Flower in the World”
– Genetic Variations –

1/2 → Cancer
1/3 → Death



Personalized Medicine Team

Extension to Whole Genome Sequencing, and More@IMSUT

Since 2013

Patient

Specimen

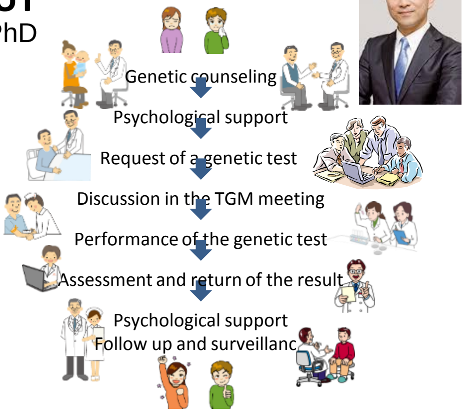
Genetic Counseling Since 2001

GCT@IMSUT

Yoichi Furukawa, MD, PhD

ELSI Team@IMSUT

Kaori Muto, PhD



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

Extension to

Whole Genome Sequence

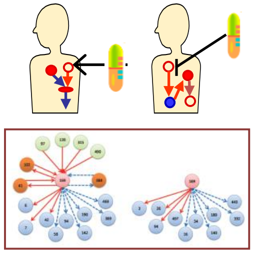
Exome Analysis

Transcriptome Analysis

Epigenome Analysis (not yet)

Personal Genomes and Omics Data

Prediction of Medical Intervention



Decision Support System (not yet)

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

Leukemia
Lymphoma
Gastrointestinal Cancer

NGS Facility

Nanopore Sequencer (not yet)

Data Analysis and Interpretation

Sequencing and Data Analysis Facilities & Management

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

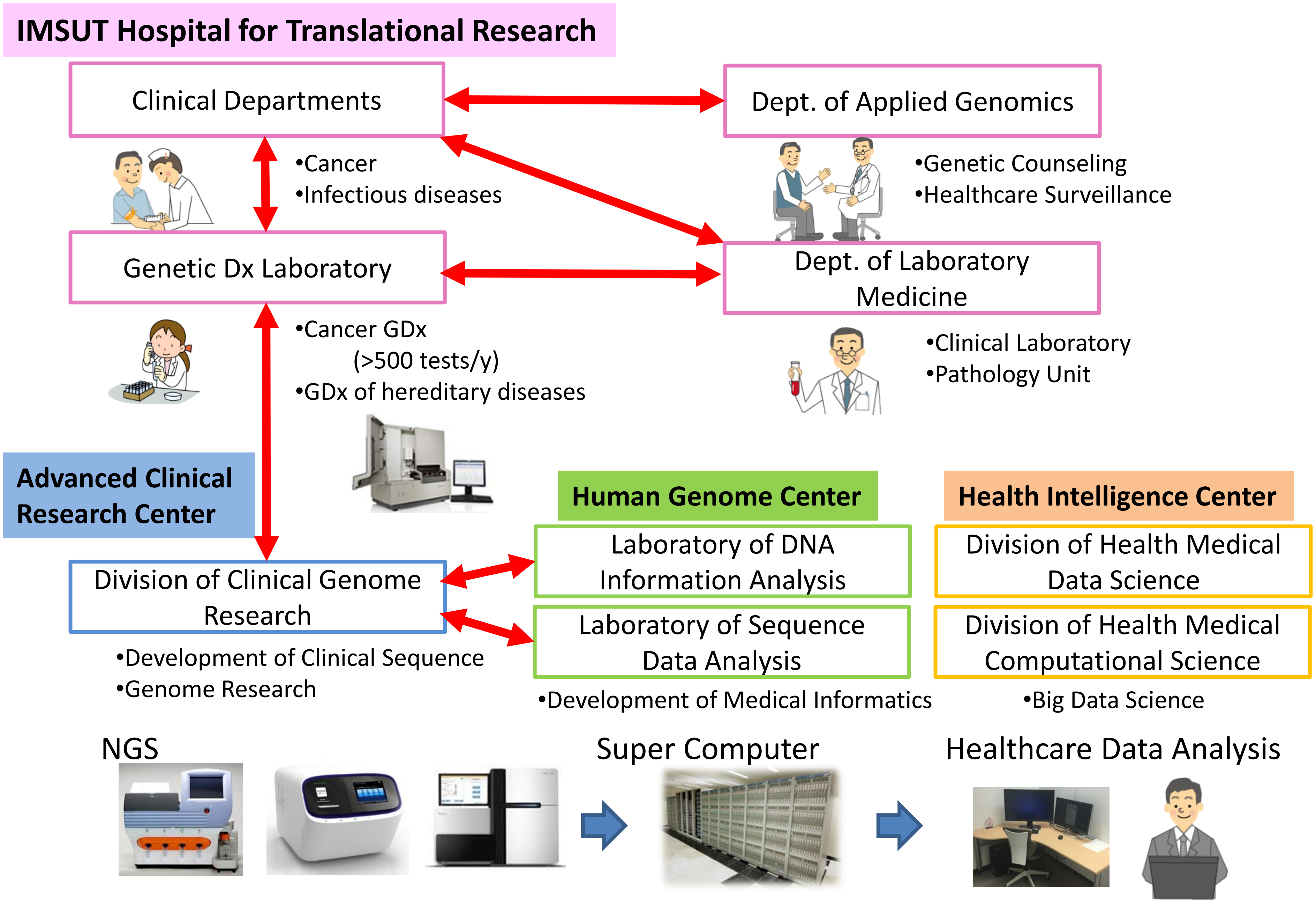
Satoru Miyano, PhD Rui Yamaguchi, PhD

Seiya Imoto, PhD

Human Genome Center

Advanced Clinical Research Center
Research Hospital

Genomic Medicine @ IMSUT



IMSUT Hospital for Translational Research

Clinical Departments

- Cancer
- Infectious diseases

Dept. of Applied Genomics

- Genetic Counseling
- Healthcare Surveillance

Genetic Dx Laboratory

- Cancer GDx
  (>500 tests/y)
- GDx of hereditary diseases

Dept. of Laboratory Medicine

- Clinical Laboratory
- Pathology Unit

Advanced Clinical Research Center

Division of Clinical Genome Research

- Development of Clinical Sequence
- Genome Research

Human Genome Center

Laboratory of DNA Information Analysis

Laboratory of Sequence Data Analysis

- Development of Medical Informatics

Health Intelligence Center

Division of Health Medical Data Science

Division of Health Medical Computational Science

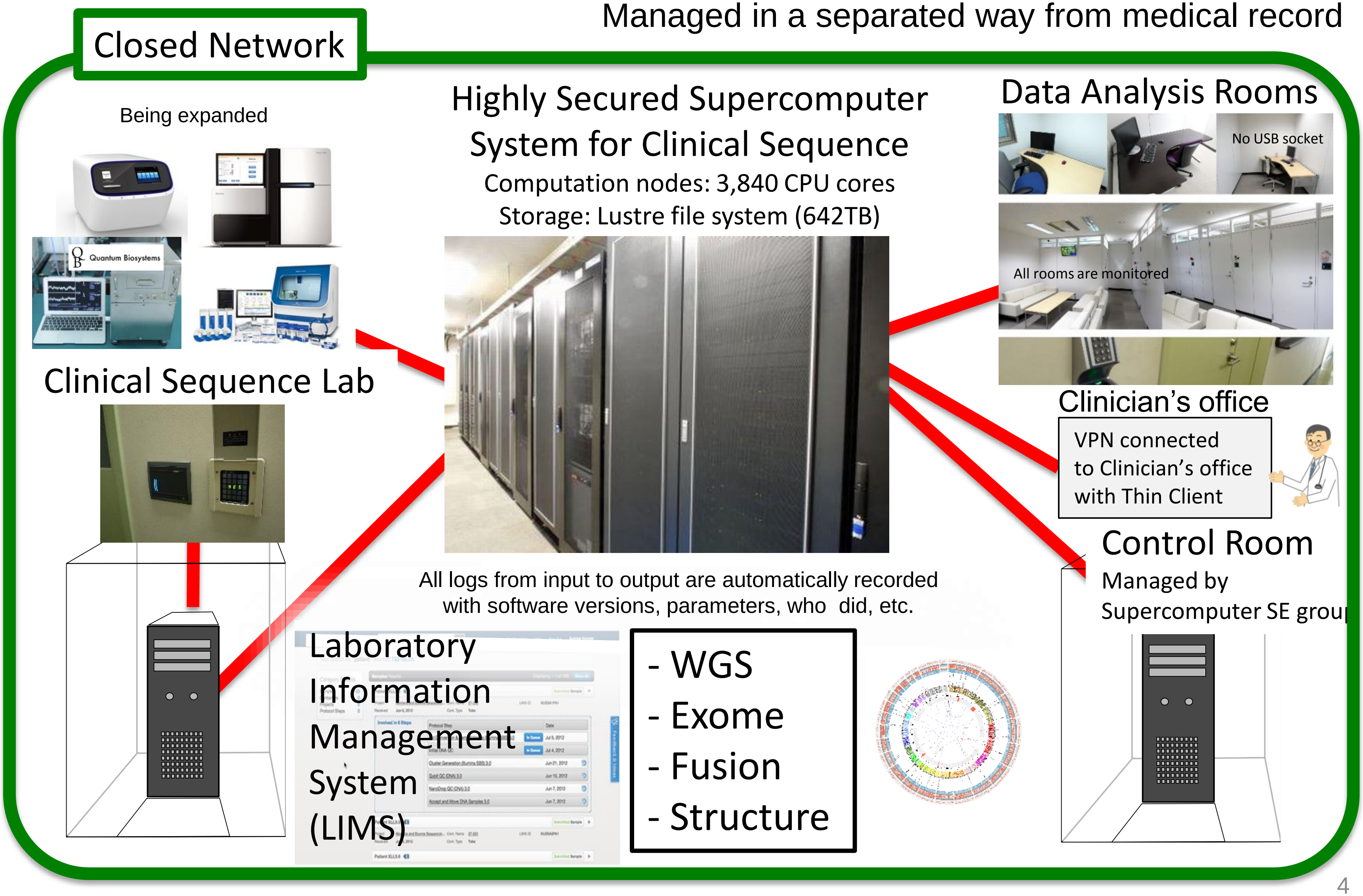
- Big Data Science

NGS

Super Computer

Healthcare Data Analysis

Informatics, Sequencing, Data Analysis Facilities & Management



Managed in a separated way from medical record

Closed Network

Being expanded

Clinical Sequence Lab

Highly Secured Supercomputer System for Clinical Sequence

Computation nodes: 3,840 CPU cores

Storage: Lustre file system (642TB)

Data Analysis Rooms

Clinician’s office

VPN connected
to Clinician’s office
with Thin Client

Control Room

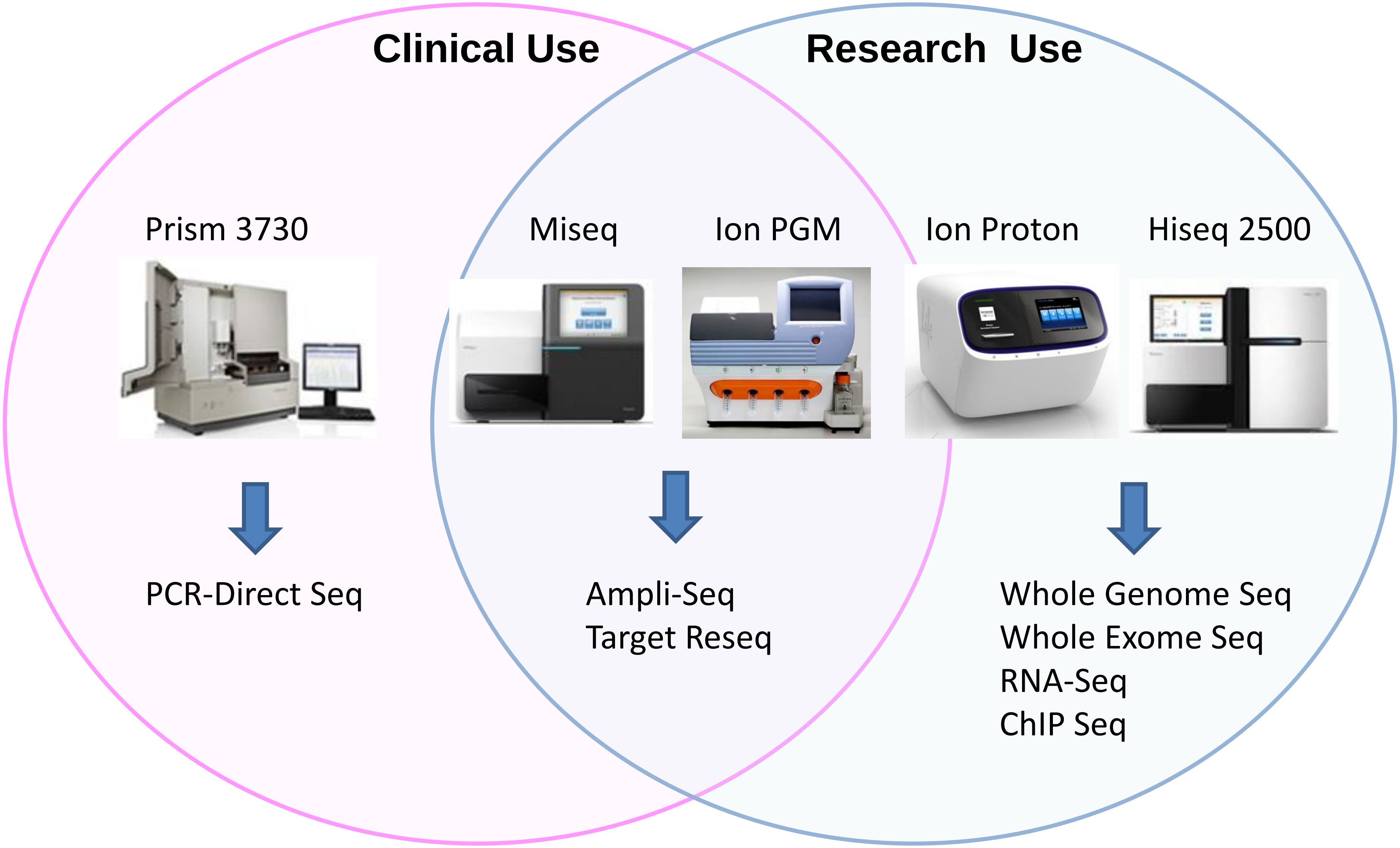
Managed by
Supercomputer SE grou

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

Laboratory Information Management System (LIMS)

- WGS
- Exome
- Fusion
- Structure

Sequencers @ IMSUT for GM



Clinical Use

Research Use

Prism 3730

Miseq

Ion PGM

Ion Proton

Hiseq 2500

PCR-Direct Seq

Ampli-Seq
Target Reseq

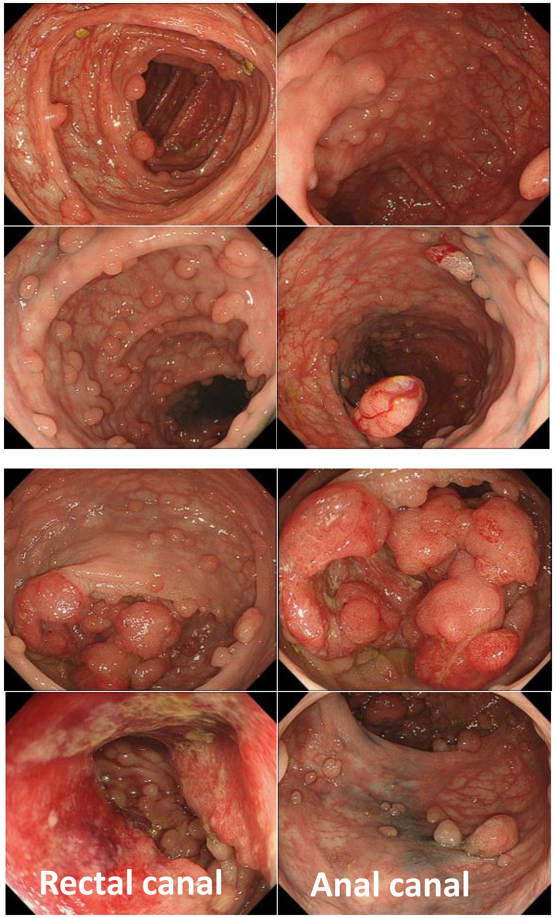
Whole Genome Seq
Whole Exome Seq
RNA-Seq
ChIP Seq

Primary Activities @ IMSUT

- **WGS-based clinical sequence**
  for colorectal cancer patients
  - FAP, Lynch, PMP, etc.
- **Panel-based clinical sequence**
  for hematological disorder patients
  - MDS, ALL, etc.
- **Utilization of AI-based interpretation system**
  - IBM Watson Genomic Analytics since 2015

Familial Adenomatous Polyposis; FAP

Colonoscopy



Multiple polyps throughout the large intestine
Advanced rectal cancer (Ra; T3N1M0)

Clinical Features of FAP

- 100s~1,000s adenomatous polyps in the colon
- Estimated penetrance for adenomas >90%
- Untreated polyposis leads to 100% risk of cancer
- Extra-colonic tumors (desmoid, osteoma, upper GI, thyroid, brain, and others)

Genetics of FAP

- Autosomal dominant inheritance
- Germline mutation in the *APC* gene

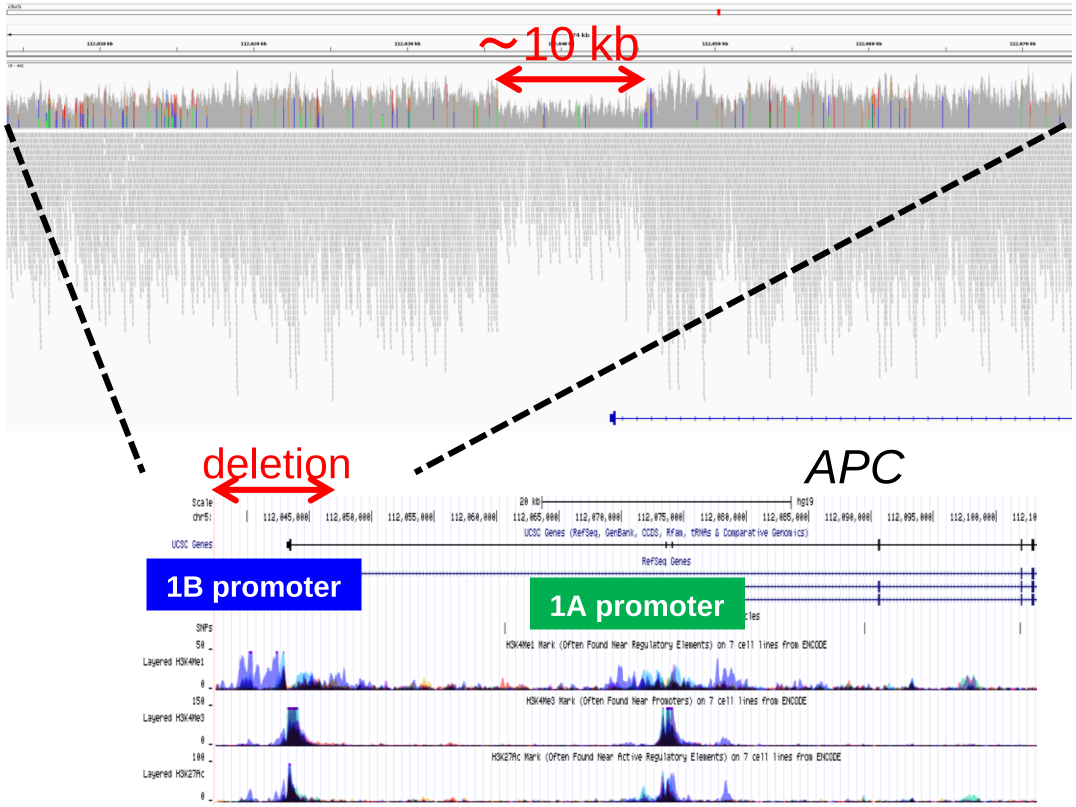
Identification of a large deletion in *APC* by WGS

(A) SNV in *APC*

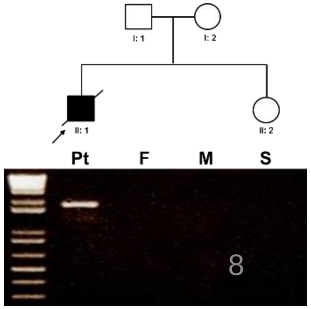
Types	Variants
intronic	c.136-53T>C
intronic	c.729+88T>C
synonymous	c.1458T>C, p.Y486Y
synonymous	c.1635G>A, p.A545A
synonymous	c.4479G>A, p.T1493T
synonymous	c.5034G>A, p.G1678G
synonymous	c.5268T>G, p.S1756S
nonsynonymous	c.5465T>A, p.V1822D
synonymous	c.5880G>A, p.P1960P

No deleterious variants

(B) SV in *APC*

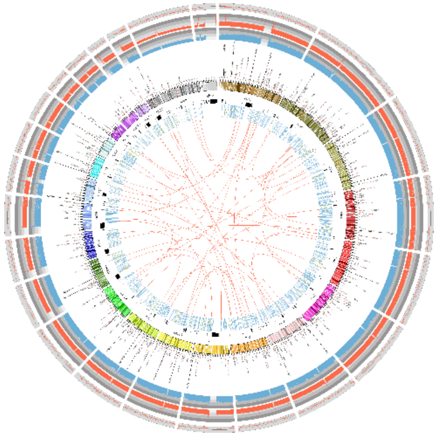


Long-range PCR confirmed a large deletion in the FAP patient.

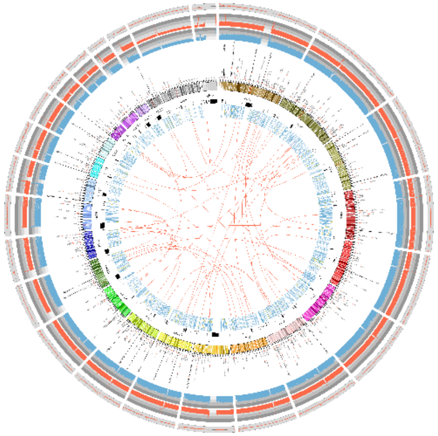


Structural Variations in FAP by WGS

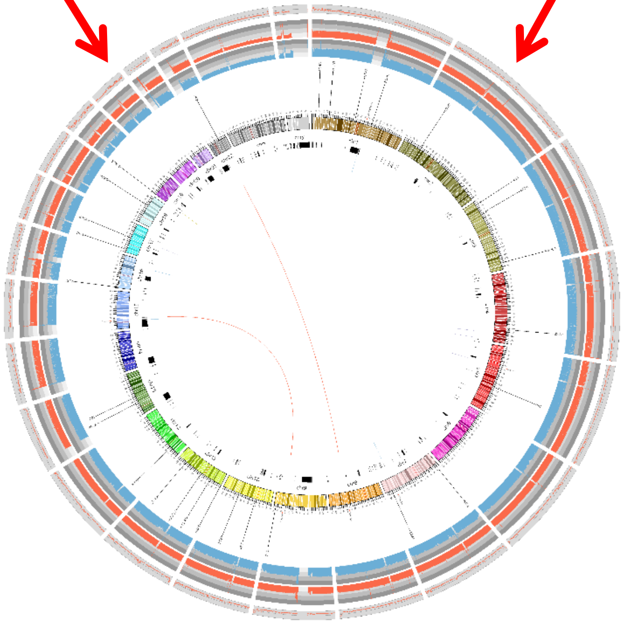
SV in Polyp



SV in Normal



Somatic SV

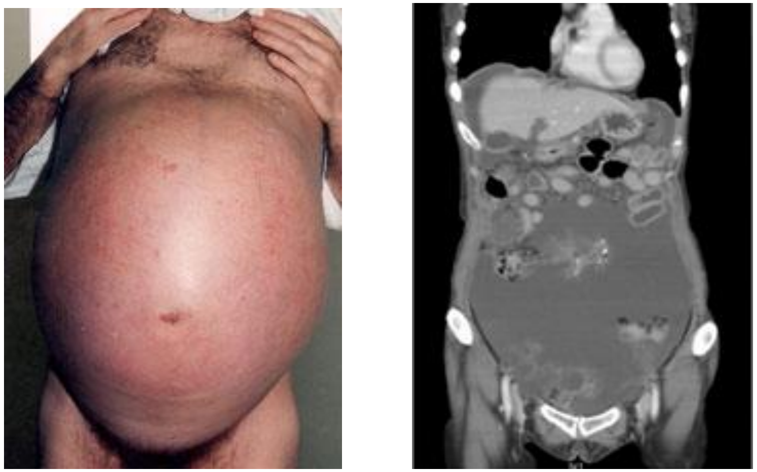


By WGS, translocations and large INDELs, non-coding mutations are detectable.

Interpretation is a big challenge.

WGS of rare & neglected tumor

- **Pseudomyxoma peritonei (PMP):** a rare disease occurring 1-2 cases in 1000,000
- The tumor cells produce mucin or gelatinous fluid, resulting in the abdominal distension.
- A slow growing disease
- But malignant transformation leads to poor prognosis..

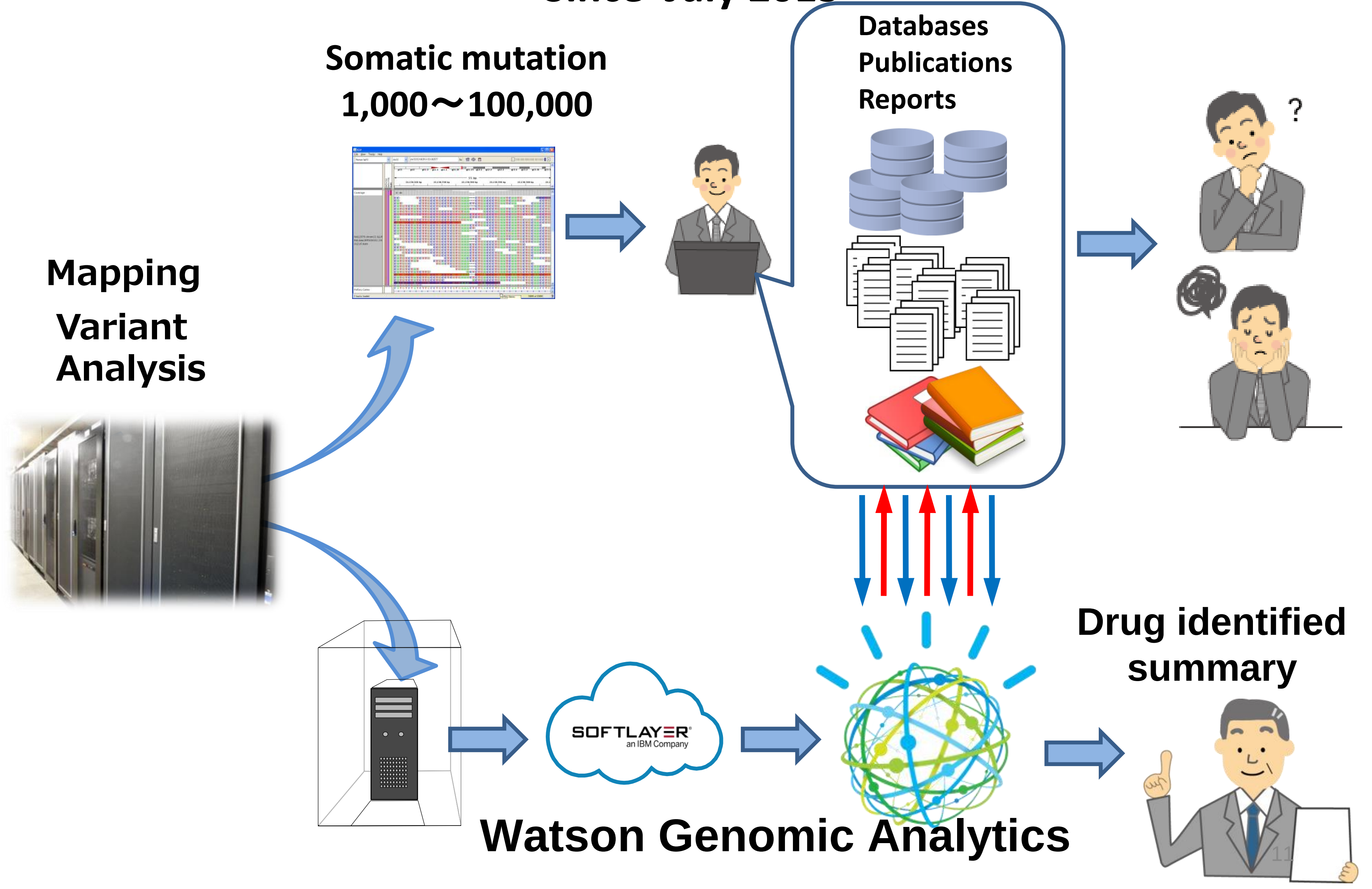


WGS!! for

Clarification of tumorigenesis
&
Identification of driver mutations

Clinical Sequencing with IBM Watson Genomic Analytics

Since July 2015



Somatic mutation
1,000～100,000

Databases
Publications
Reports

Mapping
Variant
Analysis

Drug identified
summary

Watson Genomic Analytics

A new organization was established in the University of Tokyo

April 2015 –

Medical Genomics Research Initiative, the University of Tokyo

Health Intelligence Center at IMSUT

1. **Supercomputing for genomic medicine**
2. **ELSI studies for clinical sequence**
3. **Development of data analytic and interpretation methods toward p-medicine**

Div of Health Medical Data Science

Div of Health Medical Computer Science

Clinical interpretation team

Clinical omics analysis team

Clinical sequence analysis team

Clinical epigenome analysis team

Clinical genome analysis team

Genomic counseling team

ELSI and public policy team

Bioinformatics and DB team

Genome Analysis Supercomputer

Global Genomic Medicine Collaborative

International Cancer Genome Consortium

Midwest-Asia Genome Consortium (UChicago, UT, etc.)

International Big Data Sharing

Cross-sectional study of 4 departments

Education and Training

Four-leaf clover project

Institute of Medical Science

Graduate School of Medicine

Univ of Tokyo Hospital

IMSUT Hospital

Research Center for Advanced Sciences and Technology

Grad School of Frontier of Sciences

Integration of Genome and Medical Information

Collaboration started with Kanagawa Cancer Center

地方独立行政法人 神奈川県立病院機構
神奈川県立がんセンター
Kanagawa Cancer Center

Kanagawa Cancer Center

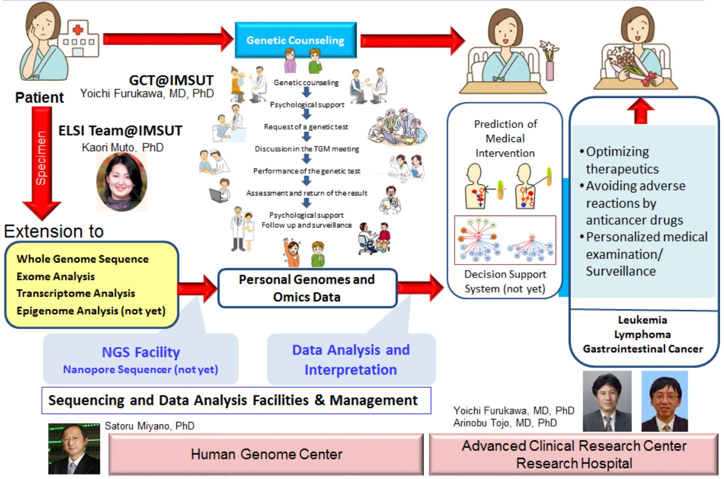
The Institute of Medical Science
The University of Tokyo

Clinics

415 beds

Basis for future cancer prevention and therapy

Clinical Sequencing Research Team



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Supercomputer
414 TFLOPS

12PB Lustre
File System

100PB
Archieve
Storage

What opportunities do you see for collaboration with G2MC or among the attendees?

- Creation of international network, especially in Asian areas
- Sharing Bioinformatics methodologies, software applications, know-how
- Use of this network to encourage/enhance the Japanese communities, especially medical communities

Cancer GM Team @ IMSUT

(About 25 members; not enumerative)

- Colorectal cancer team
  - Yoichi Furukawa, MD, PhD
  - Kiyoshi Yamaguchi, PhD
  - Rei Noguchi, PhD Student
  - Technicians: Seira Hatakeyama, Kazuko Hamada + more
- Blood cancer team
  - Arinobu Tojo, MD, PhD
  - Masayuki Kobayashi, MD, PhD
  - Kazuaki Yokoyama, MD, PhD
  - Technicians: Mika Yamazaki + more
- Bioinformatics team
  - Satoru Miyano, PhD
  - Seiya Imoto, PhD
  - Rui Yamaguchi, PhD
  - Tetsuo Shibuya, PhD
  - Rika Kasajima, PhD
  - Engineers: Eigo Shimizu, Mitsuhiro Komura + Ayumu Saito + SEs
- ELSI team
  - Koichiro Yuji, MD, PhD
  - Kaori Muto, PhD
  - Ayako Kamisato, PhD