sysmex
Lighting the way with diagnostics

The 16th R&D Meeting

March 8, 2019

SYSMEX CORPORATION

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1. Opening Remarks

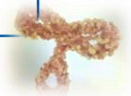
Hisashi Ietsugu, Chairman and CEO

Changes in the External Environment

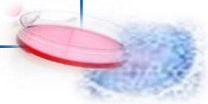
- Technological innovation

Genomic medicine

Antibody drugs



Regenerative medicine



Wearable devices

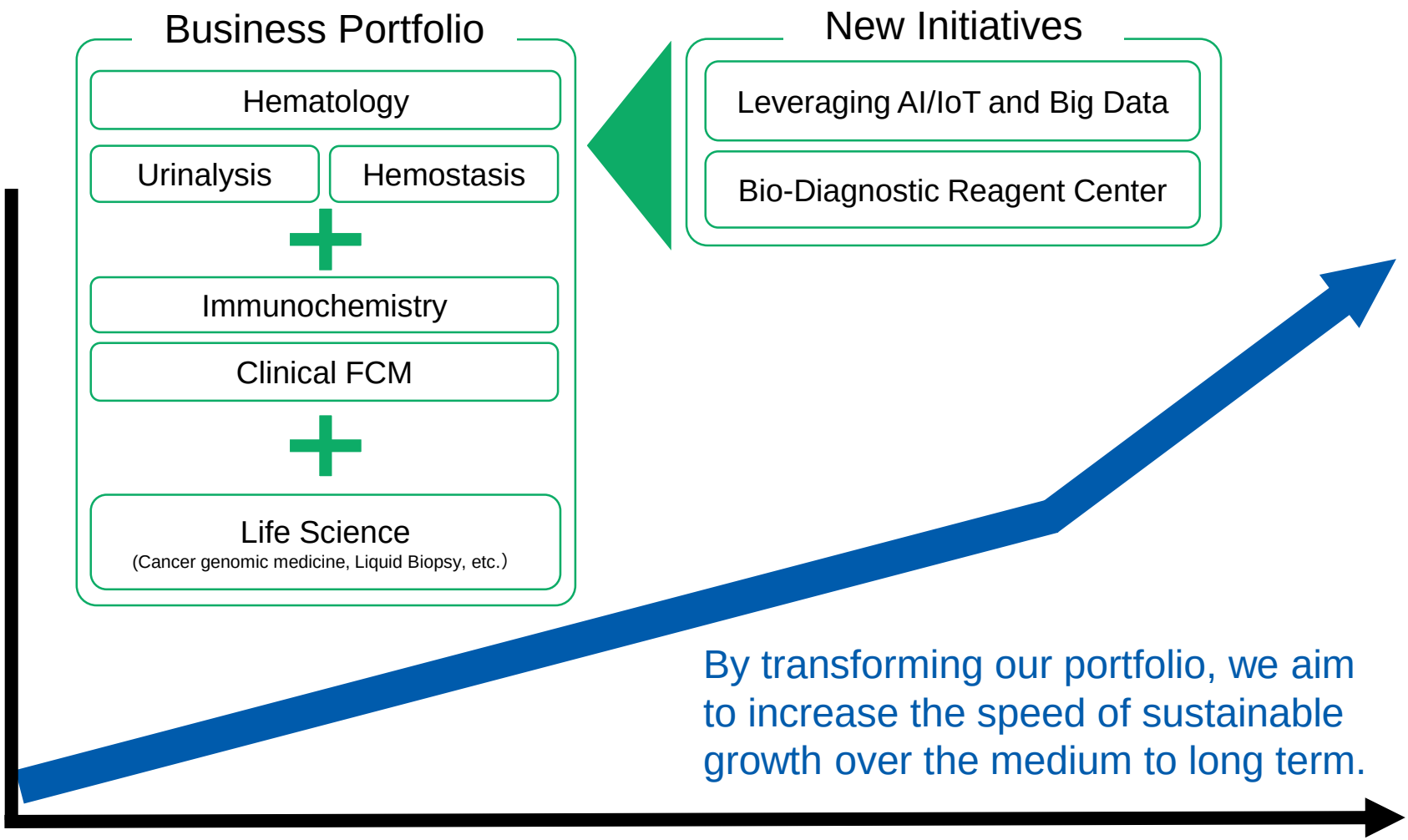
Robotics

AI/IoT

- Market environment

	Developing countries	Emerging countries	Developed countries
Changes in the external environment	Rising populations Economic growth Epidemics of infectious diseases Building of medical infrastructure		Falling birthrates and aging populations Rapidly rising medical expenses Technological innovation
Market opportunities	**Growing IVD markets in emerging and developing countries**		**Advances in personalized medicine**

Expansion and Transformation of Our Portfolio



Taking on the Challenge of Bio-Diagnostic Reagents

Taking on the challenge of advancing in the area of diagnostic reagents with the aim of providing higher-value testing

Bio-Diagnostic Reagent Center (Scheduled to commence operations in April 2019)

Handling integrated processes from procurement and development of substances for bio-diagnostic reagents to reagent development, production and distribution

(Reinforcing business in the hemostasis, immunochemistry, and life science fields)

Ensuring a steady supply of biological materials

Higher quality and performance of bio-diagnostic reagents

Accelerating development of new parameters

Shorter manufacturing lead times

Technological Developments in the AI/IoT and Big Data Domains

IT solutions and platforms to support next-generation healthcare and diagnostics

Diagnostics instruments x AI/IoT

Laboratory digitalization, more efficient service activities, etc.

Convert data to valuable information

Increase added value through data analysis

+

AI analysis

Higher diagnostic precision

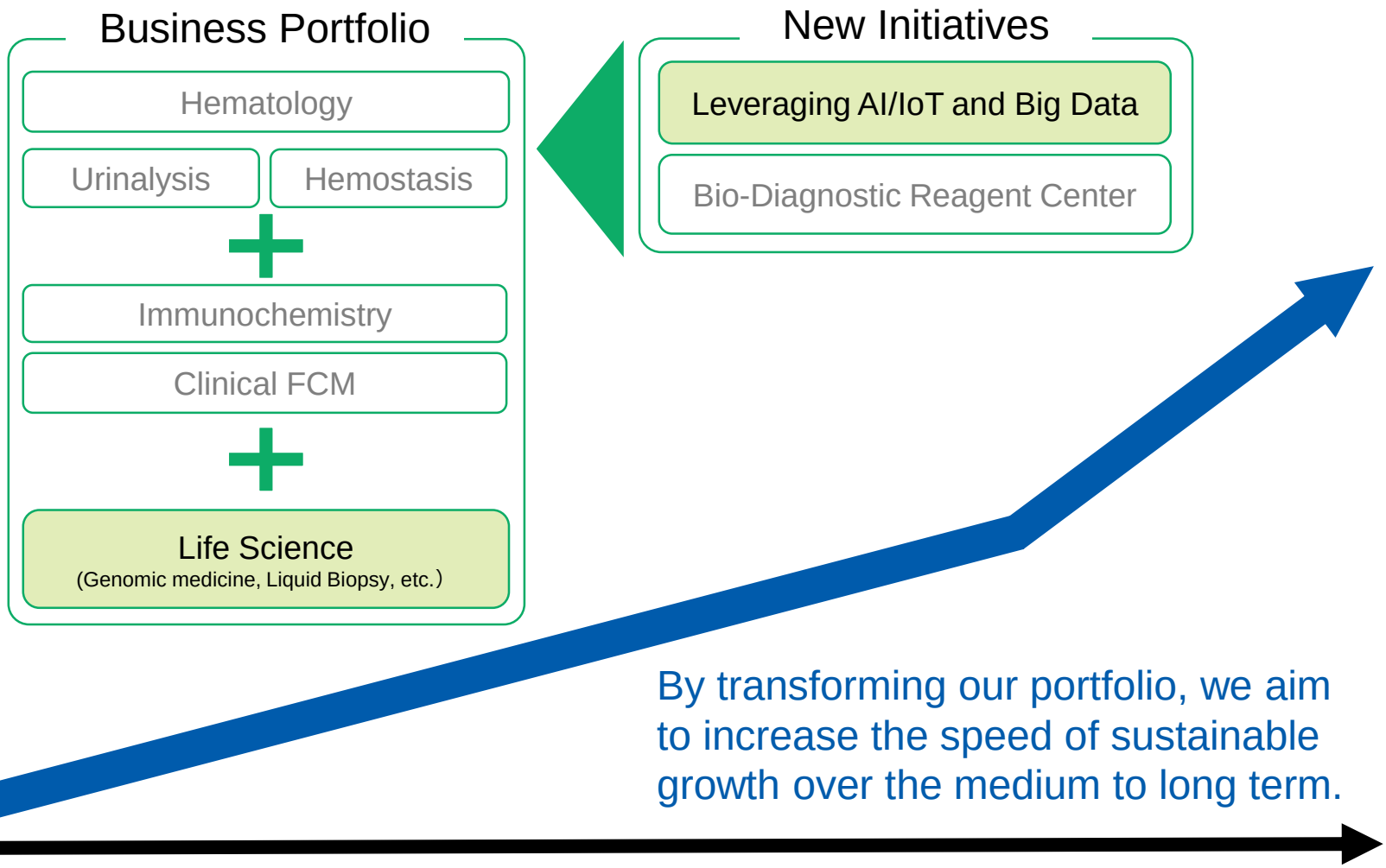
Increase the value added to testing through AI analysis of big data

Leading-edge healthcare x AI/IoT

- Remote monitoring of medical institutions
- Network services to support remote healthcare and preventive medicine
- Development of new diagnostic methods (disease prediction, image analysis), etc.

Provide medical IT solutions in the field of leading-edge healthcare

Today's agenda



2. Technology Strategy Overview and Digital Revolution Initiatives

Kaoru Asano, Member of the Managing Board and
Senior Executive Officer, Senior Managing Director

(1) Technology Strategy Overview

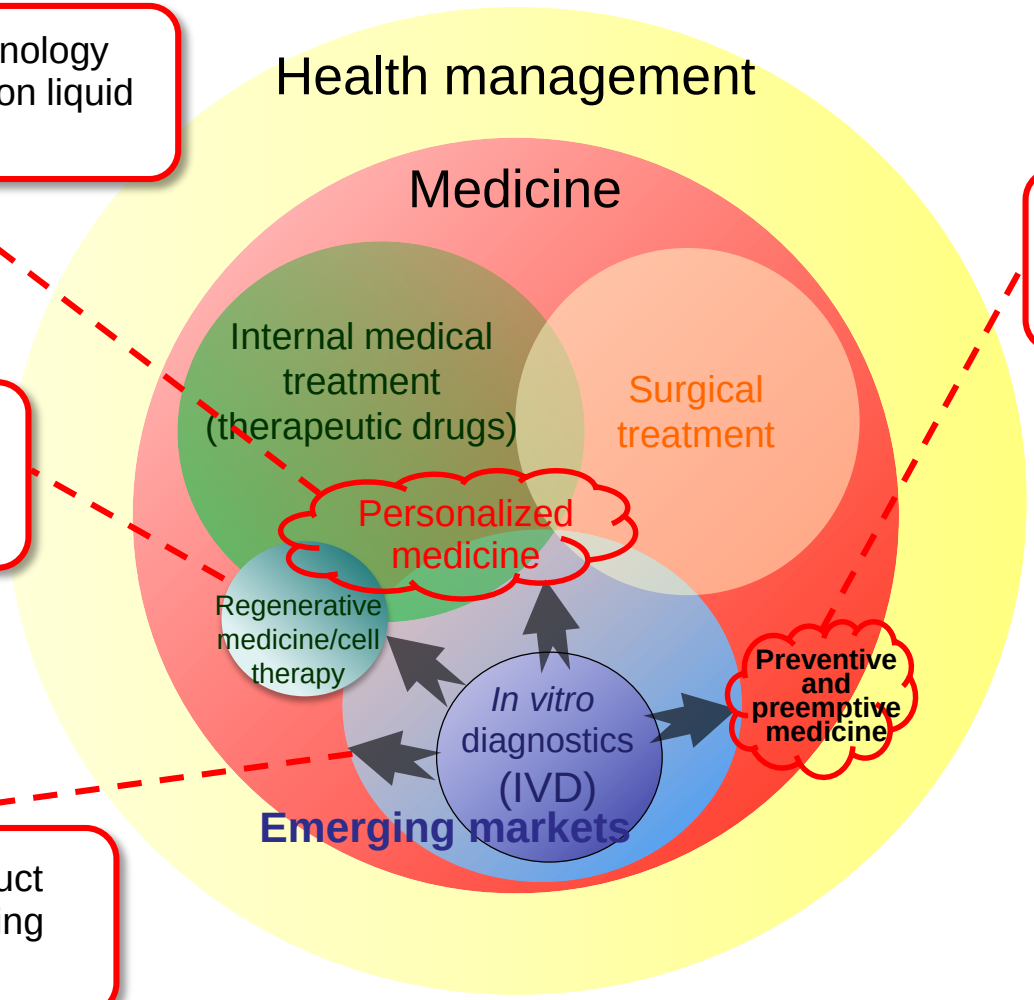
(2) Digital Revolution Initiatives

(1) Technology Strategy Overview: the Healthcare Market

Expansion of technology platforms centered on liquid biopsy

Utilization of technology assets toward new medical technologies

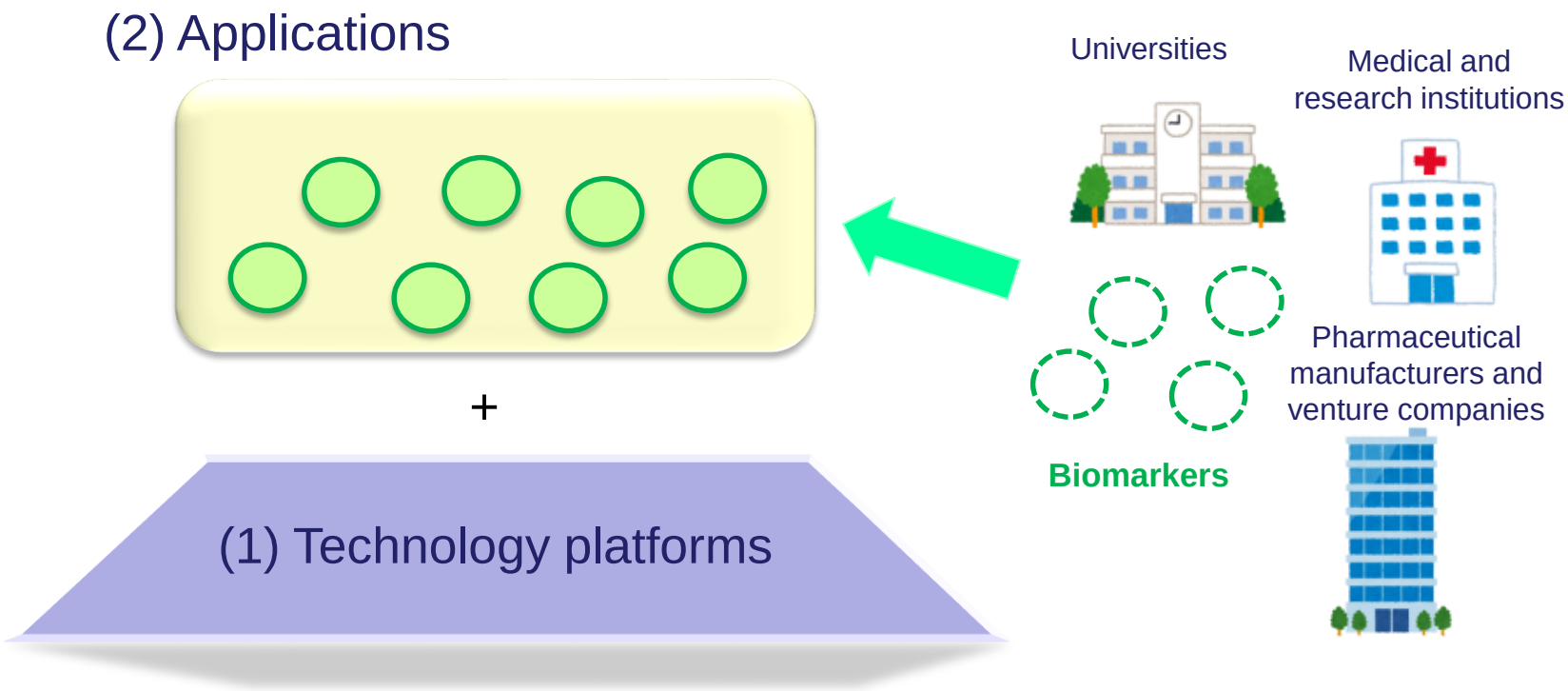
Expansion of product portfolio for emerging markets



Utilization of testing data

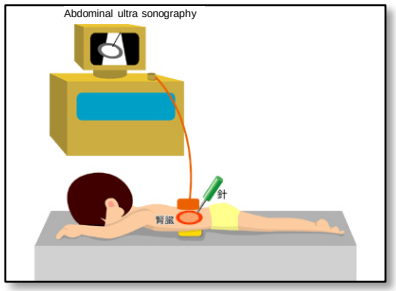
Expansion of Technology Platforms and Open Innovation

First, establish technology platforms and promote open innovation to develop applications with high clinical value



Liquid Biopsy

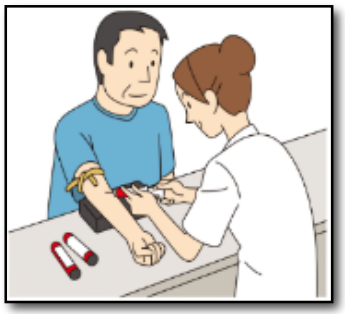
Conventionally



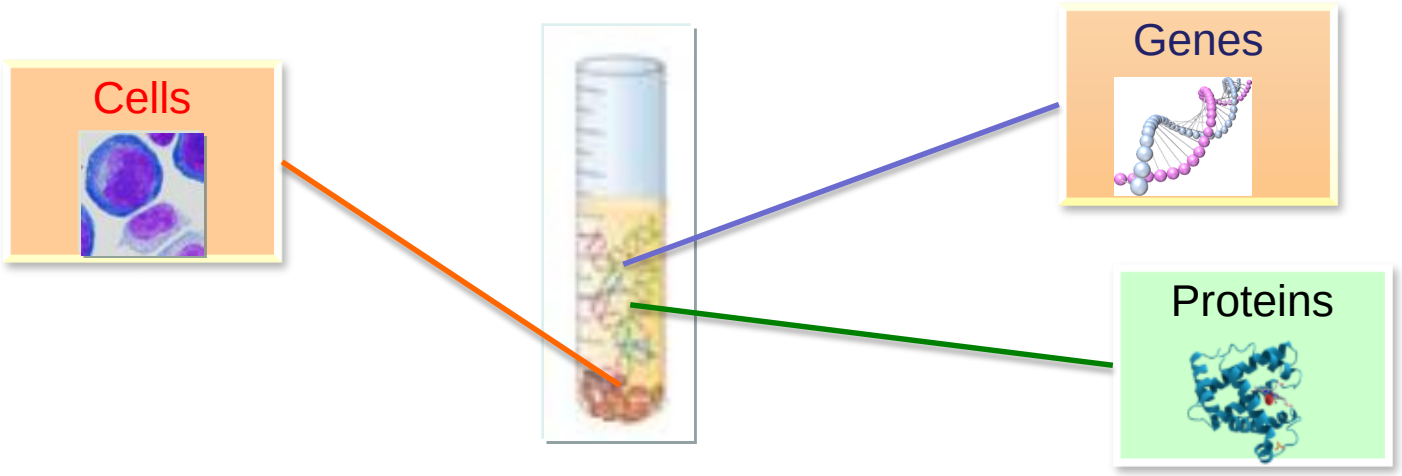
Invasive sample collection of affected organ/tissue

From biopsy to liquid biopsy

Future



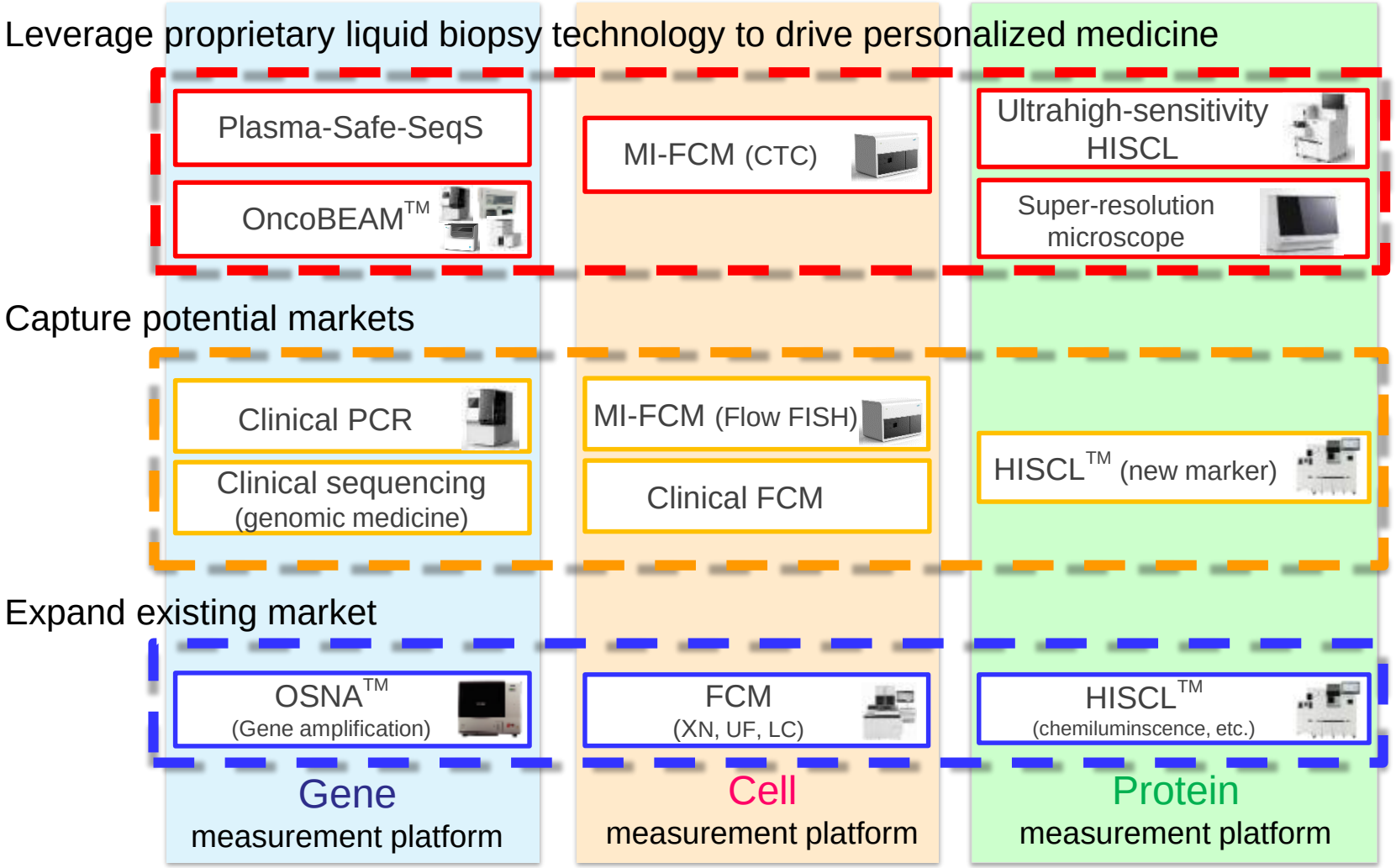
Minimally invasive sample collection of disease-derived components in the blood (bodily fluid)



Detection sensitivity will need to be 100 to 1,000 times higher than conventional methods

Expansion of Technology Platforms

We have completed the technology acquisition phase and are moving on to the commercialization stage.



Market introduction plan of Technology Platforms

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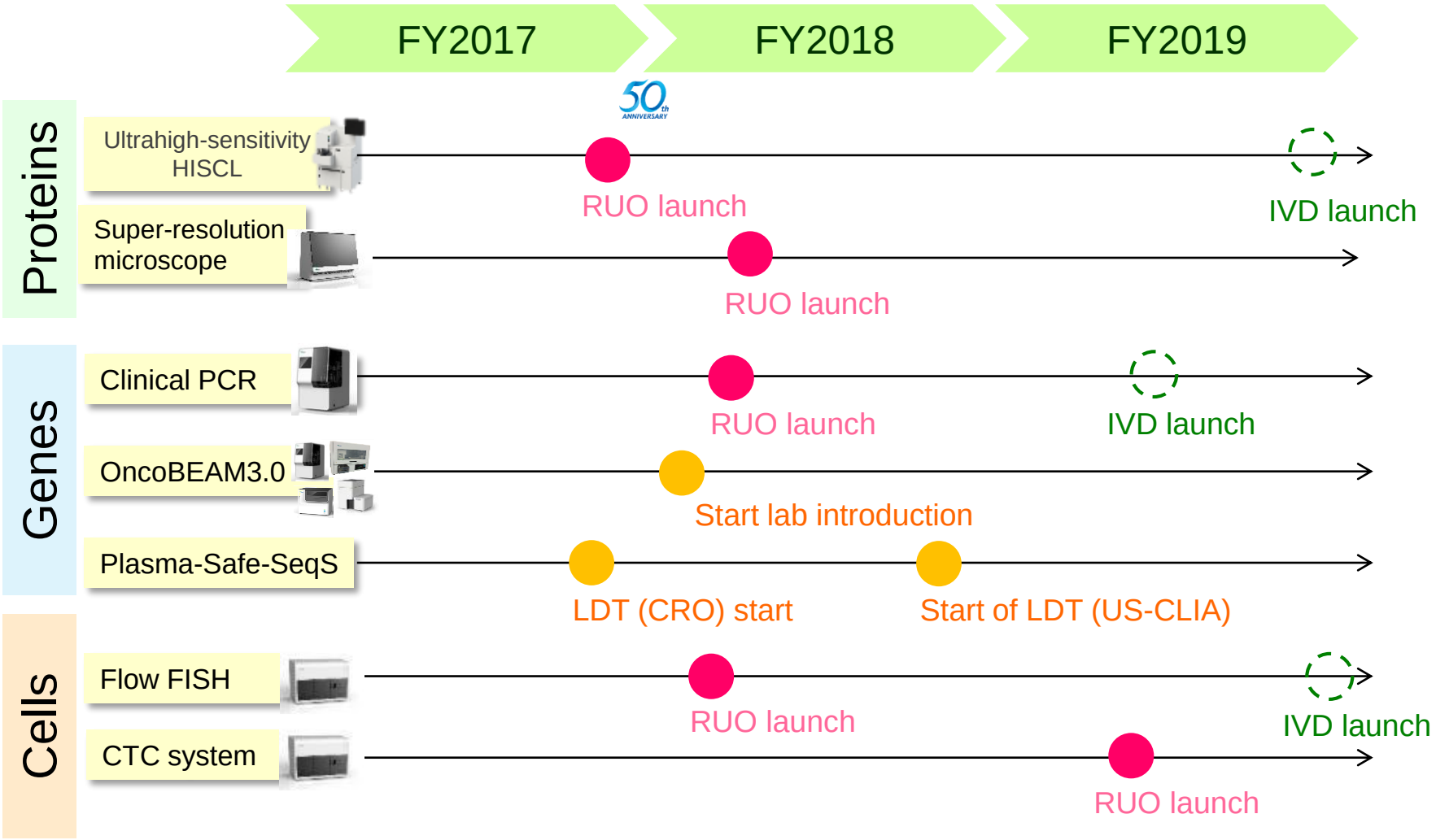
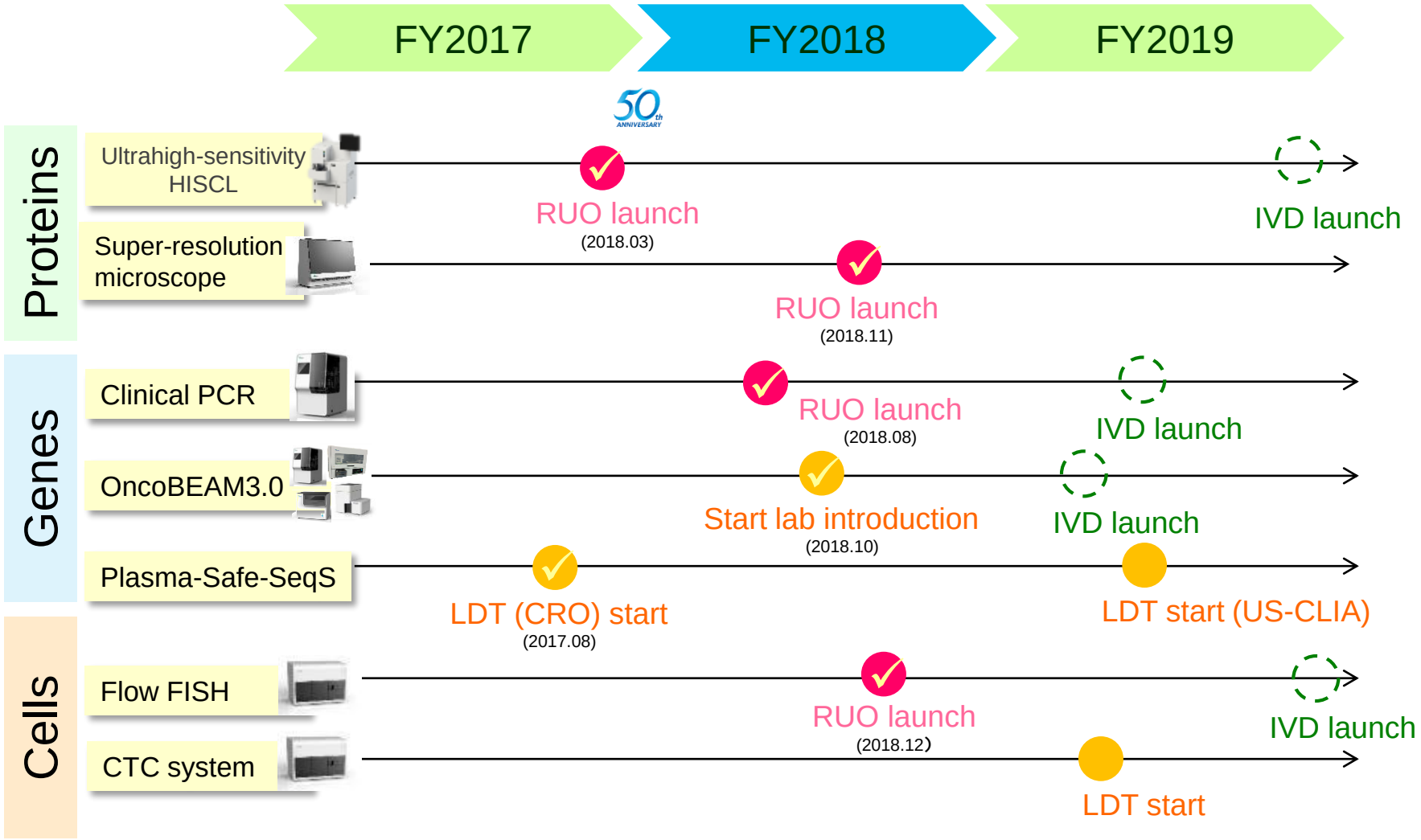


Referenced from the 15th Technology Presentation (March 2018)

Plan for the Expansion of Technology Platforms (update)



Updated from the 15th Technology Presentation (March 2018)

(2) Digital Revolution Initiatives

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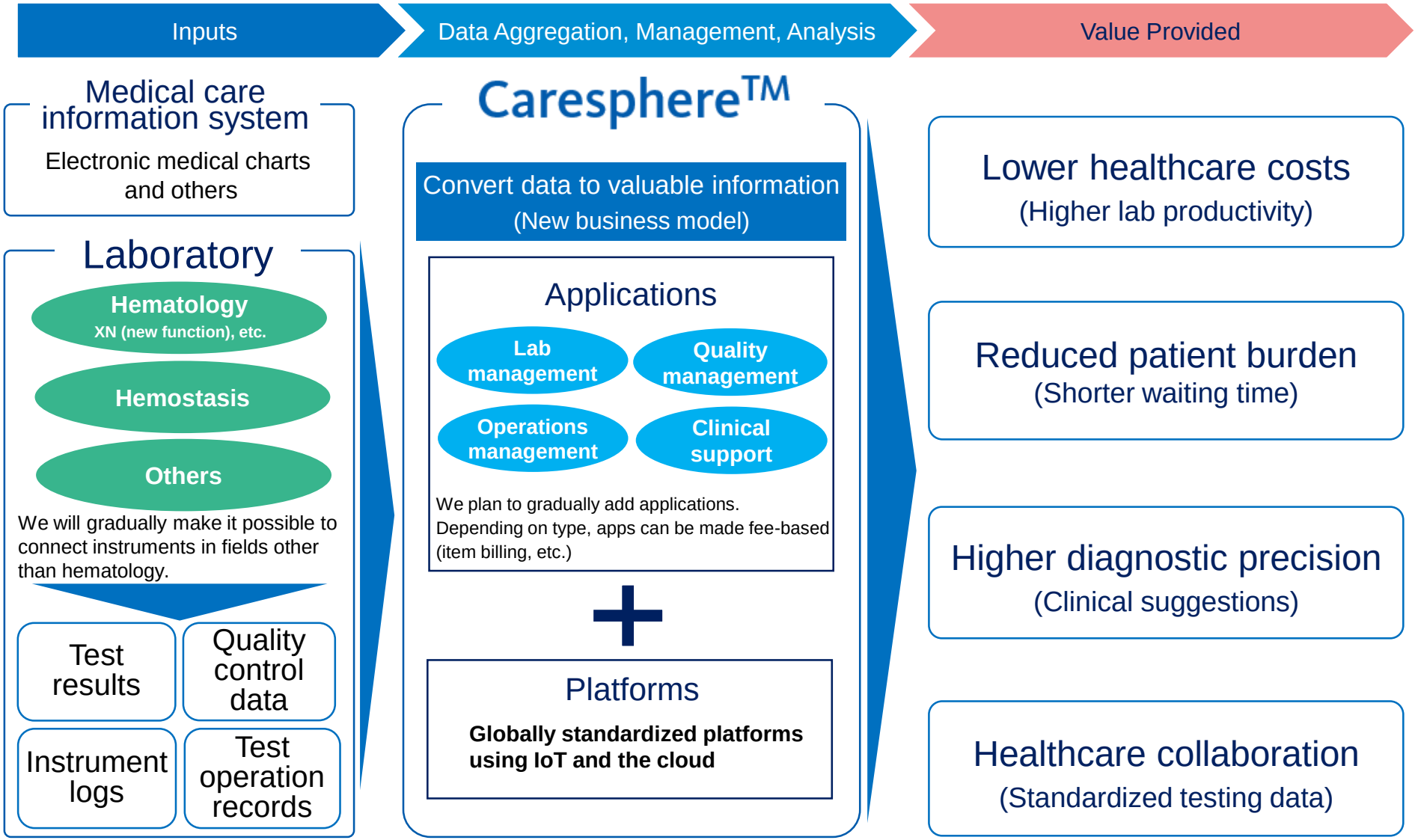
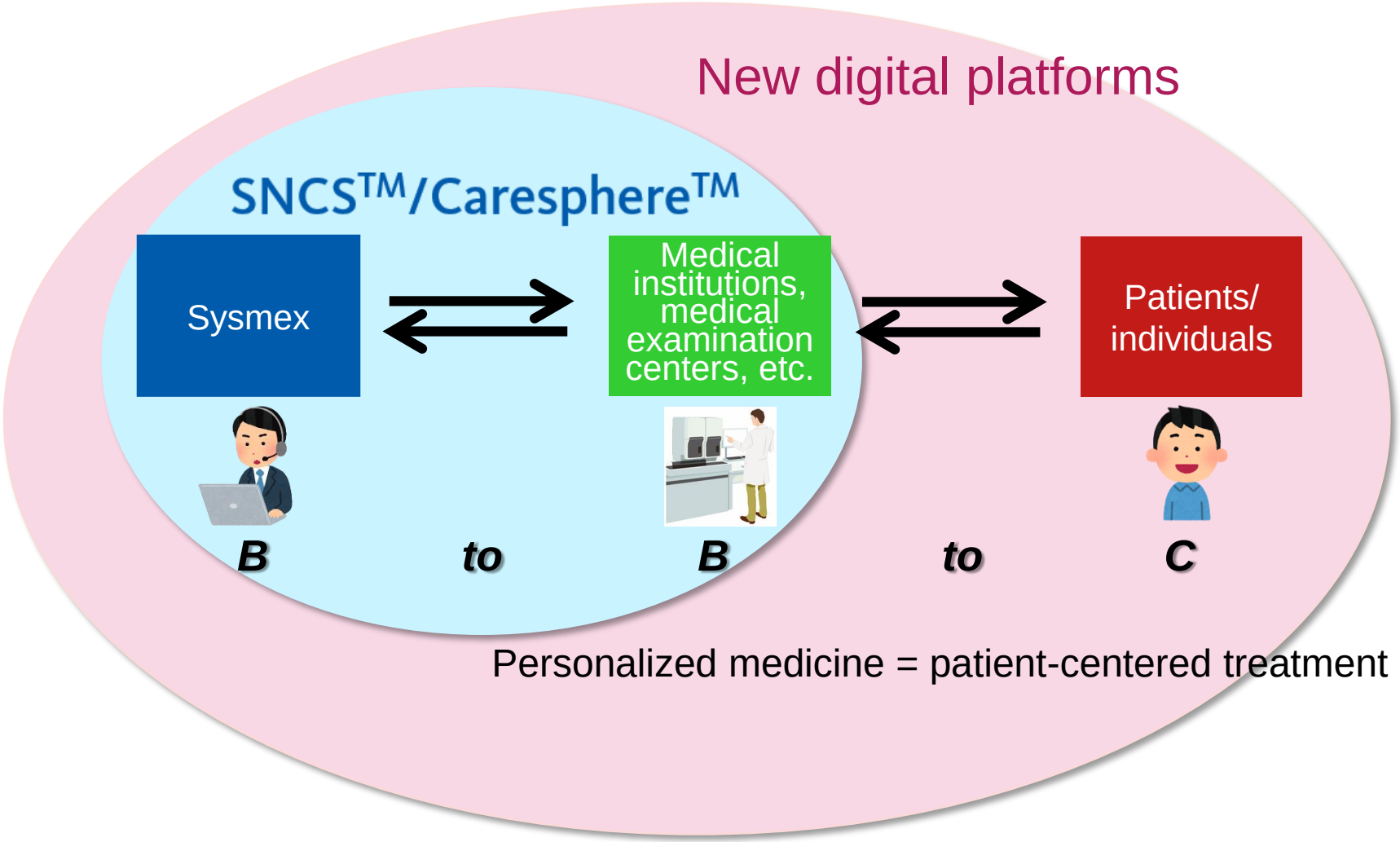


Required Digital Platforms for Establishing Personalized Medicine



Collaboration with OPTiM Corporation

Sysmex is collaborating with OPTiM Corporation in utilizing AI/IoT to develop next-generation medical IT solutions

- ✓ Development of services that will support medical institutions' efforts to enhance efficiency and quality, such as the remote monitoring of medical equipment and the use of AI to respond to inquiries
- ✓ Increase added value of products and services by combining testing data and AI analysis
- ✓ Prediction of disease onset by AI analysis of genomic information and testing data
- ✓ Development of network services to support remote healthcare and preventive medicine

System Configuration

Medicaroid Intelligent Network Support System

Sysmex Solutions

APP APP APP APP

SNCS

Caresphere™

3rd Venders Apps

APP APP APP

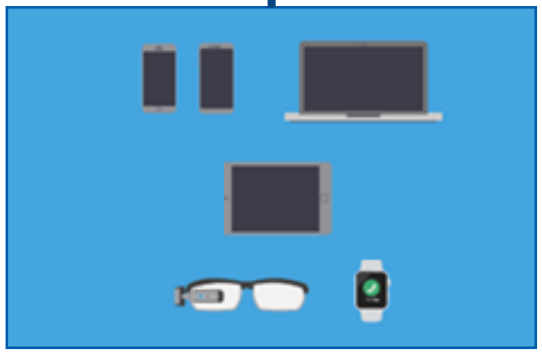
Link

API

OPTiM CLOUD IoT OS

Vision AI | AI Camera | Speech AI | Language AI

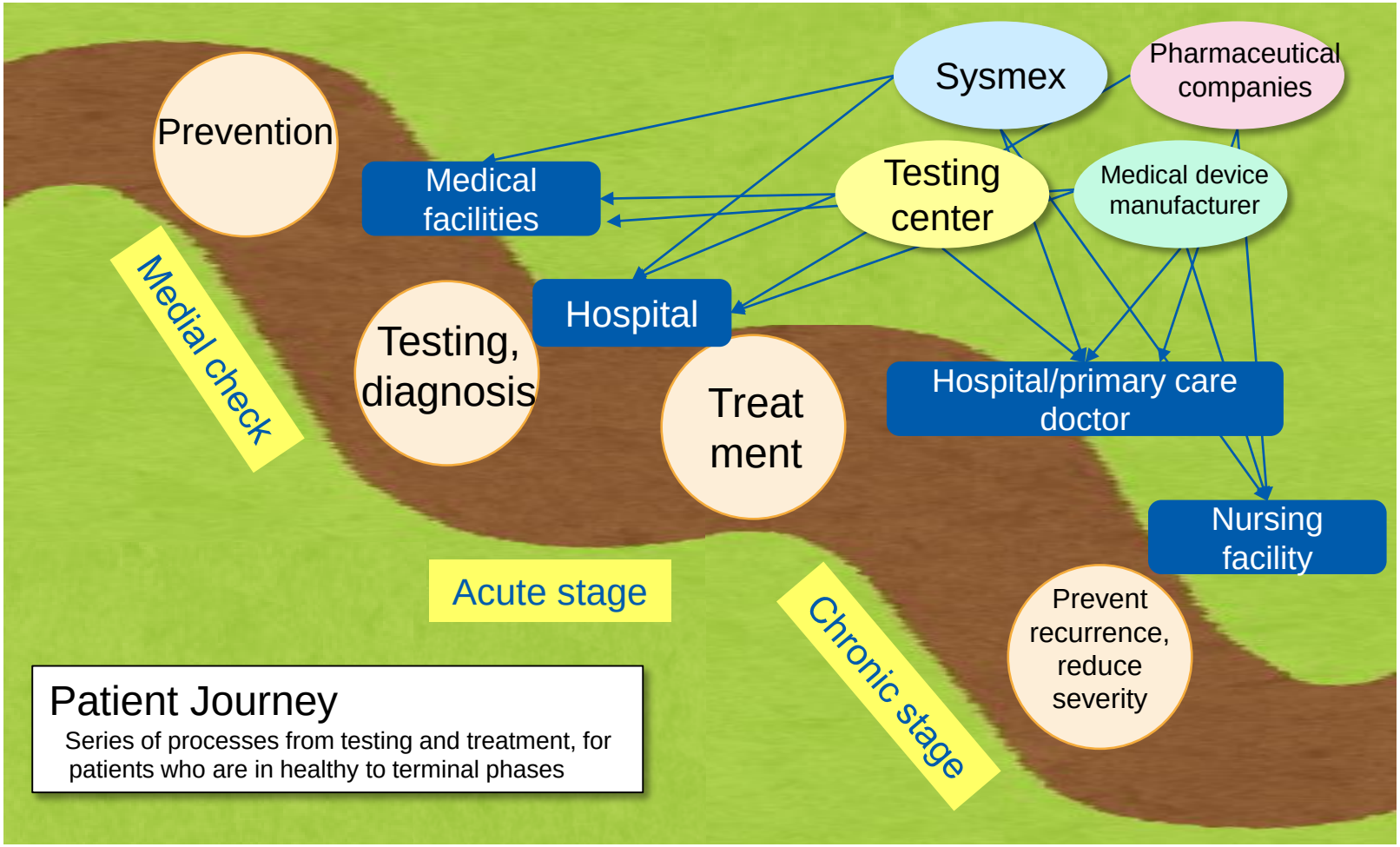
AI tools



Input/output devices

Storage

Eco System for Supporting Patient's Journey



3. Progress Report on Technology Development

Kenji Tsujimoto,
Executive Vice President of
Technology Strategy Division

(1) Genomic Medicine
(2) Liquid Biopsy
(3) New Initiatives

Overview of Cancer Genome Profiling Using the OncoGuide™ NCC Oncopanel System

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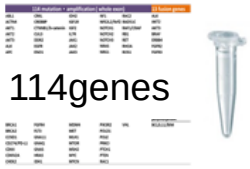
Clinical laboratories that have acquired external certification

OncoGuide™ NCC Oncopanel System

Explain tests, obtain consent, take samples

For patients with same type of solid tumor:
- Tumor tissue (FFPE)
- Non-tumor cells (whole blood)

OncoGuide™ NCC Oncopanel kit



Preparation of library for NGS analysis

NextSeq 550Dx System (Illumina K.K.)

Determine base sequences
- Tumor tissue library
- Library of non-tumor cells

OncoGuide™ NCC Oncopanel Analysis program

- Compare base sequences with the database
- Detect abnormal genes, and annotate with information

Information on candidate therapies

Therapy drugs, candidate clinical studies

Center for Cancer Genomics and Advanced Therapeutics (C-CAT)

Expert panel deliberation

Specialists (oncologists, genome researchers, counselors, etc.) determine treatment methods optimized for individual patients on the basis of abnormal gene information (conducted in core hospitals for cancer genomic medicine)

Explain results, decide treatment

Explain results to patient, select therapy drugs

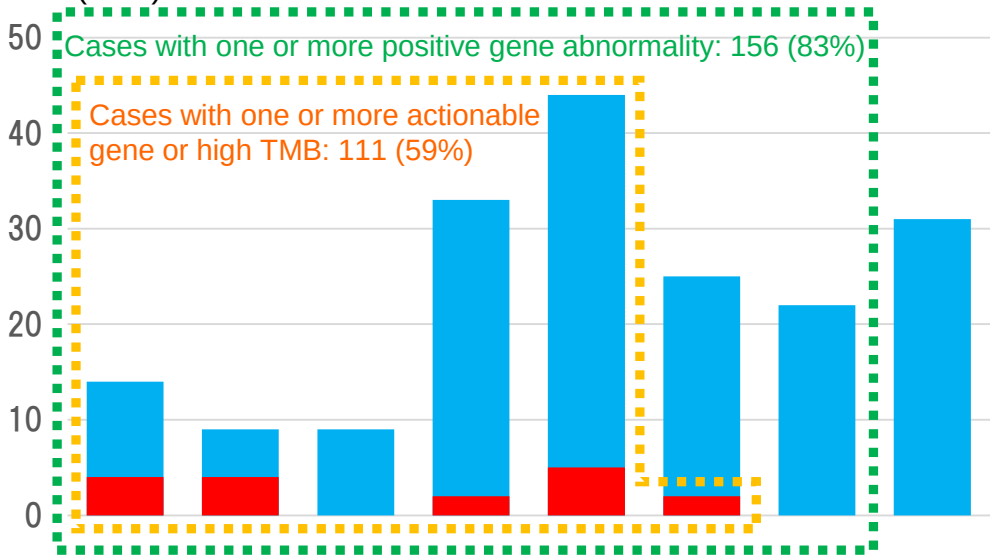
Initiatives Toward the Clinical Introduction of the OncoGuide™ NCC Oncopanel System

Oct. 2015	Opening of the Sysmex Cancer Innovation Laboratory (SCI-Lab), which conforms to international standards, in the National Cancer Center Hospital, aiming toward the clinical introduction of cancer clinical sequencing
May 2016–May 2017	Participation in Phase 2 of the TOP-GEAR Project, led by NCC In charge of clinical sequencing at the SCI-Lab
Feb. 2017	*Sakigake* Designation by the Ministry of Health, Labour and Welfare
Apr. 2018–Mar. 2019 (Registration completed Dec. 2018)	Advanced Medical Care by the National Cancer Center Hospital Lab assay testing conducted at the RIKEN GENESIS Innovation Genome Center (IGC, Kawasaki Office)
Jun. 2018	Application for manufacturing and marketing approval
Dec. 25, 2018	Receipt of manufacturing and marketing approval
Feb. 2019	Start lab assay service as healthcare services to be assessed (*Hyoka-ryoyo*)
From 2019	Promote collaboration with the Center for Cancer Genomics and Advanced Therapeutics

Clinical Research Results Phase II of the TOP-GEAR Project -Abnormal Rate of Actionable Gene-

- Of the 187 cases for which genetic profile information was obtained, genetic abnormalities based on scientific evidence gained through information on administration on humans (actionable abnormalities) were detected in 109 cases (58%).
- If the two cases with high TMB*1 (10/Mb or higher) are also included, the number of cases with actionable abnormalities was 111 (59%).

*1 TMB: Tumor Mutation Burden



Sunami Kuniko, Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting: A hospital-based study, Cancer Science (in press)

	1A	1B	2A	2B	3A	3B	4	No mutation
Patients (cases)	14 (7%)	9 (5%)	9 (5%)	33 (18%)	44 (24%)	25 (13%)	22 (12%)	31 (17%)	187 (100%)
Patients with high TMB (cases)	4	4	0	2	5	2	0	0	17

*2 Evidence level: An indicator of the therapeutic results and efficacy of anticancer drugs. A genetic abnormality for which there exist diagnostic reagents that have received regulatory approval based on scientific evidence gained through information on administration on humans is referred to as “level one.” The number becomes smaller as the level of relevance decreases.

Clinical Research Results Phase II of the TOP-GEAR Project -Drug administration that matches gene abnormality--

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- Drugs that match identified actionable gene abnormalities were administrated in 25 cases.

Drug Type	Type of Cancer	Gene Abnormality	Corresponding Drug
IND	Ovarian cancer	KRAS gene mutation	Pan-RAF inhibitor
IND	Colorectal cancer	KRAS gene mutation	Pan-RAF inhibitor
IND	Colorectal cancer	BRAF gene mutation	Pan-RAF inhibitor
IND	Pancreatic cancer	KRAS gene mutation	Pan-RAF inhibitor
IND	Pancreatic cancer	KRAS gene mutation	ERK inhibitor
IND	Esophageal cancer	FGFR2 gene amplification	FGFR2 inhibitor
IND	Angiosarcoma	MDM2 gene amplification	HDM2 inhibitor
IND	Liposarcoma	MDM2 gene amplification	HDM2 inhibitor
IND	Non-small cell lung carcinoma	High TMB	Immune checkpoint inhibitor
IND	Non-small cell lung carcinoma	High TMB	Immune checkpoint inhibitor
IND	Non-small cell lung carcinoma	RET gene fusion	Alectinib
IND	Breast cancer	HER2 gene amplification	HER2 ADC
IND	Extrahepatic bile duct cancer	HER2 gene amplification	HER2 ADC
IND	Cancer of unknown primary *1	PIK3CA gene mutation	TORC1/ 2 inhibitor
IND	Apocrine adenocarcinoma	FGFR2 gene fusion	FGFR inhibitor
Off-label use	Inflammatory pseudo tumor	ALK gene fusion	Alectinib
Off-label use	Mastocytoma	KIT gene mutation	Imatinib
Off-label use	Non-small cell lung carcinoma	RET gene fusion	Lenvatinib
Off-label use	Histiocytic sarcoma	MAP2K1 gene mutation	Trametinib
Approved drug	Cancer of unknown primary	ALK gene fusion	Alectinib
Approved drug	Non-small cell lung carcinoma	EGFR gene mutation (exon 20 insertion mutation)	Afatinib
Approved drug	Non-small cell lung carcinoma	EGFR gene mutation (rare variant)	Afatinib
Approved drug	Non-small cell lung carcinoma	EGFR gene mutation (rare variant)	Gefitinib
Approved drug	Non-small cell lung carcinoma	ROS1 gene fusion	Crizotinib
Approved drug *2	Malignant melanoma	High TMB	Nivolumab

*1 Unknown primary is diagnosed as lung.

*2 Originally an approved drug that does not require confirmation of genetic abnormality, but this drug was administrated for prospective therapeutic effect.

Lab Assay service under advanced medicine at RIKEN GENESIS

RIKEN GENESIS innovation genome center is a clinical laboratory with external certification, allowing it to conduct cancer genome profiling tests.

- RIKEN GENESIS handling lab assay for advanced medical care conducted by the National Cancer Center Hospital (April 2018–March 2019)
- Completed analysis of 317 cases at 49 core and liaison hospitals for cancer genomic medicine (As of January 31, 2019)
  (Registration of 343 cases completed in December 2018)
- Reinforcing the implementation system in preparation to handle lab assay when covered by healthcare insurance

Features of the OncoGuide™ NCC Oncopanel System

(1) Conducted entirely in Japan

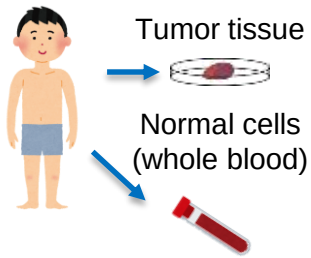
- Reporting and specialized helpdesk provided in Japanese
- Providing patients, clinical physicians, pathology departments and laboratories with the detailed services and support Sysmex has cultivated

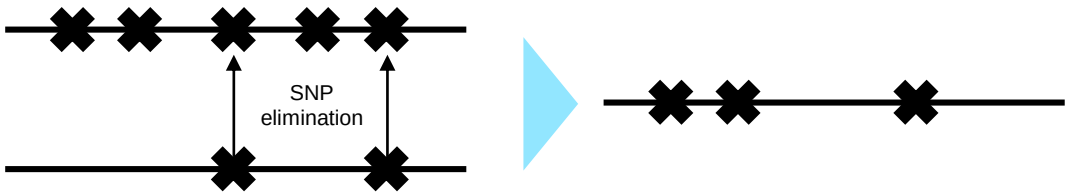
  Example: Possible to accept resubmitted samples (once) even caused by low quality of samples. Even if DNA quantities are insufficient, they can be returned as reference values.

(2) Highly reliable detection of somatic gene mutations through matched-pair analysis

- A highly precise tumor mutation burden (TMB) is calculated, allowing differentiation between somatic gene mutations and germline gene mutations

Analysis by referring to sequences in healthy cells of the same individual (matched-pair analysis)





Features of the OncoGuide™ NCC Oncopanel System

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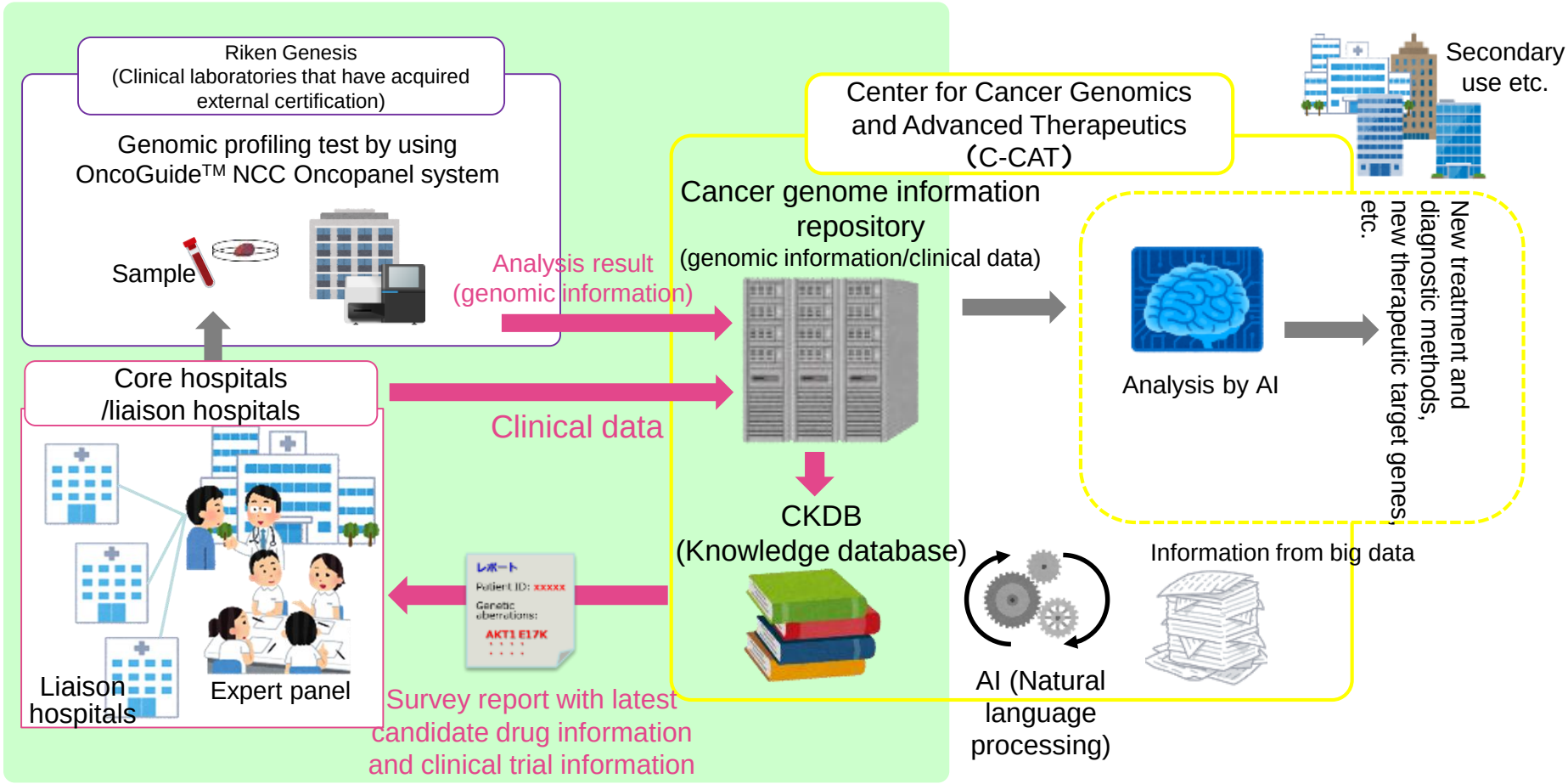
(3) By linking with the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), creates treatment opportunities benefiting from the most recent knowledge

C-CAT: This center accumulates and stores nationwide information regarding genomic medicine and creates mechanisms that enable discovery of new medical treatments.

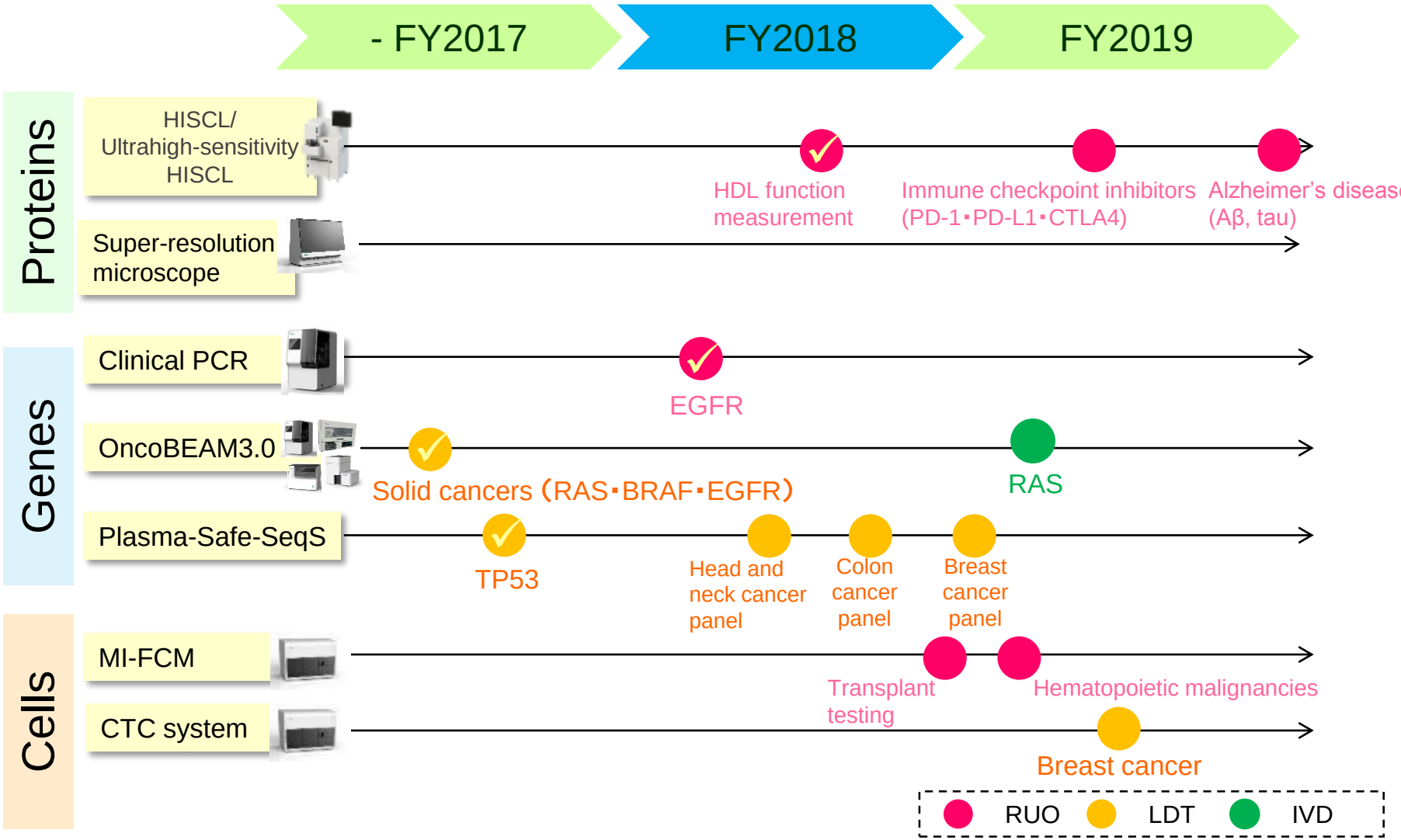


3. Progress Report on Technology Development

Tomokazu Yoshida,
Executive Officer,
Executive Vice President of
Central Research Laboratories

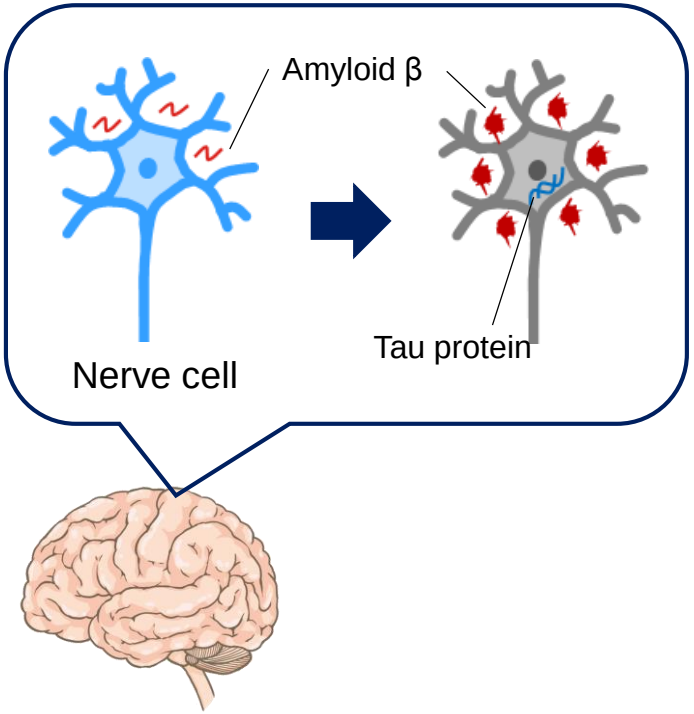
(1) Genomic Medicine
(2) Liquid Biopsy
(3) New Initiatives

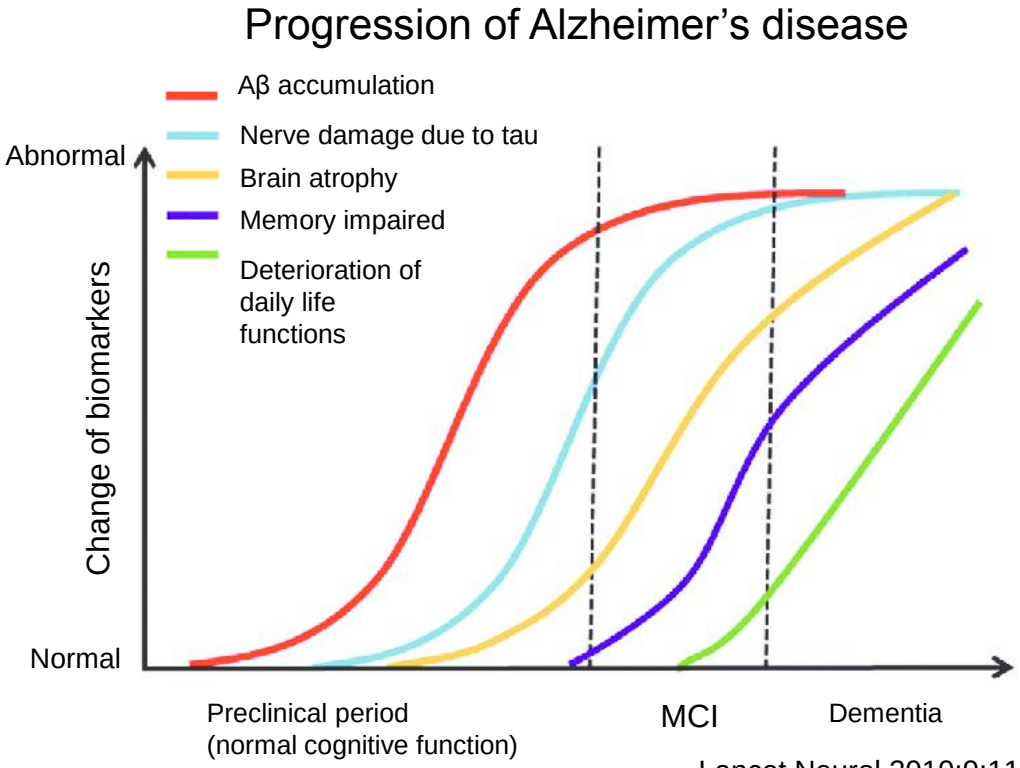
Expanding Applications



(1) Protein Measurement Platform / Application
Initiatives Targeting Alzheimer's Disease

Important focus is early detection of the accumulation of amyloid β (Aβ) and tau in the brain





Lancet Neurol 2010;9:119-128

(1) Protein Measurement Platform / Application
Initiatives Targeting Alzheimer's Disease

Post-mortem brain: confirmed diagnosis → imaging/cerebrospinal fluid → cerebrospinal fluid/blood → blood

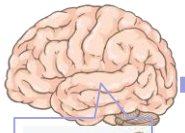
- Possibility of diagnosis with imaging and cerebrospinal fluid BM (Aβ, tau, etc.)
- Possibility of diagnosing dementia using a BM (Aβ, tau, neurofilament) profile

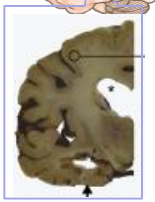
2000 — 2010 — 2018

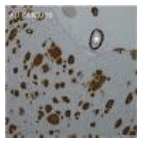
MRI/fMRI imaging

Cerebrospinal fluid protein measurement

Blood protein measurement



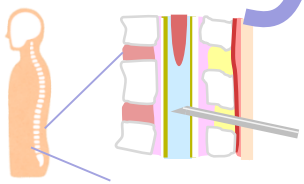




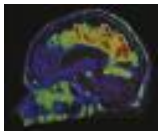
Source: Disease Models & Mechanism (2018) 11

Pathological section

Cerebrospinal fluid

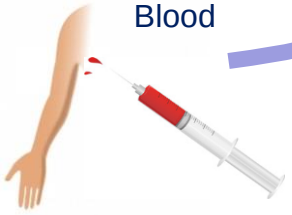


Amyloid/tau imaging



Source: Disease Models & Mechanism (2018) 11

Blood



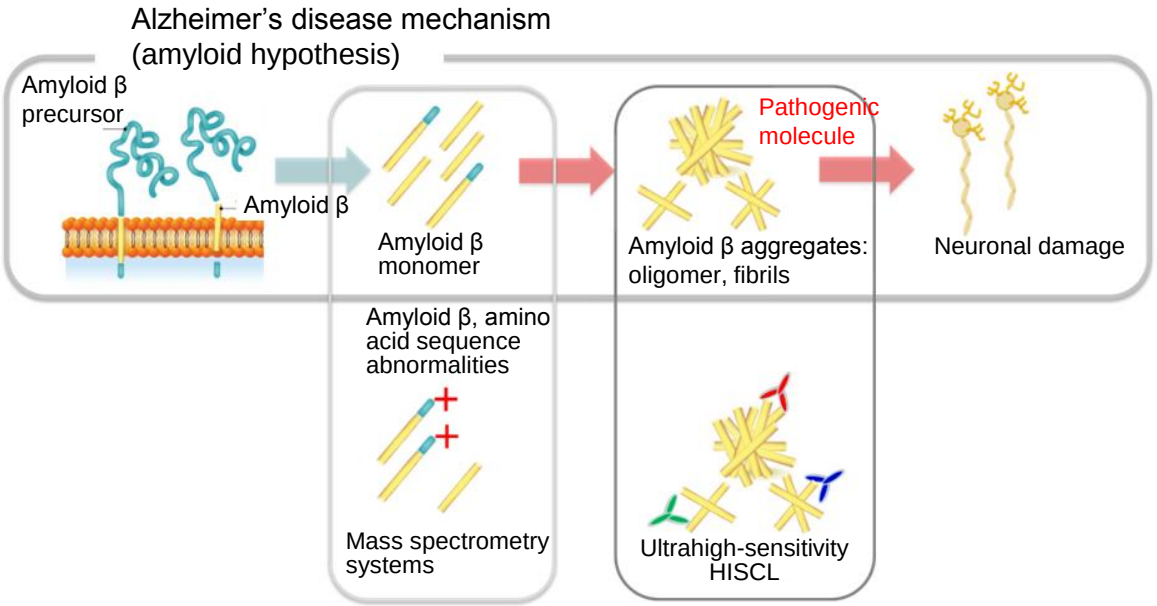
- Confirmed concordance between circulating Aβ mass and Aβ imaging

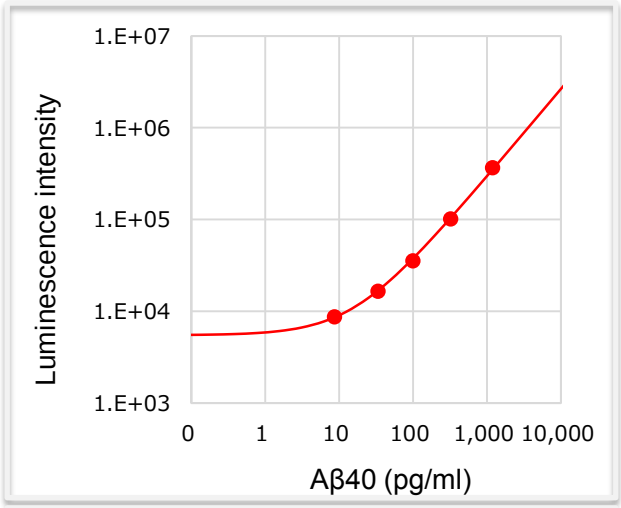
HISCL/
Ultrahigh-sensitivity HISCL
(Aβ, tau)

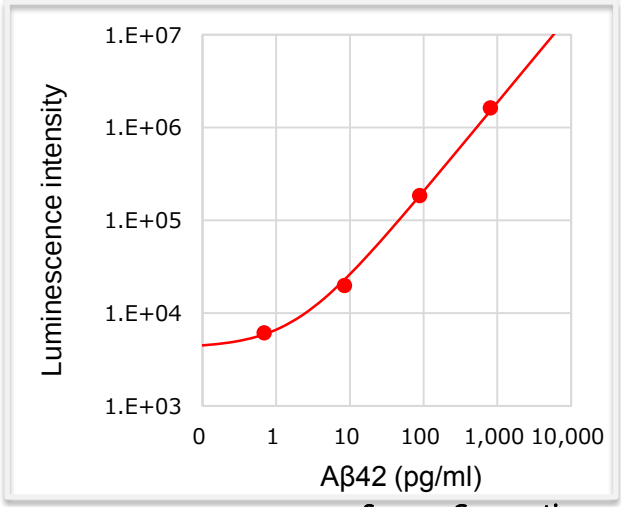
- Cerebrospinal fluid BM (Aβ, tau) measurement system designated a breakthrough device (FDA)

(1) Protein Measurement Platform / Application
Initiatives Targeting Alzheimer's Disease

Promoting multiparameter HISCL/ Ultrahigh-sensitivity HISCL for broad-based response toward measurement of related biomarkers







HISCL/
Ultrahigh-sensitivity HISCL

Development complete

- Aβ40
- Aβ42
- Tau

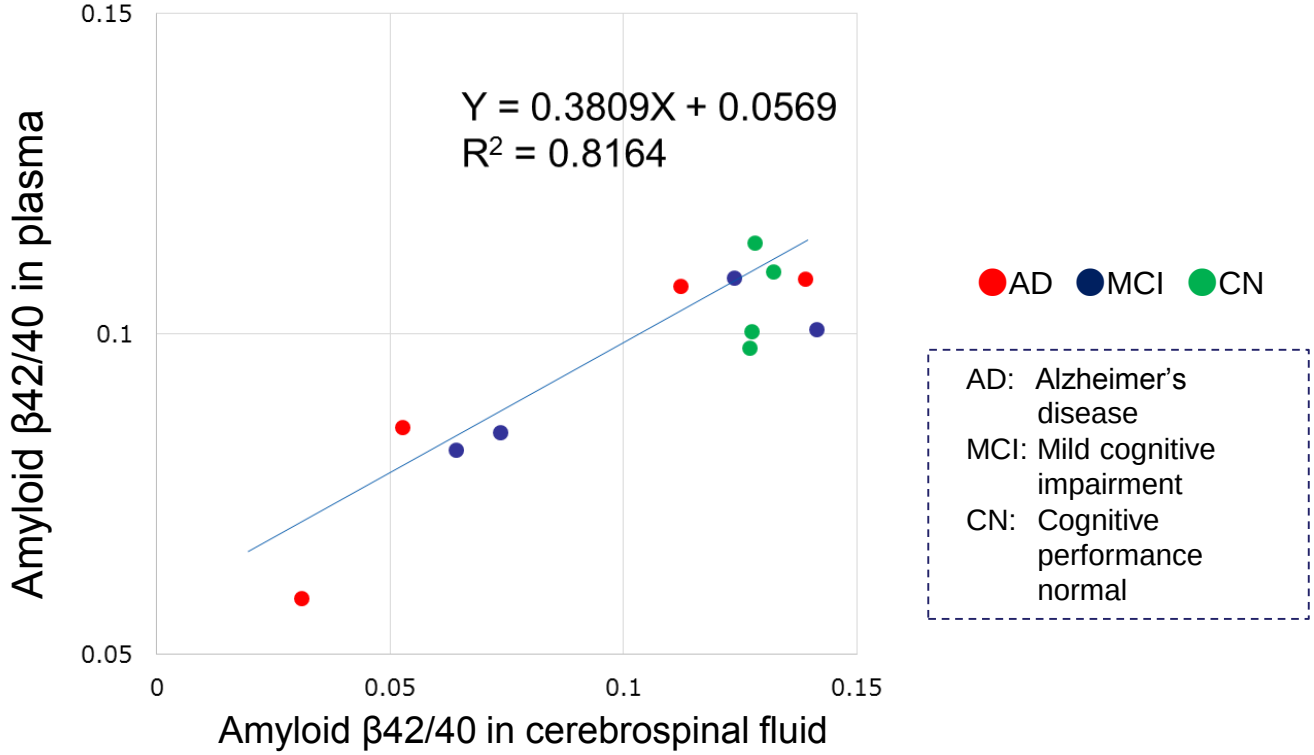
[Under development]

- Phosphorylation Tau
- Neurofilaments light chain
- Tau polymer

(1) Protein Measurement Platform / Application
Initiatives Targeting Alzheimer's Disease

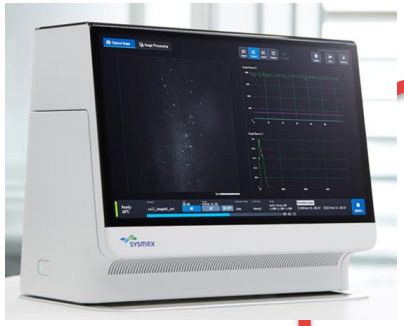
Confirmed concordance between Aβ42/40 in plasma and cerebrospinal fluid in the human body using HISCL

Possible to determine the status of brain and cerebrospinal fluid by observing the blood



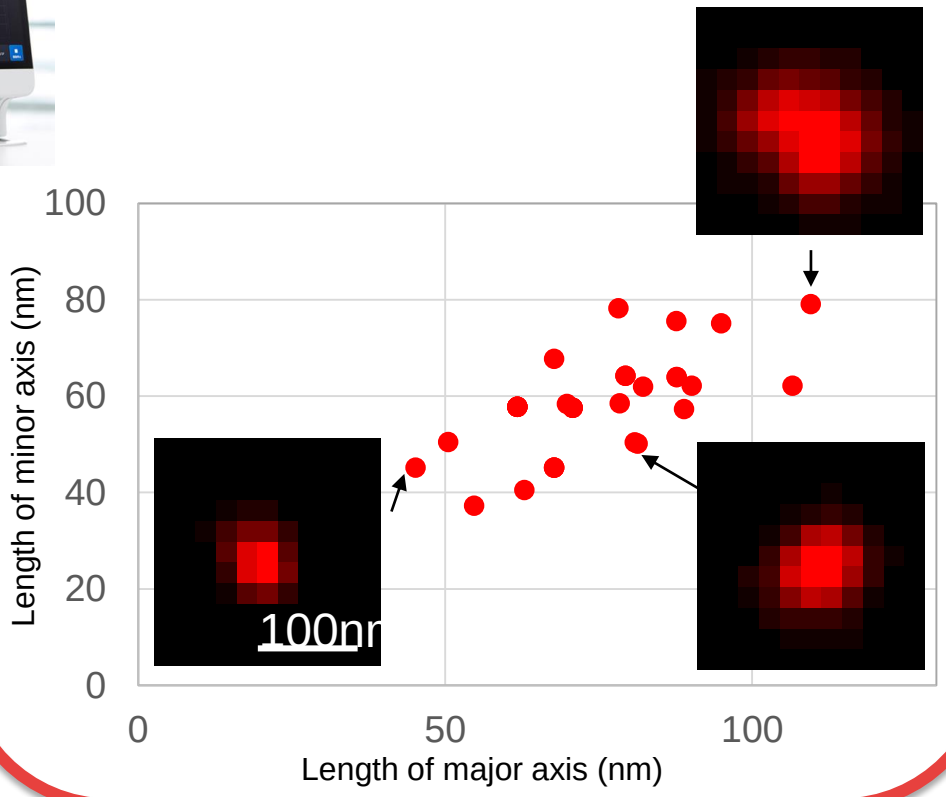
In the future, we aim to validate availability as a prescreening of amyloid PET and create new clinical usefulness by establishing multi-parameter measurement.

(1) Protein Measurement Platform / Application
Initiatives Targeting Alzheimer's Disease

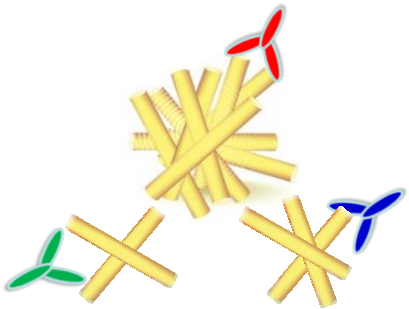


Super-resolution microscope (launched in November 2018)

Cerebrospinal fluid of a patient with dementia



Amyloid β structural abnormalities



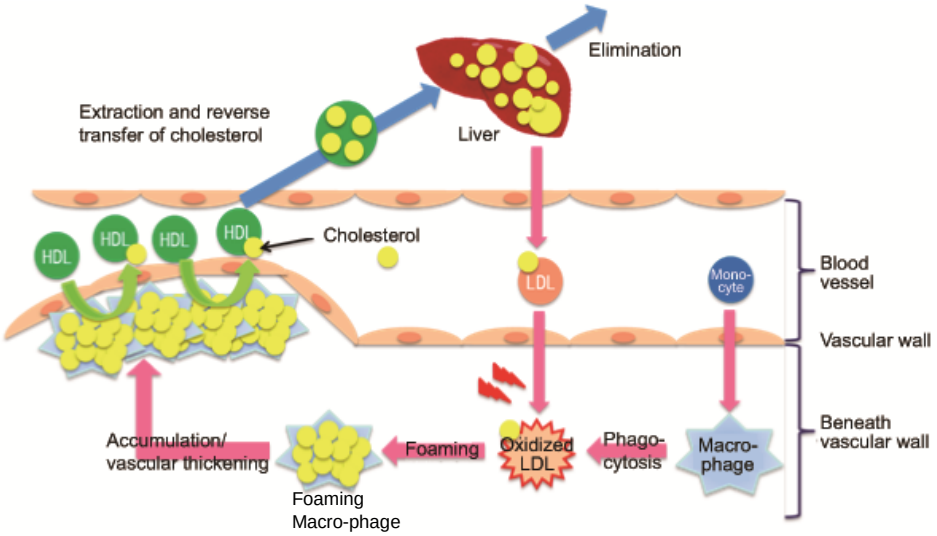
Planning to start analyzing blood samples of patients with dementia from 2019

HDL Function Assay

Development of diagnostic system for CVD risk evaluation with HDL function assay

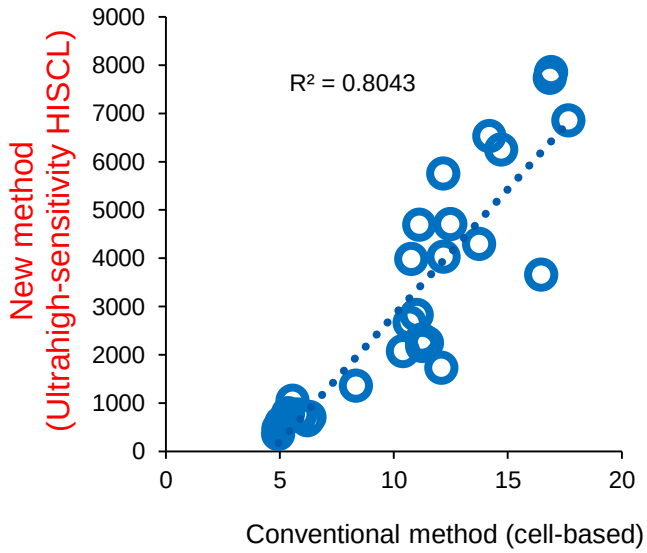
HDL function is a promising new biomarker for CVD risk assessment.

(Khera et al. Jan 13, 2011, *New England Journal of Medicine*)



[Major issues]
Conventional method requires long assay time and specialized equipment for cultured cells and radioisotope label.

Measurement by Ultrahigh-sensitivity HISCL



Good correlation with conventional method

(1) Protein Measurement Platform / Application
HDL Function Assay

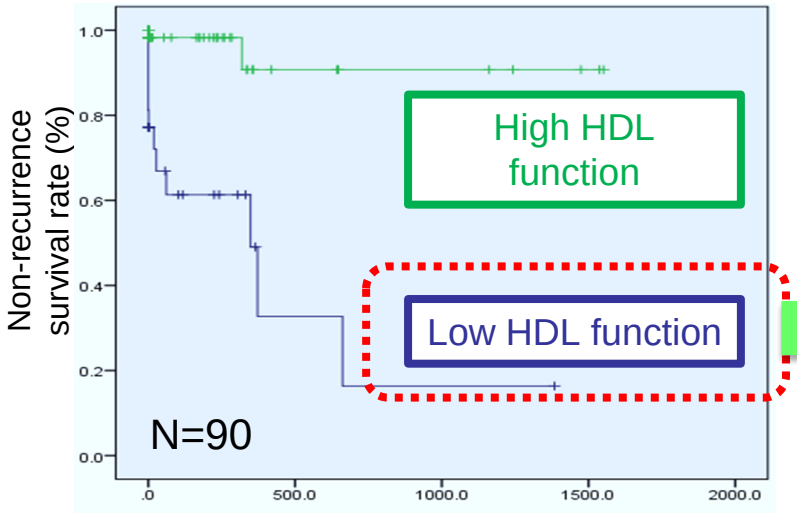
Association with prognosis after CAD treatment
(Collaborative study with Kobe Univ.)

Catheter treatment

20-30% recurrence rate

\+

HDL function assay



More aggressive intervention is needed

Potential options
- Diet therapy
- Exercise therapy
- Drugs therapy
  - Statins
  - Fibrates
  - New drugs to improve HDL function

J Atheroscler Thromb 2013 ;20: 708–16
Biochimie 2013; 95: 1278–87

* Patients with catheter treatment
  ~300,000/y (Japan)
  ~1,000,000/y (US)

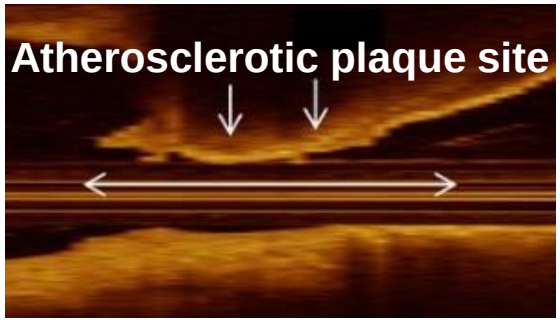
64th Japanese College of Cardiology

HDL Function Assay

Association with vulnerable plaque size

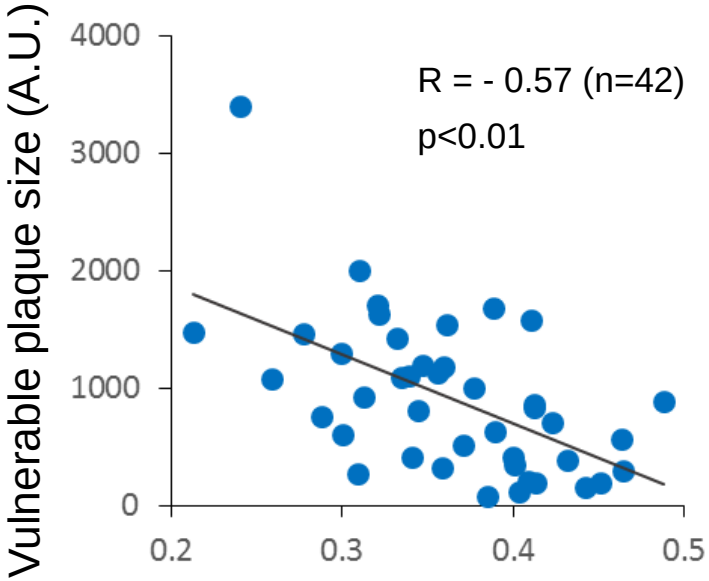
（collaborative research with Kobe Univ.）

OCT angiography of vulnerable plaque



Unstable plaque in a patient with a history of cardiovascular disease

64th Japanese College of Cardiology



HDL function（new method）

Low activity → High activity

- Comprehending the patient's clinical state by combination with diagnostic imaging
- Risk prediction of plaque size change

→ Creation of new therapeutic opportunities

Plasma-Safe-SeqS Technology

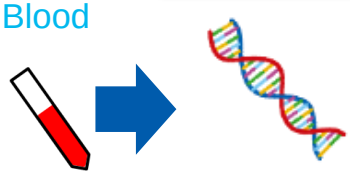
Plasma-Safe-SeqS technology for detection of rare genes in blood

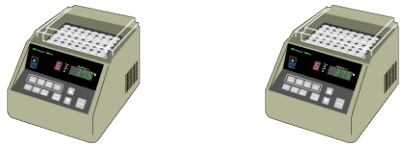
riken genesis

Handled at the RIKEN GENESIS Innovation Genome Center

Sample preparation	Pretreatment		Measurement	Analysis
DNA extraction	1st PCR	2nd PCR	NGS	Software

Blood

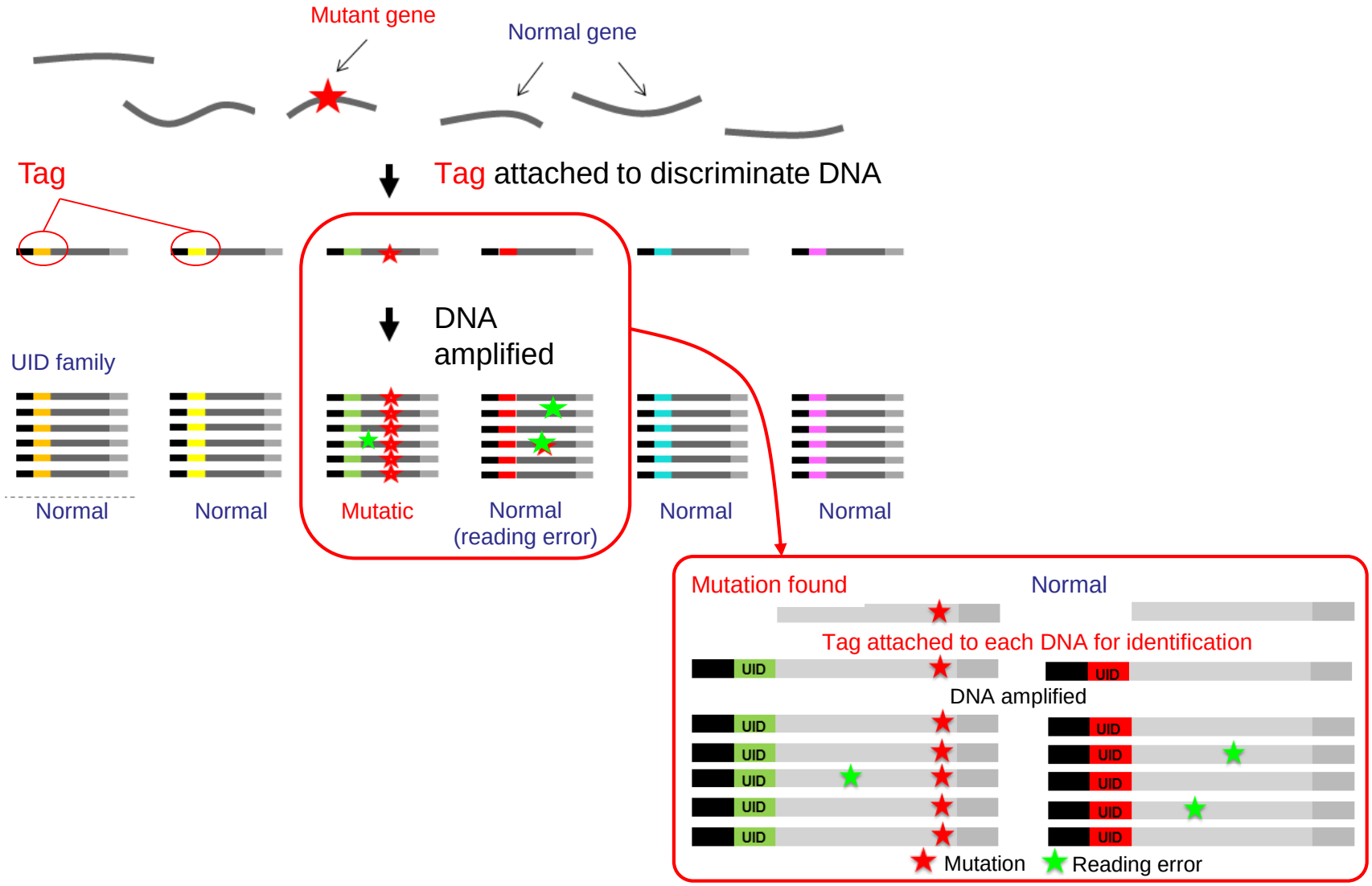




Analysis results of circulating tumor DNA mutations

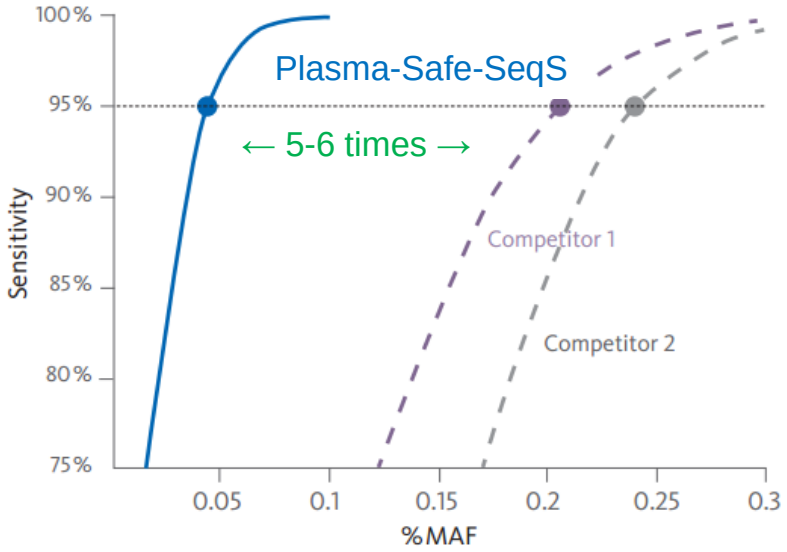
Specialized reagent supplied by Sysmex Inostics

(2) Gene Measurement Platform / Application
Plasma-Safe-SeqS Technology

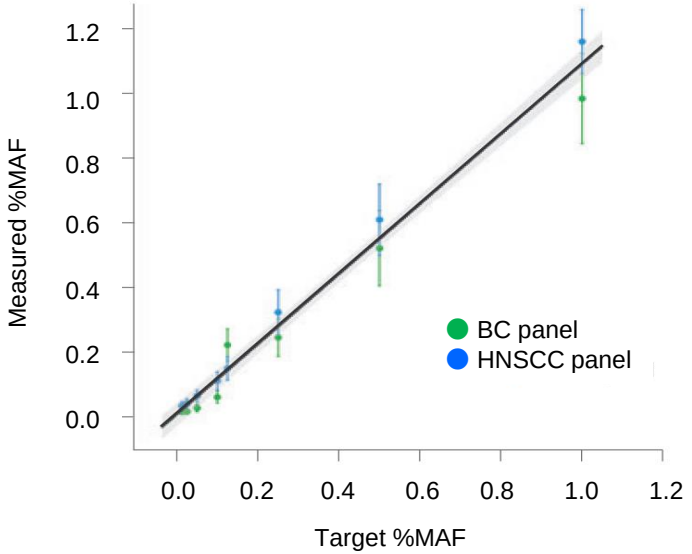


(2) Gene Measurement Platform / Application
Plasma-Safe-SeqS Technology

5–6 times higher sensitivity than competitors



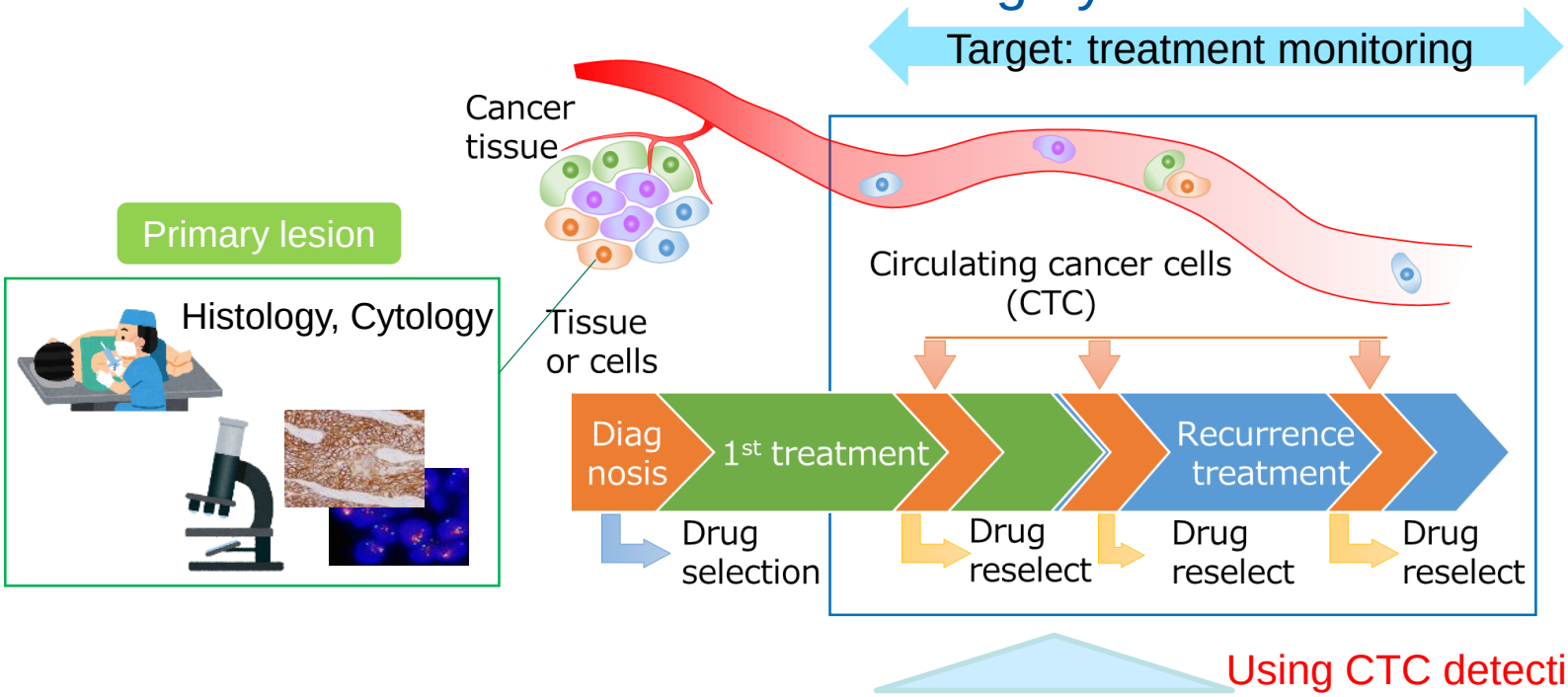
Possible to accurately detect low-frequency mutations



Ongoing development and start of CRO/LDT services for head and neck cancer, colon cancer, and breast cancer panels

(3) Cell Measurement Platform / Application
Circulating Tumor Cell (CTC) Detection

Realization of cancer monitoring by CTC detection

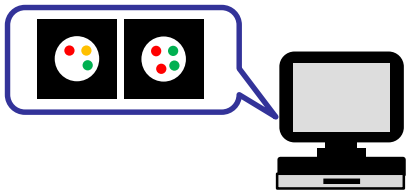


Using CTC detection system


Cell separation unit


FISH reagent (for CTCs)


MI-FCM


CTC software

Circulating Tumor Cell (CTC) Detection

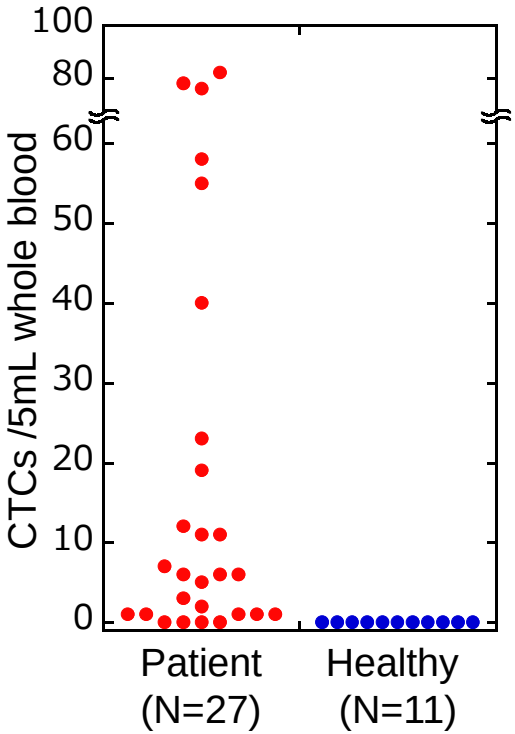
Successful CTC detection using clinical specimens

■ Clinical evaluation results

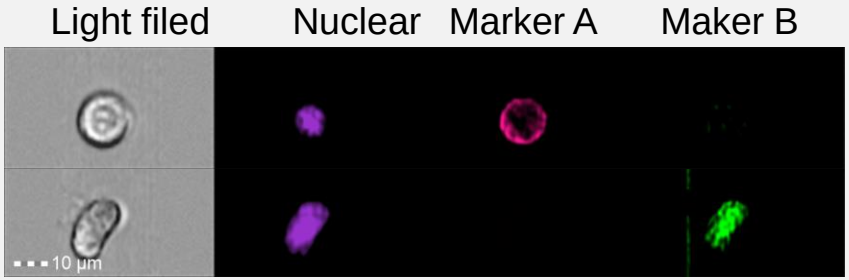
5ml of peripheral blood from patients with recurring, metastatic breast cancer*

※Stage4

5ml of peripheral blood from healthy women



CTC image sample



We continue working with the National Cancer Center to evaluate clinical specimens.
In fiscal 2019, we plan to begin offering a lab assay service.

(3) Cell Measurement Platform / Application Regenerative Medicine: Immune Compatible Test for Allotransplantation

Development of new immune compatible test by detecting immune synapse

Select suitable donor in allotransplantation → Suppress side effect, Decrease usage of immunosuppressant

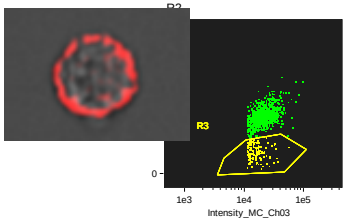
MI-FCM

Immune reaction detection

High compatibility

Lymphocytes

Donor cells

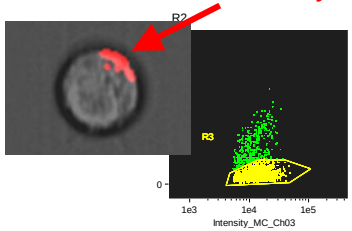


Immune synapse

Low compatibility

Lymphocytes

Donor cells

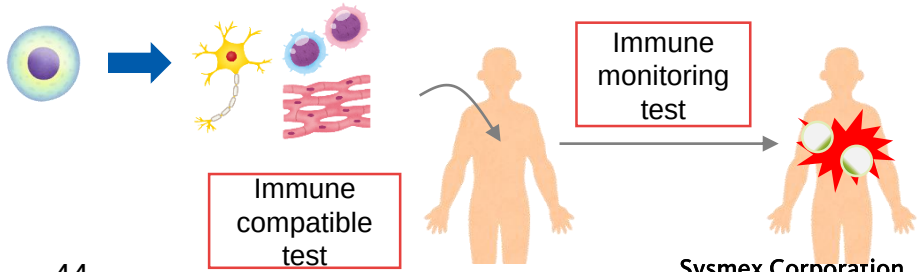


sysmex

Development of tests for side effect prediction and post-transplantation treatment using patient blood and donor cells

Collaboration research with HEALIOS, Sumitomo Dainippon Pharma and CiRA

iPS cells → Various cells and organs



3. Progress Report on Technology Development

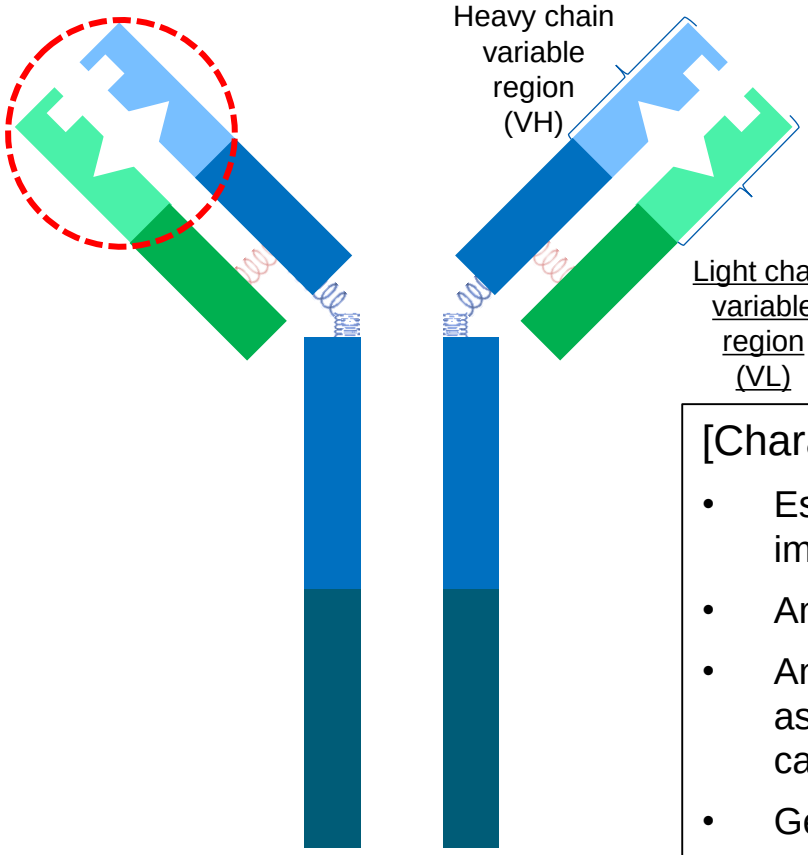
Kenji Tsujimoto,

Executive Vice President of
Technology Strategy Division

(1) Genomic Medicine
(2) Liquid Biopsy
(3) New Initiatives

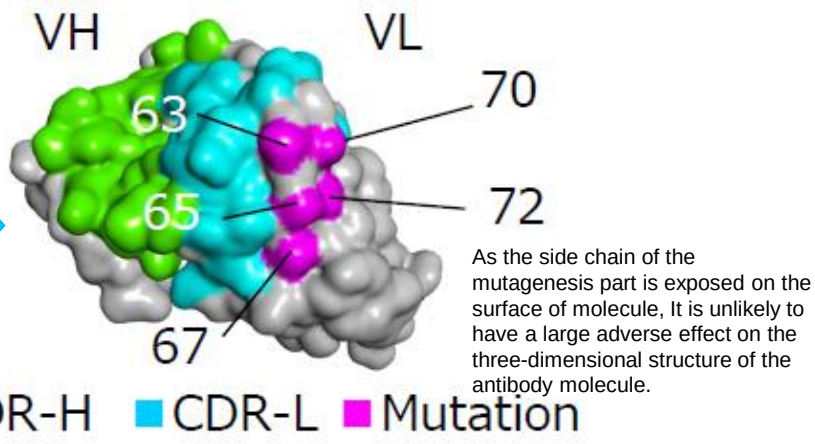
Sysmex's Antibody Affinity Modification Technology

Variable regions→CDR (Complementarity Determining Region) forms binding site by directly contacting with antigen + framework region



Structure of the antibody molecule

Image of substitution site



As the side chain of the mutagenesis part is exposed on the surface of molecule, It is unlikely to have a large adverse effect on the three-dimensional structure of the antibody molecule.

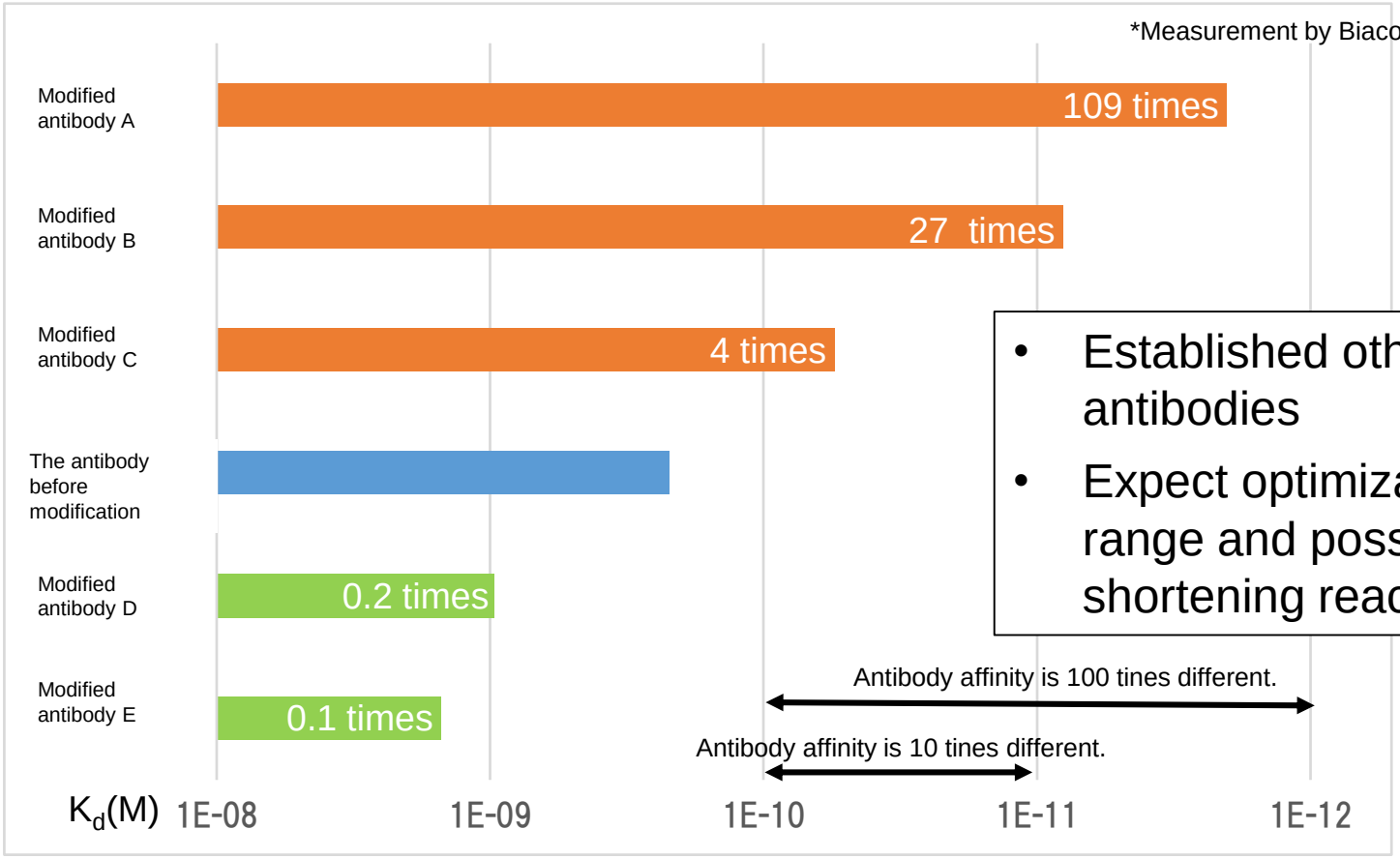
[Characteristics]

- Established in the process of technology development of immunological diagnostic reagents
- Amino acid substitution at specific part of VL region framework
- Antibody affinity (K_d: dissociation constant) dramatically changes as a results. (especially k_{on}(binding speed), a element of K_d calculation formula changed.)
- General technology (applicable for any antibody) and short-term project including evaluation (1-2 months)
- Patented in Japan.

Example of Diagnostic Antibody Modification

Anti-insulin antibody

Related papers: Biochemistry and Biophysics Reports 15 (2018) 81–85, Fukunaga et.al



- Established other modified antibodies
- Expect optimization of dynamic range and possibility of shortening reaction time

Low — Relative antibody affinity — High

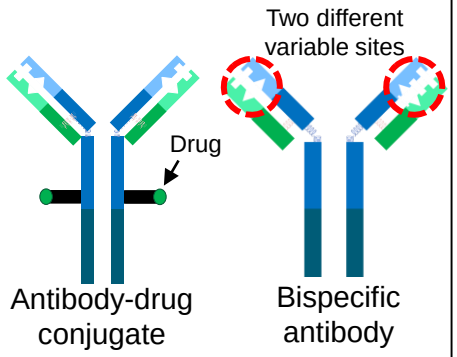
Applicability: Antibody Drug
Antibody Drug Market

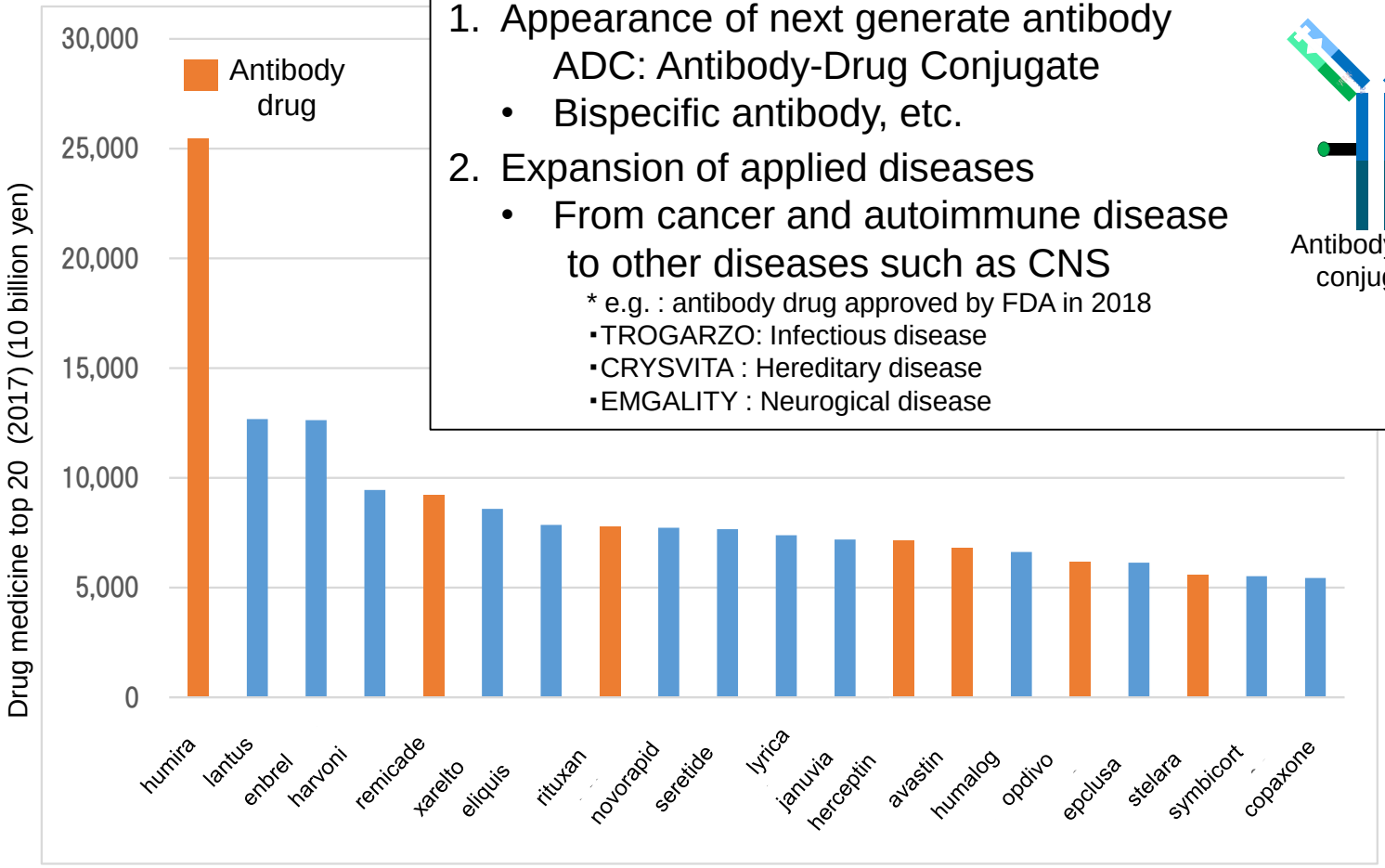
Antibodies as a major modality of drugs has continued to evolve.

[Trend of antibody drugs]

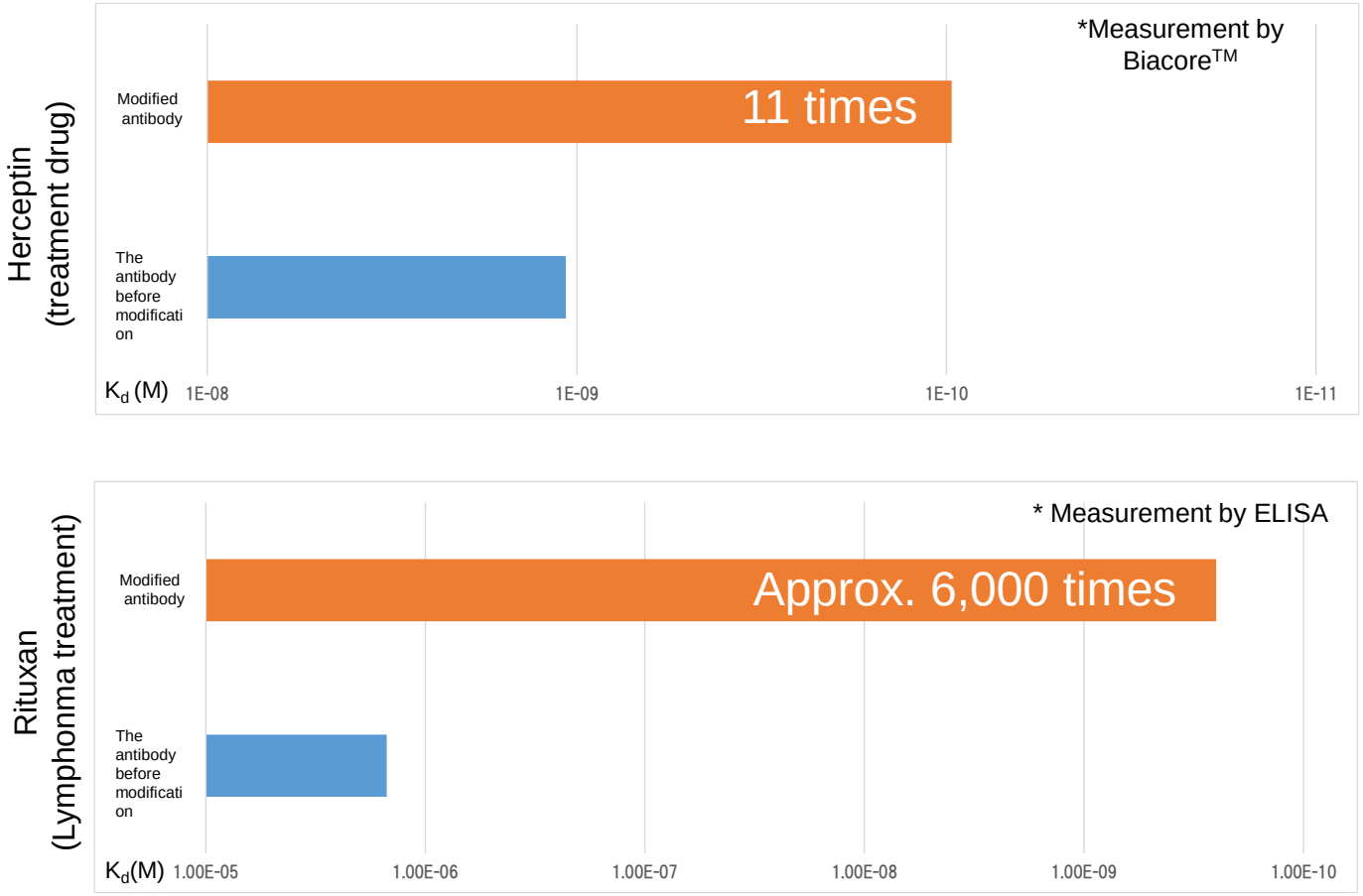
1. Appearance of next generate antibody
   ADC: Antibody-Drug Conjugate
   - Bispecific antibody, etc.
2. Expansion of applied diseases
   - From cancer and autoimmune disease to other diseases such as CNS

* e.g. : antibody drug approved by FDA in 2018
- TROGARZO: Infectious disease
- CRYSVITA : Hereditary disease
- EMGALITY : Neurogical disease





Applicability: Antibody Drug
Example of Modification



Promoting collaboration with pharmaceutical and research institutions
(*In vitro* and *in vivo* data acquisition)

* Target antibody would be selected with collaborators' concerns.

Future Policy

1. Strengthening technology

Promote mechanism analysis and performance improvement by utilizing Bio-Diagnostic Reagent Center

2. Development into diagnostics

Promote development of HISCL reagent by incorporating this technology

3. Verification of applicability to other than diagnosis, such as antibody drugs

Promote open innovation with pharmaceutical manufacturers and research institutions.

Lighting the way with diagnostics