Cancer Clinical Whole Genome Sequencing

Satoru Miyano, Ph.D.
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

Abbreviated to IMSUT
Extension to Whole Genome Sequencing, and More@IMSUT Since 2013

**Sequencing and Data Analysis Facilities & Management**

- NGS Facility
  - Nanopore Sequencer (not yet)

- Data Analysis and Interpretation

**Personal Genomes and Omics Data**

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

**GCT@IMSUT**
- Yoichi Furukawa, MD, PhD

**ELSI Team@IMSUT**
- Kaori Muto, PhD

**Human Genome Center**

**Advanced Clinical Research Center Research Hospital**

**Predictive of Medical Intervention**

- Decision Support System (not yet)

**Advantages**

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

**Personalized Medicine Team**

- Seiya Imoto, PhD
- Rui Yamaguchi, PhD
- Satoru Miyano, PhD
- Yoichi Furukawa, MD, PhD
- Arinobu Tojo, MD, PhD

**Patient**

**Extension to**

- Genetic Counseling Since 2001
- Optimization of therapeutics
- Avoiding adverse reactions by anticancer drugs
- Personalized medical examination/Surveillance

**Leukemia**

**Lymphoma**

**Gastrointestinal Cancer**

**Discussion in the TGM meeting**

- Request of a genetic test
- Performance of the genetic test
- Assessment and return of the result
- Psychological support
- Follow up and surveillance

**GCT@IMSUT**

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

**Human Genome Center**

**Advanced Clinical Research Center Research Hospital**
Informatics, Sequencing, Data Analysis Facilities & Management

Managed in a separated way from medical record

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

Data Analysis Rooms
- No USB socket
- All rooms are monitored

Clinician’s office
- VPN connected to Clinician’s office with Thin Client
- Managed by Supercomputer SE group

Clinical Sequence Lab

Laboratory Information Management System (LIMS)
- WGS
- Exome
- Fusion
- Structure

Closed Network

All logs from input to output are automatically recorded with software versions, parameters, who did, etc.
Sequencers @ IMSUT for GM

Clinical Use
- Prism 3730
  - PCR-Direct Seq

Research Use
- Miseq
  - Ampli-Seq
  - Target Reseq
- Ion PGM
- Ion Proton
- Hiseq 2500
  - 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

### 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

**Colonoscopy**
- Multiple polyps throughout the large intestine
- Advanced rectal cancer (Ra; T3N1M0)
Identification of a large deletion in APC by WGS

(A) SNV in APC

<table>
<thead>
<tr>
<th>Types</th>
<th>Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>intronic</td>
<td>c.136-53T&gt;C</td>
</tr>
<tr>
<td>intronic</td>
<td>c.729+88T&gt;C</td>
</tr>
<tr>
<td>synonymous</td>
<td>c.1458T&gt;C, p.Y486Y</td>
</tr>
<tr>
<td>synonymous</td>
<td>c.1635G&gt;A, p.A545A</td>
</tr>
<tr>
<td>synonymous</td>
<td>c.4479G&gt;A, p.T1493T</td>
</tr>
<tr>
<td>synonymous</td>
<td>c.5034G&gt;A, p.G1678G</td>
</tr>
<tr>
<td>synonymous</td>
<td>c.5268T&gt;G, p.S1756S</td>
</tr>
<tr>
<td>nonsynonymous</td>
<td>c.5465T&gt;A, p.V1822D</td>
</tr>
<tr>
<td>synonymous</td>
<td>c.5880G&gt;A, p.P1960P</td>
</tr>
</tbody>
</table>

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.

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

SoftLayer
a IBM Company
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

Genome Analysis Supercomputer

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

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

Global Genomic Medicine Collaborative
International Cancer Genome Consortium
Midwest-Asia Genome Consortium (UChicago, UT, etc.)
International Big Data Sharing

Four-leaf clover project

Institute of Medical Science
Graduate School of Medicine
Collaboration started with Kanagawa Cancer Center

**Clinics**

415 beds

**Clinical Sequencing Research Team**

Basis for future cancer prevention and therapy

**Supercomputer**

414 TFLOPS

12PB Lustre File System

100PB Archive 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