The 21st R&D Meeting

March 8, 2024
Sysmex Corporation

Together for a better healthcare journey

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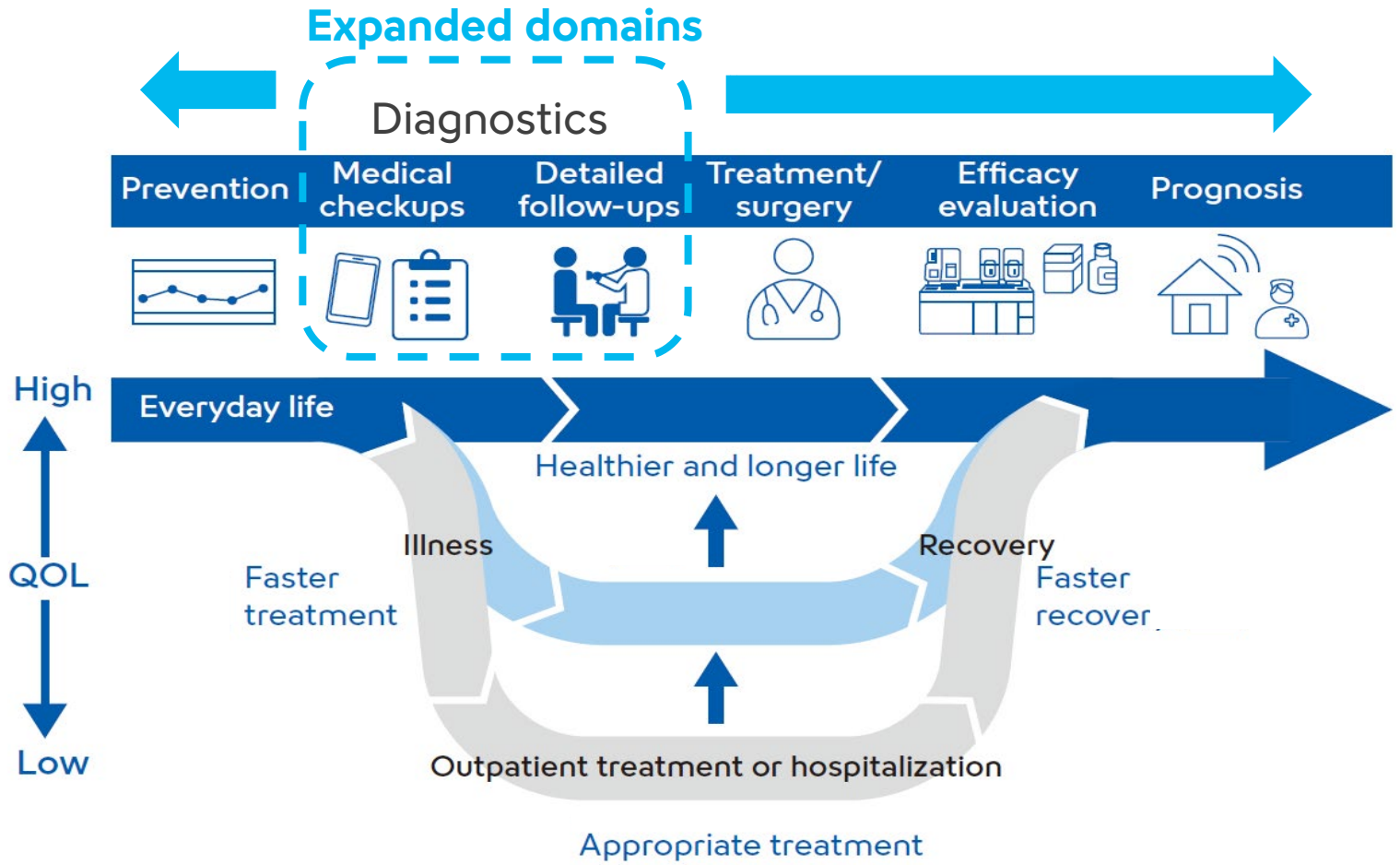
1 R&D Initiatives to Achieve the Healthcare Journey

Tomokazu Yoshida
Member of the Managing Board and
Senior Executive Officer
Managing Director, CTO

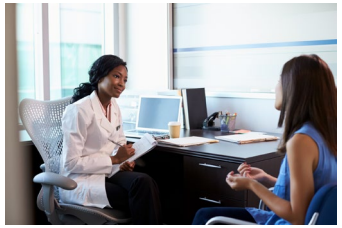
Sysmex's Long-Term Vision
"Together for a better healthcare journey"

Realizing a healthy life and a prosperous healthy society
by providing healthcare for each individual



Environmental Analysis: Responding to Advances in and the Implementation of Health Tech

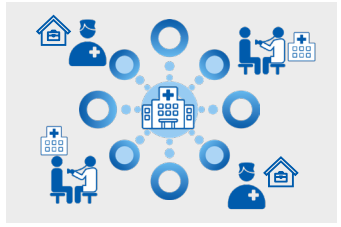
Changing healthcare awareness




- ✓ Shift from treatment to prevention
- ✓ Self-medication
- ✓ Healthcare education

Transformation of healthcare flow as healthcare becomes more personalized and decentralized

Implementation of digital technologies

- ✓ Widespread adoption of Web 3.0, AI, metaverse, etc.
- ✓ Full-scale development of remote medical care

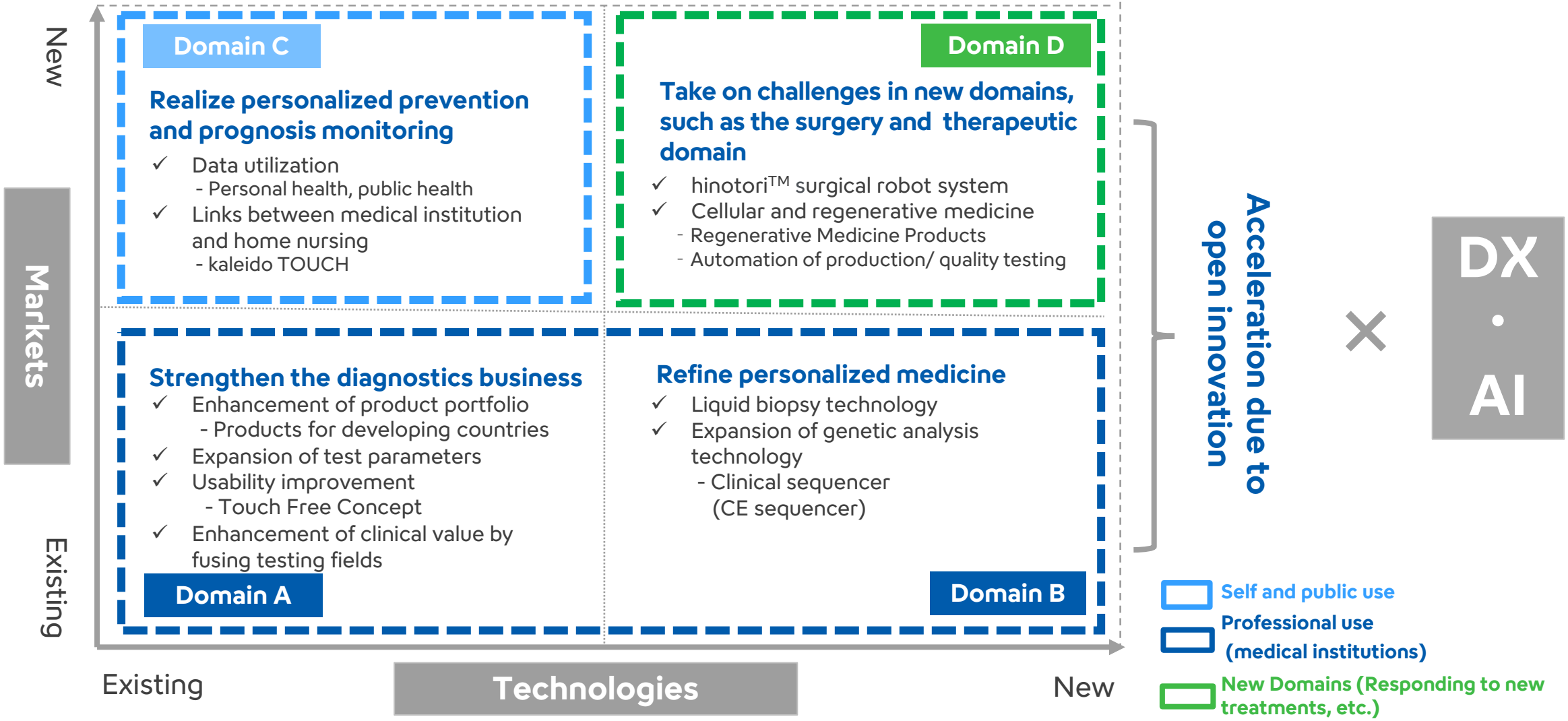
Application of digitization technology in medicine

New treatment modalities


- ✓ New Alzheimer's disease drugs
- ✓ Practical application of regenerative cell medicine

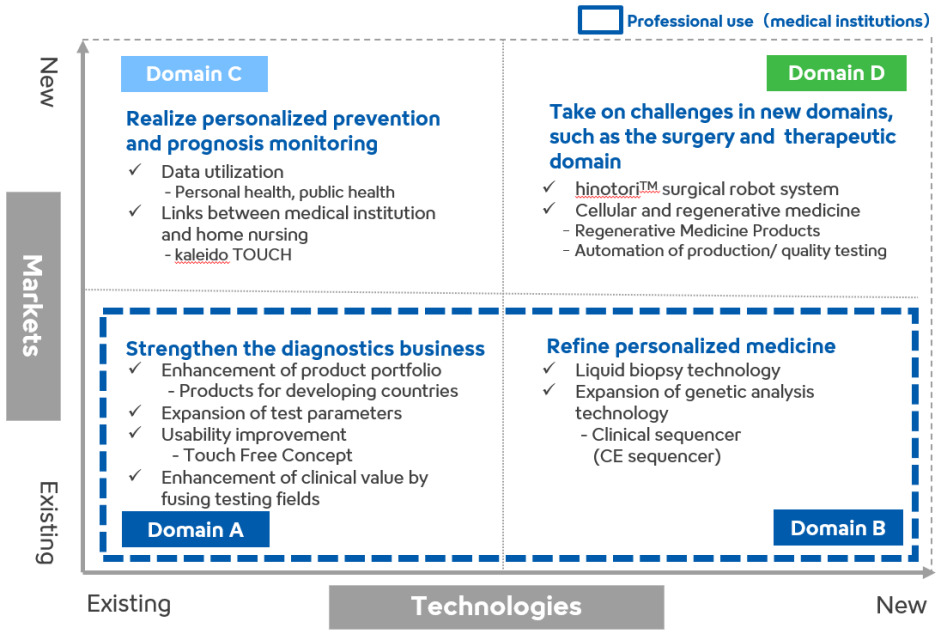
Responding to increasingly sophisticated treatment

Expansion from the Professional to the Self- and Public Health Markets



Domains A and B: Providing Value in Existing Markets (Professional)

Achieving greater efficiency and precision in healthcare



- **Strengthen the diagnostics business**
  - ✓ Expansion of testing parameters
    - Utilization of alliance partners
  - ✓ Unparalleled differentiation through operational value
    - Integration of hematology and hemostasis
  - ✓ Integration of diagnostic results across testing fields utilizing AI

- **Refine personalized medicine**
  - ✓ Expansion of liquid biopsy
    - Realization of minimally invasive and personalized medicine
    - Hepatic fibrosis, dementia, cancer
  - ✓ Realization of clinical sequencing
    - Utilization of CES technology: cancer genomics, genetic diseases

Accelerating R&D through Open Innovation (1)

Leveraging the strengths of both companies to establish a competitive advantage and realize liquid biopsy for neurodegenerative diseases

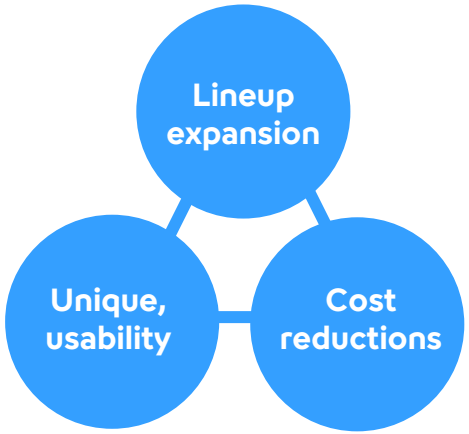
Strengthen competitiveness through collaboration and establish absolute superiority through proprietary technologies

sysmex × FUJIREBIO

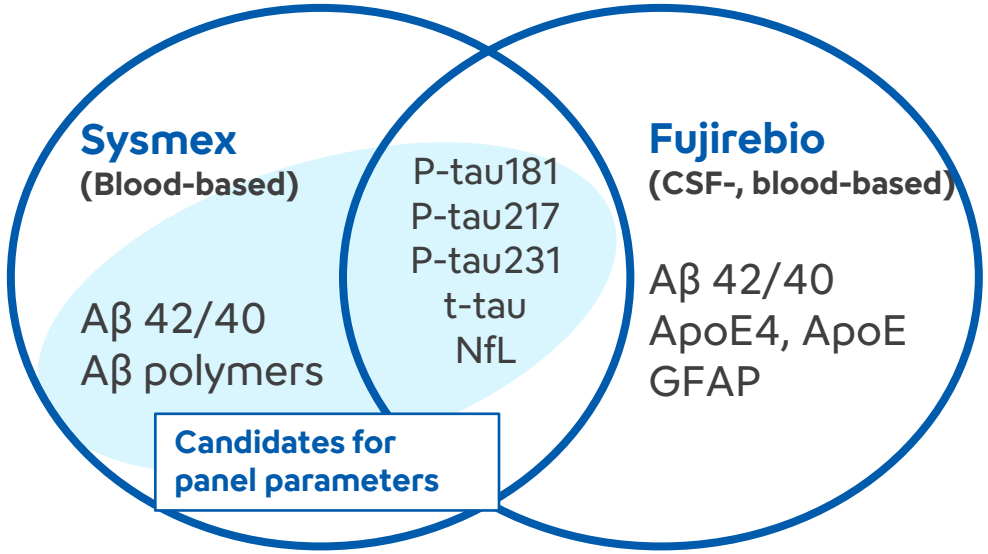
- High-quality equipment design technology
- Simultaneous development of reagents and instruments
- Global sales network

Automated Immunoassay System HISCL™-5000

- Raw material lineup
- Immunochemistry reagent development (CDMO)



Expansion of testing parameters for neurodegenerative diseases (Alzheimer's disease)



Accelerating R&D through Open Innovation (2)

Promoting IVD development of a new gene measurement analyzer using CES technology

Challenges for genomic medicine

- ✓ Insufficient clinical application of large amounts of information
- ✓ Testing costs are high, testing methods are complicated, and the tests are not versatile
- ✓ The number of medical institutions that can perform genome testing is limited

sysmex × HITACHI Inspire the Next

- High-quality instrument design technology
- Simultaneous development of reagents and instruments
- Global sales network
- NGS reagent development technology
- NGS analysis technology

- High-performance instrument design technology
- CES technology and instruments

Capillary electrophoresis sequencer

Promoting new product development through collaboration

By combining the two companies' technologies, we are working to create new clinical sequencers that can be used for testing at a wide range of medical institutions.

Domains A and B + AI: Advancing from Measurement Data to Testing Information

Increasingly sophisticated testing through the analysis of test values and measurement data

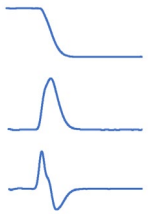
Using AI to predict causes of APTT prolongation from coagulation waveforms

Hemostasis test

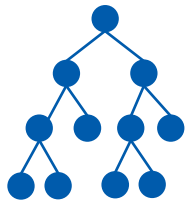
APTT, PT tests

CN-6000
Automated Blood
Coagulation Analyzer

Measurement data



Machine learning



Factor prediction

- Hemophilia
- LA
- Abnormal liver function
- Heparin
- DOACs
- Warfarin

Results with sensitivity greater than 75% and specificity greater than 95% for six causes

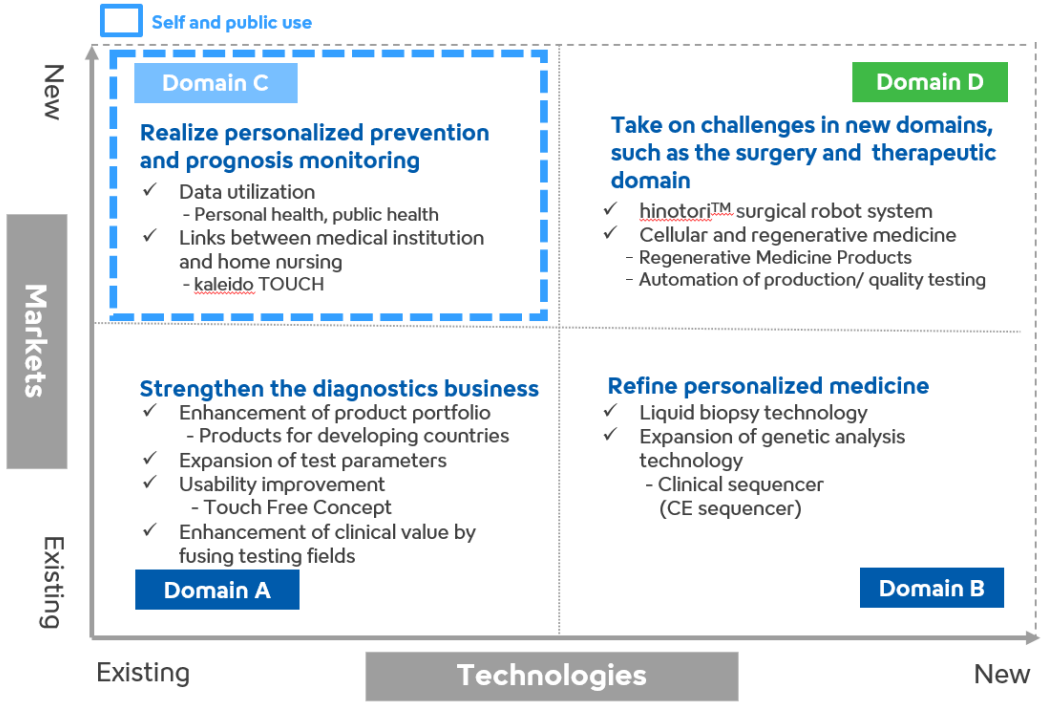
	Hemophilia	LA	Abnormal liver function	Heparin	DOACs	Warfarin
Sensitivity (%)	100.0	85.7	75.0	87.0	87.6	98.1
Specificity (%)	95.0	95.3	95.1	95.2	95.0	95.3

Joint research with Niigata University, Tenri University, and Tenri Hospital

LA: Lupus anticoagulant
DOACs: Direct oral anticoagulants

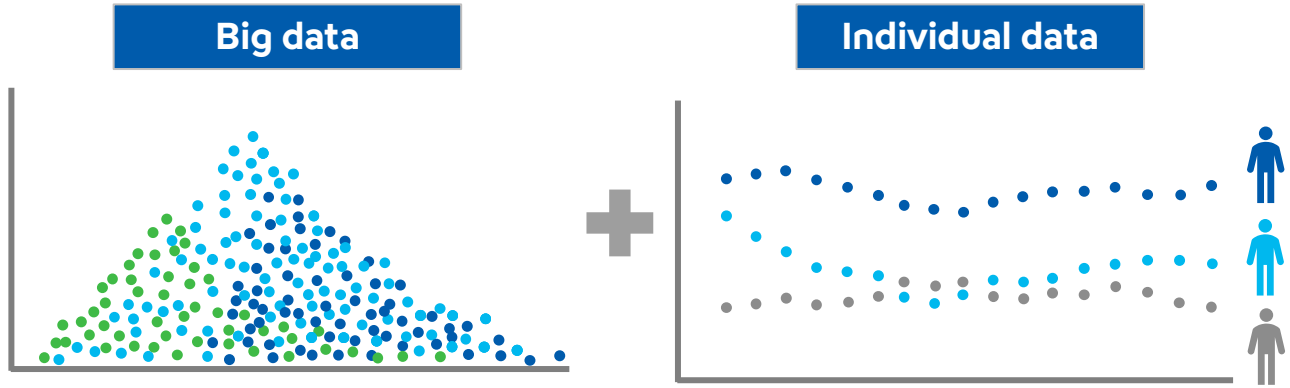
Domain C: Rolling out Existing Technology into New Markets

Creating new markets by utilizing data and strengthening medical collaboration



- **Prevention and prognosis risk monitoring**

✓ System implementation of data utilization/AI technology
✓ Provision of healthcare literacy
✓ Strengthening of cooperation between medical institutions and home healthcare (kaleido TOUCH)



Domain C: Medical Collaboration Platform

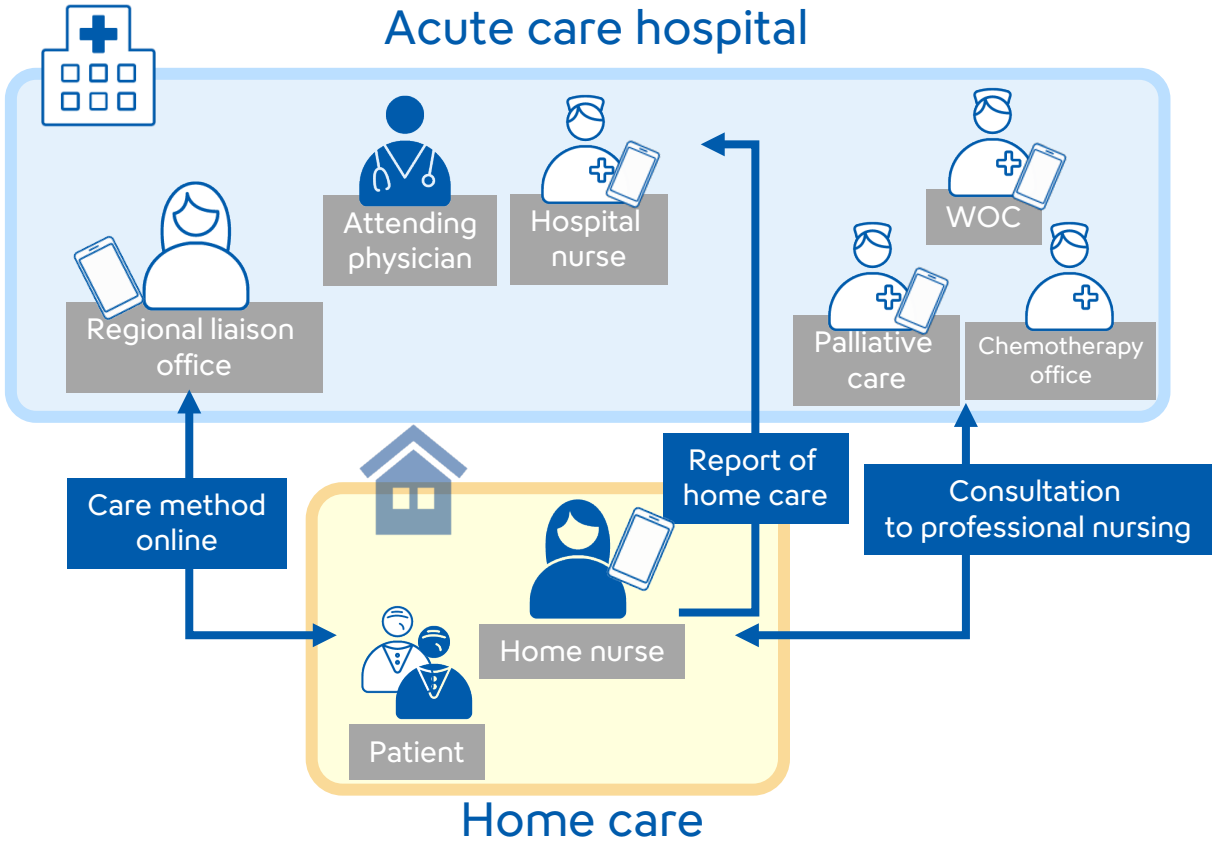
Rollout of a medical collaboration system that uses our nurse-to-nurse collaboration app (Kaleido TOUCH™) to facilitate the decentralization of medical functions

Nurse-to nurse collaboration APP connecting hospital care and home care

“Kaleido TOUCH™”

kaleido TOUCH

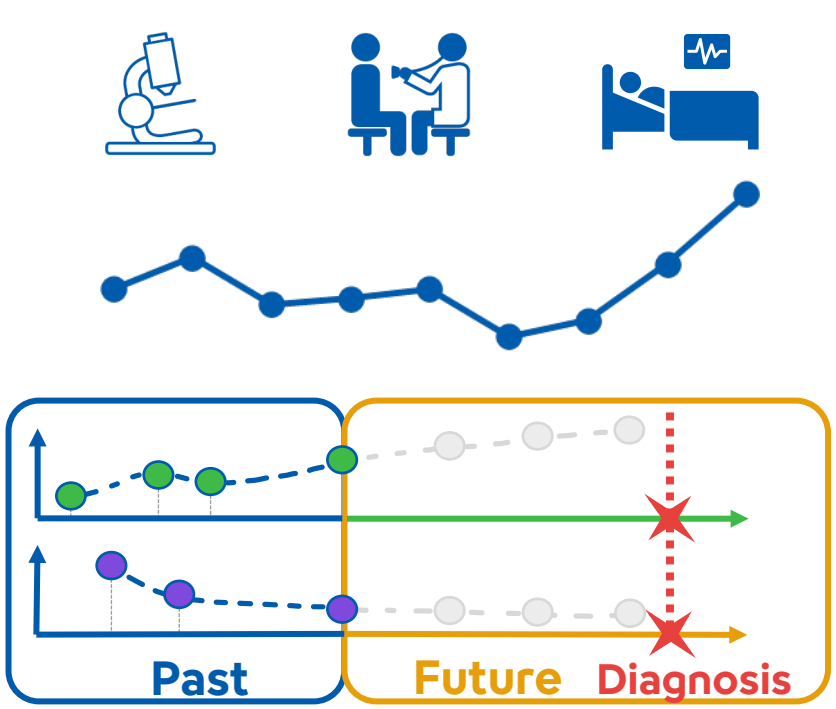
Nurse-to nurse collaboration APP “Kaleido TOUCH™”

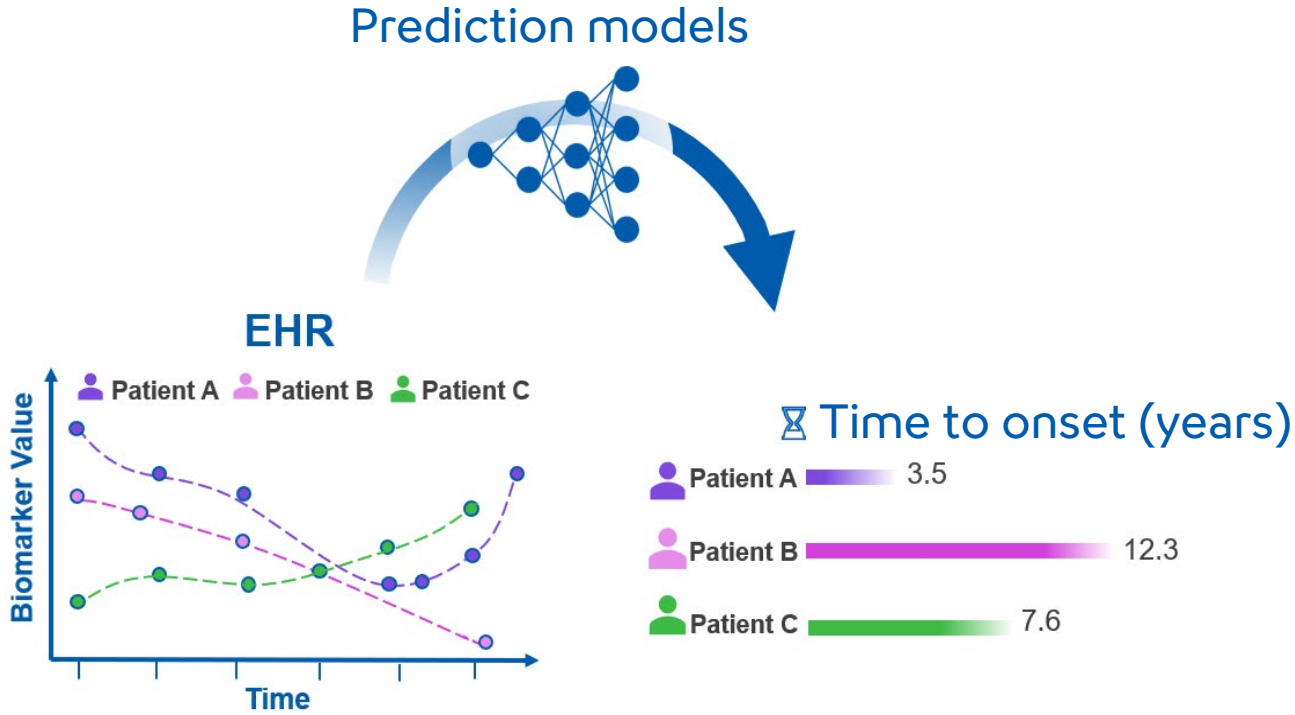


Source: https://www.dpula.co.jp/kaleidotouch/index.html（Japanese only）

Domain C + DX and AI: Behavioral Change Based on Testing Data

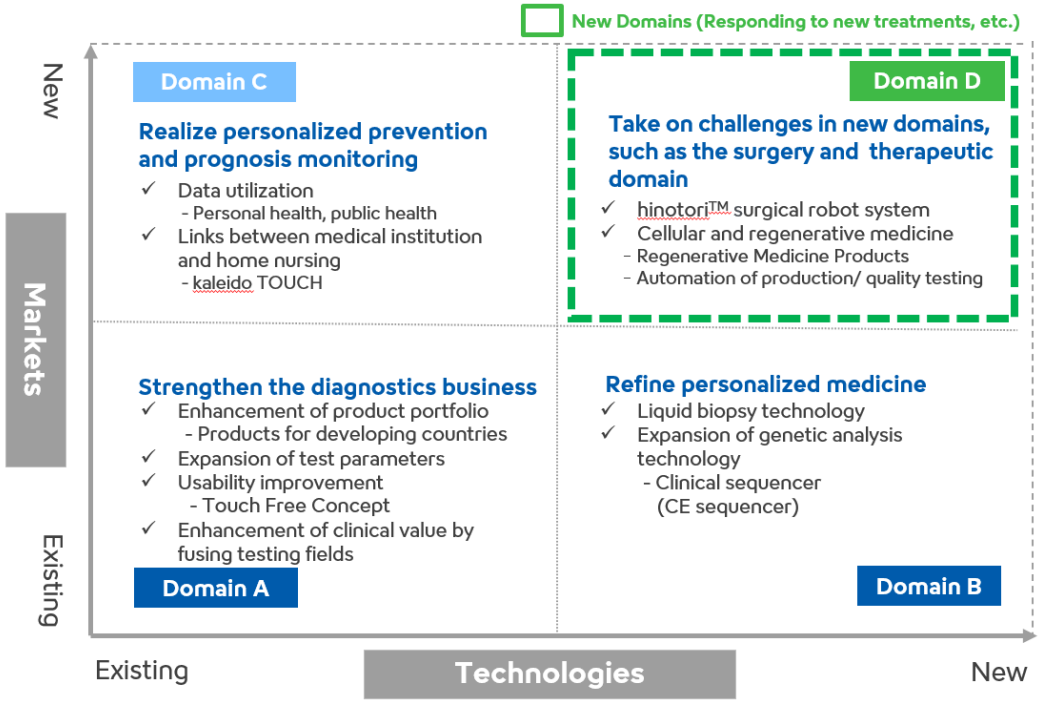
Development of technology to detect signs of disease and recurrence through accumulation and analysis of personal time-series examination data





- ✓ Established a joint research chair at Hirosaki University and began analyzing multimodal data utilizing the results of health checkups of local residents over a period of about 20 years
- ✓ Collaborating with several medical institutions in Japan and engaging in similar initiatives in Europe

Domain D: Technological Development to Take up New Market Challenges (Treatment, Surgery)



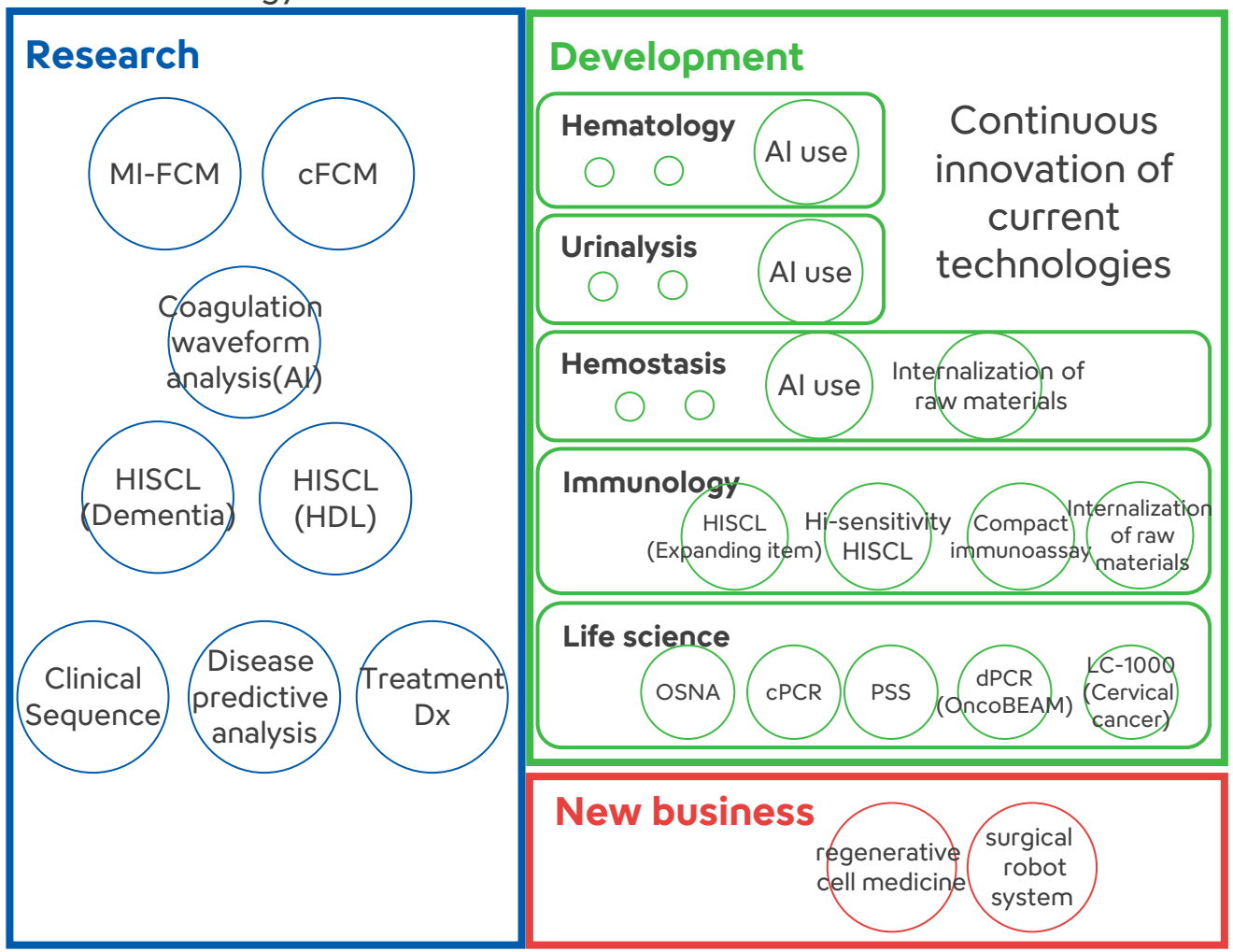
- **New treatments and diagnosis**
  - ✓ Service that integrates hinotori surgical robot system and IoT
  - ✓ Advanced quality control technology for cellular preparations
  - ✓ Creation of new highly effective therapeutics and diagnostics based on precision measurement and diagnostic plat form technology
    - Selection of treatment subjects, verification of therapeutic drug efficacy
    - Monitoring of adverse drug reactions

AlliedCel JUNTENBIO Mega karyon

Pivoting Technology Themes

Shift priorities ward expansion and clinical implementation of technology platforms and biomarkers

Main Technology Themes



Pivot index

- ✓ Market size (including future potential)
- ✓ Technological advantage
- ✓ Practical development period
- ✓ Technical difficulty (feasibility)
- ✓ Investment size
- ✓ Pharmaceutical approval requirement level

Resource allocation

Development：Research+ New business = 7 : 3

Reassessment of high-sensitivity gene assay platform

· From BEAMing to PSS (Plasma-Safe-SeqS)

Reassessment of cell measurement and analysis platform

· Discontinue development of LC-1000 (cervical cancer)

Reassessment of other development themes

Themes for Explanation Today

Strengthen the Diagnostics Business

- ✓ **Innovation in Hematology Fields**

Takaaki Nagai
Executive Officer
Executive Vice President of System Engineering Div.

Refine Personalized Medicine

- ✓ **Initiatives Targeting Central Nervous System Diseases (Alzheimer's Disease Testing)**
- ✓ **Initiatives Targeting Cardiovascular Diseases (HDL Function)**
- ✓ **Initiatives Targeting Personalized Medicine (Gene Measurement Technologies)**

Toshiyuki Sato
Executive Vice President of
Central Research Laboratories

Challenges in New Domains

- ✓ **Initiatives Targeting Regenerative and Cellular Medicine**

Kenji Tsujimoto
Executive Vice President of Next Generation
Medical Business Development Office

2 Innovation in Hematology Fields

Takaaki Nagai
Executive Officer
Executive Vice President of
System Engineering Div.

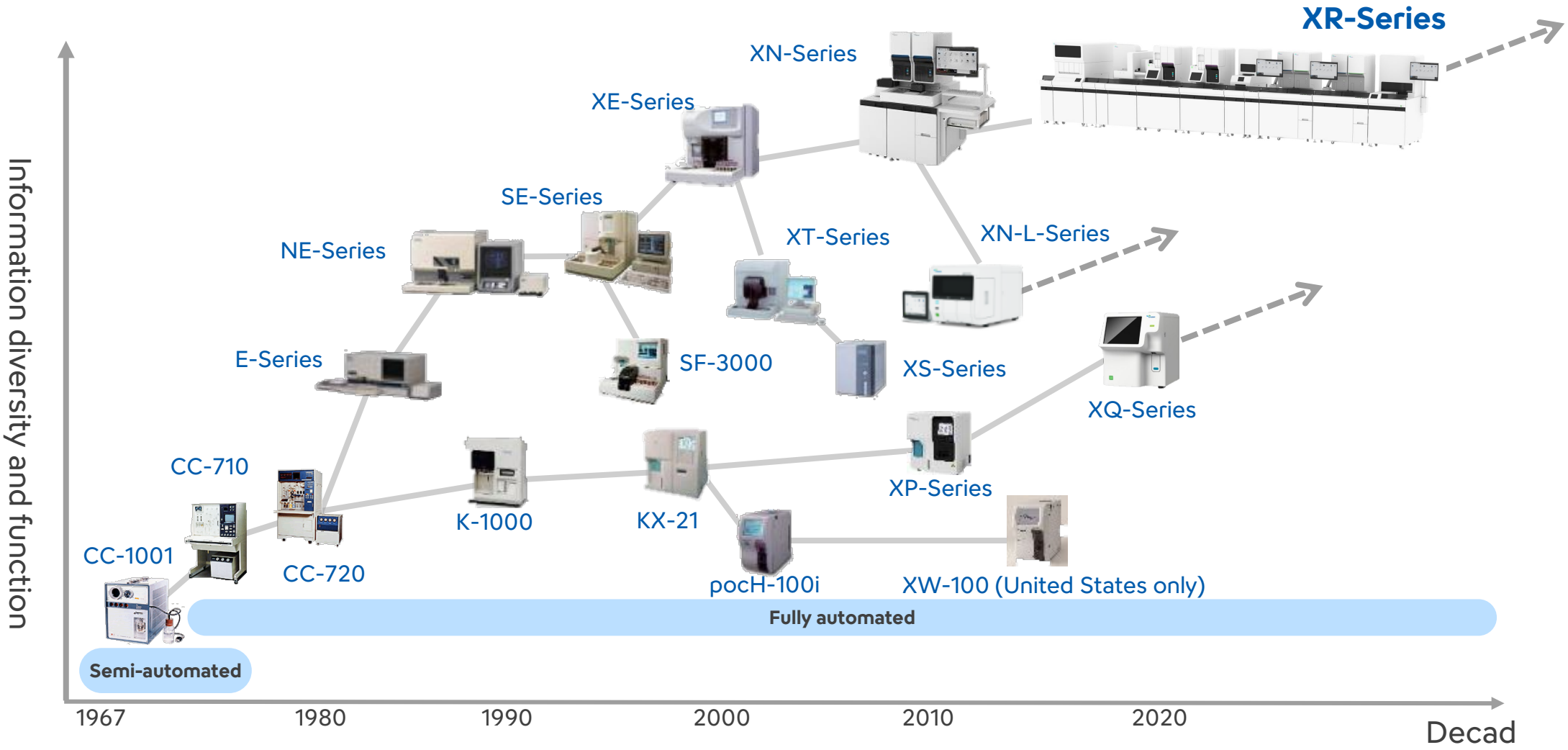
(1) History of Hematology Instruments

(2) Integration of Hematology and Other Fields

(3) Future Outlook

(1) History of Hematology Instruments

History of Hematology Instruments



We are always working to create new value by ascertaining changes in the environment.

Rollout of Transport Systems in the Hematology Field

	1980s onward	2000s	2010s
Healthcare issues, needs	✓ Reduced laboratory costs as medical costs decline ✓ Decrease in infection risk	✓ Stricter laboratory management (ISO compliance) ✓ Response to digitalization	✓ Support for a variety of laboratory needs globally ✓ More efficient testing workflows
Value provided	**Increased testing efficiency** ✓ Development of the world's first transport system improves testing efficiency and safety	**Digitalization of testing** ✓ ICT-based services and support ✓ Introduction of online quality control	**More sophisticated testing** ✓ Reduced frequency of reagent changes by introducing concentrated reagents and reagent cartridges ✓ Decrease in downtime due to preventive maintenance ✓ Automatic retesting functionality on all models

HS-Series

HST-N

XN-Series

Providing New Value through the XR-Series

Healthcare issues, needs

- ✓ Provide testing that offers higher diagnostic value and further improve overall laboratory environments
- ✓ Apply advances in AI and ICT to reduce the amount of labor needed for testing

XR-Series

Operational value

- ✓ Bringing surprise and pleasure to customer by reducing workloads (a “Wow!” experience)
- ✓ Reduce manual operations thoroughly by shifting to automation, reduction and integration, and realize an environment where customers can focus on specialized work

Touch-free concept

Clinical value

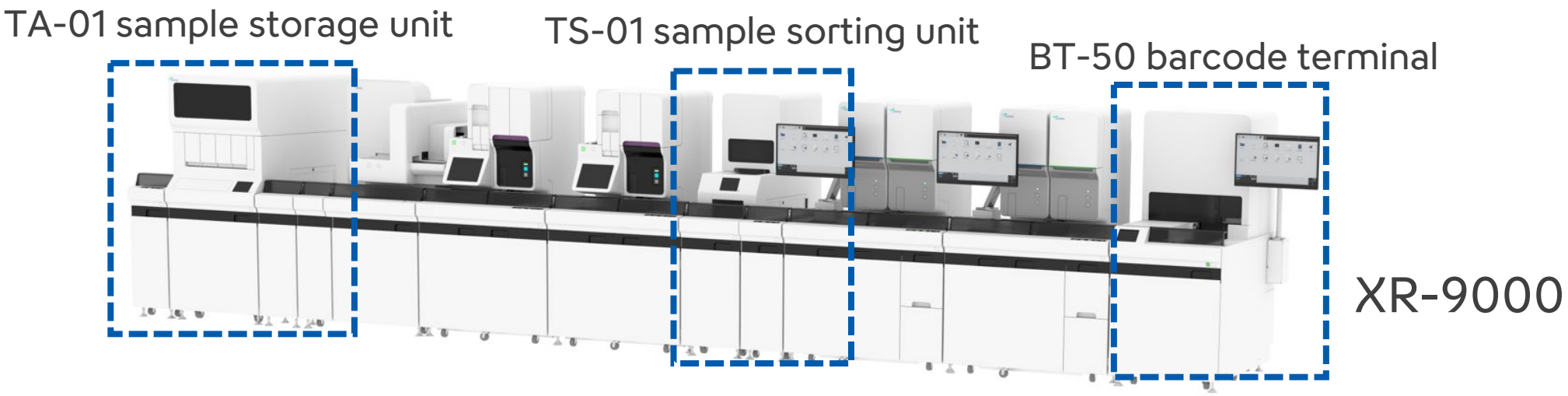
- ✓ Lighting the shortest route to diagnosis by utilizing test results
- ✓ Provide test results which are valuable for patients and clinicians

Managerial value

- ✓ Delivering best quality assurance to improve role and reliability of laboratory
- ✓ Support the smooth acquisition and operation of ISO
- ✓ Contribute to hospital management by improving laboratory operation efficiency

Touch-Free Concept, Phase 1

Note: Announced at the 19th R&D Meeting



- ✓ Startup, shutdown
- ✓ Automatic quality control
- ✓ Cleaning

Note: Patent pending

- ✓ **World's first offering a scheduling function, automatic measurement preparation and post-test cleaning, and automatic shutdown**
- ✓ **Performs automatic quality control with no manual intervention**

Eliminates manual pre- and post-testing operations

Touch-Free Concept, Phase 2

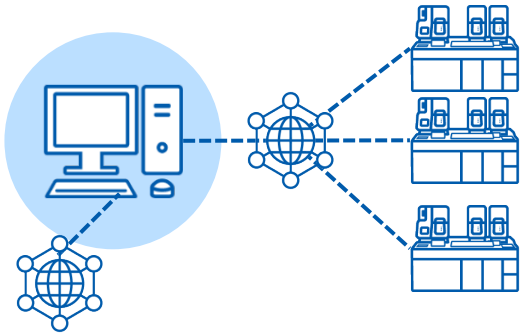
Expanding application of the touch-free concept from pre- and post-testing to the entire testing process

✓ No need to change reagents during testing

(1) RM-10 reagent supply unit

Note: Patent pending

✓ No need to perform checks in front of instruments



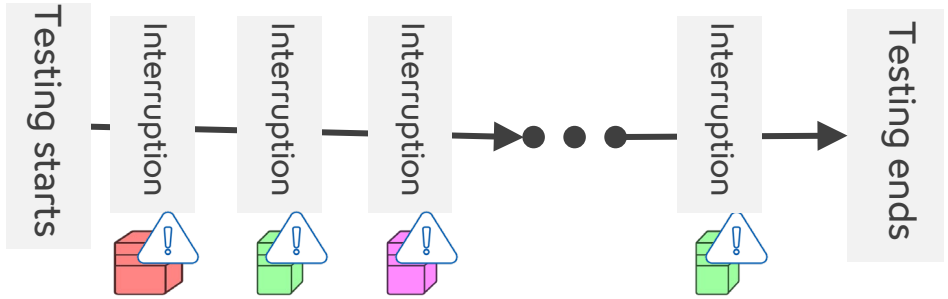
(2) Hematology dashboard

From “easy to operate” to “zero operation”

(1) Overview of the RM-10 Reagent Supply Unit

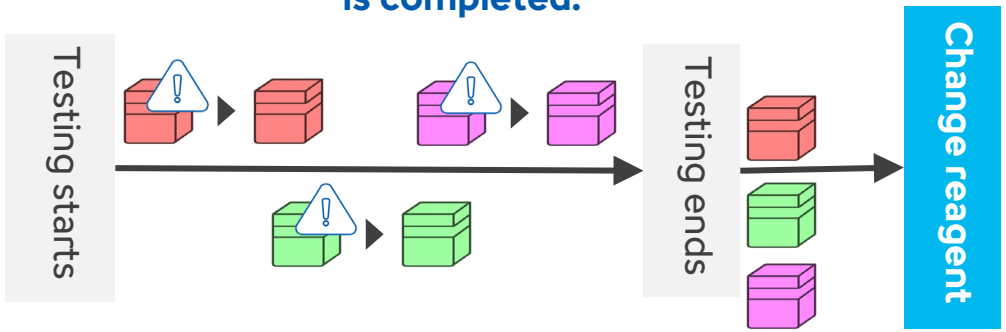
Conventionally

When a reagent runs out, testing is interrupted, and at large testing centers, reagents are changed approximately **40** times per day

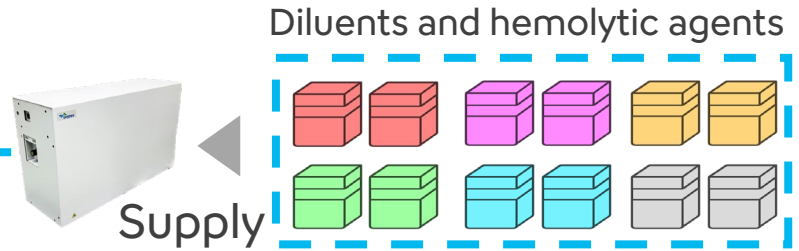


With RM-10 attached

Reagents are automatically supplied and changed at one time after testing is completed.



Reagent supply



✓ Reagent aggregation function

Rather than supplying reagents to individual instruments, they are **supplied together to the entire XR-9000**

✓ Continuous loading

Connects large reagent packs, two of each type

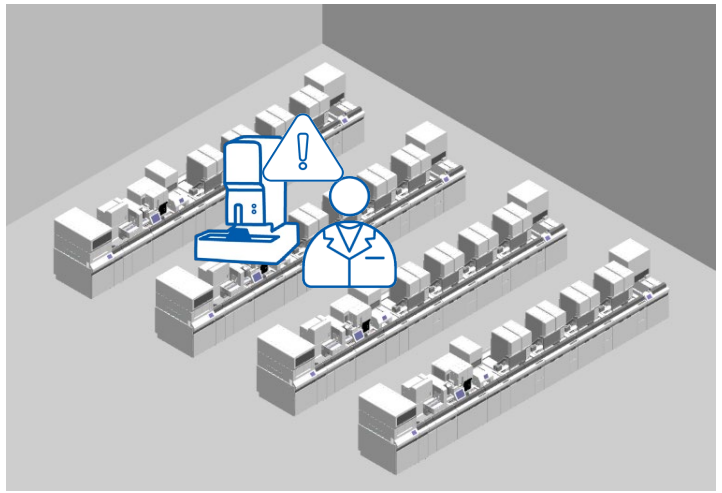
Automatic changeover and supply when reagent runs out

Prevents testing from being interrupted when reagent runs out

(2) Overview of the Hematology Dashboard

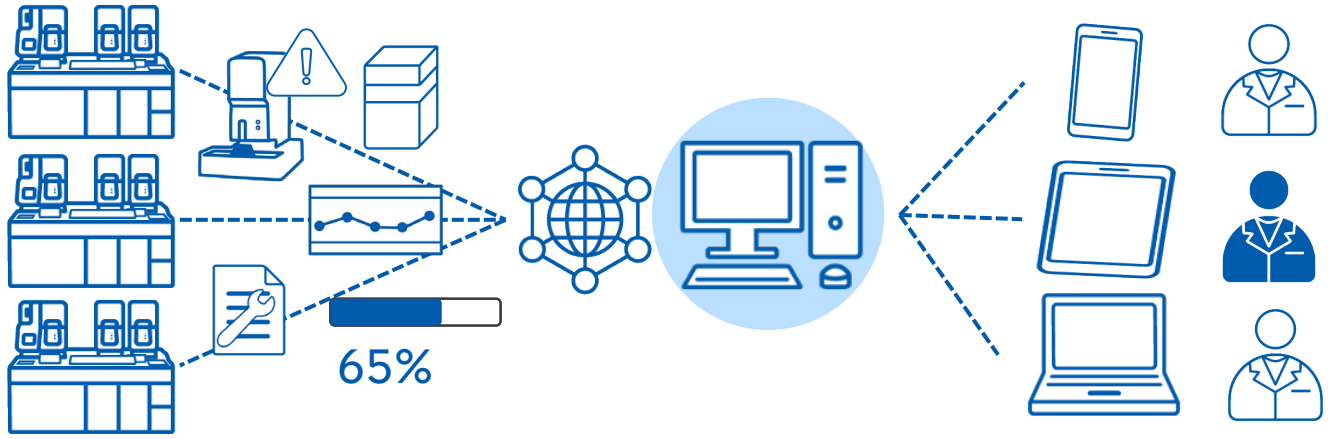
Conventionally

When an error occurs, each instrument needs to be addressed individually



With hematology dashboard attached

Capture error details and other test-related information at any location



Examples of aggregated information

- ✓ Remaining reagent volume (in conjunction with RM-10)
- ✓ Equipment status
- ✓ Quality control
- ✓ Repair records
- ✓ Overall test progress

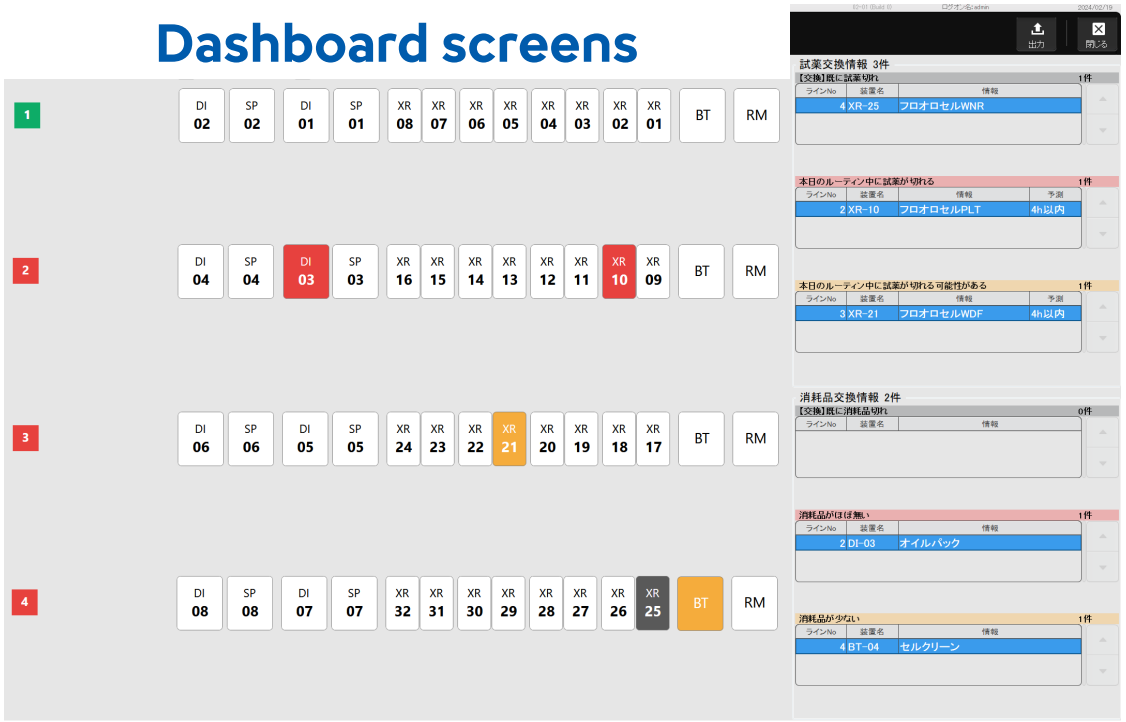
Simultaneous access from multiple terminals, even remotely

Centralized management of multiple instruments

Details of the Hematology Dashboard

- Has a function to predict when reagent/consumable supplies will be depleted

Dashboard screens



- Supply of reagents/consumables already depleted
- Supply of reagents/consumables to run out within 12 hours
- Supply of reagents/consumables to run out within 24 hours

Prevents testing from being interrupted by checking equipment status before testing starts

Example of a Large Commercial Lab

No Photo Reproduction

Each day,

during 10 hours of operation,

an average of more than

tens of thousands

of tests are performed

Makes the most of touch-free operations

Summary

Phase 1

TA-01 sample storage unit
TS-01 sample sorting unit
BT-50 barcode terminal

Phase 2

RM-10 reagent supply unit

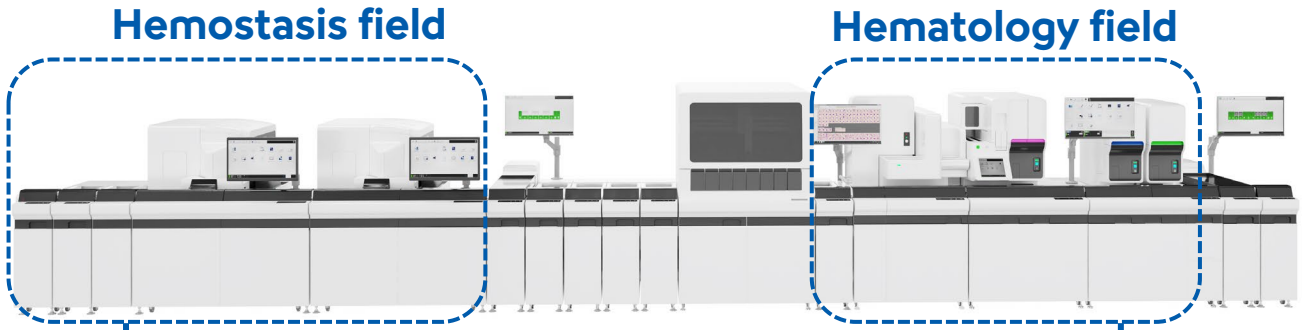
Hematology dashboard

Realizing the touch-free concept helps improve lab productivity

(2) Integration of Hematology and Other Fields

Integration of Hematology and Other Fields

Rolling out the touch-free concept, a Sysmex strength, from the hematology field to the hemostasis field



Integrated blood test, "Blood Science"

Note: Launched in the EMEA region and in South Korea

Multiparameter Automated Hematology Analyzers
XN-9000/XR-9000 + Automated hemostasis Analyzers CN-6000/CN-3000/CS-5100

+ ~~other companies' hematology instruments~~

Enhance customer retention

BloodScience Workcell web site (Sysmex Europe SE)
https://www.sysmex-europe.com/products/integrated-solutions/bloodscience-workcell.html

- ✓ Eliminate competition by offering an integrated blood system
- ✓ Potential to propose system expansion projects to existing hematology users

Demonstrate our competitive advantage by combining our leading positions in the hematology and hemostasis fields

Increasing Usability

- ✓ Systems that integrated hematology and other fields enable a single laboratory technologist to **easily operate and manage products in multiple fields**.
- ✓ **Linking measurement results** from the hematology and hemostasis fields enables the automatic selection of optimal measurement method and parameters.
- ✓ We aim to realize a **one-stop service** where Sysmex addresses everything from breakdowns to inspections and scientific support.

(3) Future Outlook

Deploying the Touch-Free Concept to Improve Diagnostic Value

Operational value

- ✓ We will be promoting a global roll-out of the touch-free concept with a view to introducing to **emerging markets** as well as developed countries.
- ✓ **Horizontally roll out design assets** cultivated in the hematology field **to the hemostasis, urinalysis, and immunochemistry fields.**
- ✓ Our ultimate goal is to **achieve unmanned labs**.

Clinical value

- ✓ The field integrated system will display diagnostic support information. We will support manual inspections **by combining AI analysis, ICT, etc.**
- ✓ We will **contribute to improve the quality of medical care in remote areas** where there are few laboratory technologists specializing in hematological diseases.

We are working to resolve healthcare disparities, which are a social issue.

3 Toward the Refinement of Personalized Medicine

Toshiyuki Sato
Executive Vice President of
Central Research Laboratories

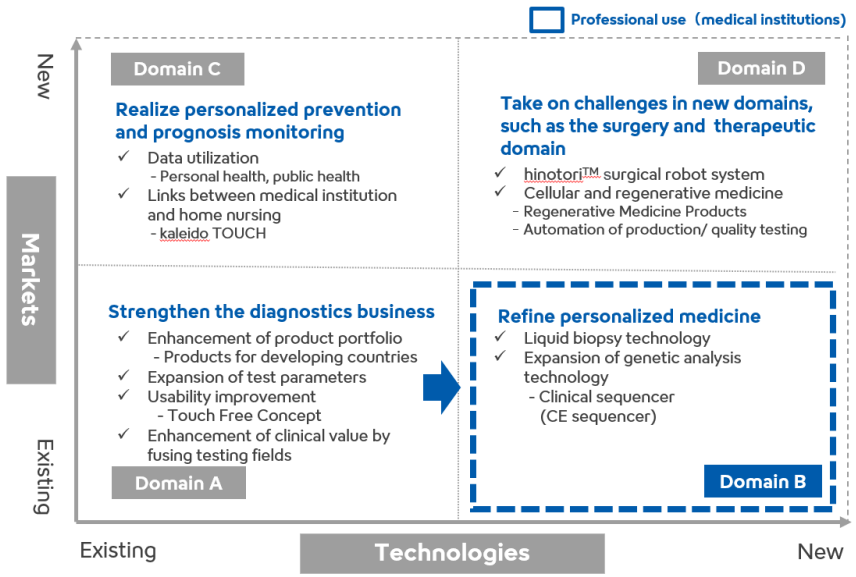
(1) Initiatives Targeting Neurological Diseases (Alzheimer's Disease Testing)

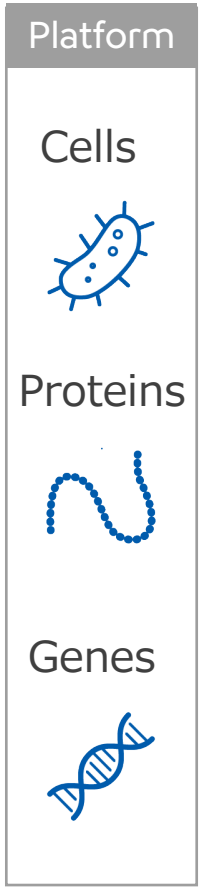
(2) Initiatives Targeting Cardiovascular Diseases (HDL Function)

(3) Initiatives Targeting Personalized Medicine (Gene Measurement Technologies)

Domain B: Toward the Refinement Personalized Medicine

Expanding technologies and verifying their clinical values to realize the healthcare journey





Utilization, Acquisition, Innovation

Direction of R & D

Bold : Launched

①Realization of Liquid Biopsy by Utilizing High Sensitivity PF

✓Expaning into proteins and cells in addition to genes

Protein:

- Liver fibrosis marker (M2BPGi)

- Alzheimer's disease test

- Immune checkpoint (sPD-1/sPD-L1/sCTLA-4)

Cell:

- Immune synapse (transplant rejection test), CTC

Gene:

- Plasma-Safe-SeqS

②In addition to conventional tests (quantitative changes), acquisition of technologies for detecting qualitative changes

- HDL function, TTR stability, vWF size

③Innovations in sensitive testing systems for genetic mutations

- **NGS：NCC OncoPanel、IRD Panel**
- Clinical sequencing：a new system based on CES

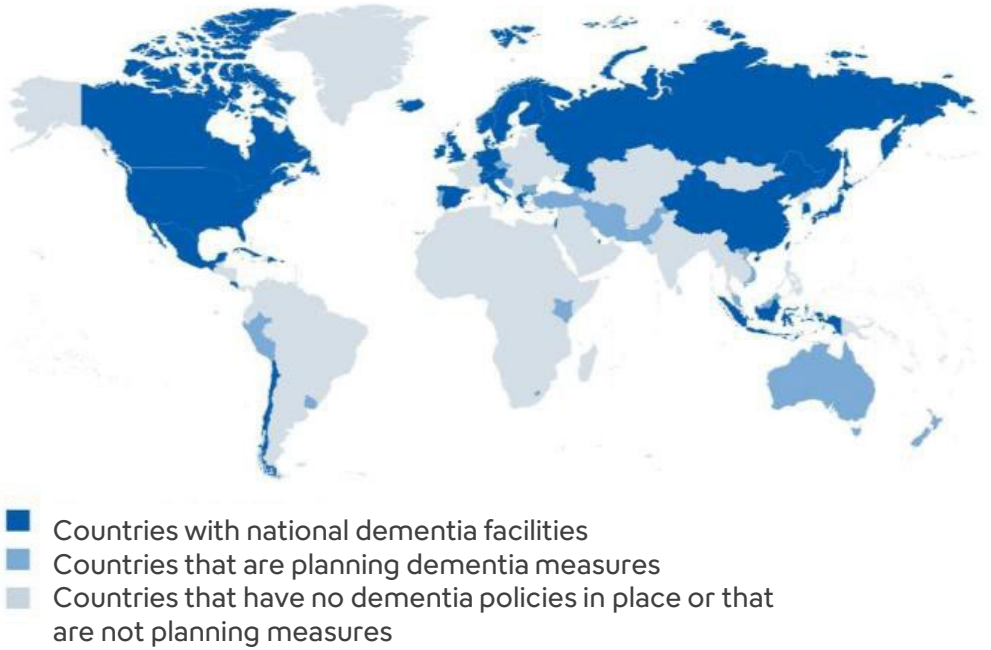
(1) Initiatives Targeting Neurological Diseases (Alzheimer's Disease Testing)

Global Dementia Trends

Contributing to the advancement of healthy lifespans and an aging society

- ✓ By 2030, 20% of people over 65 years old will have dementia.
- ✓ Dementia prevention and treatments are under active development worldwide.
- ✓ While various therapeutic agents are being developed, identification of dementia is important.

Status of development of national strategies for dementia (As of April 2021)



Emergence of disease-modifying drugs

- ✓ New new therapeutic drug targets Alzheimer's disease
- ✓ Drug acts directly on Aβ, inhibiting or eliminating its aggregation and deposition, thereby reducing the progression of AD and slowing the decline in cognitive and daily life functions
- ✓ Development of new therapeutic drugs targeting other molecules, such as tau, is also underway

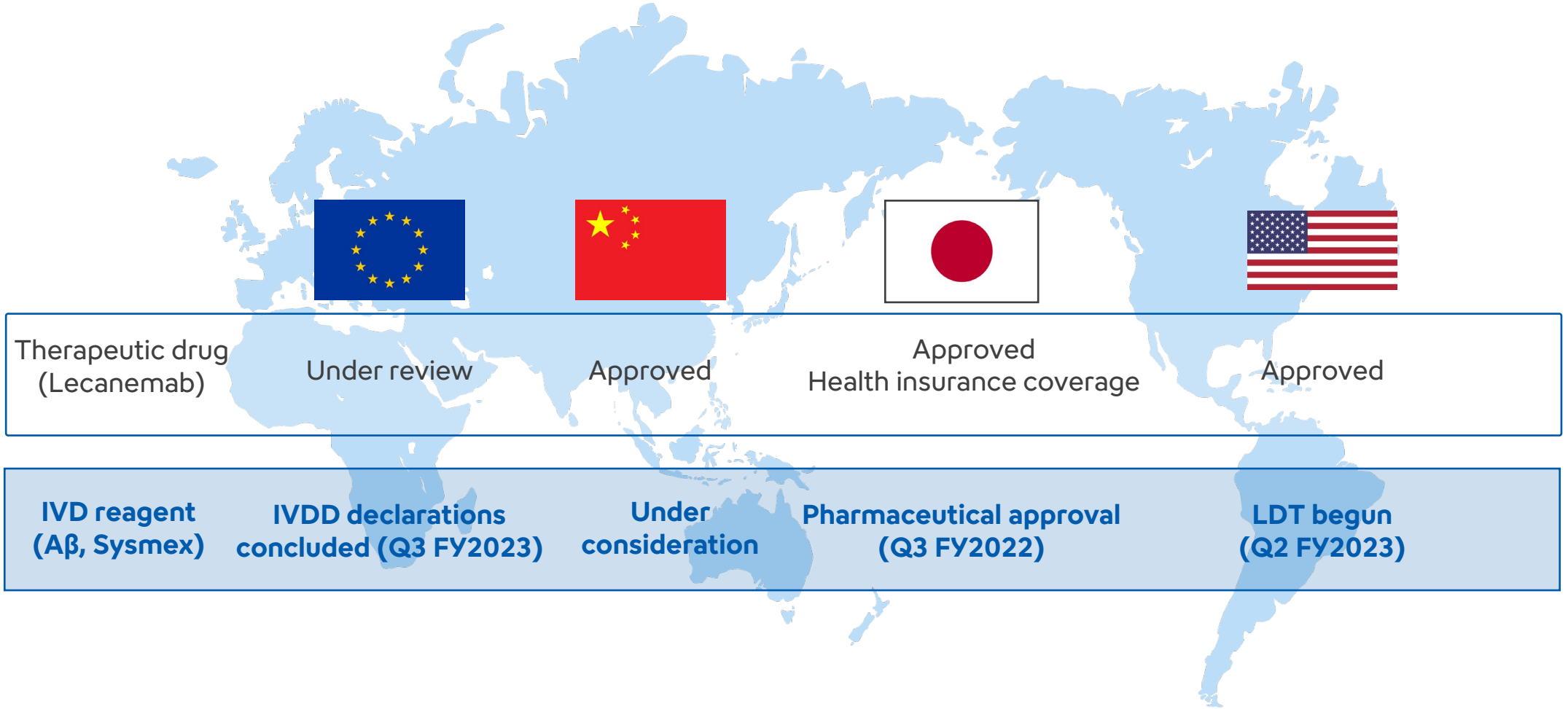
Therapeutic drug	Developed by
Lecanemab (LEQEMBI®*)	Eisai, Biogen
Donanemab (Under review)	Eli Lilly

*Drug for Alzheimer's disease developed by Eisai in collaboration with BioArctic AB

Asada, T., et al.: Prevalence of Dementia and Measures for Impairment of Life Functioning of Dementia in Urban Areas. In: FY 2012 Health and Labour Science Research Grants (Comprehensive Research Project for Dementia Control) Comprehensive Research Report [https://mhlw-grants.niph.go.jp/system/files/2012/123021/201218011B/201218011B0001.pdf]

Global Status of Dementia Treatment and Diagnosis

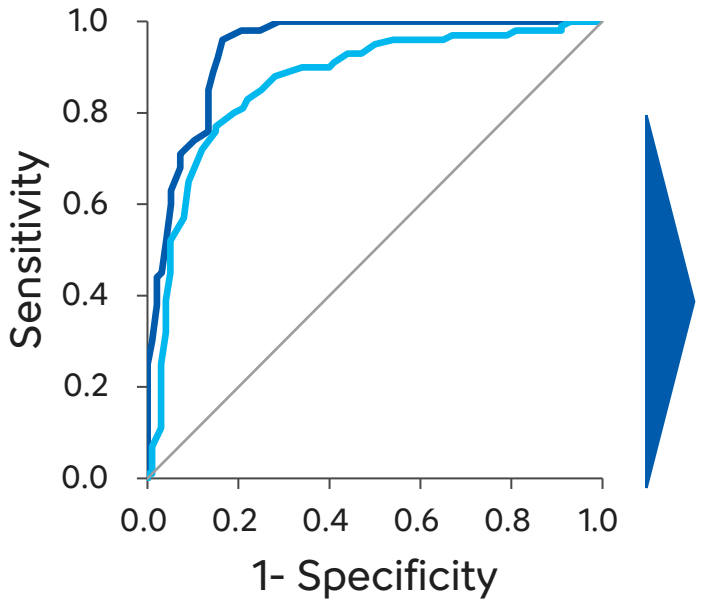
Regional deployment underway to provide blood testing conditions that keep up with drug approvals



Therapeutic drug (Lecanemab)	Under review	Approved	Approved Health insurance coverage	Approved
IVD reagent (Aβ, Sysmex)	**IVDD declarations concluded (Q3 FY2023)**	**Under consideration**	**Pharmaceutical approval (Q3 FY2022)**	**LDT begun (Q2 FY2023)**

Performance of Alzheimer's Disease Test Reagent (Aβ42/40) (External Evaluation)

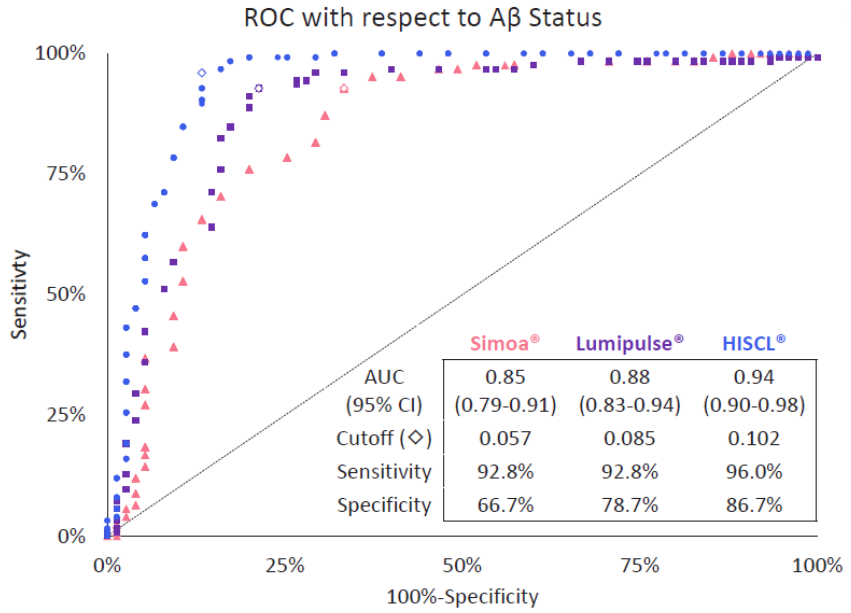
Excellent diagnostic performance for amyloid pathology confirmed at multiple facilities



In-house data (exploratory and validation studies)

AUC: 0.868～0.941

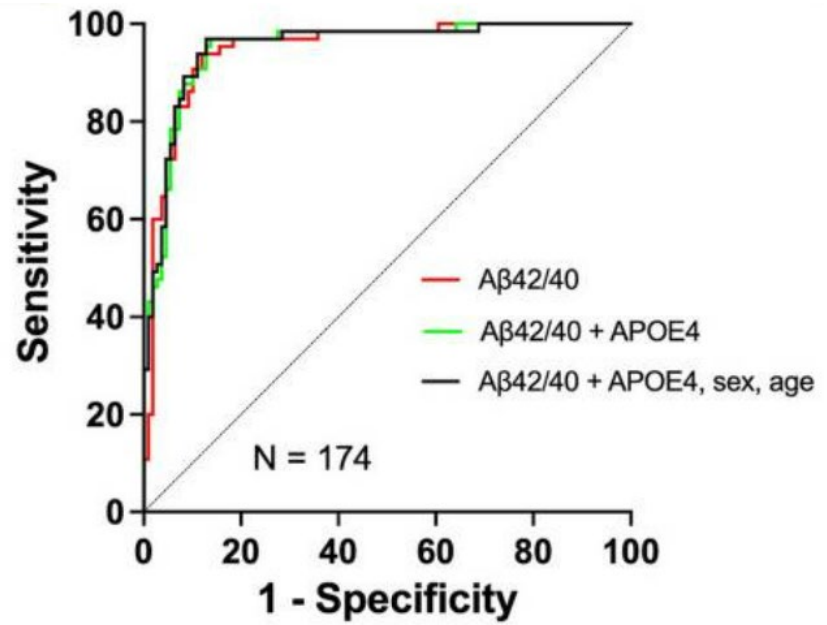
Cited from Kazuto Y. et al., Annual Meeting of Japan Society for Dementia Research (2022)



AIBL cohort (Australia)

AUC: 0.94

Cited from Ayla B. Harris (Labcorp), et al., CTAD (2023)



Keio University Memory Clinic and others

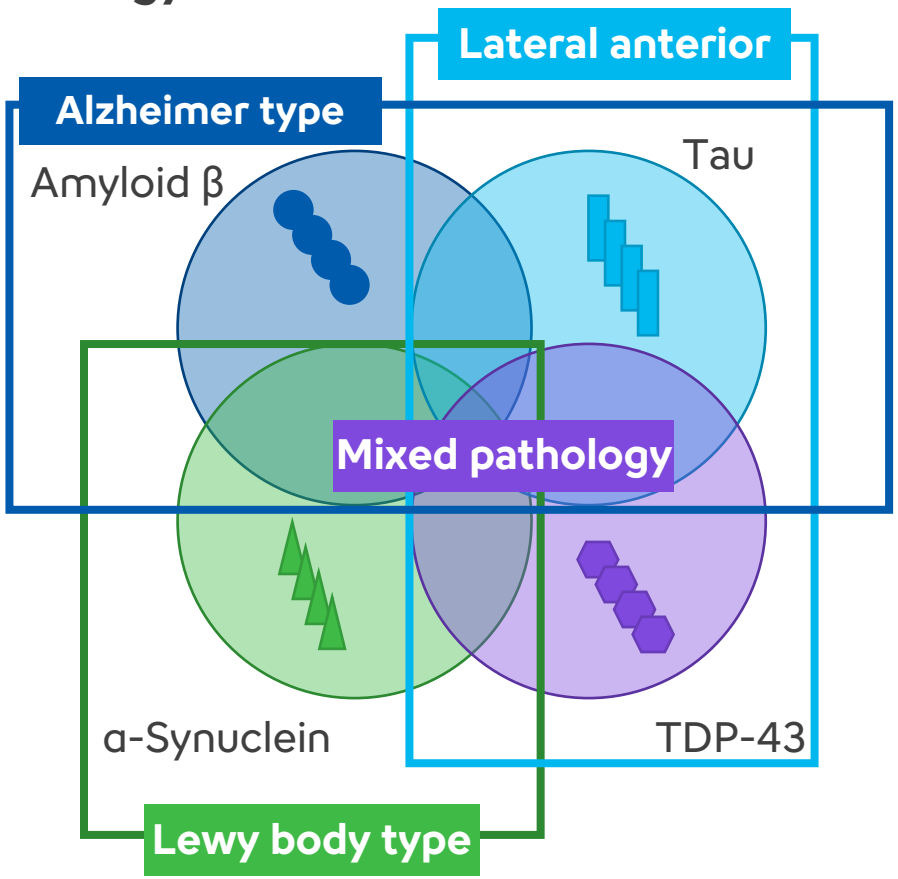
AUC: 0.949

Cited from Shogyoku B. et al., Alzheimers Res Ther. 15: 149 (2023)

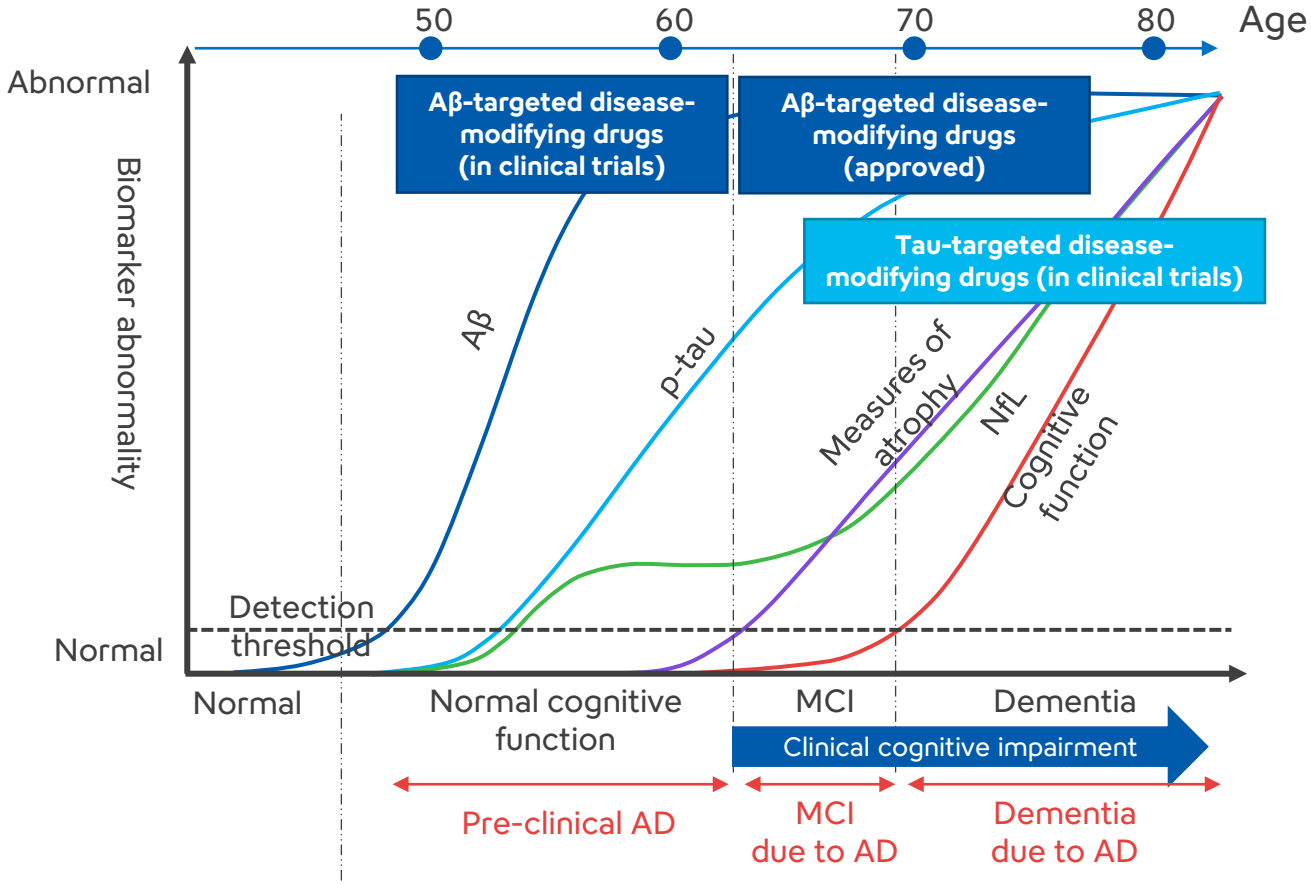
The Growing Need for Dementia Biomarkers

The development of biomarkers corresponding to the stratification of dementia patients and therapeutic agents for each disease stage is required.

Accelerating trend toward dementia stratification based on background pathology



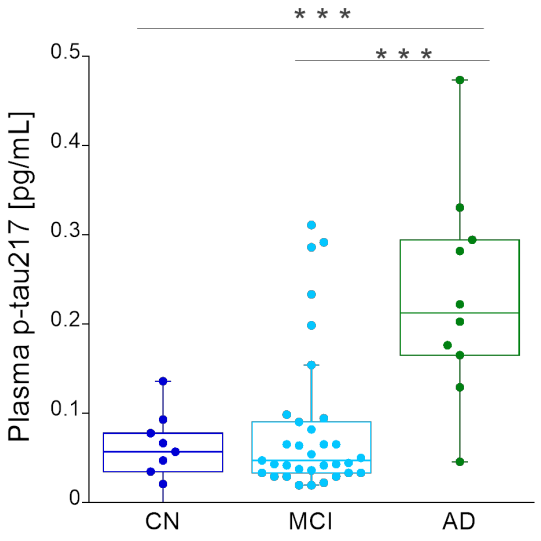
Progress in the development of therapeutic agents according to disease stage



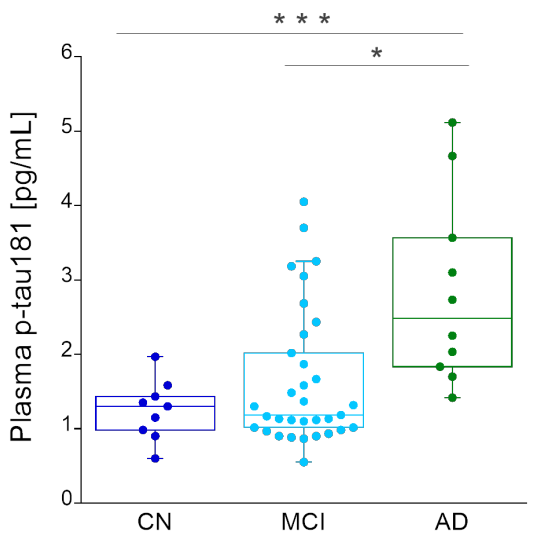
Modified from O. Hansson Nat. Med.27, 954-963 (2021), Tokuda Journal of the Society for Gerontological Dementia Vol21 No.4 2017

Progress in Multi-Paneling of dementia diagnosis

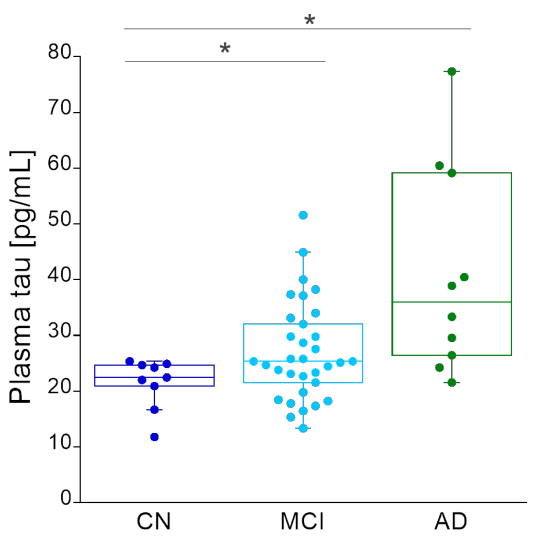
Similar disease stage dependence confirmed for new parameters (p-Tau217, 181, and Tau) as for the existing parameters (Aβ42/40)



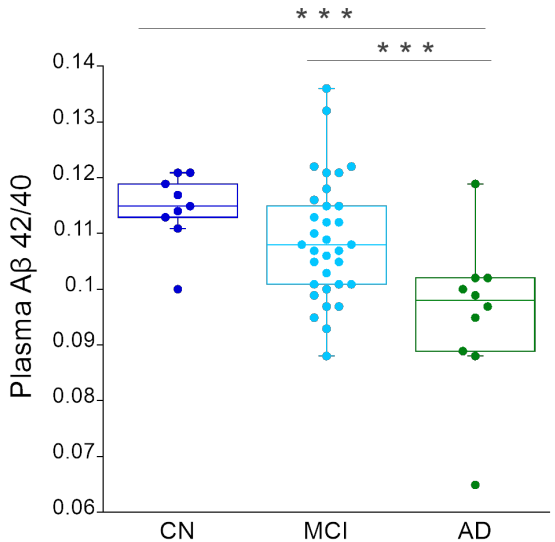
p-Tau217



p-Tau181



Tau



Aβ42/40

Cited from Matsumoto K. et al., AAIC, (2023)

Started product development of p-Tau217 (scheduled to launch in FY 2025,RUO)

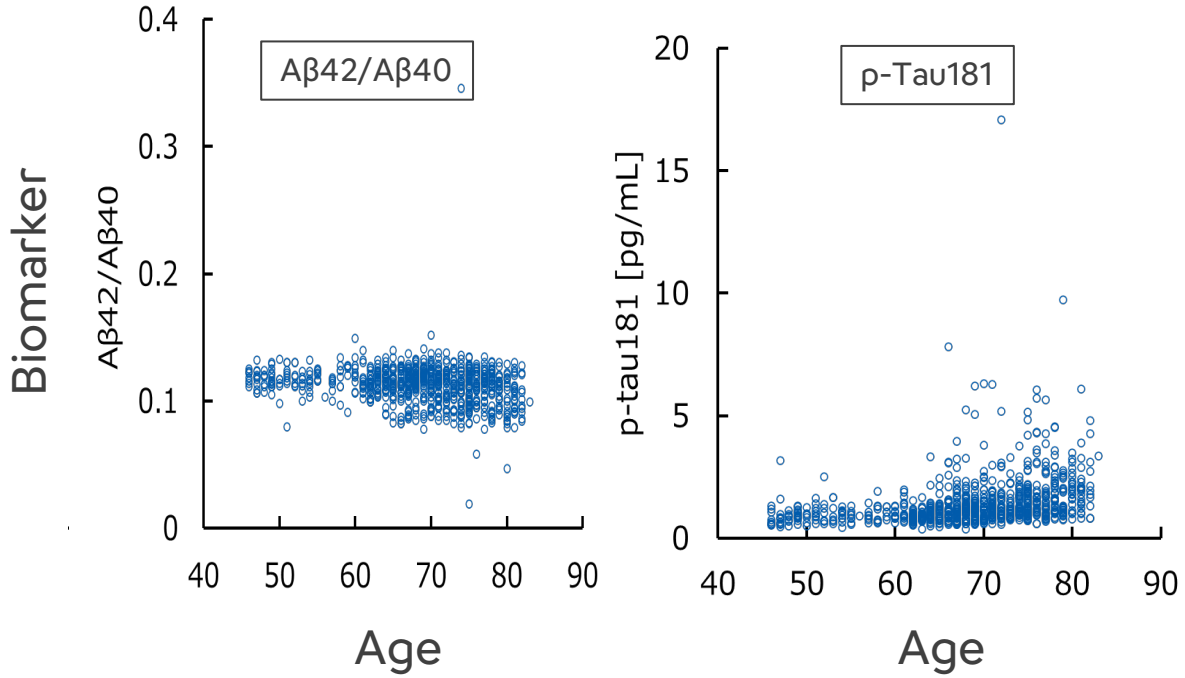
Future R&D Directions

Promote cohort studies in parallel with biomarker panel expansion to accumulate evidence for greater clinical applications

Expand biomarker panels

Change in pathological state	Biomarker		
	Image diagnosis	CSF	Blood
Amyloid accumulation	Amyloid PET	Aβ42/40 comparison	Aβ42/40 comparison, etc.
Tau accumulation	Tau PET	p-Tau	**p-Tau181 p-Tau217, etc.**
Neuro-degenerative	FDG PET, MRI	Tau	Tau, etc.

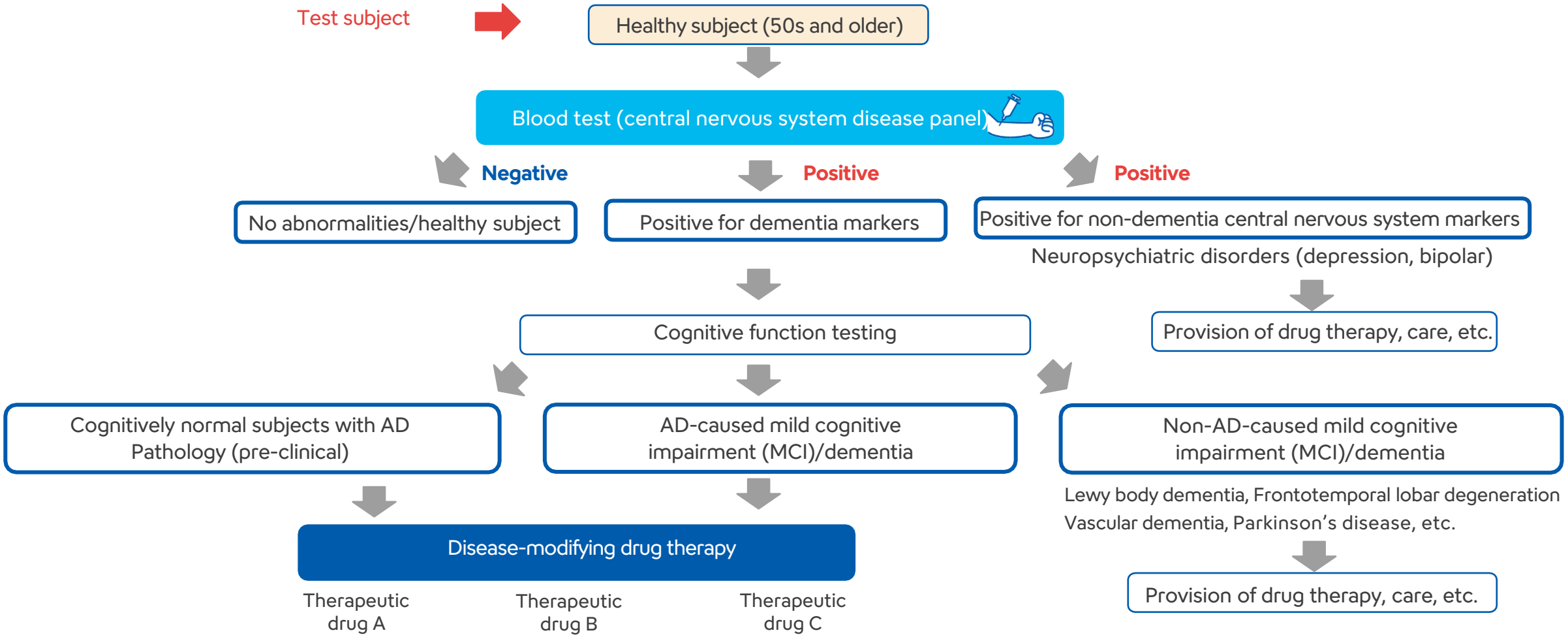
Promote cohort studies (Age dependency, etc.)



Diagnostic Flow of Central Nerve System Disease Realized by Multi-paneling

(From the 20th R&D Meeting)

Realization of a healthy society with reduced physical burden and social costs

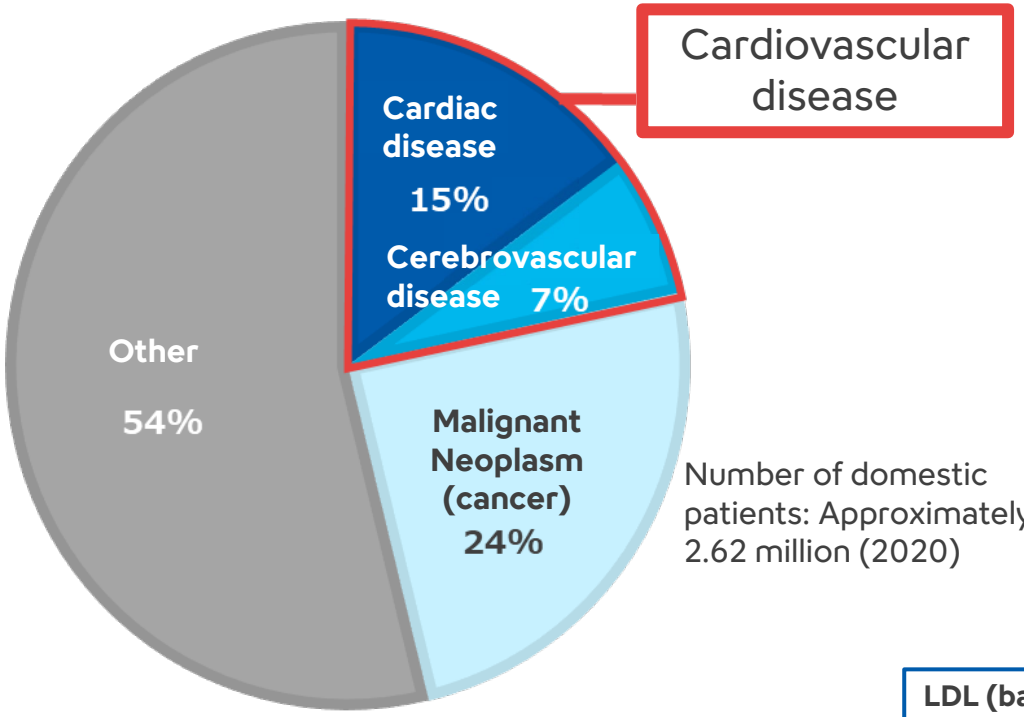


(2) Initiatives Targeting Cardiovascular Diseases (HDL Function)

Status of Circulatory Disease (Cardiovascular Disease)

Lipid management is important to control the progression of cardiovascular disease, and residual risk reduction is a key factor.

Rate of deaths by major causes



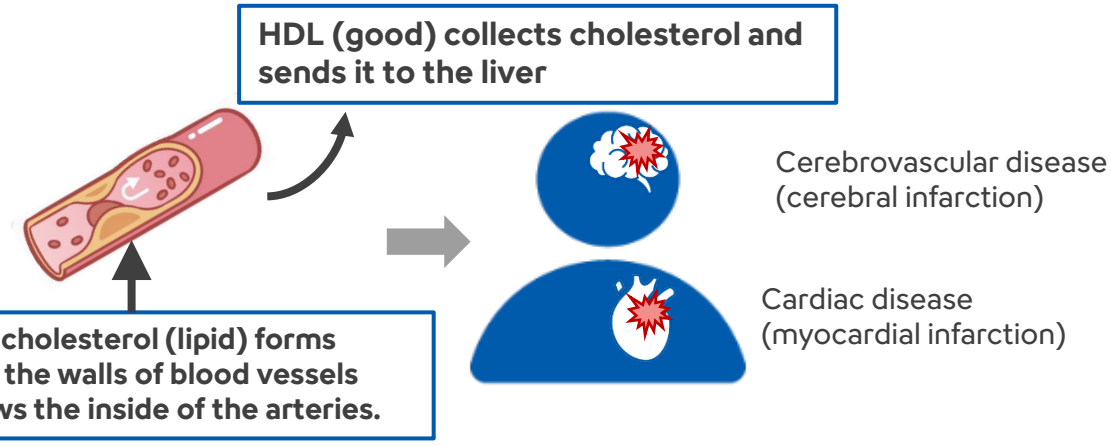
Number of domestic patients: Approximately 2.62 million (2020)

Overview of the Annual Report on Monthly Demographic Statistics 2022 (Approximations) (partially revised)

Risk factor of cardiovascular disease

Hypertension	**Dyslipidemia**	Diabetes	Smoking
Alcohol	Obesity	Age Male Family history	Other

Estimated number of patients with dyslipidemia: About 32 million people



CVD risk remains even after management targets are reached (residual risk)

Focus on HDL, a negative correlate of cardiovascular risk

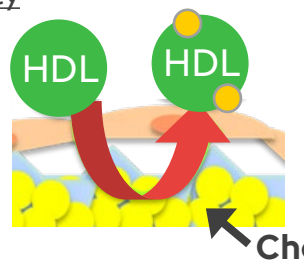
Background and Technological Concepts behind HDL Function Testing

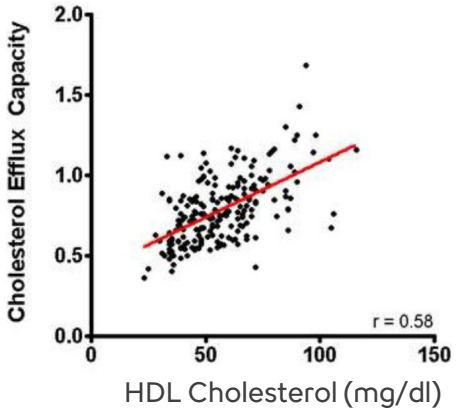
Completed construction of a HISCL system to simply measure HDL function

Even at same HDL-C values, function differs

HDL function

Cholesterol efflux capacity

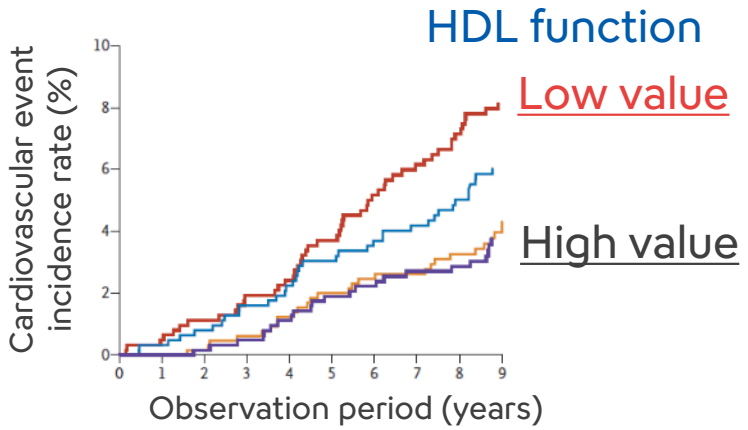




HDL-C

N Engl J Med. 2011

Reduced HDL function a risk of cardiovascular disease incidence



N Engl J Med. 2014

Conventional method

Clinical application, standardization are difficult

Assess cholesterol efflux capacity from cultured cells

- ✓ Use cells, RI
- ✓ Cumbersome process, requiring three days

New concept

Measurement can be automated
→Can be measured in 17 minutes with HISCL

Assess HDL's cholesterol uptake capacity (CUC)

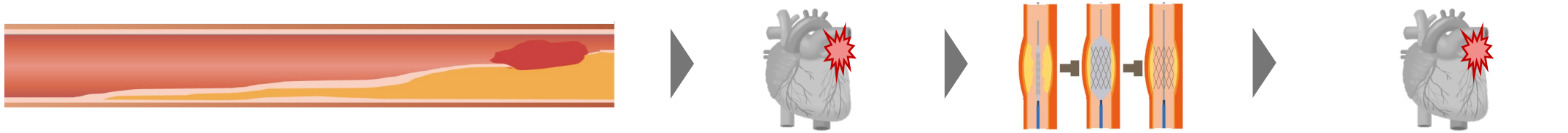
- ✓ Cultured cells, RI unnecessary
- ✓ Simple, standardized, easy process

Harada, et al. ***J Appl Lab Med.*** 2017
Murakami, et al. ***Sci Rep.*** 2023

Monitoring and Screening for Cardiovascular Disease

Advance clinical benefit verification from patients at high risk of developing cardiovascular disease

Healthy subject | Dyslipidemia | Arteriosclerosis | Onset of coronary artery disease | Treatment | Recurrence of coronary artery disease



Primary prevention
Risk assessment
Lipid management

- Exercise/diet
- Medication

Secondary prevention
Risk assessment
Lipid management

- Exercise/diet
- Medication
- Surgical treatment (revascularization)

Patients at risk of cardiovascular events diagnosed by HDL function tests

Screening

Step 3
Clinical research underway in the United States

No history of coronary artery disease

New
Step 2
Today's Topic

Hereditary disease with no history of coronary artery disease

Monitoring

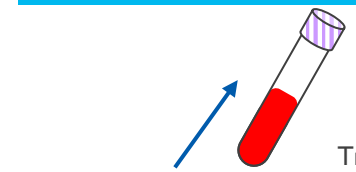
New
Step 1
Today's Topic

History of coronary artery disease

Step 1: Verification toward Recurrence Risk Testing

In patients undergoing revascularization, an association with serious postoperative cardiovascular events was observed, indicating the potential for appropriate intervention in high-risk patients.

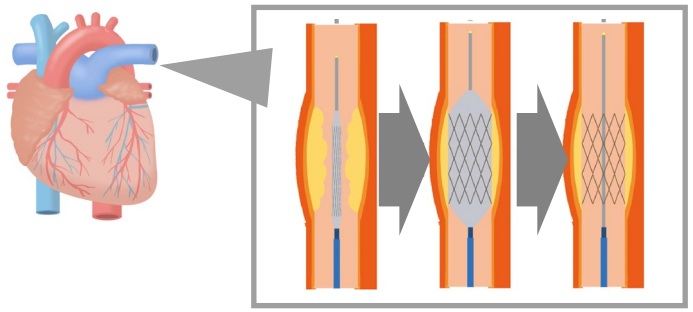
HDL function (CUC) testing



Treatment, follow-up

Revascularization → CVD composite outcome evaluation

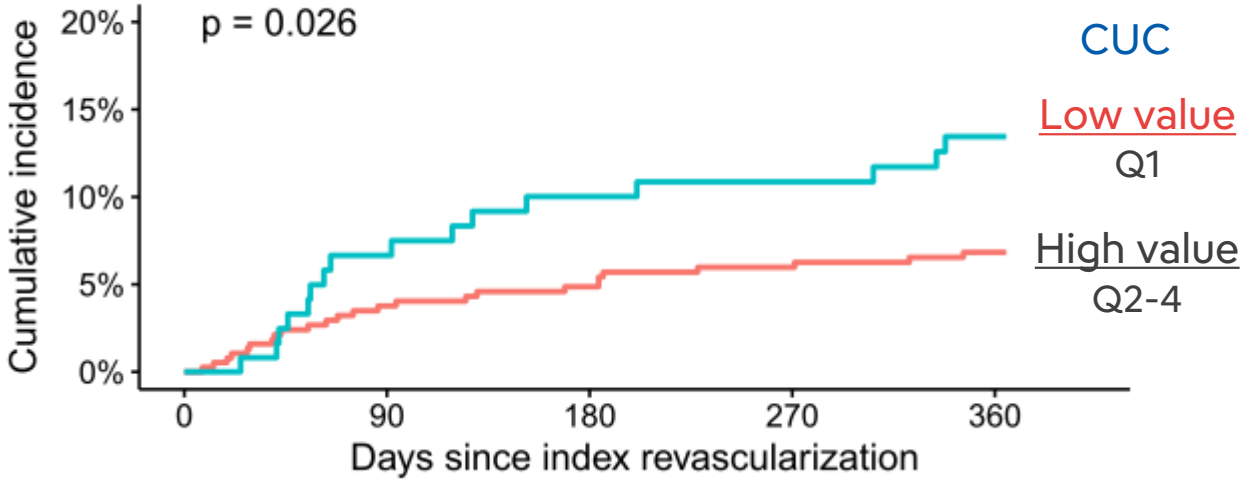
Number of cases in Jpan: approx. 250,000/year



- Myocardial infarction
- Stroke
- Hospitalization for heart failure
- Peripheral arterial disease
- Total death

New

Evaluation in a case at the National Cerebral and Cardiovascular Center

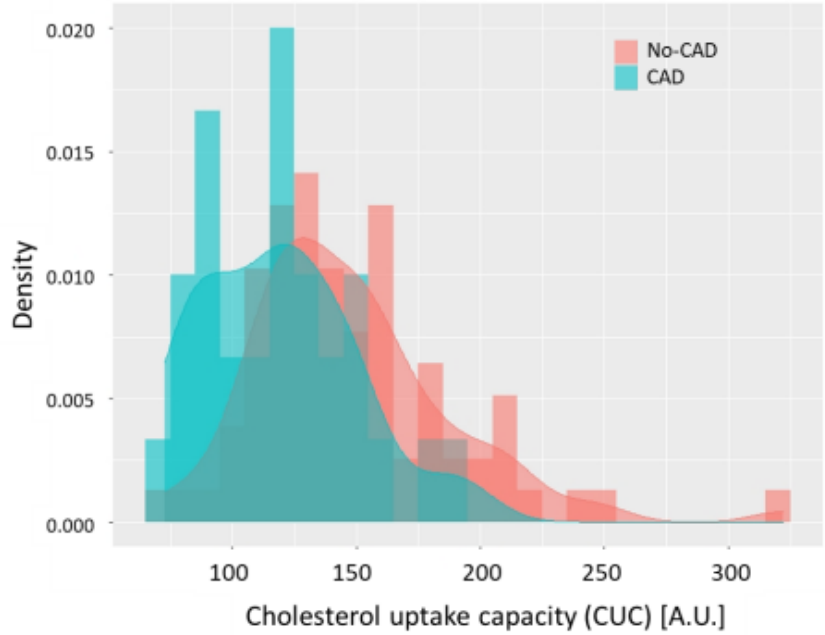


Step 2: Verification Aimed at Monitoring CVD Risk among Patients with Hereditary Disease

HDL function suggests greater utility than traditional risk indicators in stratifying risk of cardiovascular events in patients with familial hypercholesterolemia

New

Evaluation of cases in Kanazawa University



Variable	Odds ratio	95% CI	*P*-value
Age (per year)	1.12	1.02 – 1.29	0.017
Male (yes vs. no)	2.30	0.75 – 3.85	0.27
Hypertension (yes vs. no)	7.85	2.10 – 13.60	0.033
Diabetes (yes vs. no)	11.45	1.46 – 21.44	0.0021
Smoking (yes vs. no)	14.2	0.21 – 27.9	0.26
HDL cholesterol (per 1 mg/dl)	1.21	0.96 – 1.46	0.22
LDL cholesterol (per 10 mg/dl)	0.77	0.45 – 1.09	0.18
Lipid-lowering therapy	0.96	0.08 – 1.84	0.48
Cholesterol uptake capacity (per 10 A.U.)	0.86	0.76 – 0.96	0.033

Familial hypercholesterolemia

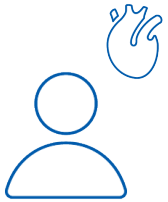
- LDC-C level is elevated significantly due to genetic mutations.
- Frequency is estimated to be 1 in 200 to 500 people and life expectancy is reduced by around 15 years, so early intervention is necessary.

Tada, et al, ***Circ J.*** 2023.
(Circulation Journal Award)

Future Initiatives

Social implementation of cardiovascular disease risk monitoring through CUC testing

High-risk patients
- History of coronary artery disease
- Presence of hereditary disease (e.g., FH)



Medical examination

Blood test (CUC test)

Cardiovascular risk assessment

- High risk → Enhanced treatment, Increased frequency of testing
- Low risk → Maintain conventional treatment plan

Medication and exercise therapy
Follow-up

Promote research and development of novel biomarkers for total management of cardiovascular diseases

Metabolic abnormality → Arteriosclerosis

→ Angina pectoris

→ Heart muscle infarction → Pathological remodeling, Myocardial fibrosis → Heart failure

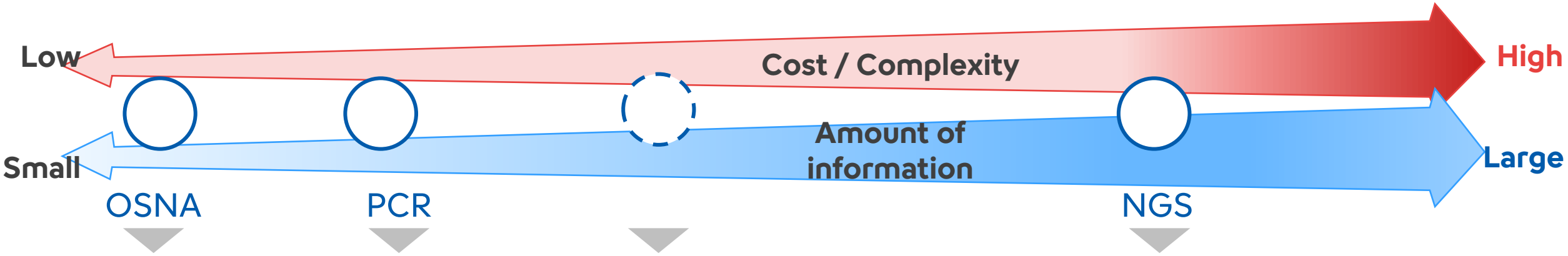
Risk assessment of disease onset, early intervention			Disease identification	Malignancy assessment	Therapeutic drug selection
Lipid markers	Vascular calcification markers	Coagulation molecular markers	Myocardiopathy markers	Fibrosis markers	Cardiac amyloidosis markers
HDL function (CUC test)	**Calcified EV**	**vWF size**	**cMyC**	**M2BPGi**	**TTR stability**

(3) Initiatives Targeting Personalized Medicine (Gene Measurement Technologies)

Overview of Gene Measurement Technology

In addition to expanding technological assets, resolve clinical issues in genome testing and promote commercialization

Rapid testing, few parameters	Genome profiling



OSNA LYNOAMP™ CK19/CK19E (IVD) diagnosis of cancer lymph node metastasis

ROS1 fusion gene detection kit, lung cancer multigene PCR panel, SARS-CoV2 PCR kit (IVD)

Develop a new system based on CES

＊Collaborated with Hitachi High-Tech Corporation

Plasma Safe-SeqS (IVD/RUO)
CDx, LDT assay, breast cancer, solid cancer, colorectal cancer

Genetic Panel Testing System for Inherited Retinal Dystrophy
IVD approval
Insurance coverage

NCC Oncopanel System
Solid cancer
Bile duct cancer

Spread of genetic testing using systems that are low-cost and that produce data in quantities sufficient for diagnosis

Development of a new genetic testing technology platform

Combines Hitachi High-Tech's CES technology with Sysmex's reagent development expertise and analysis technology to solve problems of genome testing

	Reagent	Instrument	Analysis/ report
			
	sysmex	HITACHI Inspire the Next	sysmex
Roles	Optimization of preprocessing/ Development of parameter	medical device registration/ Optimization of developed items	

Focus initially on clinical implementation in the field of cancer and gradually expand to other disease areas.

Technical issue and approaches to clinical implementation of CES technology

Utilizing our company's proprietary technology and know-how to enhance the sensitivity of CES technology

Issue of CES

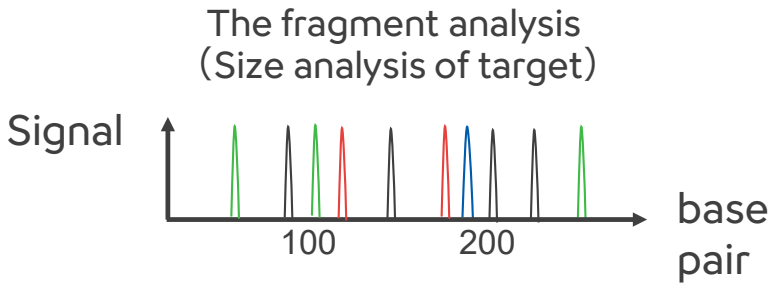
Although CES fragment analysis is simple, low-cost, and capable of measuring multiple parameters, its sensitivity is insufficient for clinical application.

Initiatives of issues

Preprocessing

- Extraction of nucleic acid
- **Use of artificial bridged nucleic acid (BNA) technology for PCR amplification**

measurement

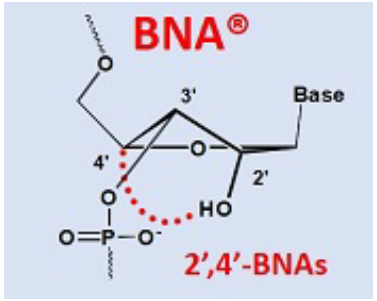


Achieve high sensitivity and multi-molecule measurement in fragment analysis

Enhance Sensitivity Using Artificial Nucleic Acid (BNA) Technology

Highly selective PCR amplification is possible by using artificial nucleic acid (BNA), a proprietary Sysmex technology.

RIKEN genesis holds patent



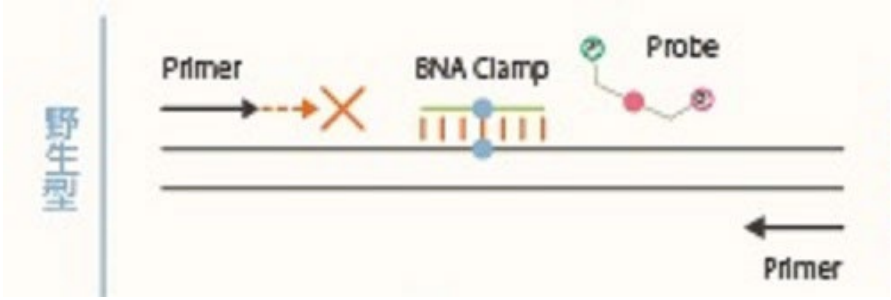
- ✓ **BNA is a new artificial nucleic acid in which sugar moieties of natural nucleic acids are cross-linked and structured.**
- ✓ It forms more stable duplexes than natural nucleic acids and **can amplify only the target (mutant gene) in a highly selective manner.**

BNA

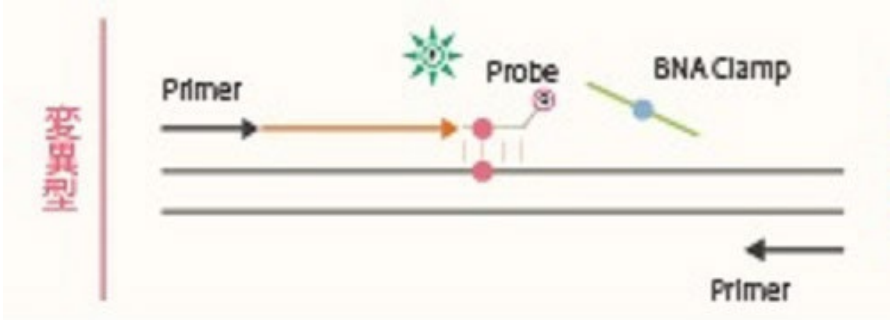
mRNA　etc..

Stable doble chain nucleic acid

Non-target（wild type） ➡ Non-amplify



Target（mutation） ➡ Amplify



4 Initiative Targeting Regenerative Cell Medicine

Kenji Tsujimoto
Executive Vice President of
Next Generation Medical Business Development

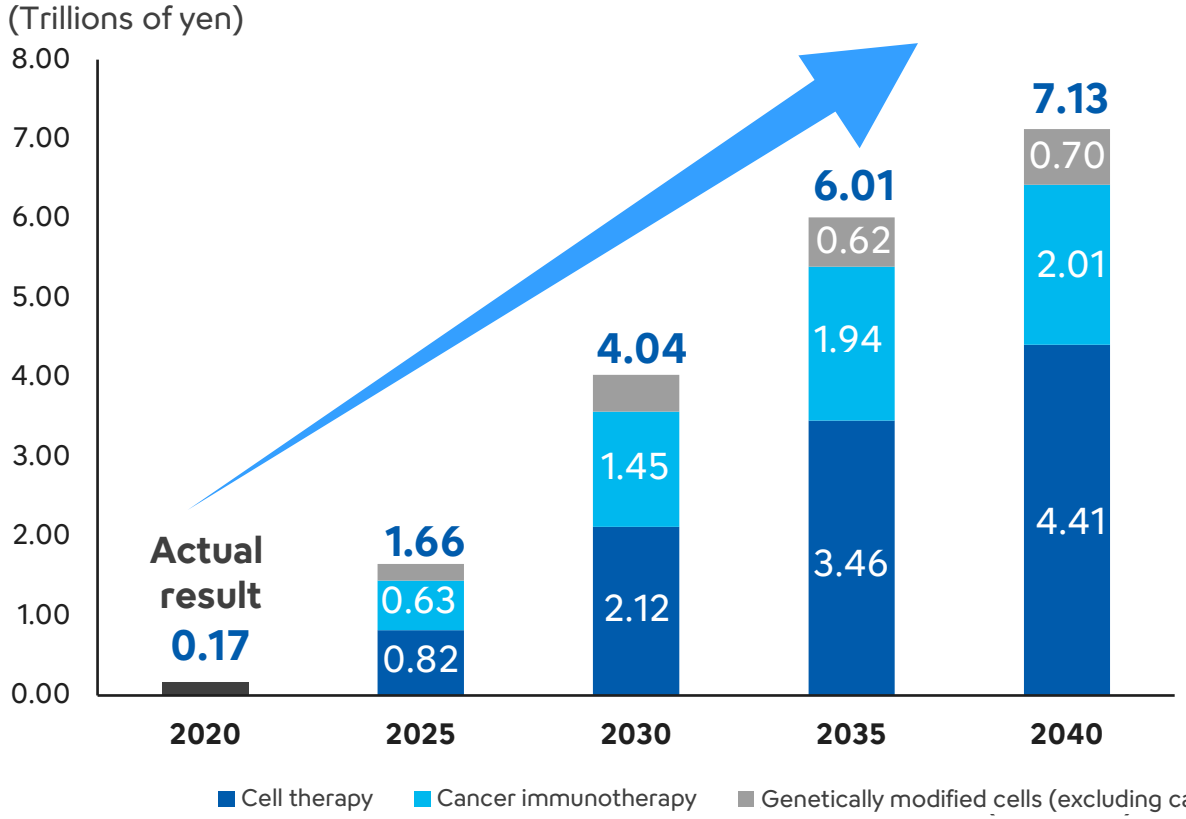
(1) Significance of Our Commitment to Regenerative Cell Medicine

External Environment

In order to provide regenerative cell medicine, which is expected to grow, to a wide range of patients, it is important to resolve issues related to cell manufacturing.

Market expanding at a rapid pace

Forecast of the global market for regenerative cellular medicine

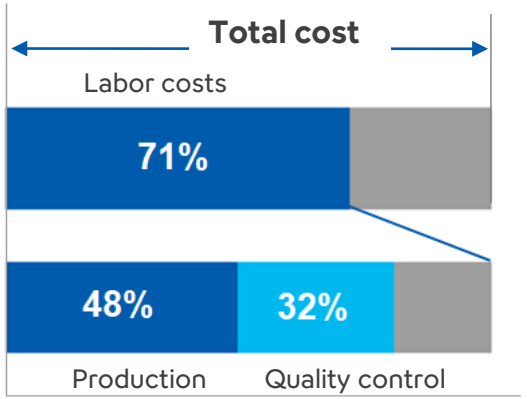


Source: BB Bridge 2023: The Current Status and Future Prospects of Global Cellular Drug Development, compiled by Arthur D. Little, Inc.

The challenges of regenerative cellular medicine

- ✓ Cumbersome manufacturing processes raise costs
- ✓ Unstable quality due to manufacturing idiosyncrasies
- ✓ Lack of cell manufacturing personnel

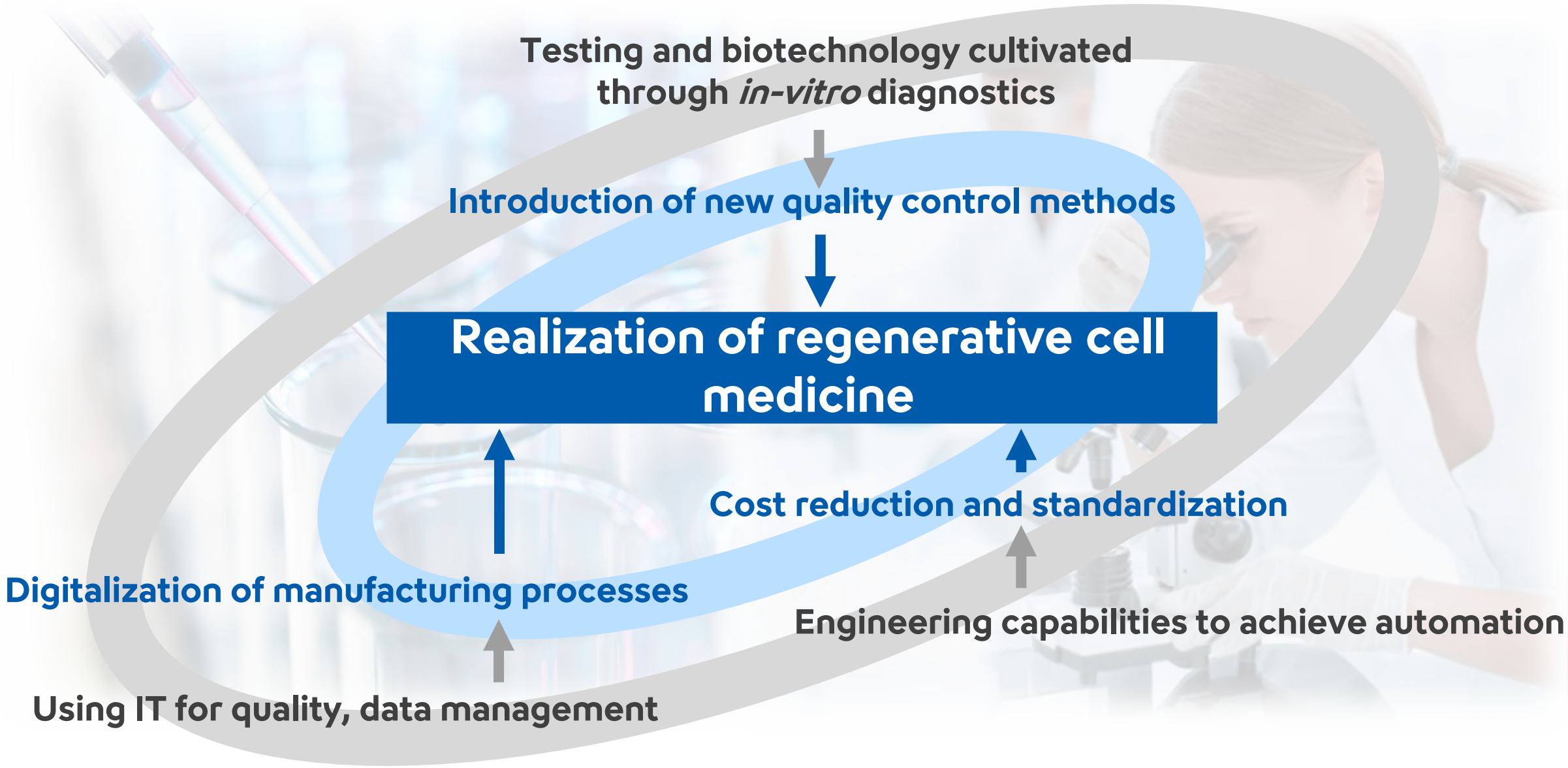
Labor costs as a percentage of total manufacturing costs and breakdown (Example of CAR-T production)



Breakdown of cost of production (%)

Source: V. Papavasileiou et.al(2007), K Spink and A Steinsapir (2018)

Why is Sysmex Getting Involved in Regenerative Cell Medicine



Sysmex's technologies in the Regenerative Cell Medicine

Sysmex's cell evaluation technology and digital platform contribute to the stable production and supply of cellular medicine

Use hematology analyzer to count cell, determining absolute quantities

More accurate measurement of blood cells

XR-Series

Automated protein assays using the HISCL automated immunoassay system

ELISA fully automates protein assays

HISCL-Series

Evaluation of undifferentiated iPS cell content using miRNA in culture medium

Non-destructive testing to ensure against iPS cell contamination

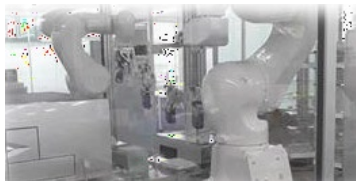
Localization analysis of intracellular molecules using molecular imaging FCM (MI-1000)

Pre-transplant compatibility testing for allogeneic transplants

MI-1000

Using robotics technology for lab automation

Automation of cell production and quality testing

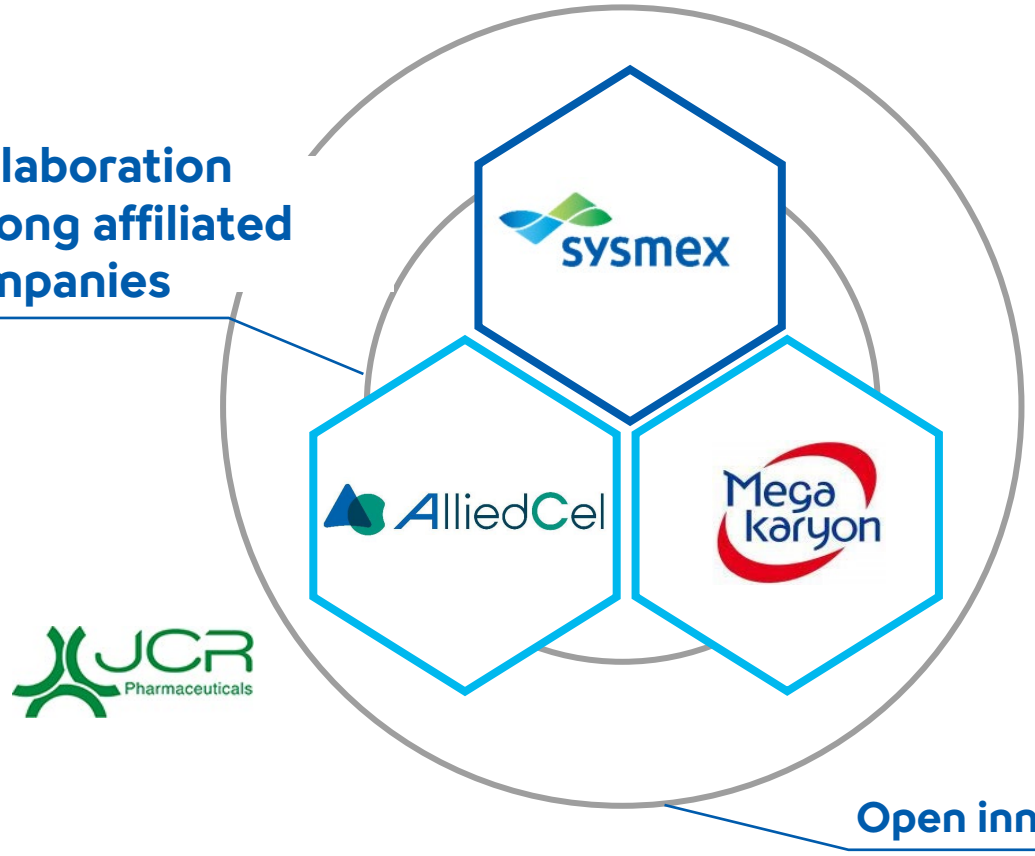


Systems for aggregating, managing, and analyzing Caresphere™ and other data

Linkage and analysis of manufacturing and quality control data

Our Overall Approach to Regenerative Cell Medicine

Taking up the challenge of creating regenerative medicine products and novel manufacturing processes based on open innovation



Creating regenerative medicine products

- ✓ Inducible inhibitory T-cells* (AlliedCel)
- ✓ Cultured hematopoietic stem cells (AlliedCel)
- ✓ Platelet derived from iPS cells (Megakaryon)

* Obtained manufacturing and sales license from JUNTEN BIO in November 2023

Automation and digitization of cell production/quality testing

- ✓ Laboratory automation for efficient manufacturing and quality control
- ✓ Digitization of manufacturing processes and utilization of data through integrated information management systems

(2) Initiatives for the Creation of Regenerative Medicine Products

Regenerative Medicine Product Pipeline

Promoting the development of innovative regenerative medicine products that offer new hope to patients

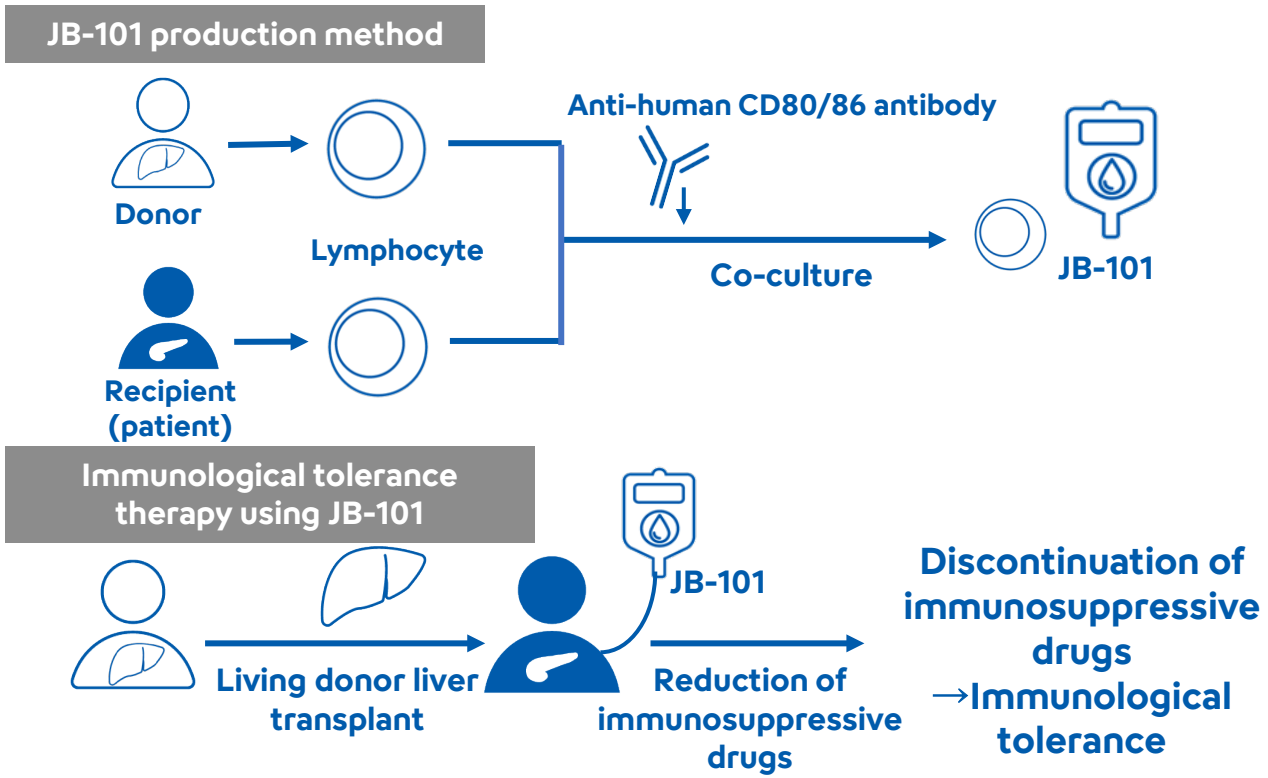
Cells	Target indication	Clinical value	Submission to Regulatory approval (expected)
(1) Inducible inhibitory T-cells AlliedCel	Organ transplants	Induction of immune tolerance in recipient T cells	Around FY2026
(2) Cultured hematopoietic stem cells AlliedCel	Hematopoietic tumors	Restoration of hematopoietic function by cultured hematopoietic stem cells	Around FY2030
(3) Platelet derived from iPS cells Mega karyon	Thrombocytopenia	Restoration of hemostatic function with artificial platelets	Around FY2029

(1) Inducible Regulatory T Cells （Under the clinical trial）

The world's first cell-based drug that induces sustained immune tolerance in organ transplantation, significantly helping to improve the quality of life of transplant recipients

Inducible regulatory T cells (JB-101*) are cells to prevent the patient's body from rejecting a transplanted donor organ.

* Subject to the Ministry of Health, Labour and Welfare's "Sakigake Designation System"



Significance of immunological tolerance therapy

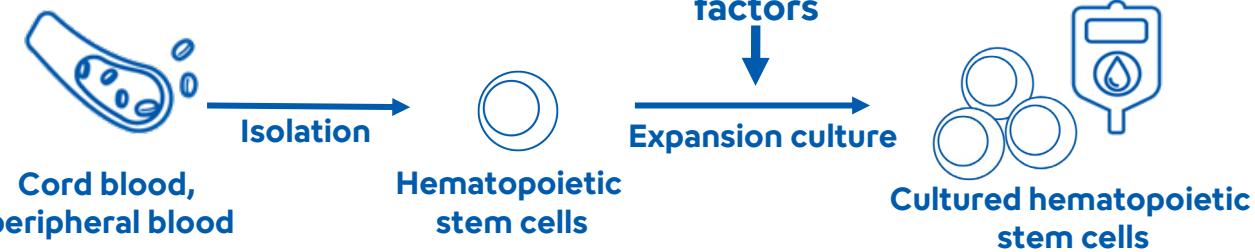
- Improvement of transplant organ viability by induction of immune tolerance
- Decreased risk of complications by reducing or withdrawing immunosuppressive drugs
- Decreased medical costs by reducing or weaning patients off immunosuppressive drugs

(2) Cultured Hematopoietic Stem Cells

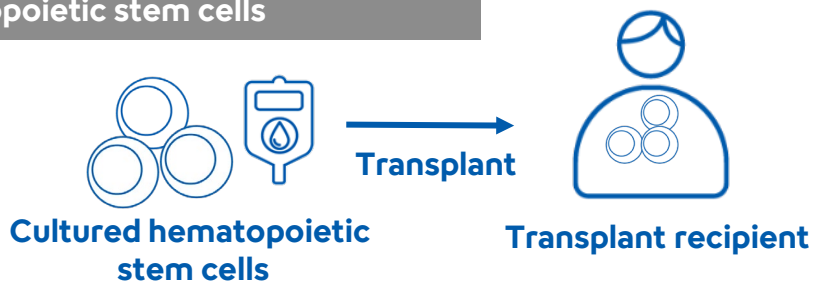
The realization of amplified culture of hematopoietic stem cells in cord blood and peripheral blood could be a new therapeutic approach for hematopoietic stem cell transplants.

A culture technology to amplify hematopoietic stem cells, which are important for post-transplantation engraftment, at a high rate in a short period of time

Cultured hematopoietic stem cell production method



Indication for transplant of cultured hematopoietic stem cells



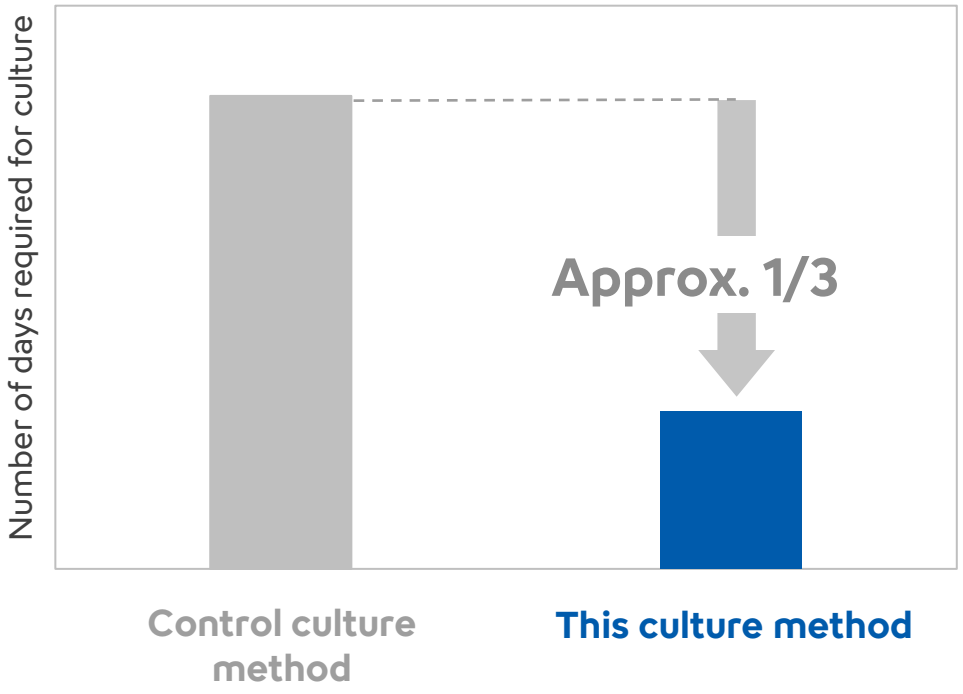
Significance of cultured hematopoietic stem cell transplants

- Improved treatment efficacy due to shortened implantation period
- Reduced risk of infection due to early live births
- Possible to utilize cord blood with low cell count for transplantation

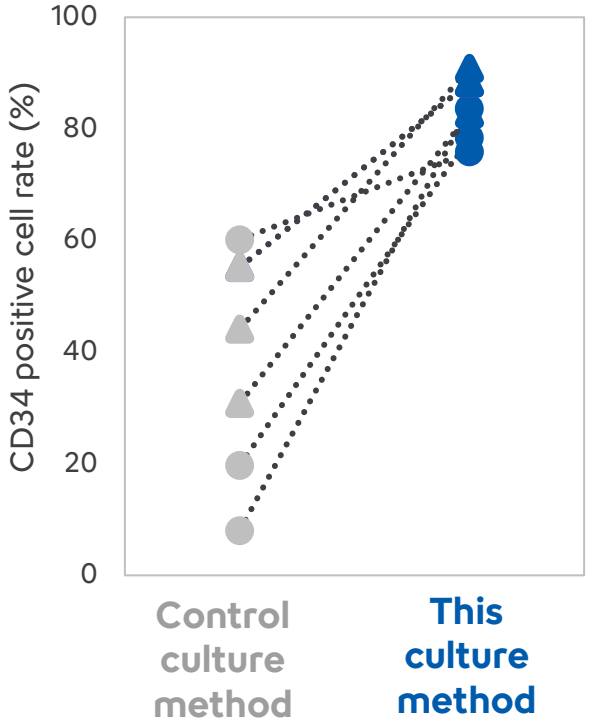
(2) In-vitro Performance of Amplified Culture Technology for Hematopoietic Stem Cells

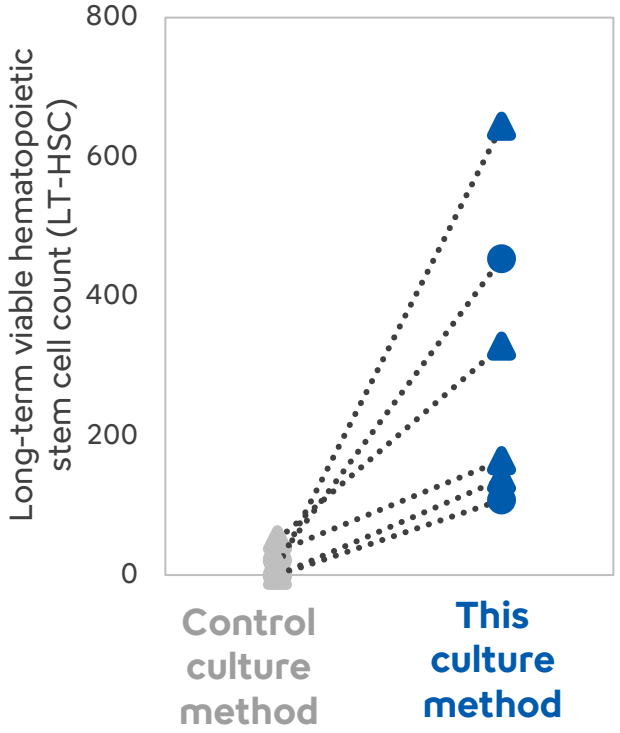
Successful amplification of hematopoietic stem cells involved in long-term viability in a short period of time

Significantly shortens the time required for cell amplification



Efficient amplification of hematopoietic stem cells involved in long-term viability

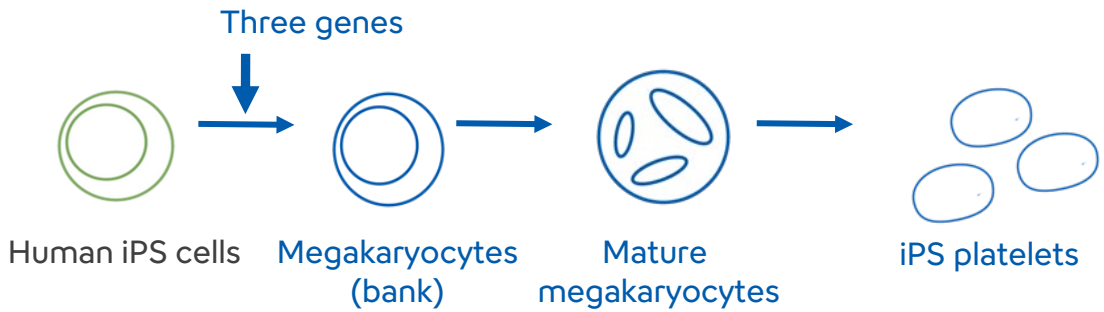




(3) Platelets from iPS Cells

We are aiming for the early commercialization of platelet preparation products derived from human iPS cells by leveraging synergies with Megakaryon, which has become a member of the Sysmex Group.

iPS cell-derived platelet technology



- ✓ Establishment of immortalized megakaryocyte line from iPS cells
- ✓ Successful mass production of platelets from immortalized megakaryocytes

Human iPS cell-derived HLA homologous platelet trial

JRCT No.: jRCT2053210068

- ✓ World's first administration in humans (April 2022)
- ✓ No side effects/adverse events reported
- ✓ Confirmed increase in platelet count after administration

Thrombocytopenia patients

Synergies between the companies

Mega karyon × sysmex

- ✓ Development, manufacturing and sales of formulations
- ✓ Provision of raw materials for reference materials etc.
- ✓ Support for manufacturing automation
- ✓ Provision of quality control testing etc.

In addition to the development of regenerative medicine and other products, beginning to consider collaboration in existing businesses

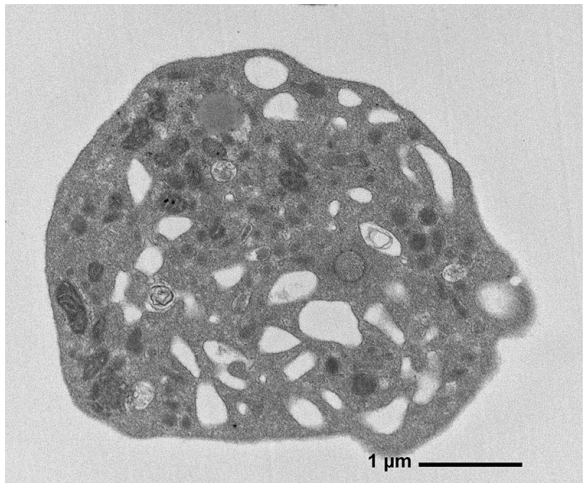
- ✓ Development of automated large scale manufacturing system
- ✓ Verification of quality control tests using our hematology analyzers, etc.
- ✓ Feasibility study for use as a reference material

(3) Platelets Derived from iPS Cells

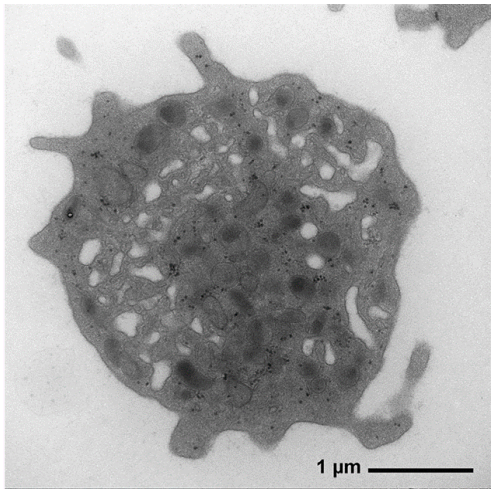
iPS cell-derived platelets showed comparable performance to human-derived platelets.

Platelets derived from iPS cells exhibit the microscopic morphology necessary for their physiological function.

Microstructural analysis of platelets by transmission electron microscopy



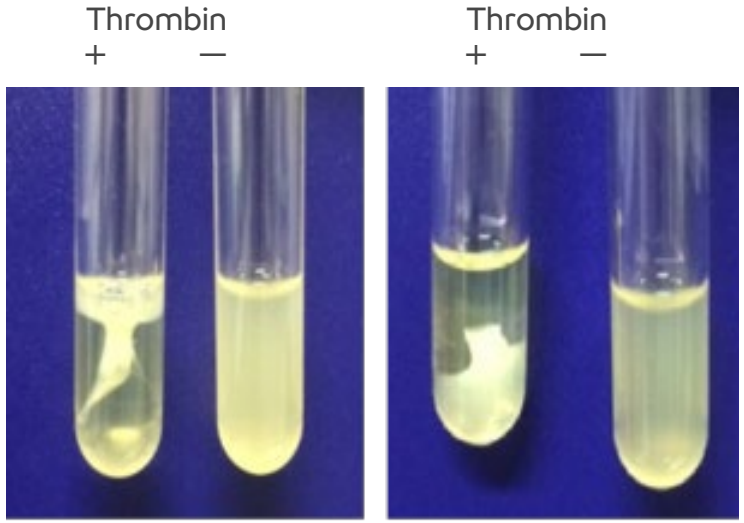
iPS cell-derived platelets



Normal human peripheral blood platelets

iPS cell-derived platelets showed clot retraction in the brain similar to that of human-derived platelets

In-vitro functional evaluation by blood clot retraction test



iPS cell-derived platelets Normal human peripheral blood platelets

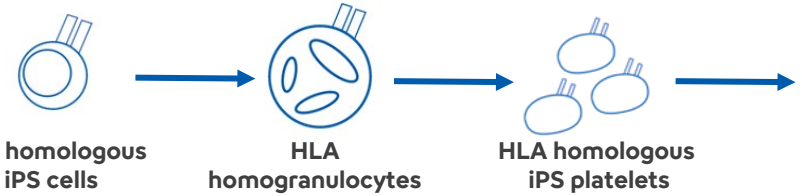
To be presented at the 23rd Annual Meeting of the Japanese Society for Regenerative Medicine (March 2024)

(3) Platelet Preparations Derived from iPS Cells

Delivering platelet preparations that can be administered to platelet transfusion-refractory patients

World's first basic technology to produce platelets lacking HLA expression (HLA-deficient platelets)

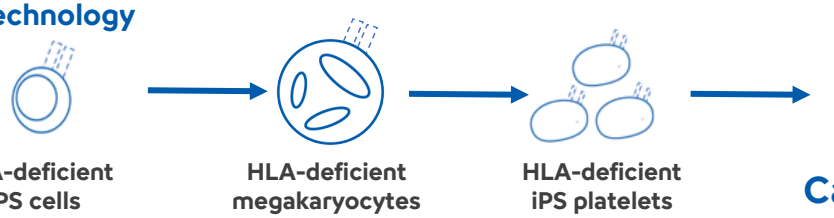
Conventional technology



Can be administered to some patients

This technology

Gene editing technology



Can be administered to almost all patients

Significance of platelet preparations derived from iPS cells

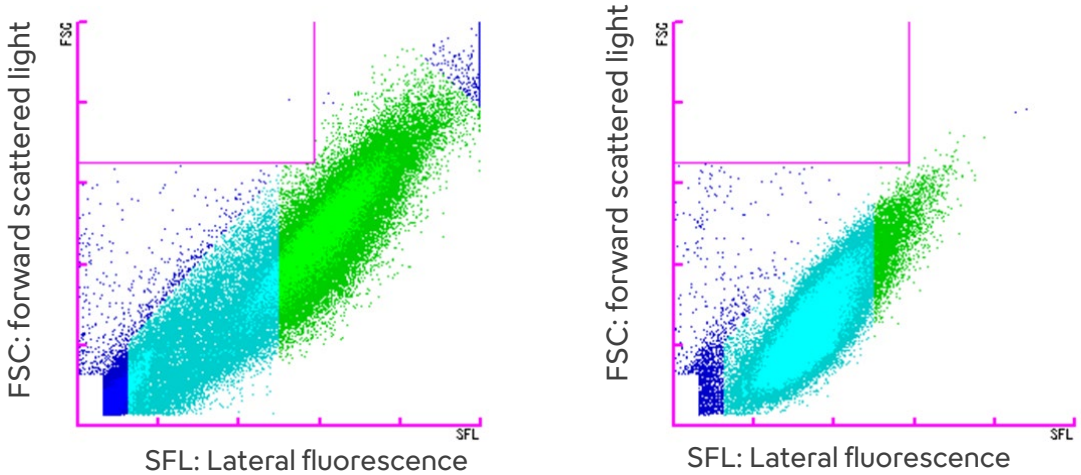
- Versatility allows transfusion to transfuse patients of any HLA type
- Safety without pathogenic or carcinogenic risk
- Contribution to the world's medical infrastructure through stable supply

(3) Platelet Preparations Derived from iPS Cells

Platelets derived from iPS cells have the potential to be a raw material for standard materials for our hematology analyzers.

Platelets derived from iPS cells can be measured with our hematology analyzer.

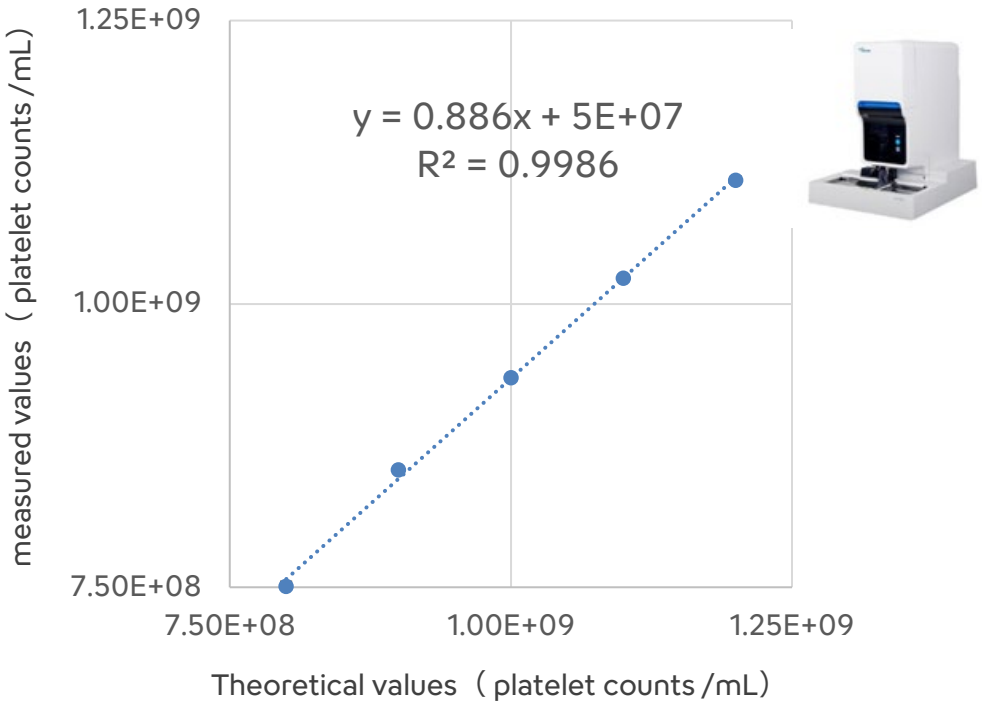
Comparing scattergrams



Platelet Preparations Derived from iPS Cells

Normal human peripheral blood platelets

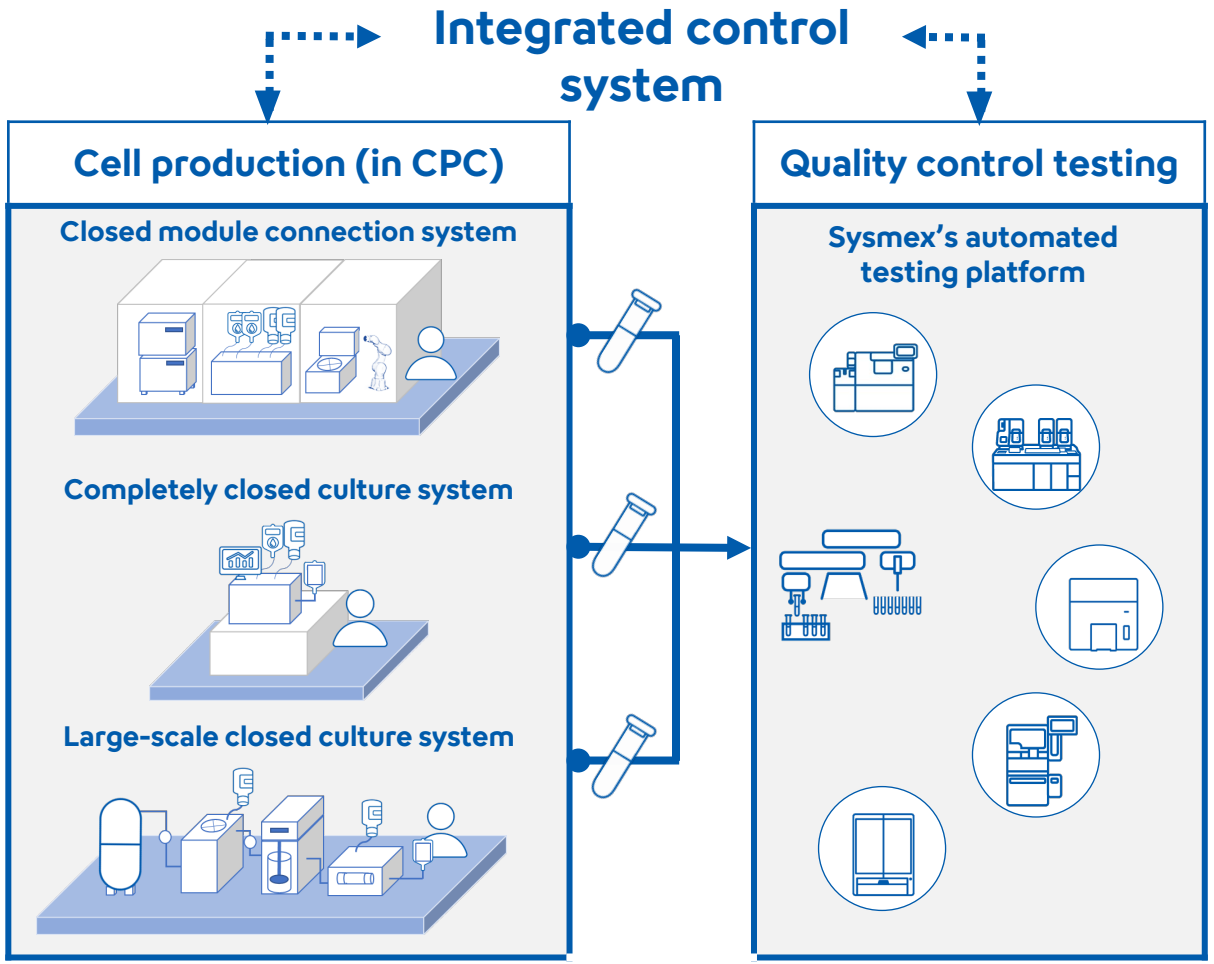
Linearity evaluation of iPS cell-derived platelet counts



(3) Initiatives toward the Automation of Manufacturing and Quality Testing

Innovations in Manufacturing Being Advanced by Sysmex

Automated manufacturing systems and quality control testing tailored to cell characteristics ensure both stable cell quality and cost optimization



Help realize sustainable regenerative cell medicine

- Cost reduction
- Scalability
- Labor-saving
- Easy technology transfer

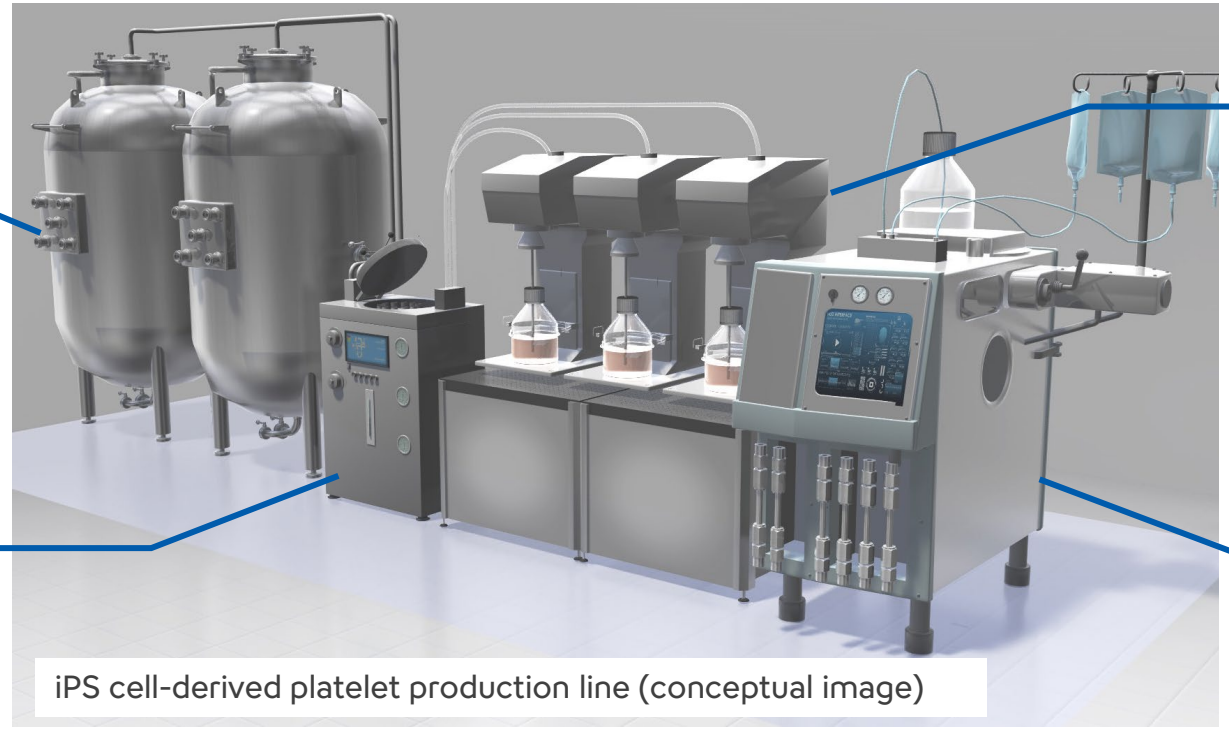
Promote early business development in cell manufacturing and quality control automation

(Example) Initiative with Megakaryon

Large-scale culture reactor and coupled purification system for efficient mass production of platelet preparations derived from iPS cells

Concept

- ✓ Large-scale closed-loop consolidated manufacturing system
- ✓ Linked automation and information integration of manufacturing and quality control
- ✓ Scalability and specifications to accommodate manufacturing scale and site expansion



iPS cell-derived platelet production line (conceptual image)

Quality Control Testing Automation Initiatives: Fully Automated Immunoassay System

Introducing fully automated protein measurement with high usability cultivated in IVD to the regenerative cell medicine market

Launch of HISCL VEGF/PEDF Assay Kits* (Q1 2024)

*Launched as research use

Characteristics

- ✓ Fully automated measurement of 1 test in 17 minutes
- ✓ One test can be measured at a time
- ✓ Wide measurement range without dilution
- ✓ High correlation with ELISA

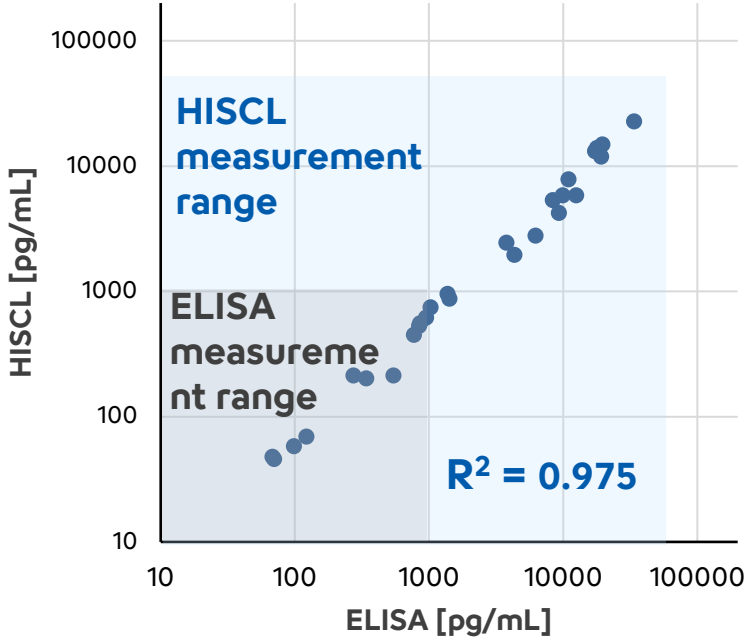
Vascular endothelial growth factor (VEGF)

Central molecule for angiogenesis, an indicator of organ bioproduction

Pigment epithelium-derived factor (PEDF)

Molecules that serve as indicators of cell survival and maintenance for eye regenerative medicine, which is now being implemented in clinical practice

Correlation evaluation of the existing method and this development method (n = 27)

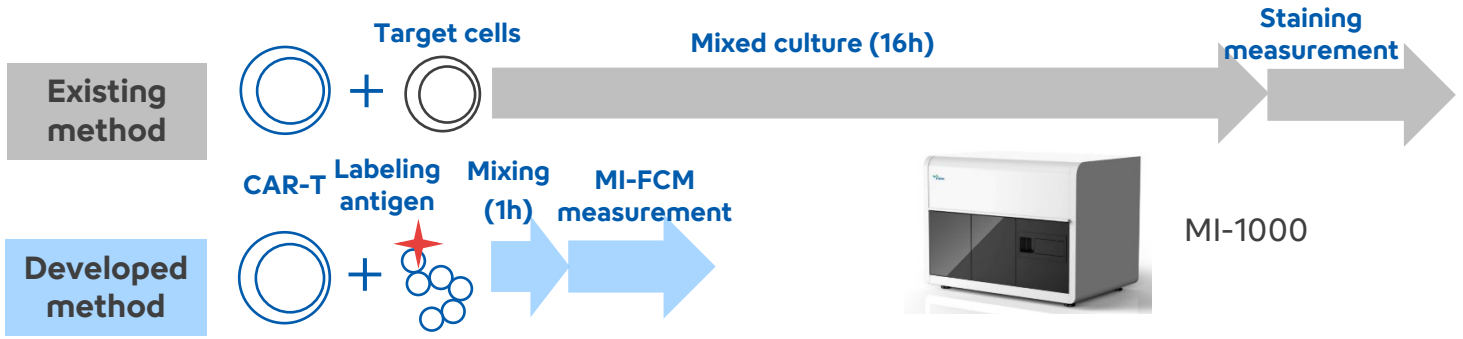


- ✓ Completed feasibility verification with several pharmaceutical and bio-venture companies
- ✓ Prompt dissemination after market introduction

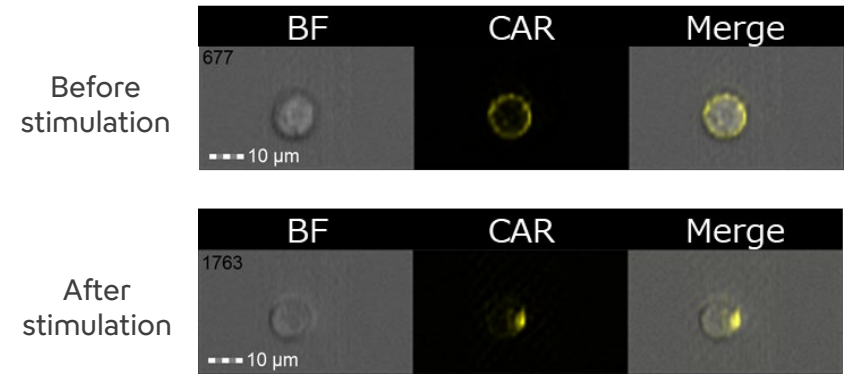
Quality Control Testing Automation Initiatives: Molecular Imaging FCM

Cytotoxicity of CAR-T cells is possible to evaluate automatically by detecting CAR molecular localization after stimulation

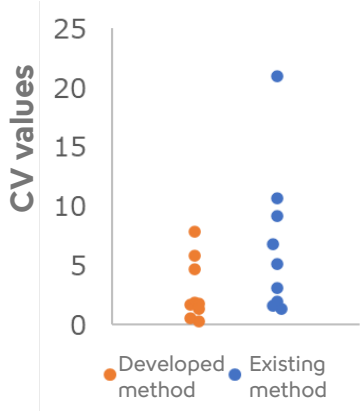
Comparison of our method with existing method in evaluation of cytotoxicity of CAR-T cells



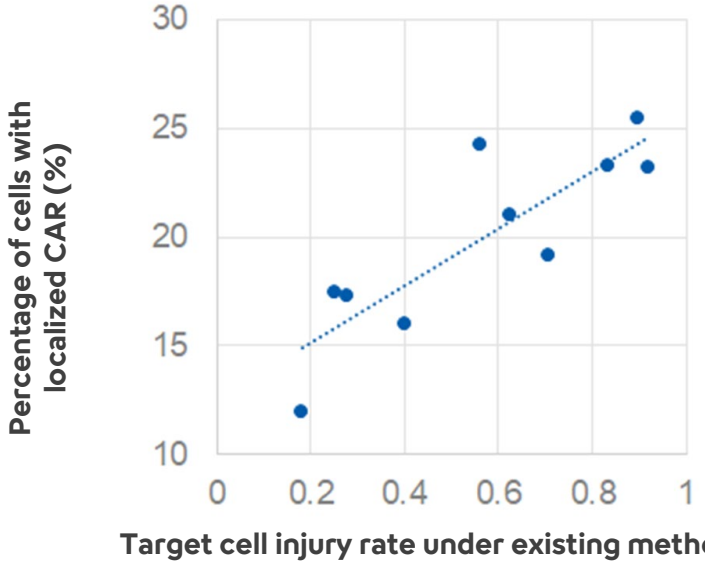
Localization change of CAR before and after stimulation



Comparison of measured CV values



Correlation evaluation of existing method and developed method



Our method enable to visualize the cytotoxic activity (≒ cell killing effect) of CAR-T cells against target cells.

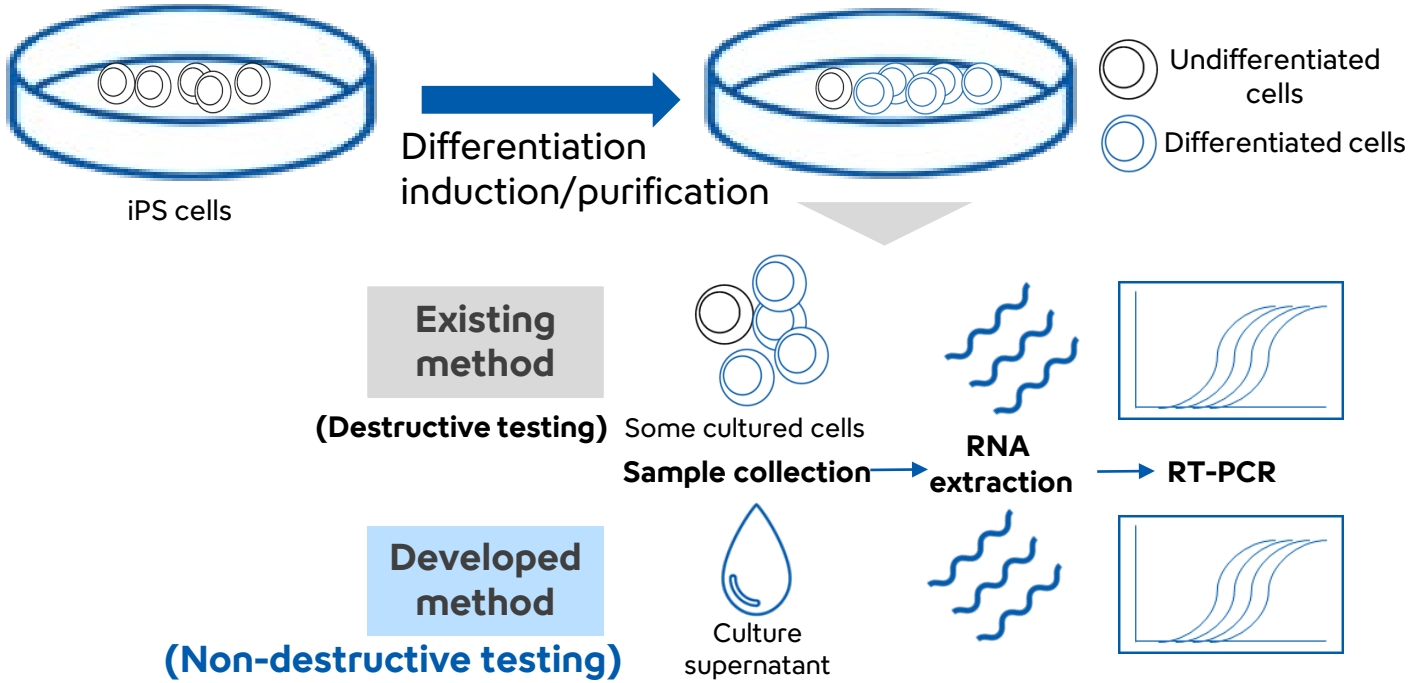
Molecular imaging FCM
FCM using high-speed imaging of cell morphology and fluorescence images and having the ability to automatically analyze images

Quality Control Testing Automation Initiatives: Undifferentiated iPS Cell Detection Technology

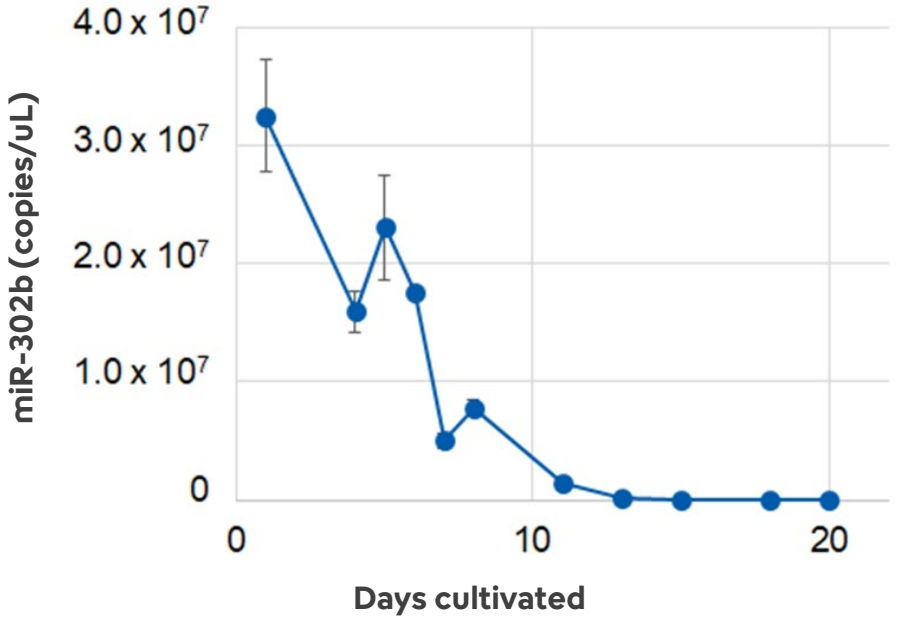
Collaborative study suggests utility as a non-destructive quality control test for safety of iPS-derived cellular medicine

Undifferentiated iPS cell detection technology

- Use PCR to detect miRNA produced by iPS cells in the culture process
- Evaluate residual undifferentiated iPS cells that may cause tumorigenesis
- Conduct non-destructive assay using culture supernatant



Changes during induction of differentiation of iPS cells into neurons



Remaining iPS cells, which decrease with cell differentiation, can be evaluated by the amount of miRNA in the culture supernatant.

Glossary

Glossary

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.
APOE4	An isoform of apolipoprotein E (ApoE), a protein that contributes to lipid metabolism, APOE4 is the gene product of ApoE ε4. ApoE ε4 is thought to be a risk factor for Alzheimer's disease.
APTT	Activated partial thromboplastin time (APTT) is a test parameter used to determine the cause of abnormalities in endogenous coagulation function.
BNA clamp PCR	BNA is an artificially created nucleic acid that binds stably to complementary nucleic acids, forming stable duplexes. This method uses the properties of BNA to bind (clamp) to genes other than the target of detection to suppress amplification and specifically amplify and detect the target.
Calcified EV	Calcified EV is a certain extracellular vesicle (EV) that causes vascular calcification (hardening of the blood vessels wall and restriction of blood flow).
CAR-T cells	Chimeric antigen receptor T cells (CAR-T cells) have been engineered to recognize specific cells such as cancer cells.
CDMO	A contract development and manufacturing organization (CDMO) is an organization that is contracted to develop and manufacture pharmaceuticals.
CDx	Short for "companion diagnostics." Clinical testing performed to predict the efficacy and side effects of drugs before using them for treatment.
cMyC	A myocardial-specific protein that is released more rapidly after acute myocardial infarction.
CPC	Cell processing center (CPC) is a facility that manufactures cell processing products for cell therapy and regenerative medicine.
CSF	A general term for tests using cerebrospinal fluid. Indispensable test for diagnosing diseases of the brain and spinal cord
CUC	An acronym for "cholesterol uptake capacity," CUC means the ability of HDL to take up cholesterol.
Cultured hematopoietic stem cells	Hematopoietic stem cells which expanded and cultured in-vitro in the presence of proprietary growth factors, compounds, etc.
Disease-modifying drug	A drug that suppresses the onset and progression of a disease by targeting the substance that causes the disease
ELISA	A method for detecting and quantifying target antigens or antibodies contained in a sample solution by using specific antibodies or antigens as well as enzymatic reactions.

Glossary

Expert panel	A multidisciplinary investigative commission that meets to medically interpret gene panel testing results. 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.
GFAP	Glial fibrillary acidic protein (GFAP) is a component protein of astrocytes, which refers to the glial cells responsible for immunity that arise in the central nervous system. GFAP is a marker of astrocyte activation during central neurvous system injury and repair.
HDL	High-density lipoprotein (HDL) is involved in the transport of cholesterol. HDL function is the function of collecting excess cholesterol.
Healthcare education	Education about healthcare provided in schools, companies, homes, etc.
Hematopoietic stem cells	Cells that produce red blood cells, white blood cells and blood platelets in the bone marrow.
HER	Electronic health records (EHRs) provide a system for the comprehensive and central management of patient medical information accumulated at medical institutions.
HLA	Human leukocyte antigens (HLAs) are distributed in almost all cells and body fluids. They serve as histocompatibility antigens (important molecules involved in self-recognition in the human immune system). HLA compatibility is a key factor in hematopoietic stem cell transplantation, organ transplantation, and regenerative medicine.
Immune tolerance	Immune-system's state of unresponsiveness to substances that would otherwise trigger an immune response.
Inducible inhibitory T-cells	T cells that suppress immune responses to specific antigens induced by antigens and anti-CD80 and anti-CD86 antibodies.
IVDR	The European In Vitro Diagnostic Medical Device Regulation (IVDR).
LDL	Low-density lipoprotein (LDL) is responsible for transporting cholesterol.
LDT	Acronym for “laboratory developed test.” LDTs, often testing methods that have not received regulatory approval, include highly sophisticated and complex IVD-testing that can only be performed in specific clinical testing labs.
M2BPGi	Abbreviation for Mac2 Binding Protein Glucosylation Isomer, a glycosylated isomer of Mac2 binding protein. It is thought to be clinically useful as a disease biomarker because it has tissue cell specificity and reflects the degree of cell differentiation and canceration.
miRNA	MicroRNA (miRNA) is a single-stranded RNA molecule of around 20 nucleotides in length involved in controlling the expression of numerous genes and proteins, thereby making fine adjustments in vital phenomena. In recent years, attention has focused on the miRNA present in exosomes for diagnosing disease, as they are stable, preventing them from being broken down by enzymes in the blood, and their quantities and types vary substantially depending on various disease pathologies and degree of progression.

Glossary

NfL	Neurofilament light chain (NfL) is a neuron-derived protein, which is used as a biomarker for cognitive function.
NGS	Acronym for “next-generation sequencer.” May also refer to a next-generation sequencer, an instrument for reading gene base sequences at high speed.
Plasma-Safe-SeqS	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.
PT	Prothrombin time (PT) is a test parameter used to examine the coagulation function of the extrinsic pathway responsible for hemostasis.
Quality control	A management method used to guarantee the values measured by customers’ testing equipment and to confirm that a customer’s equipment is functioning correctly
Recipient T cells	T cells of a patient who receives a transplant operation.
Revascularization surgery	A surgical treatment for cerebrovascular disorders, especially cerebral infarction.
RI	RI is a radioisotope testing.
RPE cells	Retinal pigment epithelial (RPE) cells comprise the tissue covering the outermost layer of the retina. These cells contain the pigment melanin, which absorbs excess light entering the retina and prevents scattering.
Self-medication	Taking responsibility for your own health and examine and treat minor physical ailments on your own.
Tau	A microtubule associated protein that exists in neuronal cells. Along with senile plaque, inordinately phosphorylated deposits of tau protein can be observed in the brains of patients with Alzheimer’s disease.
TMB	Tumor Mutational Burden (number of somatic mutations)
TTR	TTR is transthyretin, A carrier protein in the blood that carries the thyroid hormones thyroxine (T4) and retinol to the liver. Its stability is studied as a marker of cardiac amyloidosis.
Variants	Variants are differences in DNA sequences.
vWF	The von Willebrand factor (vWF) is a high molecular weight plasma glycoprotein with stabilizing effects on initial platelet adhesion, platelet aggregation, and coagulation factor VIII at the site of vascular injury.

Together for a better
healthcare journey