The 17th R&D Meeting

March 6, 2020

Sysmex Corporation

- The information contained in these materials is based on current judgements and assumptions of the Sysmex Group in light of the information currently available to it. Uncertainties inherent in such judgments and assumptions, the future course of our business operations and changes in operating environments in Japan and overseas may cause plans to change.

- These materials contain information about products, service and support (including those under development). This information is not intended for advertising or promotional purposes.

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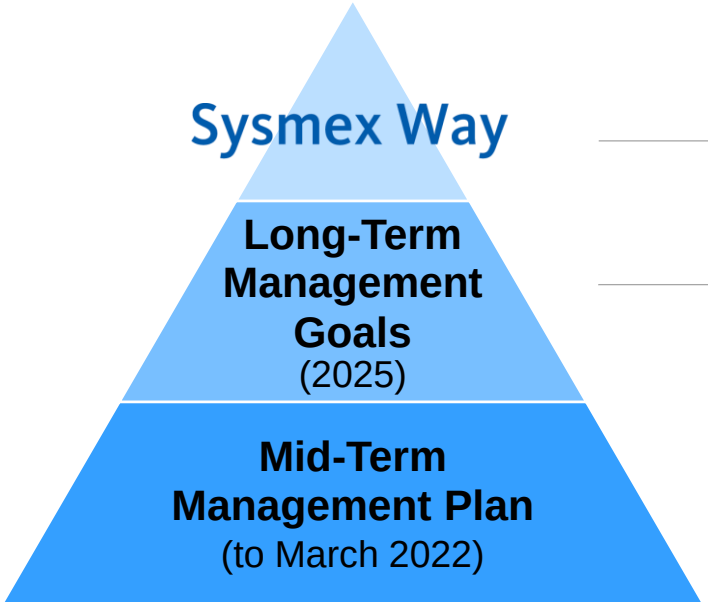
Opening Presentation

Hisashi Ietsugu, Chairman and CEO

Sysmex's Long-Term Management Goals



Mission

Shaping the advancement of healthcare.

Value

We continue to create unique and innovative values, while building trust and confidence.

Mind

With passion and flexibility, we demonstrate our individual competence and unsurpassed teamwork.

Long-Term Vision

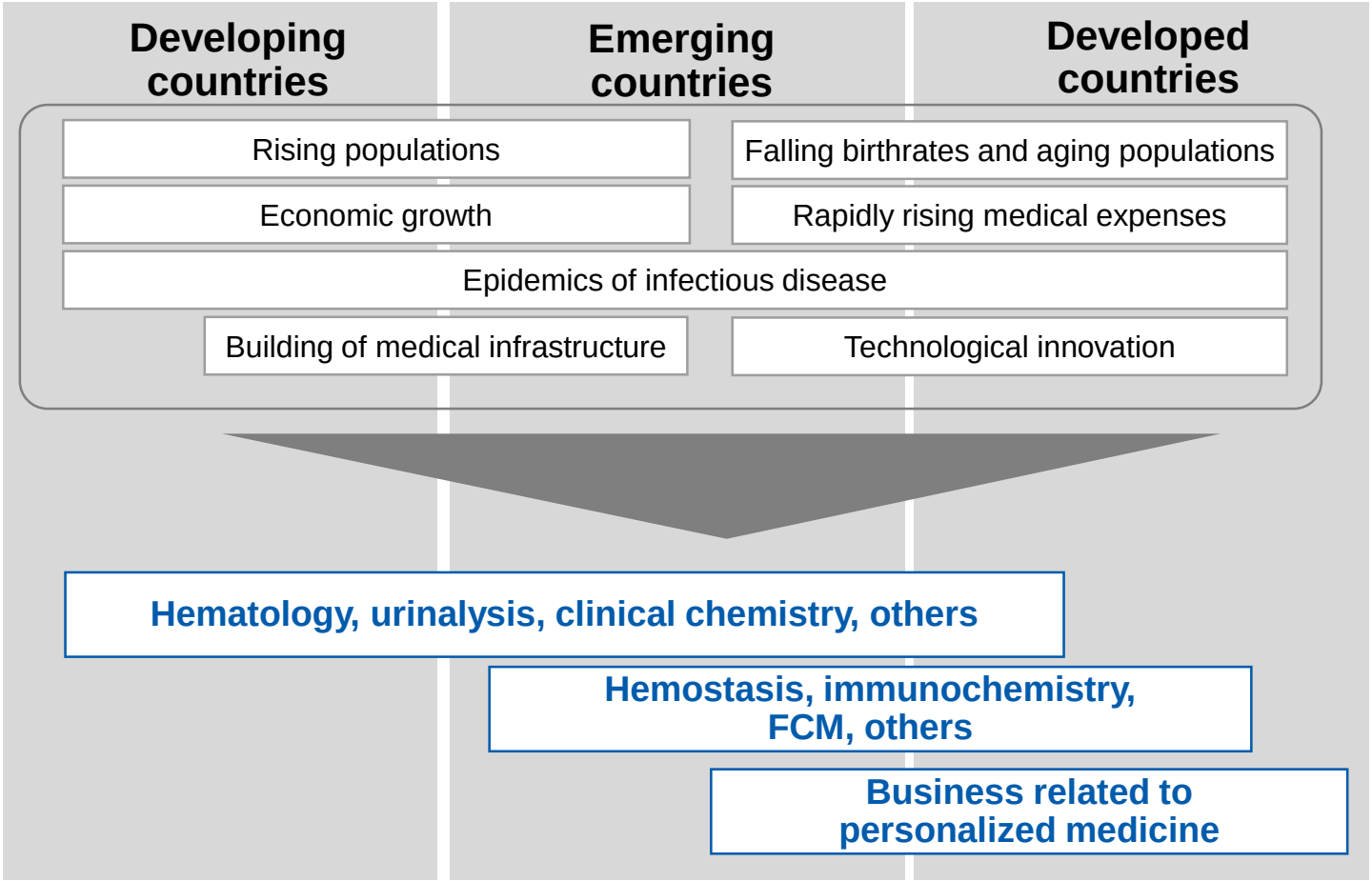
Unique & Advanced Healthcare Testing Company

Positioning

- Creating innovative diagnostic value as a global top-five company in IVD
- A leading company in personalized diagnostics for optimizing medical treatment
- A solution provider contributing to the advancement of primary care diagnostics
- An attractive company providing value and instilling confidence
- One Sysmex carrying out high-speed management

Recognition of the External Environment

Demographic changes and accelerating technological innovation are giving rise to a host of medical issues and growing markets to address these issues.



Sysmex's Technologies and Value Creation

Helping to realize a fulfilling and healthy society through unique technologies

Sysmex's Technologies

Engineering technologies
- Mechanics
- Fluids
- Optics
- Electronics

Reagent development technologies
- Chemical reagents
- Bio reagents

ICT technologies
- Data management
- Services and support

+

Acquire technologies through open innovation and M&A

Outputs
To medical institutions in 190 countries

- **Contribution to the creation of new diagnostic and treatment methods**
- **Improvements in testing productivity**
- **Development of reagents with high clinical value**
- **Environmentally considerate product development (energy conservation, other aspects)**
- **Network solutions providing more efficient healthcare and enhanced services and support**

Outcomes
For 7.0 billion patients and people undergoing screening around the world

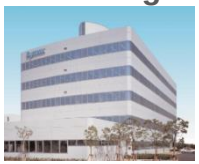
- **Contribution to extending healthy lifespans**
- **Help in curtailing healthcare expenses**

Expanding Our R&D Bases

Strengthening our R&D and technology bases, creating new products and services

Techno Center (From 1991)

Main building



Central Research Laboratories (2000)

- Reinforce product development in the IVD business
- Start moving into the life science field

Technopark (From 2008)

40th anniversary of establishment

- Accelerate initiatives targeting personalized medicine
- Acquire diverse and specialized human resources and technologies

Technopark East Site (From 2019)

50th anniversary of establishment

- Procure materials for, develop and produce bio-diagnostic reagents, and strengthen the logistics function

Enhancing our R&D functions overseas,
acquiring technologies through M&A, promoting open innovation

IVD Business

XN Series multiparameter automated hematology analyzer

Automatic measurement of red blood cells infected by malaria parasites

New network solution

Reagents in environmentally conscious paper packs

Unique reagents for HISCL Series automated immunoassay systems

CN Series fully automated blood coagulation analyzer

Life Science Business

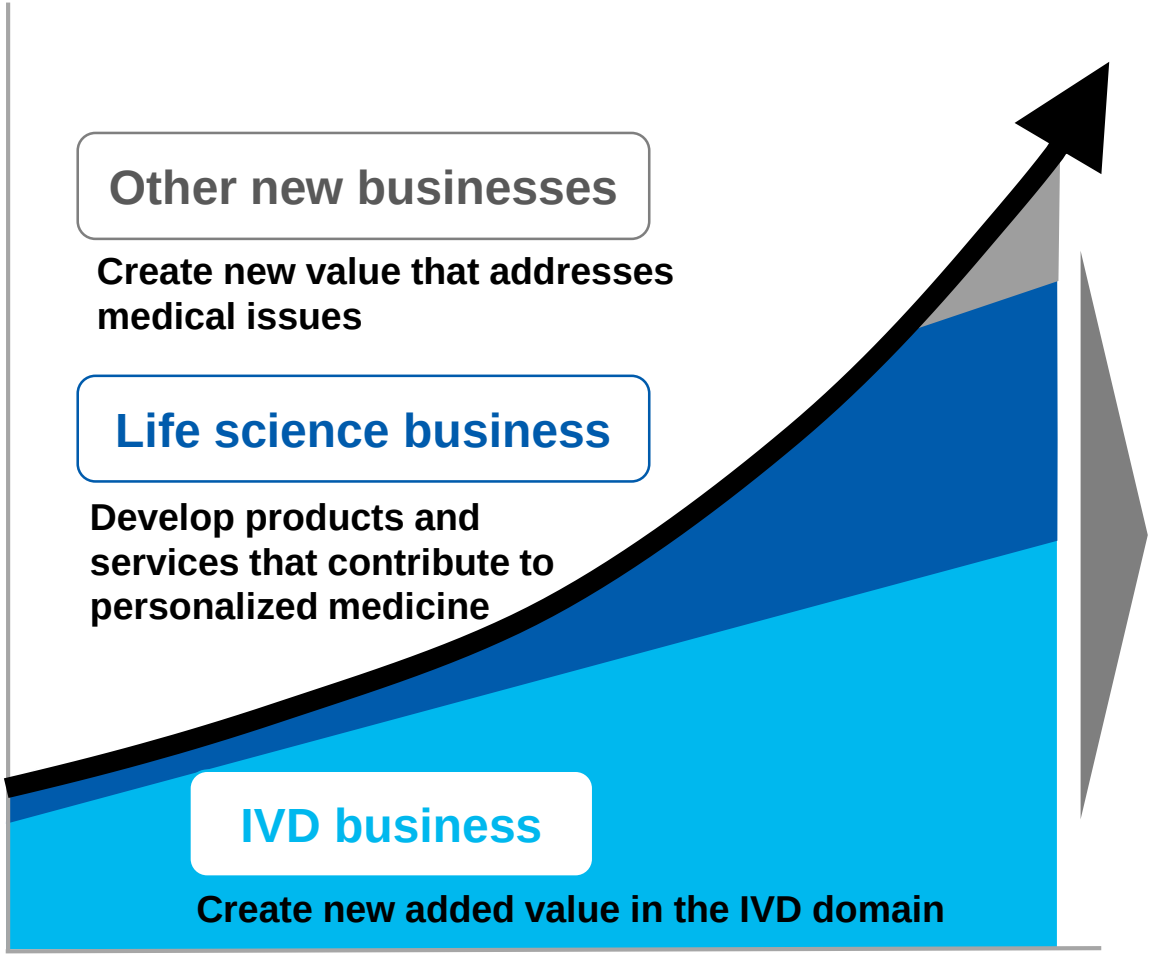
RD-200 gene amplification detector

OncoBEAM RAS CRC kit

OncoGuide NCC OncoPanel System

Sysmex's Growth Strategy

In addition to sustainable growth in the IVD business, increase the rate of growth by transforming our portfolio



Today's agenda

Initiatives targeting personalized medicine

- Cancer genomic medicine
  - BEAMing
  - NCC OncoPanel
- Liquid biopsy
  - Alzheimer's disease
  - CTC

Innovations in the IVD business

- Enhancing the Operational Value of Blood Coagulation Analyzers
- Applying Astrego's Microchannel Technology
- Using AI Technology for Blood Imaging Analysis

2

Technology Strategy Overview

Kaoru Asano
Member of the Managing Board and Senior Executive Officer,
Senior Managing Director,
COO LS Business Unit and CTO

(1) Progress on Initiatives for the Realization of Personalized Medicine

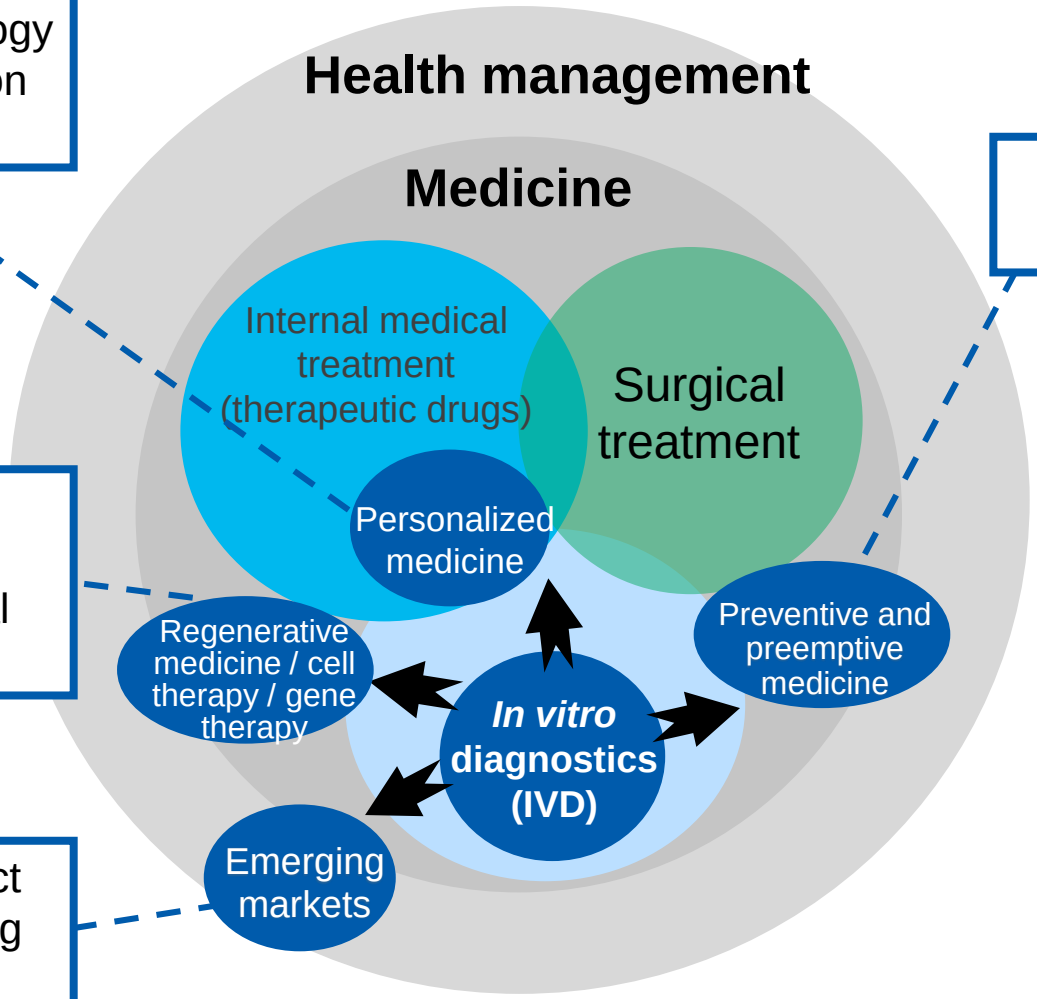
(2) Compact Immunoassay System and Initiatives Targeting Coronavirus

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

Liquid Biopsy

Biopsy

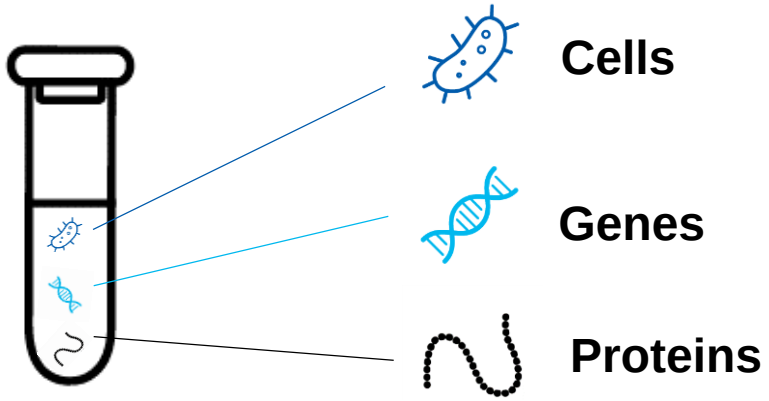
Invasive sample collection of affected organ/tissue

Technology Platform

Liquid biopsy

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

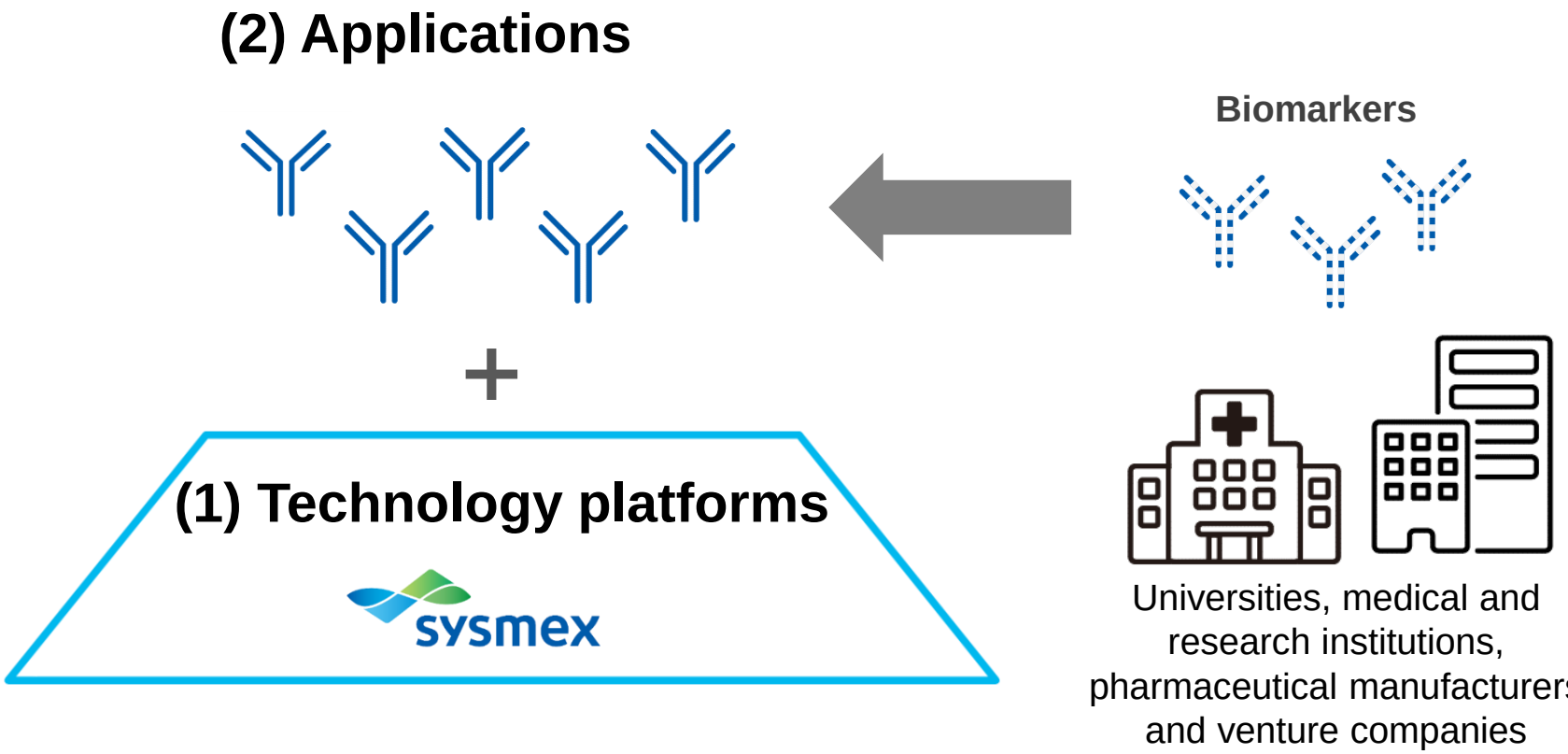
Detection sensitivity: 100 to 1,000 times higher than conventional methods



Compared with conventional methods, liquid biopsy is in the spotlight for its potential for imposing less of a burden on patients, increasing opportunities for testing and helping to determine treatment methods at an early stage.

Open Innovation

Promote open innovation to develop applications with high clinical value and place them on the technology platforms we have established



Established Technology Platforms

We have completed the establishment of technology platforms and are promoting the development applications with a view toward commercialization.

Leverage proprietary liquid biopsy technology to drive personalized medicine

Capture potential markets

Expand existing market

Gene measurement platform	Cell measurement platform	Protein measurement platform
Plasma-Safe-SeqS	MI-FCM (CTC) 	**Breast cancer CTC**
OncoBEAM3.0 		Ultrahigh-sensitivity HISCL HISCL™ 
OncoBEAM™ RAS CRC		Super-resolution microscope 
		Alzheimer's disease
Clinical PCR 	MI-FCM (Flow FISH) 	HISCL™ (new markers) 
Clinical sequencing	Clinical FCM	Compact immunoassay 
NCC Oncopanel		
Panel for hereditary retinal degenerative diseases		
OSNA™ (RD) 	FCM (XN, UF, LC) 	HISCL™ 
		CS, CN 

Application Launch Plans

As indicated at the 16th R&D Meeting (Mar. 2019)

(Fiscal years to March 31)

	~2019.3	~2020.3	~2021.3	~2022.3
Proteins				
Immunoassay systems		HDL function measurement		Alzheimer's disease Immune checkpoint inhibitors (PD-1, PD-L1, CTLA4)
Super-resolution microscope				
Genes				
Clinical PCR		EGFR		
OncoBEAM3.0			RAS	
Plasma-Safe-SeqS		Head and neck cancer panel Colon cancer panel	Breast cancer panel	
Clinical sequencing				
Cells				
Flow FISH			Transplant testing	Hematopoietic malignancies
CTC system				Breast cancer

● RUO ● LDT ● IVD ● Other Note: Dotted lines indicate expectations

Application Launch Plans (Update)

(Fiscal years to March 31)

	~2019.3	~2020.3	~2021.3	~2022.3
Proteins				
Immunoassay systems	HDL function measurement	Immune checkpoint inhibitors (PD-1, PD-L1, CTLA4)	Alzheimer's disease	HDL function
Compact immunoassay			Gynecology biomarker	Special biomarkers
Genes				
Clinical PCR	EGFR			4 Gene panel (EGFR, ALK, ROS1, BRAF)
OncoBEAM3.0		RAS		
Plasma-Safe-SeqS	Head and neck cancer panel / Colon cancer panel		Breast cancer panel	
Clinical sequencing	NCC Oncopanel	NCC Oncopanel	Developmental delay / GIMS	NCC Oncopanel (next version) / IRD panel
Cells				
Flow FISH			Transplant testing	Multiple myeloma / Hematopoietic malignancies
CTC system			Breast cancer	Prostate cancer

● RUO ● LDT ● IVD ● Other Note: Dotted lines indicate expectations

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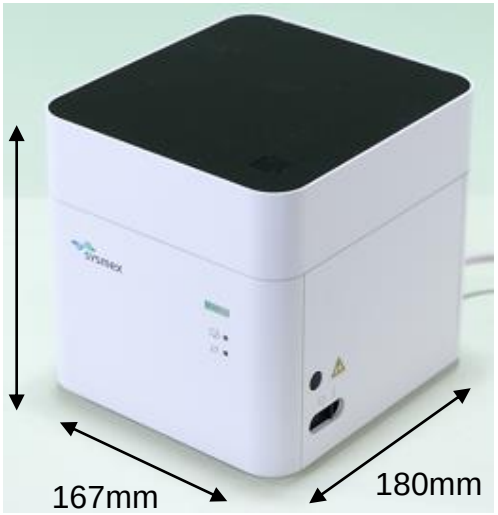
Technology Strategy Overview

(1) Progress on Initiatives for the Realization of Personalized Medicine

(2) Compact Immunoassay System and Initiatives Targeting Coronavirus

Compact Immunoassay System



- High-sensitivity and rapid measurement (within20 min.) provided by use of HISCL, an automated immunoassay system, reagents
- Compact unit allowing clinical installation
- Equipped with IoT function
- Simple to operate with smart phones or other IT devices

Cartridge reagents
φ120mm t1.2mm

・All reagents pre-sealed
・No effluent

Jointly developed products with JVCKENWOOD Corporation

Operating Principle

Movie of Compact Immunoassay

Analytical Performance (TSH)

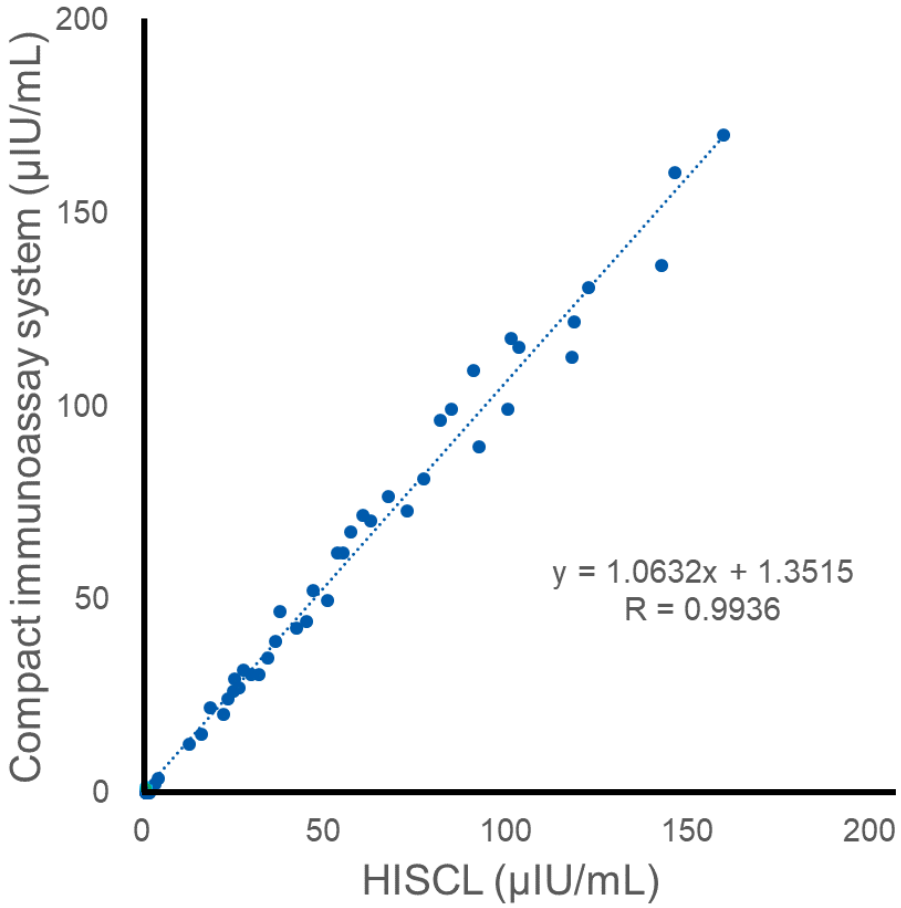
Confirmed that its performance is almost the same as HISCL

Measurement range

	Lower limit		Upper limit
μIU/mL	0.02	~	100

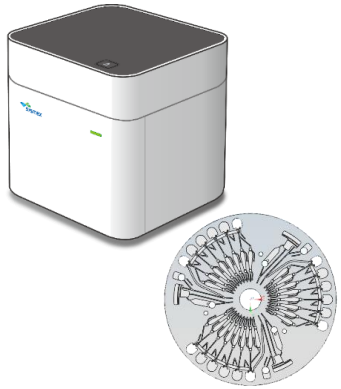
Reagent cartridge

Correlation

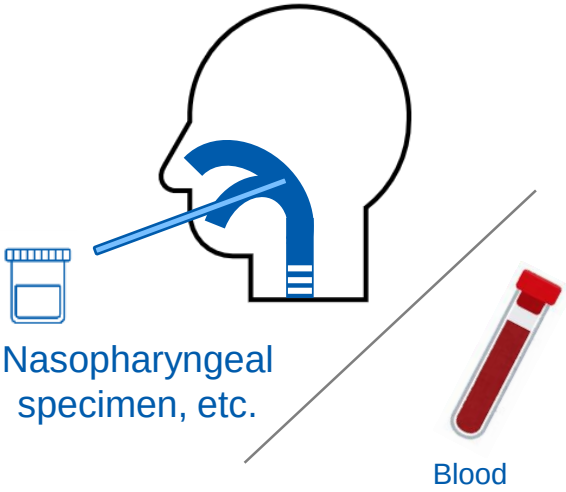


TSH: Thyroid stimulating hormone

Start Consideration for Coronavirus Testing



Compact immunoassay system



Nasopharyngeal specimen, etc.

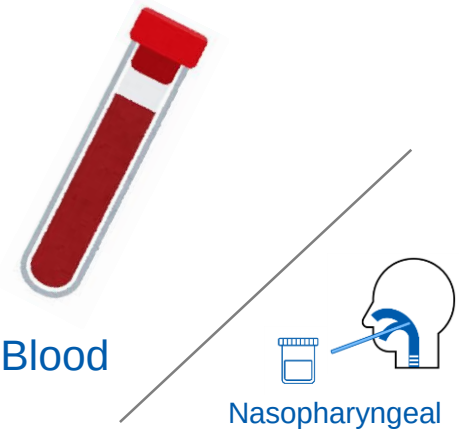
Blood

On-site testing (at clinics, etc.)

COVID-19 Ag Test

- Easy and rapid
- Lower price than PCR

HISCL



Blood

Nasopharyngeal specimen, etc.

For clinical laboratories and testing institutions

COVID-19 IgM Ab Test
COVID-19 IgG Ab Test
COVID-19 Ag Test

- Antigen / antibody test
  (test the infection of patients who have few virus in their specimen)
- Capable of processing a large number of samples

3

Initiatives for the Realization of Personalized Medicine I

Mamoru Kubota
Senior Executive Officer

(1) Overview of Cancer Gene Testing in the LS Business

(2) Liquid Biopsy Gene Testing Initiatives

(3) Cancer Genomic Medicine Initiatives

Overview of Cancer Gene Testing in the LS Business

(1) OSNA method (molecular detection of metastases in lymph nodes)
Breast cancer, colorectal cancer, gastric cancer, lung cancer: Covered by insurance

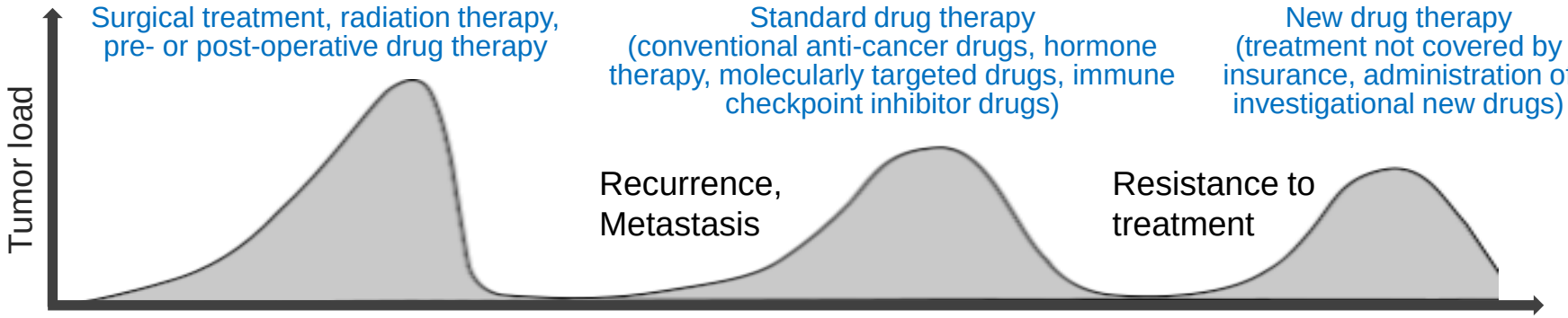
(2) Curebest™ 95GC Breast / 55GC Colon (recurrence risk tests)
Gene expression analysis in primary tumor for breast cancer and colorectal cancer: LDT/not covered by insurance

(3) OncoPrime, MSK-IMPACT (clinical sequence testing)
Genome profiling of solid tumors: LDT/not covered by insurance

(4) OncoBEAM RAS CRC kit (liquid biopsy CDx)
Determine suitability of anti-EGFR antibody drugs for colorectal cancer: Approved by the Ministry of Health, Labor and Welfare, insurance coverage expected within 2020

(5) PSS/NGS (liquid biopsy gene panel test)
Panel ctDNA profiling for breast cancer and colorectal cancer: LDT/not covered by insurance

(6) OncoGuide™ NCC Oncopanel system (cancer gene testing)
Solid tumor genome profiling: Covered by insurance



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Initiatives for the Realization of Personalized Medicine I

(1) Overview of Cancer Gene Testing in the LS Business

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(3) Cancer Genomic Medicine Initiatives

Liquid Biopsy Gene Testing Initiatives

OncoBEAM RAS CRC kit

First companion diagnostic drug in the world to receive approval for ctDNA testing using the digital PCR method (July 19, 2019)

Detection of RAS (KRAS and NRAS) gene mutations in genomic DNA extracted from blood plasma <used to help determine suitability of Cetuximab (genetic recombinant) and Panitumumab (genetic recombinant) for patients with colorectal cancer>

KRAS	NRAS
• Codon 12	• Codon 12
• Codon 13	• Codon 13
• Codon 59	• Codon 59
• Codon 61	• Codon 61
• Codon 117	• Codon 117
• Codon 146	• Codon 146

Configuration of a lab assay system at the lab of SRL, Inc. (introduction of the BEAMing 3.0 system)

November 2019
Application for insurance coverage

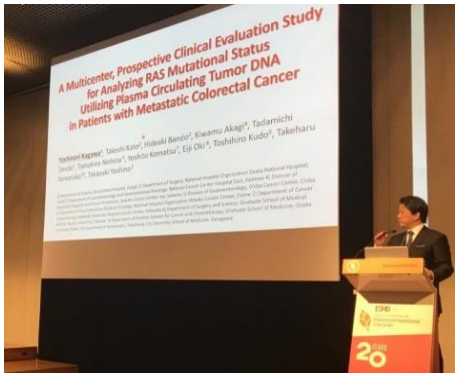
April 2020
Expected start of assessment

July 2020
Expected start of insurance coverage

Clinical Performance of OncoBEAM RAS CRC kit

ESMO WCGC2018

Oral presentation by Dr. Yoshinori Kagawa, Department of Gastroenterological Surgery, Kansai Rosai Hospital



ARTICLE
Clinical Study

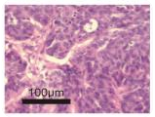
A multicentre, prospective study of plasma circulating tumour DNA test for detecting *RAS* mutation in patients with metastatic colorectal cancer

Hideaki Bando[1], Yoshinori Kagawa[2], Takeshi Kato[3], Kiwamu Akagi[4], Tadamichi Denda[5], Tomohiro Nishina[6], Yoshito Komatsu[7], Eiji Oki[8], Toshihiro Kudo[9], Hiroshi Kumamoto[10], Takeharu Yamanaka[11] and Takayuki Yoshino[1]

British Journal of Cancer volume 120, pages982–986(2019)

RASKET
tissue sample

N=294 93.9 %*



OncoBEAM RAS
tissue sample

N=280 86.1% （89.2%**）

OncoBEAM RAS
blood plasma sample

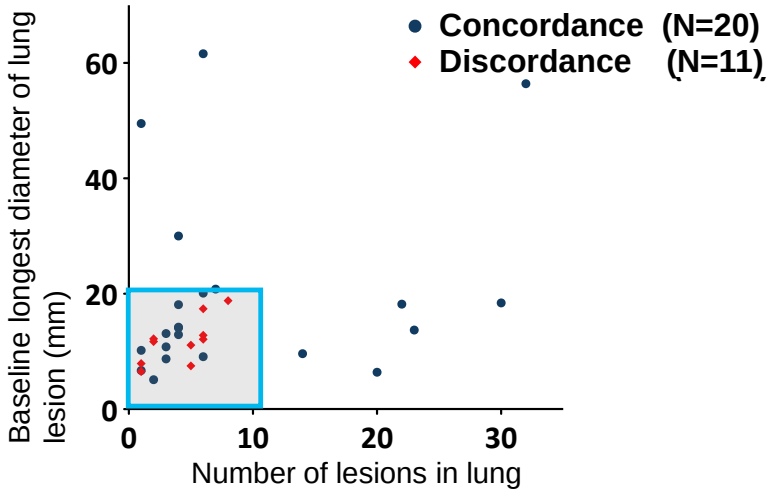
N=100 96.0 %*

NGS
blood plasma sample

*Concordance rate

**Excluding cases of lung metastasis only

Analysis of cases of **lung metastasis only**



As false negatives are possible, as much as tissue tests were considered for patients with lung metastasis only.

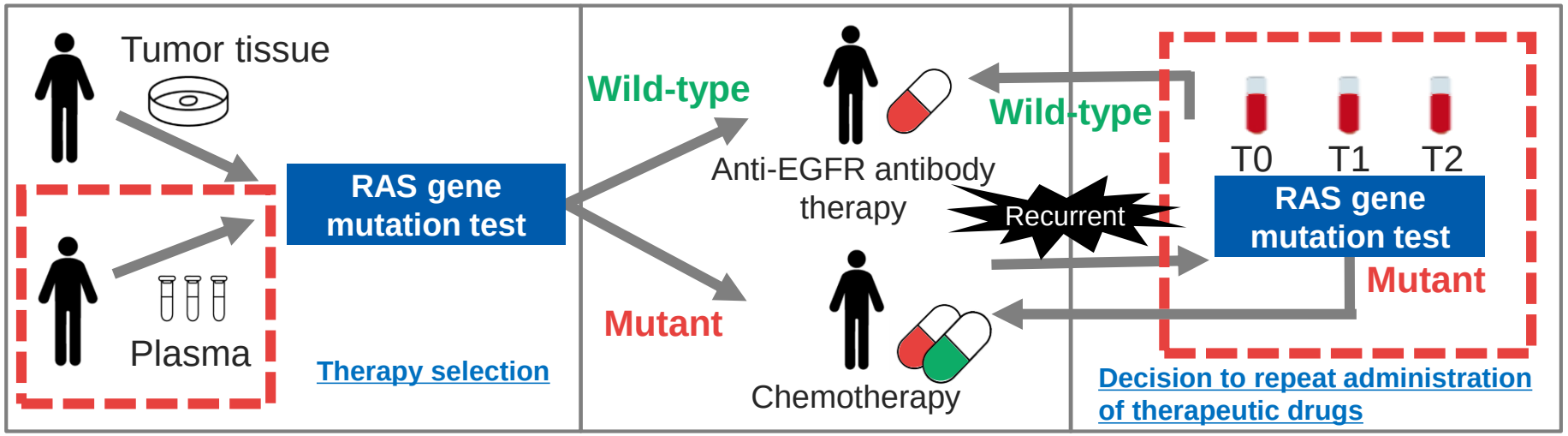
Clinical Utility of OncoBEAM RAS CRC kit

Market scale

Number of patients in Japan with colorectal cancer: **158,127 pts/year**
Number of RAS gene mutation tests: **25,546 test/year**

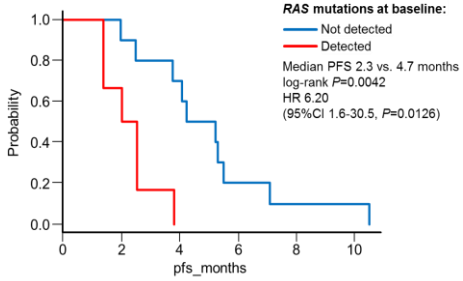
Cancer Incidence in Japan*, Ministry of Health, Labour and Welfare (January 1 to December 31, 2016) *Excluding intraepithelial cancer
"Cancer Statistics '18," Foundation for Promotion of Cancer Research (2018)

Patients with advanced or recurrent colorectal cancer



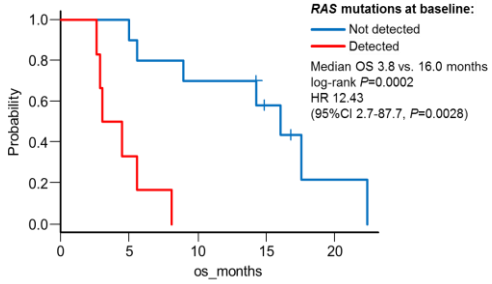
PFS

Progression-free survival rate



OS

Overall survival rate



Retrospective study indicates a positive prognosis (PFS and OS) for the patient group with wild-type RAS genes in blood plasma before administration of anti-EGFR antibody drugs.

Sunakawa Y, *et al*. *ESMO-GI 2019*.

3

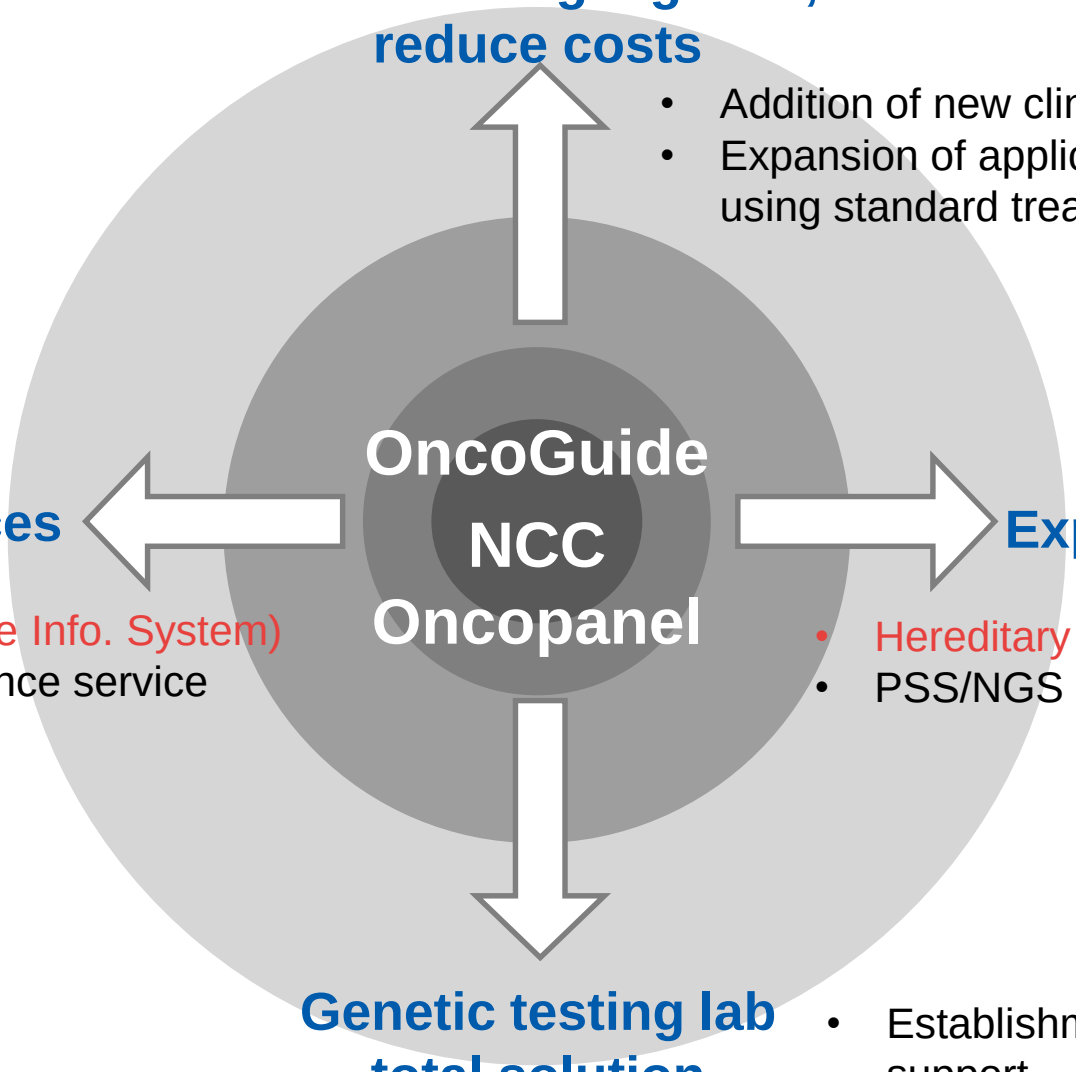
Initiatives for the Realization of Personalized Medicine I

(1) Overview of Cancer Gene Testing in the LS Business

(2) Liquid Biopsy Gene Testing Initiatives

(3) Cancer Genomic Medicine Initiatives

Cancer Genomic Medicine Initiatives



Increase target genes, reduce costs

- Addition of new clinical items
- Expansion of application before using standard treatments

Analysis services

- GIMS (Genome Info. System)
- Quality assurance service

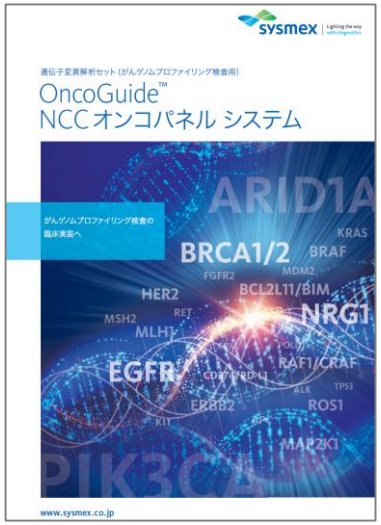
Expand portfolio

- Hereditary disease gene panel
- PSS/NGS liquid biopsy

Genetic testing lab total solution (on-site business)

- Establishment and operational support
- Analysis support

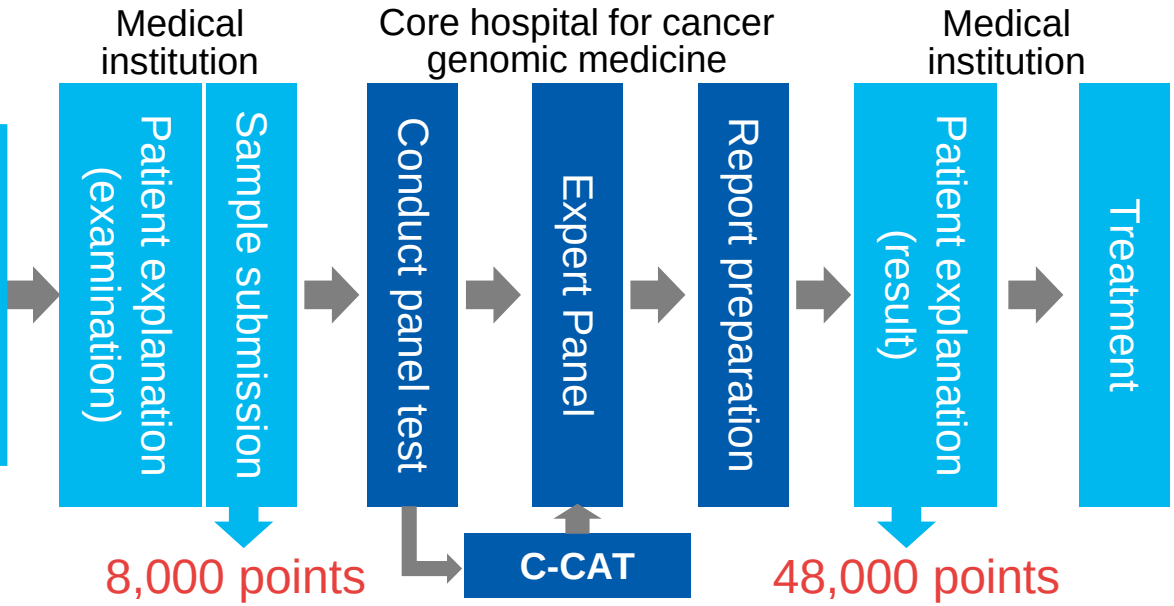
OncoGuide NCC Oncopanel



Name:	**OncoGuid NCC Oncopanel System** OncoGuid NCC Oncopanel analysis program OncoGuid NCC Oncopanel kit
Application:	Obtaining a comprehensive genomic profile of tumor tissue in patients with solid tumors
Target market:	Japan
Target institutions:	Medical institutions that have in place diagnostic systems appropriate for cancer genome profiling
Medical equipment production sales authorization number:	23000BZX00398000 (approved as a combination medical device)

June 1, 2019
Insurance coverage of cancer genome profiling using OncoGuid NCC Oncopanel (56,000 points)

<u>Target patients</u>
Patients with solid tumors for which:
(1) No standard treatment exists
(2) Standard treatment has been concluded
(or is expected to conclude)



Clinical Implementation of OncoGuide NCC Oncopanel

Establish a flow of cooperation connecting affiliated institutions to conduct cancer gene testing

Core hospitals (11)
Hub hospitals (34)

Liaison hospitals (161)

Note: As of January 1, 2020

Clinical testing company

riken genesis

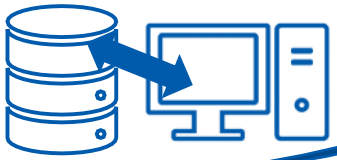
Center for Cancer Genomics and Advanced Therapeutics (C-CAT)

AGAAGCACCTGGAGAACTCATG.
....
TGCACACATTGACTTACCCACT.
....
AAGCAAAAATCCAGCCCATCAC.
....
CTTGGAAAAGGACTGCACTTGG.
....
CCTGGTGGTCTGGAAGATCTTC.
....
GCACCAGGAGGGACTTAGTTTA.
....

公益財団法人 日本適合性認定協会 Japan Accreditation Board

Expert Panel

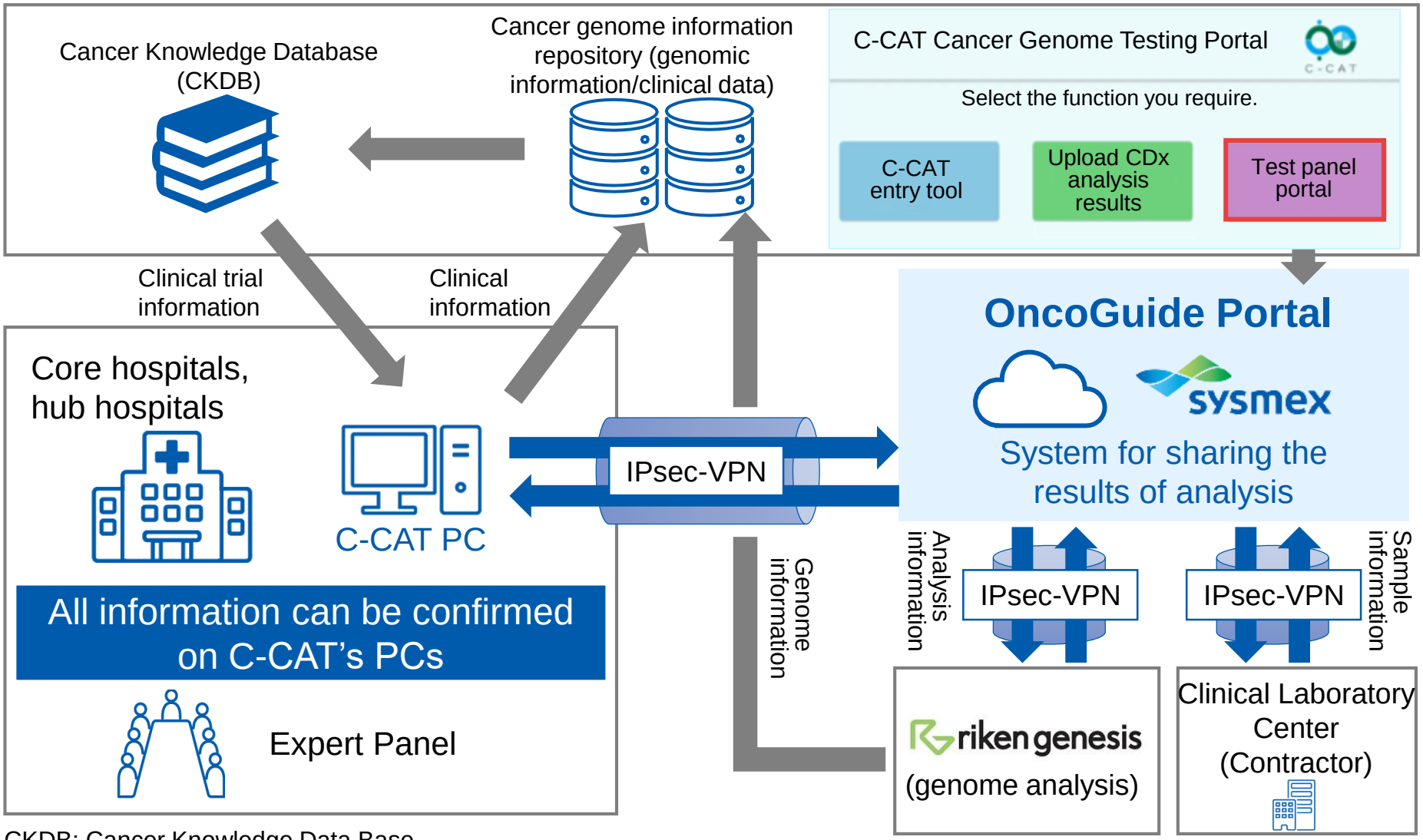
C-CAT portal



Open up the road to the use of therapeutic drugs not covered by insurance and participation in clinical trials

Contribution of ICT Technologies: OncoGuide Portal

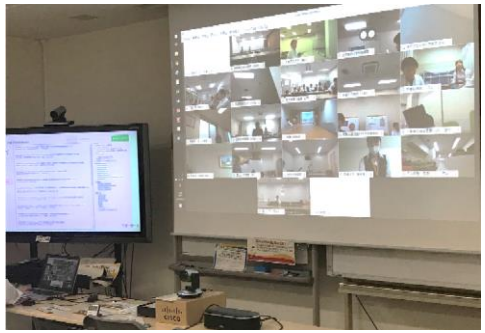
Creation of a system compliant with the security measures outlined in the Three Guidelines from Three Ministries



CKDB: Cancer Knowledge Data Base

Contribution Using ICT Technologies: GIMS

Leveraging IT/AI and contributing to the standardization of cancer gene testing



Issues with Expert Panel

- Needed to reduce the amount of time and effort needed to arrange schedules among multiple institutions and participants
- Sharing information across multiple systems was complicated and complex

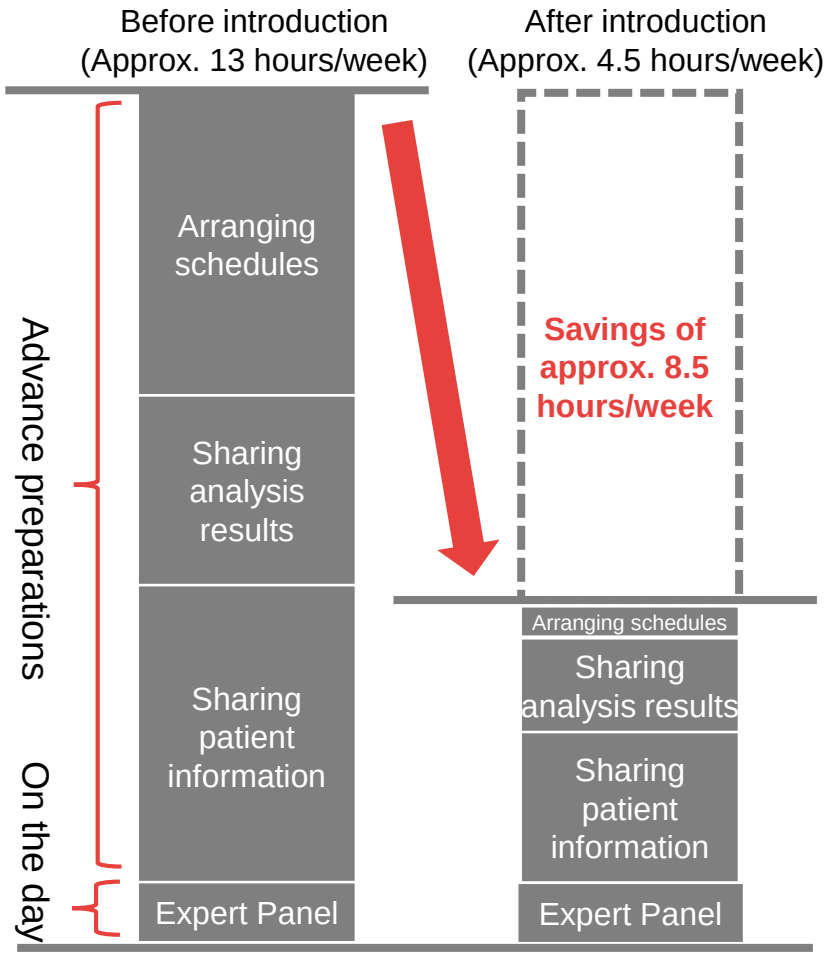
Genome Information System (GIMS)

➢ Expert Panel support system

Connects with OncoGuide Portal and provides support for advance preparations

- Simplifies the arrangement of schedules
- Analysis and patient information can all be shared on this system

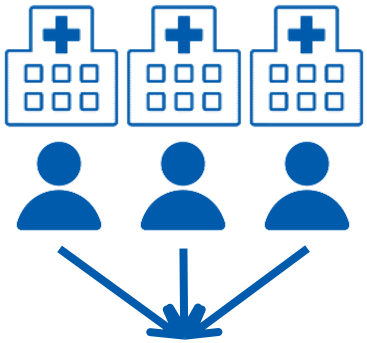
Expert Panel support system results



Expert Panel Support Provided by GIMS

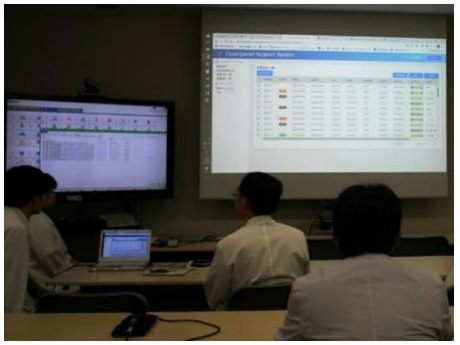
Core hospitals, hub hospitals

Liaison hospitals



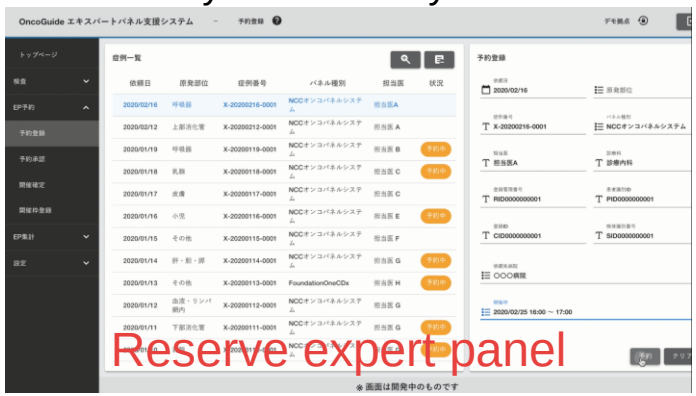
Core hospitals, hub hospitals

Prepare framework

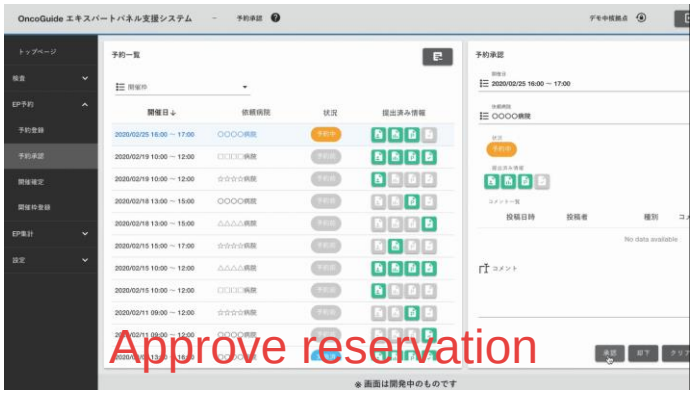


Trial underway at hospital affiliated with Kyoto University

Register information on cases, test reports (communicate with portal)



Reserve expert panel



Approve reservation

Panel fixed

Note: Images are all provisional

Comments about GIMS

GIMS has essentially eliminated the labor required to arrange schedules and confirm materials for Expert Panel. Once schedules have been set, the system also automatically sends out information to all the people involved at related institutions. The system has significantly reduced the amount of work needed for arranging and holding Expert Panel.

The system is convenient, as it allows information to be checked easily and facilitates the advance review of case data scheduled for review. The system provides solid peace of mind, because information security is maintained whether viewing information from inside or outside the hospital. We can browse information easily and quickly.

Manabu Muto, M.D., Ph.D., Professor, Department of Therapeutic Oncology, Graduate School of Medicine and Faculty of Medicine, Kyoto University

In the past, arranging for expert panels involved security issues and the efforts of two or three people. Now, all the doctors (including those from other departments) have accounts, so each one can manage the cases for which he is responsible.

In addition to reducing the burden on those of us who handle arrangements, I am impressed that the system is covered under health insurance and can be managed directly by doctors as part of their everyday operations.

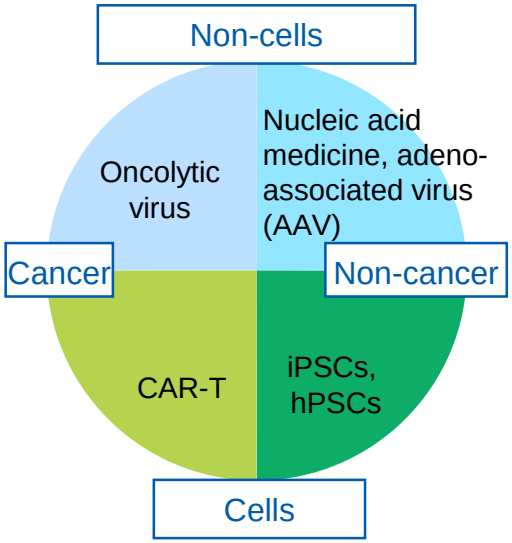
Kumi Mukai, Specialist/Clinical Laboratory Technologist, Department of Therapeutic Oncology, Graduate School of Medicine and Faculty of Medicine, Kyoto University

Handling the data for cancer gene panel testing is very cumbersome. In the past, we had to transfer data and reports manually, which presents the risk of mishandling. Now data can be shared between OncoGuide Portal and the Expert Panel support system, allowing reports to be checked, which significantly reduces the load on us.

Masashi Kanai, Program-Specific Associate Professor, Department of Therapeutic Oncology, Graduate School of Medicine and Faculty of Medicine, Kyoto University

Development of Gene Panels for Hereditary Diseases

Gene therapy:
Providing treatment to normalize the **disease-causing genes** resulting from gene mutations (hereditary diseases)



Key gene therapy drugs that have recently been approved

Drug (company)	Target disease	Transgene	Regions of approval: Price
Glybera (UniQure)	Lipoprotein lipase deficiency	Lipoprotein lipase	Europe: €820,000/pt (sales discontinued)
Imlygic (Amgen)	Malignant melanoma	GM-CSF	US: $65,000/pt Europe: unknown
Strimvelis (Orchard Therapeutics)	Adenosine deaminase deficiency	Adenosine deaminase	Europe: €594,000/pt
Zalmoxis (MolMed)	Graft-versus-host disease	HSV-TK Mut2	Europe: €149,000/time
Kymriah (Novartis)	Acute lymphoblastic leukemia	CD19-directed CAR molecule	US: $475,000/time Europe: €360,000/time Japan: ¥33,490,000/time
Yescarta (Kite Pharma)	Large B-cell lymphoma	CD19-directed CAR molecule	US: $373,000/time Europe: unknown
Luxturna (Spark Therapeutics)	Retinal dystrophy	RPE65	US: $425,000/eye Europe: €345,000/eye
Zolgensma (AveXis)	Spinal muscular atrophy	SMN1	US: $2,125,000/time Japan: under review

Reference: Drug Delivery System 34-2, 2019. The price is according our research.

Aiming to create a gene panel for hereditary diseases (IVD/CDx)

CAR-T: Chimeric Antigen Receptor-T cell、iPSCs: Artificial pluripotent stem cells、hPSCs: Human pluripotent stem cells

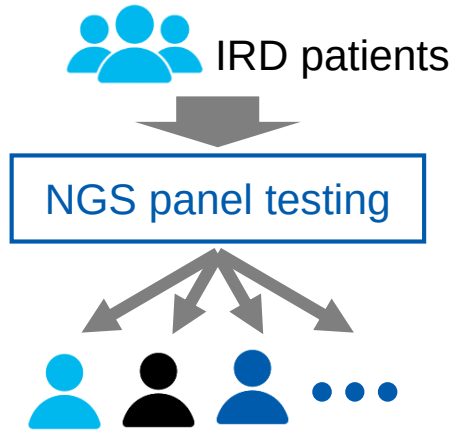
Development of Genomic Medicine for IRD

Comprehensive collaboration with the Kobe Eye Center Hospital (March 5, 2020 release)

Inherited Retinal Disease(IRD)

- Hereditary diseases characterized by abnormalities of abnormalities in the photoreceptor cells or epithelial cells that adhere to the retina.
- No fundamental treatment method exists, but gene therapy drugs have been approved in the United States and Europe.
- At least 40 types of underlying genes exist. Not every genes are clear yet.

Testing is needed to elucidate the underlying gene in order to select the optimal method of treatment



Provide therapy optimized for each **underlying gene**

Aim to develop NGS panel testing (identification of the disease-causing genes) by leveraging specialized skills at the Kobe Eye Center Hospital and the Sysmex Group's technologies and experience

Kobe Eye Center
- First institution in Japan specialized in ophthalmology
- Actively conduct clinical researches and genetic counselings

sysmex
- Development of cancer genome profiling system
- Experience in obtaining regulatory approval and insurance coverage

ogt A Sysmex Group Company
- Development of rare disease arrays
- Development of the NGS panel system

riken genesis
- Gene analysis expertise
- Quality-assured consignment system

IRD：Inherited Retinal Degeneration Dystrophy/Disease/Disorder

4

Initiatives for the Realization of Personalized Medicine II

Tomokazu Yoshida
Executive Officer
Executive Vice President of Central Research Laboratories

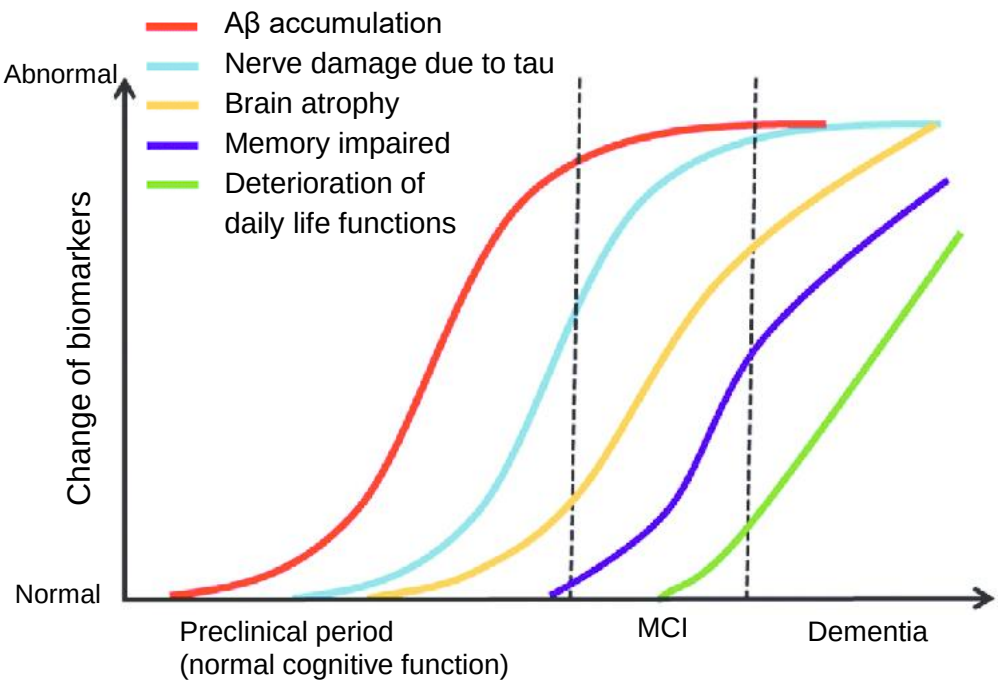
(1) Initiatives Targeting Alzheimer's Disease

(2) Applying Circulating Tumor Cells（CTC）Measurement Technology

Liquid Biopsy (Alzheimer's Disease)

Early-stage detection and pre-emptive medical attention at the mild cognitive impairment stage of Alzheimer's disease are important.

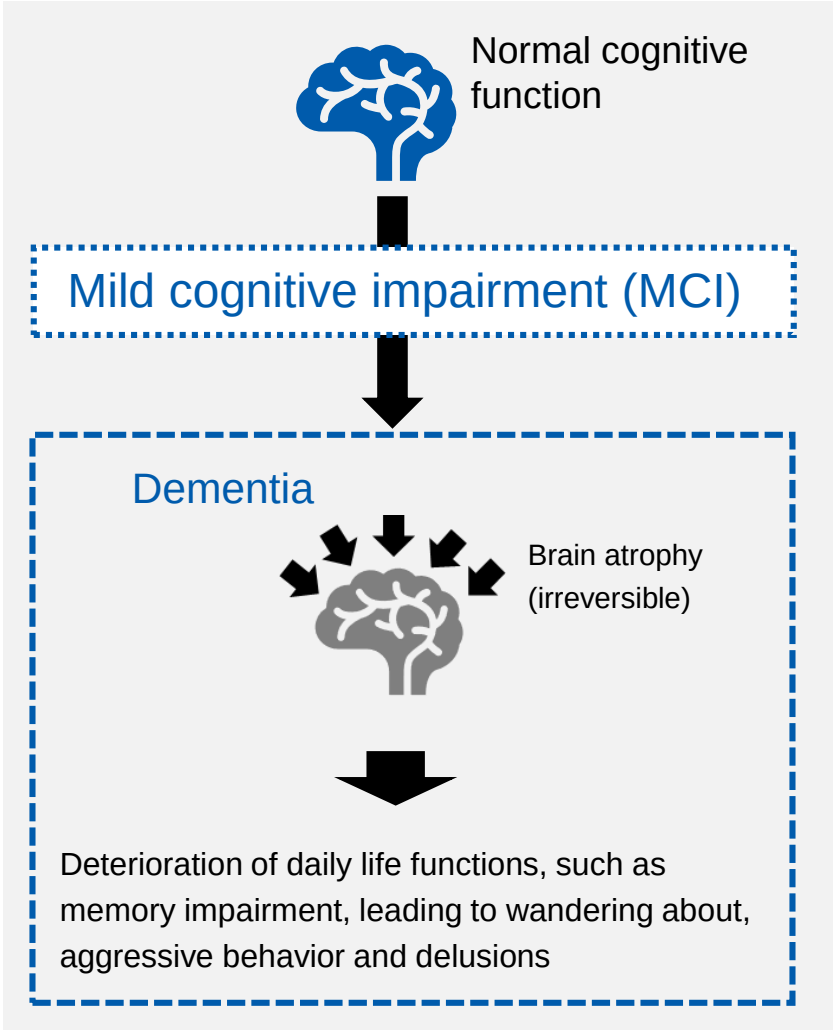
Progression of Alzheimer's disease



Adapted from Lancet Neurol 2010; 9:119-128

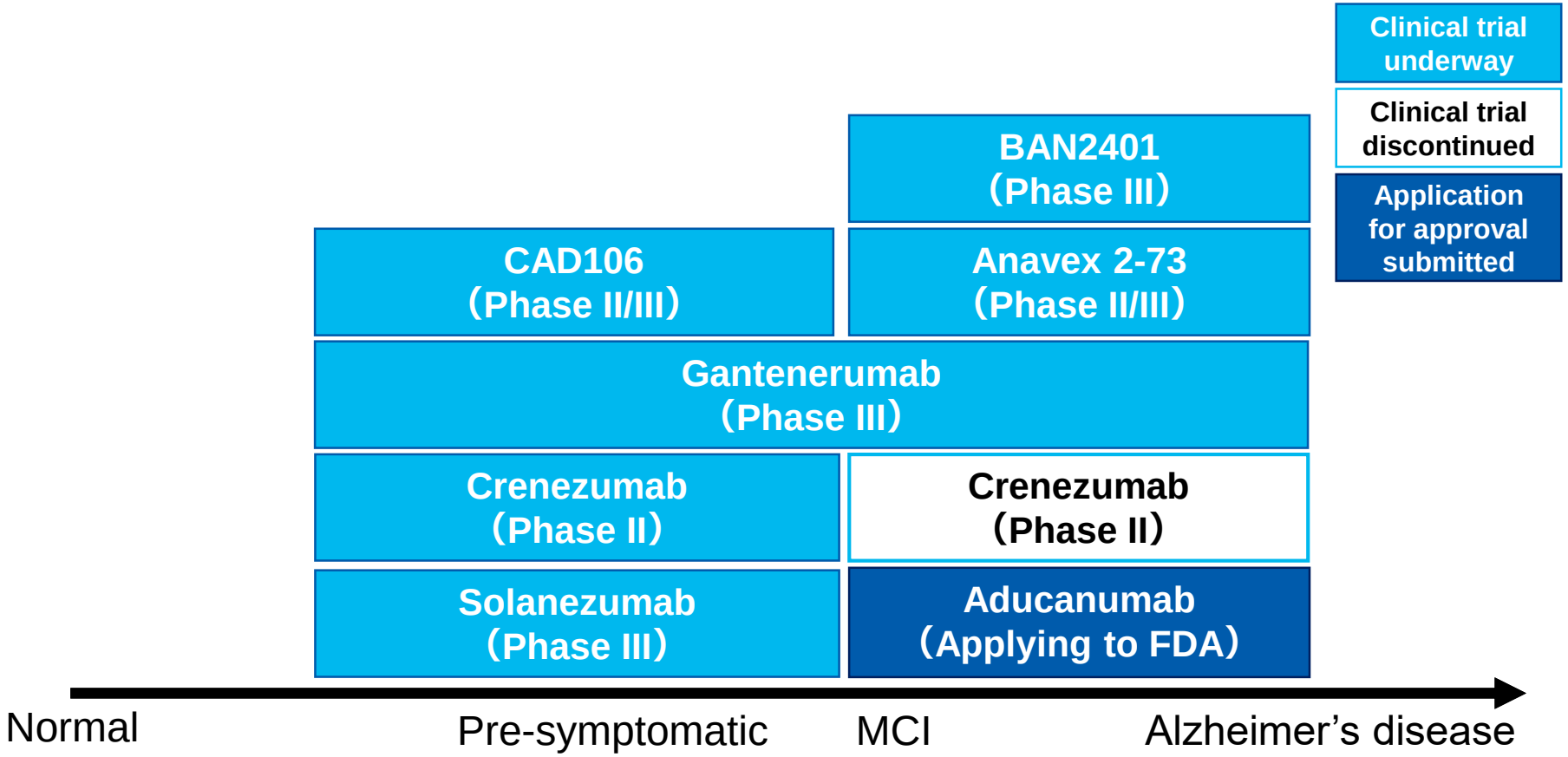
No clear standards currently exist for diagnosing MCI.

A quantitative, standardized system for diagnosis is needed.



Liquid Biopsy (Alzheimer's Disease)

Drugs targeting amyloid β are being developed to curtail disease-base deterioration at an earlier stage.



Alzheimers Dement (N Y). 2019; 5: 272–293.
Sources: Revised and adapted by Sysmex based on information from ClinicalTrials.gov, individual companies' press releases, and materials from a 2017 Eisai information meeting

Liquid Biopsy (Alzheimer's Disease)

The realization of blood tests for Alzheimer's disease will help provide new therapeutic opportunities.

Medical interview
(evaluation of cognitive function)

▶ MCI × Not objective or quantitative

Imaging (MRI/CT, PET, etc.),
spinal fluid tests

× Cost-prohibitive, require special facilities

× Invasive, inadequacy of testing items

Dementia

Diagnosis by exclusion

Vascular, Lewy bodies

Alzheimer's disease × Differentiation of biomarkers an issue

Symptomatic treatment

Symptomatic treatment

Confirmed diagnosis
(post-mortem brain pathology)

MCI early-stage diagnosis (screening)

Distinguishing Alzheimer's Disease

CDx

Blood tests

- Simple (easy to standardize)
- Quantitative
- Minimally invasive
- Multi-marker (therapeutic target molecules, etc.)

Liquid Biopsy (Alzheimer's Disease)

Elements required for realization of blood tests

1. Highly sensitive measurement: Because target markers are present in the blood in minute quantities
2. Highly specific measurement: To reduce the impact of blood-based similar molecules and impurities
3. Scientific basis: Consistency of changes between marker behavior and brain imaging
4. Medical basis: Relationships between marker behavior and status of cognitive function

HISCL

Sysmex's initiatives

1. **Creation of a highly sensitive measurement system using HISCL**
2. **Verification of specificity of captured molecules (amyloid β)**
3. **Verification of concordance with PET test results (accumulation of amyloid β in the brain)**
4. **Verification of results of markers related to Alzheimer's disease other than amyloid β**

Liquid Biopsy (Alzheimer's Disease)

Measurement with HISCL enables highly sensitive and accurate detection of target amyloid β.

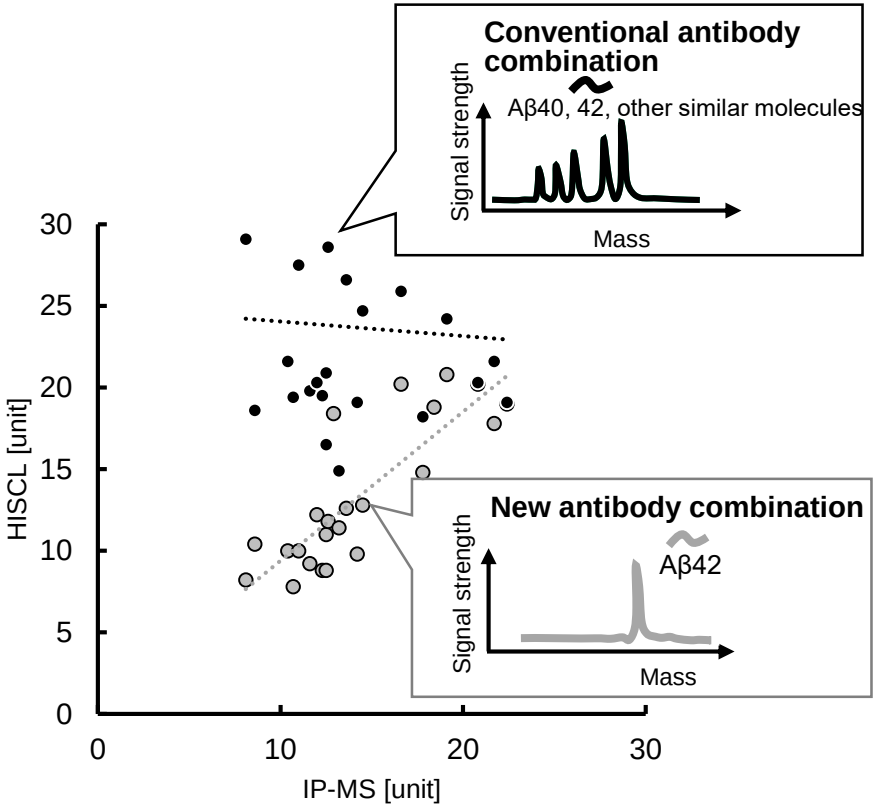
nature
LETTER
doi:10.1038/nature25456

High performance plasma amyloid-β biomarkers for Alzheimer's disease

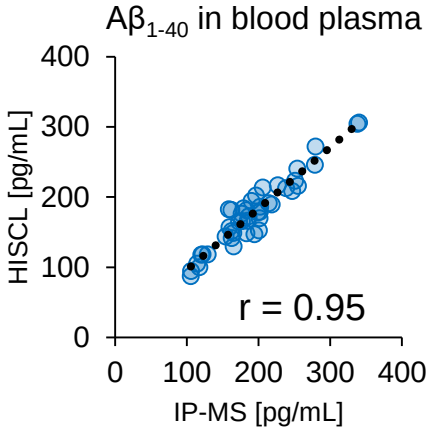
Akinori Nakamura[1], Naoki Kaneko[2], Victor L. Villemagne[3,4], Takashi Kato[1,5], James Doecke[6], Vincent Doré[3,6], Chris Fowler[4], Qiao-Xin Li[4], Ralph Martins[7], Christopher Rowe[3,4], Taisuke Tomita[8], Katsumi Matsuzaki[9], Kenji Ishii[10], Kazunari Ishii[11], Yutaka Arahata[1], Shinichi Iwamoto[2], Kengo Ito[1,5], Koichi Tanaka[2], Colin L. Masters[4] & Katsuhiko Yanagisawa[1]

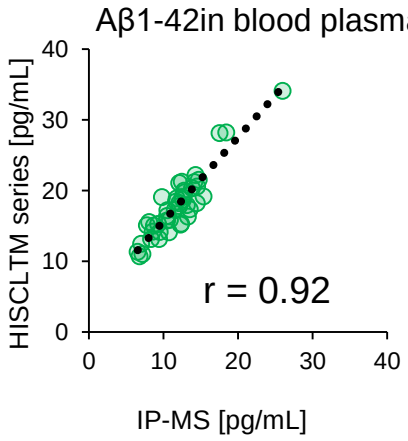
Mass spectrometry

The accurate detection of amyloid β (Aβ40, Aβ42) in the blood reportedly enables prediction of the status of amyloid β accumulation in the brain.



	$Aβ_{1-40}$	$Aβ_{1-42}$
Dynamic range [pg/mL]	8.6 – 975	0.7 – 895
Reproducibility CVs [%]	2 - 5	2 – 6





From a CTAD2019 poster

Liquid Biopsy (Alzheimer's Disease)

A high degree of concordance has been determine with amyloid PET (status of amyloid β accumulation in the brain)

Results of positive PET predictions in clinical subjects (n= approx. 200 cases) in amyloid PET diagnosis

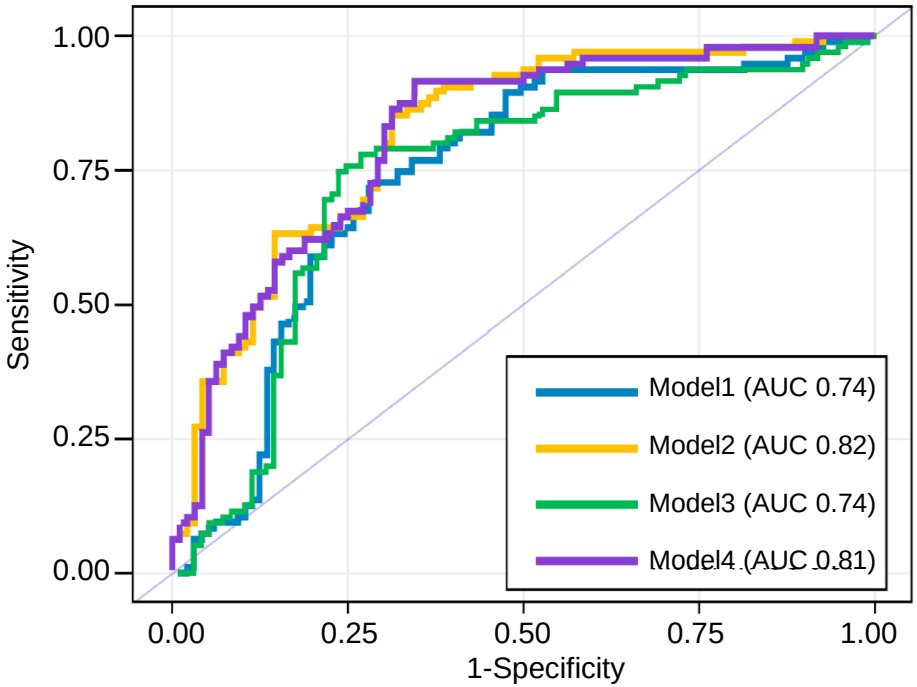
Background of subjects (n=192)	
Average age (standard deviation)	73.3 years (6.28)
Race: Caucasian / other	92.7% / 7.3%
Gender: Male / female	51.0% / 49.0%
APOE4: - / +	57.3% / 42.2%
MCI due to Alzheimer's disease	84.9%
Early stage of mild Alzheimer's disease	10.4%

Amyloid positivity in patients with clinical cognitive dysfunction in clinical trials

Negative: Cognitive dysfunction without amyloid β accumulation in the brain

Positive: MCI, mild AD with amyloid β accumulation in the brain

◆Prediction performance of amyloid β accumulation in the brain by IP-MS (Comparison with PET using flutemetamol)
Sensitivity: 78.7% / specificity: 82.4%
(From Nature. 2018 Feb 8; 554(7691): 249-254)



Model1 = Aβ1-42/Aβ1-40, Model2 = Model1 + age + ApoE4
Model3 = Aβ1-42 + Aβ1-40, Model4 = Model3 + age + ApoE4

CTAD2019 ポスターより

Sensitivity: 73%
Specificity: 71%

Note: When using cutoffs based on Youden Index in Model 1,

Liquid Biopsy (Alzheimer's Disease)

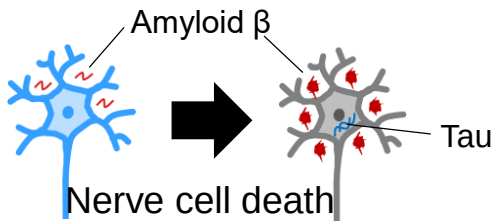
Creation of an HISCL measurement system for parameters other than amyloid β (total tau, phosphorylated tau)

Around the world, efforts are underway to classify the stages of cognitive impairment by using ATN.
(Research framework from the National Institute on Aging and the Alzheimer's Association)

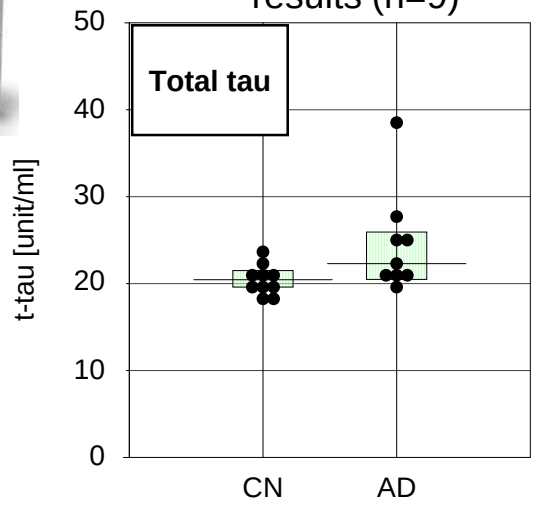
Biomarker profile				Stage of cognitive impairment		
	A	T	N	Normal	Mild cognitive impairment	Dementia
	−	−	−	Normal		Non AD
	+	−	−			AD cognitive impairment
	+	−	+			AD and Non AD
	+	+	−	Pre-symptomatic AD	Prodromal AD	AD
	+	+	+			

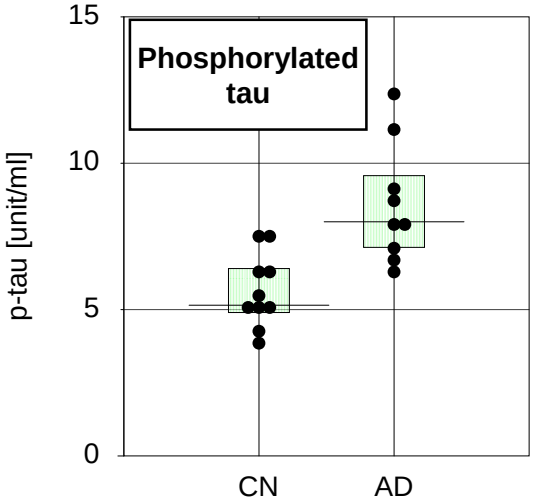
A: Amyloid β, T: Tau protein, N: Neurodegeneration / nerve damage

Adapted from Alzheimer's Dementia. 2018 Apr; 14(4): 535-562



Blood: Subject measurement results (n=9)





4

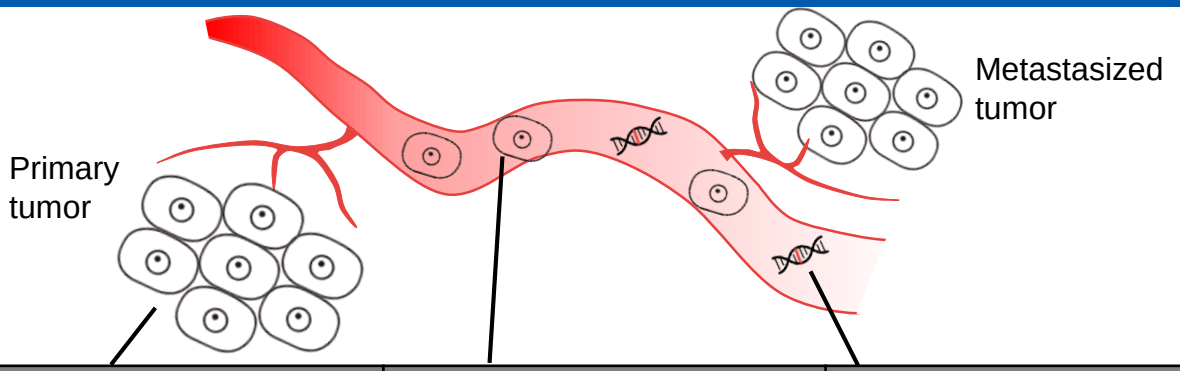
Initiatives for the Realization of Personalized Medicine II

(1) Initiatives Targeting Alzheimer's Disease

(2) Applying Circulating Tumor Cells（CTC）Measurement Technology

Liquid Biopsy (CTCs)

Circulating tumor cells (CTCs), in combination with genetic information, have the potential to facilitate optimized treatment.



	Body	Tissues or cells	Circulating tumor cells (CTCs)	Circulating tumor DNA (ctDNA)
Testing method	MRI, CT, PET	Immunostaining, FISH NGS (cancer genome)	**CTC measurement system**	High-sensitivity PCR NGS
Invasiveness	None	High (surgery, biopsy)	Low (only blood sampling via liquid biopsy)	
Main measurement targets, characteristics	Location, size	Shape / gene / protein	Detailed analysis of protein expression within a single cell	Simultaneous measurement of multiple genetic mutations
Originating tissue			Can be identified	Difficult to identify
Information obtained	Whole body	Localized	Whole body	
Impact on treatment	Screening, severity, monitoring of treatment effects	Confirmed diagnosis, severity, selection of therapeutic drugs	Selection of drugs to target expressed proteins	Selection of drugs to gene mutations

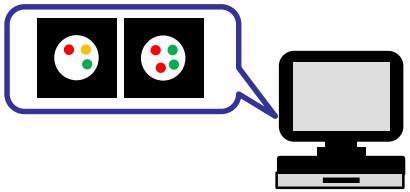
Liquid Biopsy (CTCs)

We have finished building a system and plan to begin offering a lab assay service in Japan and Singapore.

Cell separation and concentration unit

Reagent (CTC panel)

MI-FCM



CTC software

Collaborative research

Biological and medical verification

- Obtain pathological data on CTCs
- Analyze single cells

Clinical verification

- Monitoring of treatment effects / consideration of potential for treatment of metastatic tumors

Colo-rectal cancer | Lung cancer | Prostate cancer | Breast cancer

Creation of clinical value with a view to development for IVD

Lab Assay Services for Research

Customer verification of clinical utility

Development of image analysis methods leveraging data

Liquid Biopsy (CTCs)

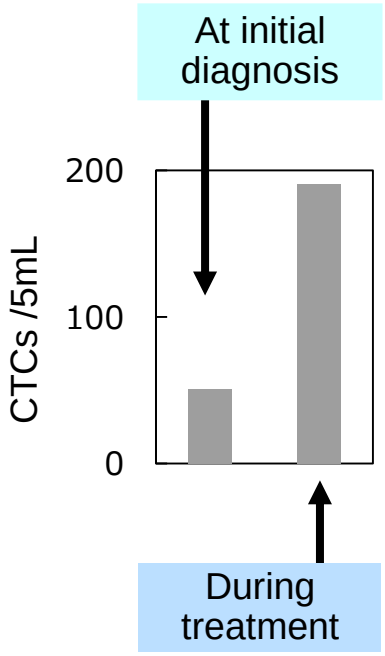
It is suggested that CTCs could be used to track changes in the expression status of the molecules a drug targets.

Patient with untreated stage 4 breast cancer

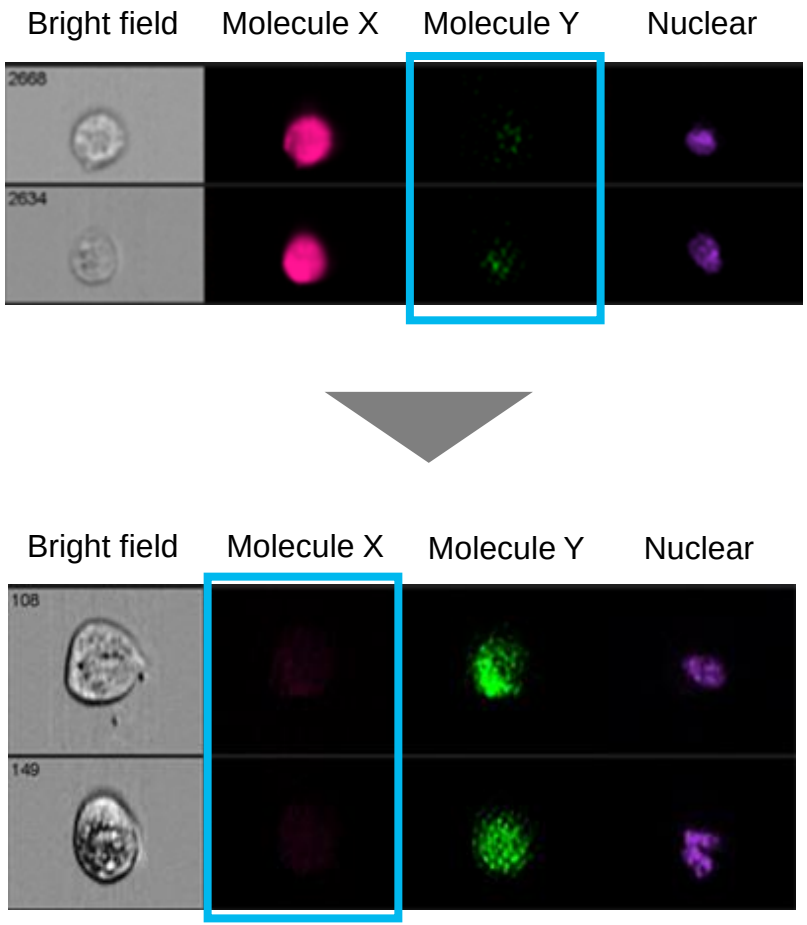
Pathology results
Molecule X expression: Yes
Molecule Y expression: No

Treatment with drugs that target X

Potential for changing the treatment by changing the drug used for treatment



Images of detected CTCs



Going forward, we plan to consider the clinical utility of drug selection based on CTC information.

5

Technology Innovation in the IVD Business

Hiroshi Kanda
Member of the Managing Board and Senior Executive Officer
Managing Director

(1) Enhancing the Operational Value of Blood Coagulation Analyzers

(2) Applying Astrego's Microchannel Technology

(3) Using AI Technology for Blood Imaging Analysis

CN Series
(Launched in Japan in December 2018)

CN-6000/CN-3000 automated blood coagulation analyzers

New CN Series meets the call for further advances in in vitro diagnostics

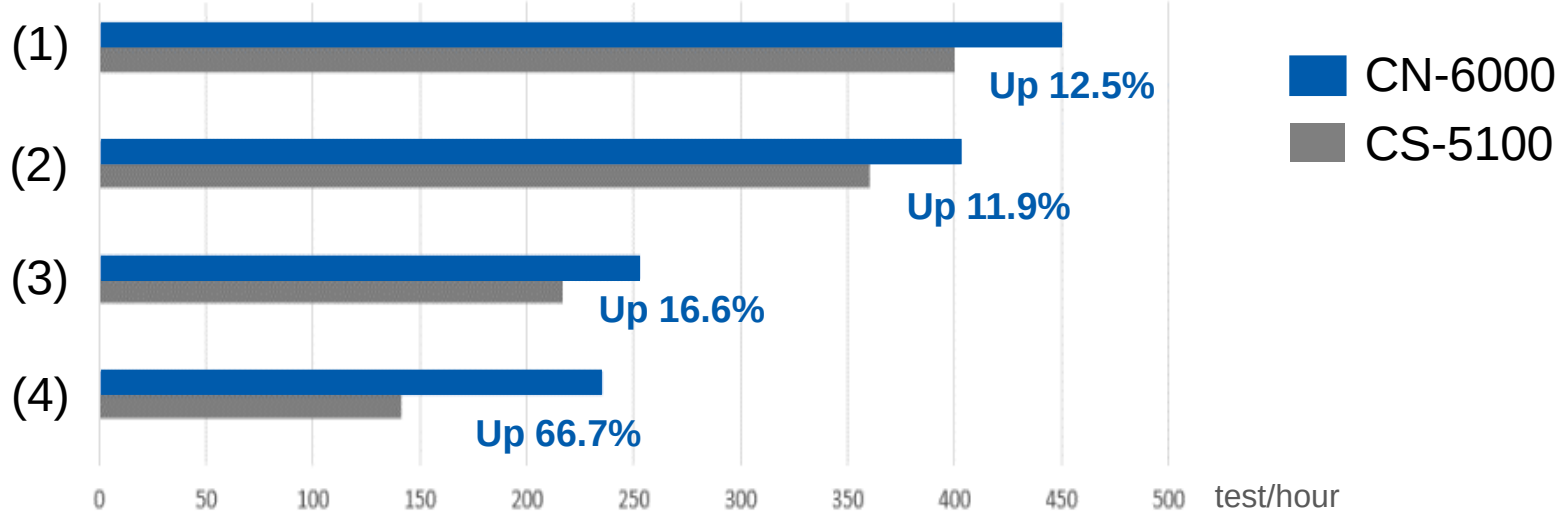
- High-speed processing
- Space-saving
- Transport-compatible
- Network support

Developed by installing new engineering technologies

CN Series
(Launched in Japan in December 2018)

Achieves high-speed processing when measuring multiple parameters

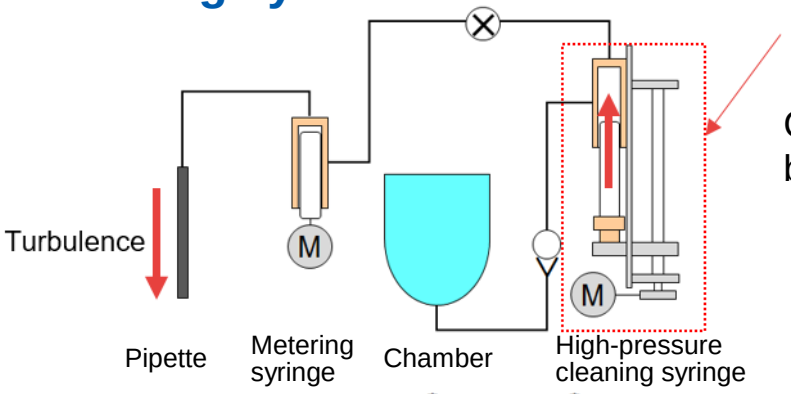
Order pattern (ratio of sample numbers)	
(1) Coagulation principle, single parameter	PT
(2) Coagulation principle, multiple parameters	PT(10)+APTT(10)+Fbg(10)
(3) Coagulation, turbidimetric immunoassay and chromogenic substrate principles, multiple parameters	PT(10)+APTT(8)+Fbg(5)+AT(2)+DD(3)+FDP(3)
(4) Coagulation, turbidimetric immunoassay and chromogenic substrate principles, multiple parameters	PT(10)+APTT(10)+Fbg(10)+AT(10)+DD(10)+FDP(10)



Technologies Incorporated into the CN Series

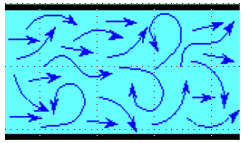
Using high-pressure cleaning to shorten cleaning time

High-pressure cleaning system



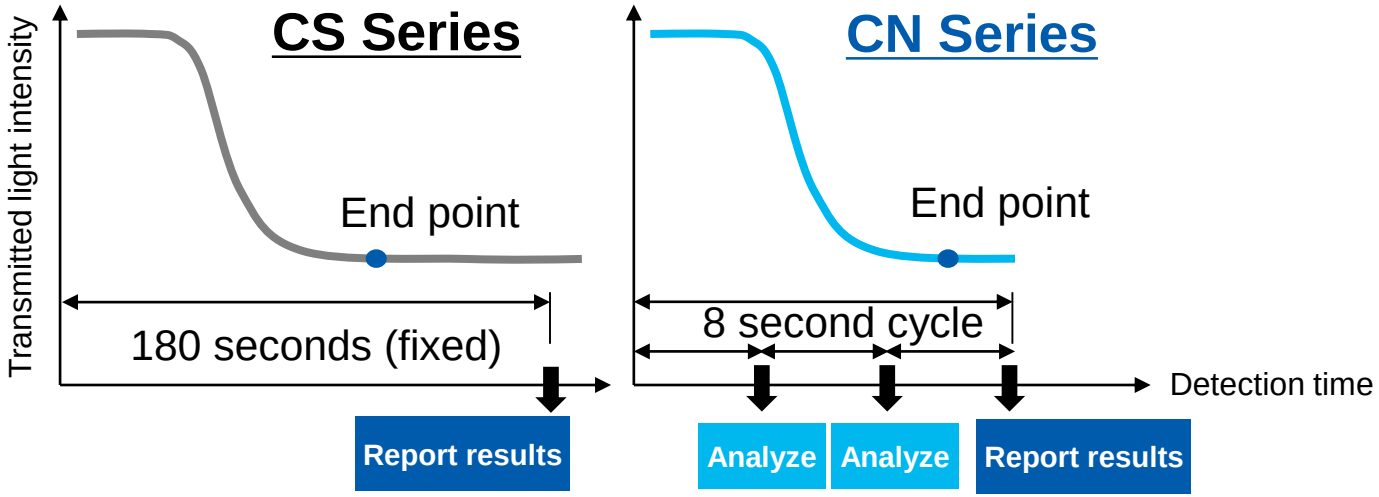
Cleaning liquid forced out at high speed

Generates turbulence for better cleaning



Inside the pipette

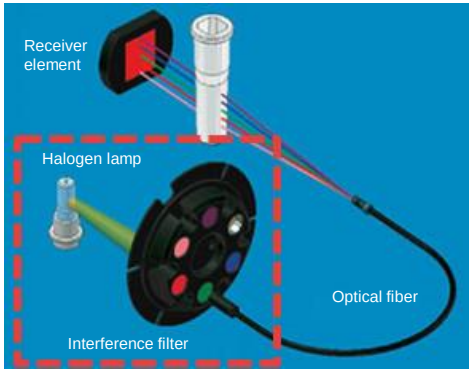
Faster reporting due to an improved analysis algorithm



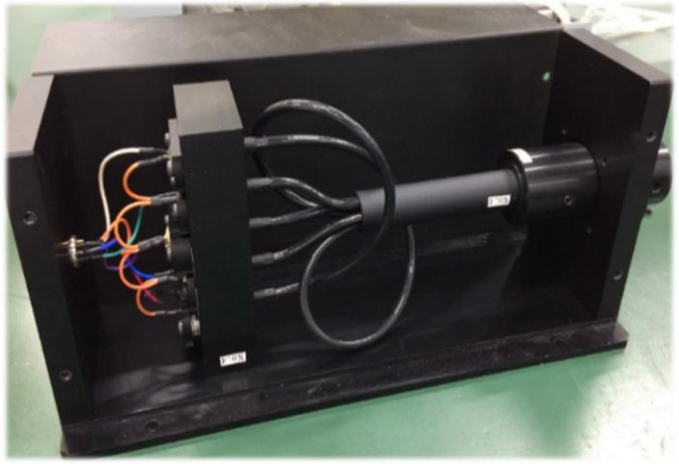
Technologies Incorporated into the CN Series

Life of maintenance-free light source: Five years or more

Multi-wavelength detection method



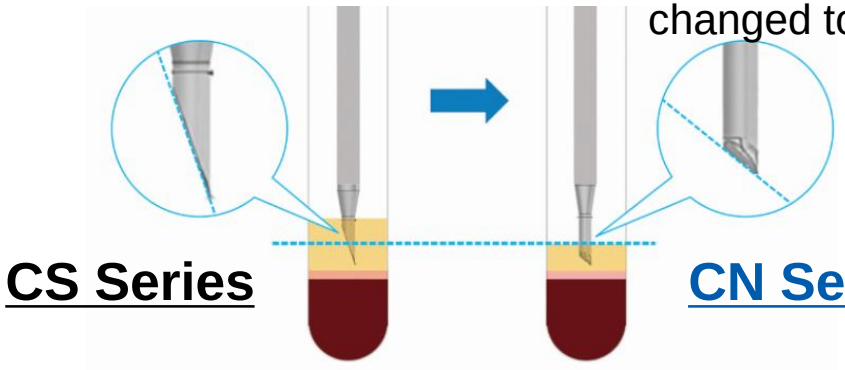
Note: The halogen lamp on the CS needed to be changed periodically, having a life of 1,000 hours (less than three months if operated 24 hours a day)



LED unit that takes over the multi-wavelength function

Enhanced durability and usability

Shape of the needle tip changed to an obtuse angle



CS Series **CN Series**

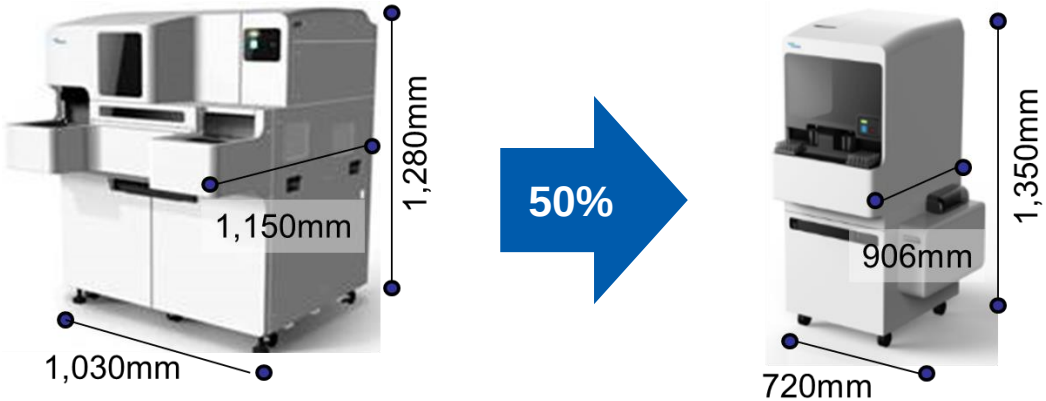
Tripled the durability (to 120,000 piercings) and reduced the dead volume when blood cells are layered

Environmental Considerations in the CN Series (Compared with the CS-5100)

Initiatives contribute to SDGs

1. **More compact and space saving**
   Volume **reduced by approx. 50%**
2. **Power consumption**
   1,700VA→1,080VA
   Reduced by approx. 36% due to improved Pelteir element for cooling reagent
3. **Transport efficiency**
   Weight: 420kg→370kg **12% CO_2 reduction effect**
   Dimensional weight*: 516.6kg→376.5kg **27% reduction**

*Dimensional weight (kg)
= Depth (cm) x width (cm) x height (cm) ÷ 6,000 (cm^3/kg) container box size



CS-5100 **CN-6000/3000**

5

Technology Innovation in the IVD Business

(1) Enhancing the Operational Value of Blood Coagulation Analyzers

(2) Applying Astrego's Microchannel Technology

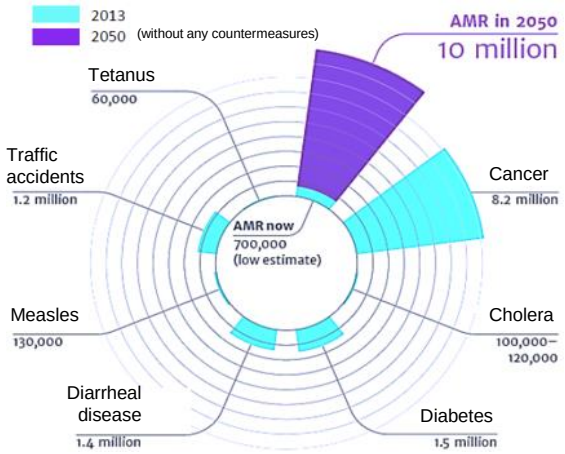
(3) Using AI Technology for Blood Imaging Analysis

Environment Surrounding Urinary Tract Infections

- Currently, infectious diseases still account for around 1/4 of deaths around the world. Malaria, tuberculosis, AIDS and enteral infections are major problems in developing countries, and present urgent issues for multidisciplinary studies (such as health and development studies) as well as infectious disease studies.

- In developed countries, in addition to emerging and re-emergent infectious diseases the spread of bacteria with antimicrobial resistance is becoming a public health issue. Developments in advanced medical care and a growing elderly population are leading to an increase in opportunistic infections among postoperative patients and patients in an immunosuppressive state. Thus routine infectious disease are also becoming an issue.

- A number of people are affected by infectious respiratory-tract diseases, such as those of the upper respiratory tract, as well as bladder infections and other urinary tract infections. This situation is emphasizing the importance of proper early-stage diagnosis and treatment, including the proper use of antimicrobial drugs.

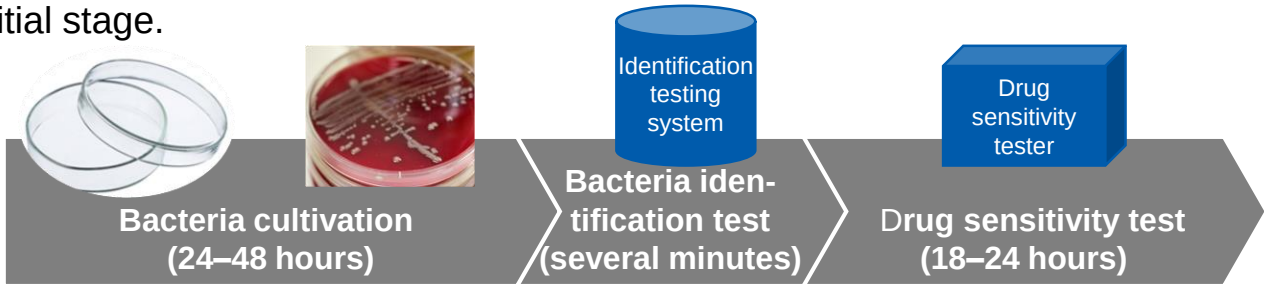


Source: Antimicrobial Resistance: Tackling a crisis for health and wealth of nations, the O'Neill Commission, UK, December 2014

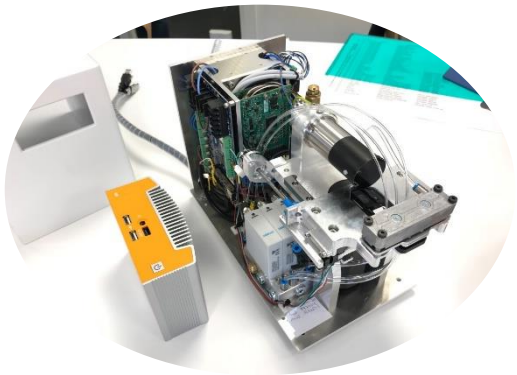
In 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance (AMR). Various countries are pursuing AMR countermeasures, and progress is being reported by the WHO.

Technology for the Rapid Cultivation of Bacteria in Liquid Using Microchannels

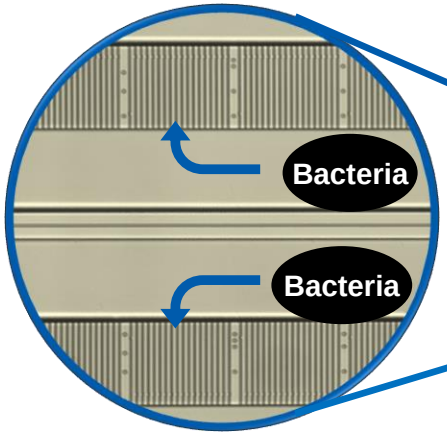
- The process of obtaining test results needed for the appropriate diagnosis and treatment of infectious disease involves cultivating bacteria and running identification and drug sensitivity tests. Currently, results are reported in one–two days for hospitalized patients and more than four days for patients handled by private practices. This situation does not contribute to the proper use of antimicrobial drugs at the initial stage.



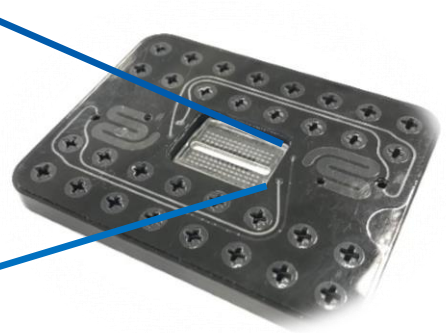
- When cultivated in Petri dishes, bacteria grow in all directions, forming colonies, and the process generally takes 24 hours or more. Astrego's technology involves growing bacterial in one direction within microchannels. This approach allows small changes in growth to be observed, facilitating rapid, 30-minute tests. This is expected to contribute to appropriate diagnosis and treatment at the initial stage.



Prototype machine



Exploded view of microchannel

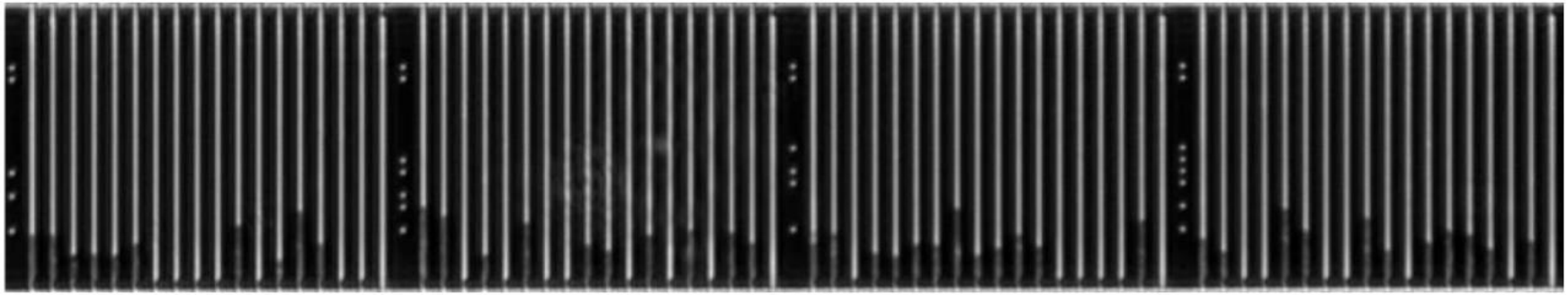


Prototype cartridge

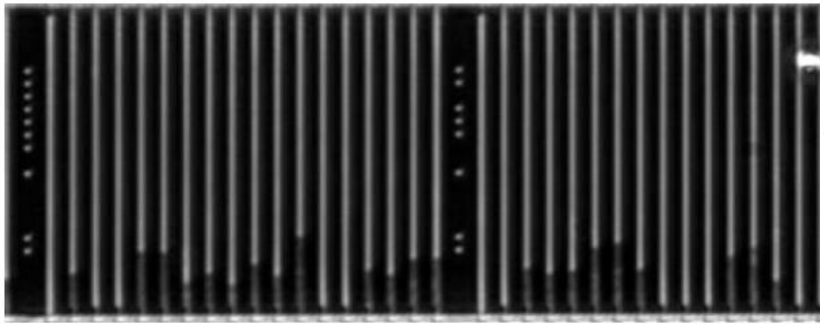
Applying Microchannel Technology to Drug Sensitivity Tests

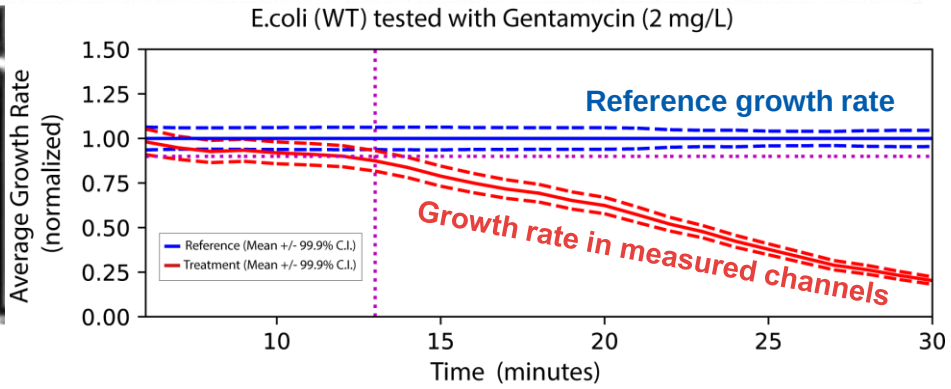
- Multiple channel conditions (different drugs and densities) can be set, allowing changes in growth rate under different conditions to be compared to the reference channels. This approach allows measurement for resistance to multiple antibacterial drugs.
- Different from gene testing, “living bacteria” are used to reveal drug resistance, providing more accurate drug sensitivity test results. (Dead bacteria that do not express resistance are outside the scope of measurement.)

Reference channels (culture liquid only)



Measured channels (with antibacterial drugs)





Leveling off of growth: drug sensitivity exists

5

Technology Innovation in the IVD Business

(1) Enhancing the Operational Value of Blood Coagulation Analyzers

(2) Applying Astrego's Microchannel Technology

(3) Using AI Technology for Blood Imaging Analysis

Using AI Technology in Hematology

Hematology testing flow

Assumes university hospital-class facility using SP-50/DI-60

Laboratory

Blood test

XN Series multiparameter automated hematology analyzer

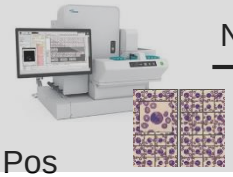
Neg

Pos

SP-50 slide preparation unit

30%-50% of all samples

DI-60 blood image analyzer



Neg

Pos

Microscopic examination by expert technologists (visual)

Cell counting / abnormality detection

10%-15% of all samples

Approx. 2 min./patient

Caresphere™ LWS laboratory information system

Report

- Disease prediction
- Assumptions for additional testing
- Preparation of sample comments

Summarize information used for diagnosis and consultation by doctors

Diagnostics and treatment

Tests are needed that can reduce the burden on laboratory technologists and are not skill-dependent.

Using AI Technology in Hematology

Potential to leverage AI

Assumes university hospital-class facility using SP-50/DI-60

Laboratory

Blood test

XN Series multiparameter automated hematology analyzer

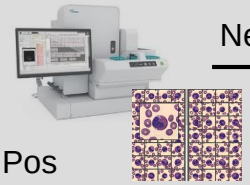
Neg

Pos

SP-50 slide preparation unit

30%-50% of all samples

DI-60 blood image analyzer



Neg

Pos

AI image analysis technology

Cell counting / abnormality detection

10%-15% of all samples

Several seconds/patient

Caresphere™ LWS laboratory information system

Report

- Disease prediction
- Assumptions for additional testing
- Preparation of sample comments

Summarize information used for diagnosis and consultation by doctors

Diagnostics and treatment

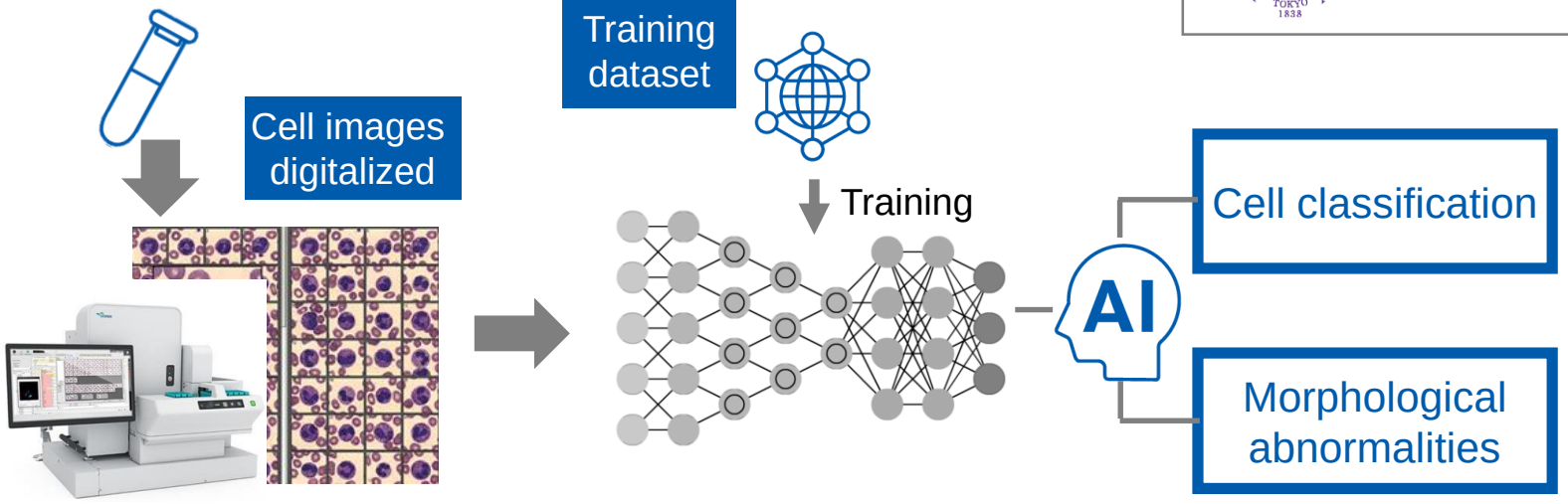
Configuration of an automated system that performs at least as well as expert laboratory technologists

Current initiatives and performance

■ Initiative

Department of Next-Generation Hematology Laboratory Medicine

Extract and learn features of blood cell images using convolutional neural networks



■ Skills needed for AI image analysis and current performance

(1) Ability to differentiate images of blood cells

➡ For all 19 cell types, differentiate to accuracy of 95% or higher

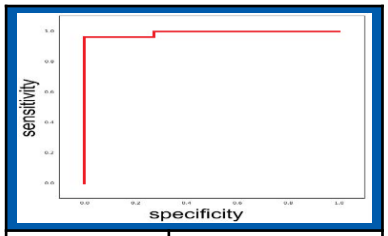
(2) Ability to detect cell abnormality

➡ For 80% of abnormal cells, detect with an accuracy of 90% or higher

New initiatives

- Challenging to realize the technology to distinguish disease using AI image analysis

AI image analysis technology



AUC	0.990

In cases of hematopoietic stem cell abnormalities, ability to distinguish(*1) between MDS(*2) and AA(*3) → reaching 90%

Paper published in *Scientific Reports*(*4), a series by *Nature*, a UK-based journal (Published September 16, 2019)

https://www.nature.com/articles/s41598-019-49942-z

(*1) Sensitivity, specificity
(*2) Myelodysplastic syndrome
(*3) Aplastic anemia
(*4) Scientific Reports : Impact factor 4.011

Increase the performance of AI image analysis technology, combine with existing hematology technology, and achieve new technological advances

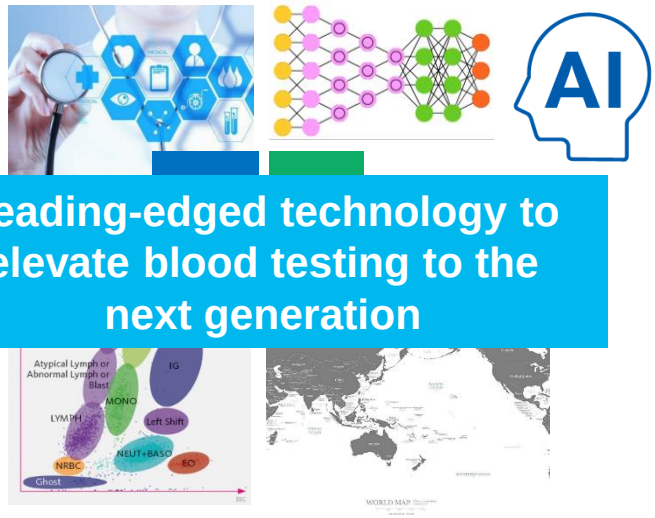
Transform into clinical value that helps support diagnosis

Future developments

Sysmex Way

Mission

Shaping the advancement of healthcare.



Leading-edged technology to elevate blood testing to the next generation

×

Global standard in blood testing

Roll out a hematology digital platform as the foundation of next-generation hematology testing technology

Appendix

Glossary

Glossary

Slide No.		
4	**Primary care**	The initial care provided at clinics or other locations when a patient first falls ill.
4	**IVD**	Acronym for “in vitro diagnostics.” Refers to in vitro diagnostic pharmaceuticals and products that have received regulatory approval.
5	**Personalized medicine**	This type of medicine goes beyond the conventional practice of providing selected predetermined or uniform treatment for a given disease. Instead, the selection of treatment is optimized for individual patient characteristics, based on gene and other testing data.
7	**RAS**	One of the gene that is known to cause cancer when it mutates.
8	**BEAMing**	An acronym for “Bead, Emulsion, Amplification, and Magnetics,” this gene analysis method combines ultrahigh-sensitivity PCR and flow cytometry technologies for analysis of genetic mutations.
8	**Liquid biopsy**	This is a general name for technology using blood or body fluid samples for diagnosis and the prediction of treatment impacts rather than through the conventional practice of tissue biopsy, in which diagnosis is performed on diseased tissue that has been collected. Liquid biopsy is less invasive than tissue biopsy, but more highly sensitive detection technologies are required.
8	**CTC**	Acronym for “circulating tumor cell.” CTCs refer to cancer cells that have broken away from primary or metastatic cancer sites and are circulating in the blood.
8	**Urinary tract infections**	The urinary tract runs between the kidneys and the urethral opening. Inflammations due to the incursion of bacteria into the urinary tract are known as urinary tract infections. Such infections can lead to bladder inflammation and pyelonephritis (inflammation of the kidneys).
8	**Drug susceptibility test**	A test to determine the efficacy of various antimicrobial drugs against pathogenic bacteria detected in a sample.
10	**Technology platform**	Refers to Sysmex’s three technologies - gene measurement, cell measurement and protein measurement - and the measurement platforms that utilize them.
10	**Regenerative medicine**	This type of medicine seeks to repair, regenerate and restore function of tissues and organs that have been lost, injured or lost function due to disease or accident by using cells and tissues cultivated outside a patient’s body.
10	**Preventive/preemptive medicine**	Preventive medicine uses gene testing and other types of testing to diagnose and prognosticate diseases that are likely to occur, and seeks to prevent their occurrence. Preemptive medicine follows the onset of symptoms and seeks to prevent disease from becoming more serious.
12	**Application**	Corresponds to a “test item” in Sysmex’s technology platforms.

Glossary

Slide No.		
13	**Plasma-Safe-SeqS (PSS)**	Acronym for “Plasma-Safe-Sequencing.” This pretreatment technology is used to discern between gene mutations and read errors by attaching tags to genes to be amplified.
13	**PCR**	Acronym for “polymerase chain reaction.” A gene amplification technology for copying small quantities of DNA to produce larger quantities.
13	**FISH**	An abbreviation of Fluorescence In Situ Hybridization. The term refers to a testing method that uses fluorescent probe that binds only to specific genes to detect target genes within a chromosome.
14	**LDT**	Acronym for “laboratory developed test.” LDTs, often testing methods that have not received regulatory approval, include highly sophisticated and complex gene testing that can only be performed in specific clinical testing labs.
15	**GIMS**	Acronym for "Genome Information Management System."
22	**CDx**	Short for “companion diagnostics.” Clinical testing performed to predict the efficacy and side effects of drugs before using them for treatment.
22	**NGS**	Acronym for “next-generation sequencer.” May also refer to a next-generation sequencer, an instrument for reading gene base sequences at high speed.
22	**ctDNA**	Cancer-derived DNA circulating in the blood. A focus of growing attention as a non-invasive cancer biomarker for testing using liquid biopsy.
29	**Expert panel**	A multidisciplinary investigative commission that meets to interpret gene panel testing results medically. Convened at core hospitals for cancer genomic medicine, expert panels recommend treatment methods optimized for individual patients on the basis of abnormal gene information. Members of such panels include oncologists, genome researchers, counselors, etc.
29	**Center for Cancer Genomics and Advanced Therapeutics (C-CAT)**	A new cancer genomic medicine base established by the National Cancer Center. It was created to collect and store nationwide information regarding genomic medicine and to create mechanisms that enable the discovery of new medical treatments via the appropriate utilization and application of this information.
31	**Three Guidelines from Three Ministries**	Three guidelines established by three Japanese ministries (the Ministry of Health, Labour and Welfare; the Ministry of Economy, Trade and Industry; and the Ministry of Internal Affairs and Communications) for the handling of electronic medical information.
35	**iPSCs, hPSCs**	iPSCs are induced pluripotent stem cells. hPSCs are human pluripotent stem cells. hPSCs include human-derived embryonic stem cells and iPSs.
38	**Amyloid-β (Aβ)**	A key constituent of senile plaque, a pathological characteristic of the brain tissue of patients with Alzheimer’s disease, composed of around 40 amino acids.

Glossary

Slide No.		
38	**Tau**	A microtubule-associated protein that exists in central neuronal cells. Along with senile plaque, inordinately phosphorylated deposits of tau protein (neurofibrillary tangle) can be observed in the brains of patients with Alzheimer's disease.
38	**MCI**	Acronym for "mild cognitive impairment."
40	**Lewy body dementia**	A cognitive disease caused by the expression of clusters of proteins (called Lewy bodies) in nerve cells in the brain.
56	**Antimicrobial resistance**	This phenomenon occurs when living organisms develop a resistance to a drug, whose efficacy is reduced or nullified as a result. Bacteria that have developed microbial resistance are known as antimicrobial-resistant bacteria.
57	**Identification test**	A test to determine the name of bacteria that are the source of an infectious disease detected in a sample.
60	**Blood smear sample**	Prepared for microscopy of blood cell morphology by placing a drop of blood on a glass slide, and then drying and staining it.
60	**Caresphere™**	Caresphere utilizes IoT and the cloud to establish a platform for the real-time linking and analysis of a variety of information managed using testing instruments and clinical laboratory information systems. It is a new network solution that provides support for increasing the operational efficiency of professionals involved in testing and healthcare, enhancing quality and raising patient satisfaction.
63	**Hematopoietic stem cells**	Cells that produce red blood cells, white blood cells and blood platelets in the bone marrow.
64	**Digital platform**	New platforms for business that are based on digital technology. Within the healthcare market, this term refers to IoT platforms that support healthy lives and enable seamless care in terms of prevention, diagnosis, treatment and home care.

Lighting the way with diagnostics