# The 22nd R&D Meeting

March 7, 2025

Sysmex Corporation

Together for a better
healthcare journey

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・The information on products and other matters contained herein is not intended as advertising or medical advice, whether or not regulatory approval has been obtained.

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# 1

# Initiatives to Realize the Healthcare Journey and Strengthen R&D Functions and Systems
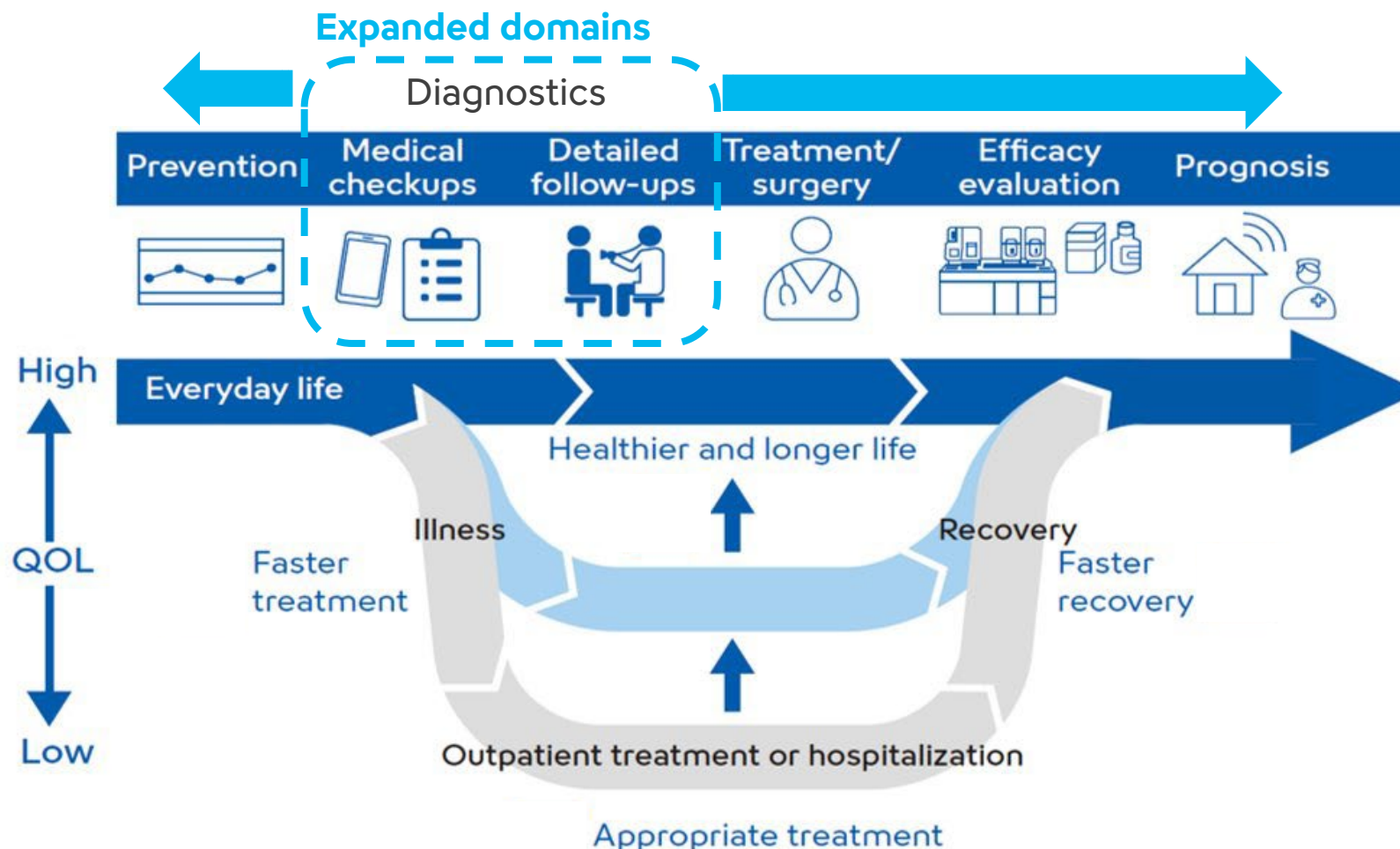
Tomokazu Yoshida
Member of the Managing Board and
Senior Executive Officer
Managing Director, CTO

# 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

# Accelerating Evolution of Health Tech

| Changing healthcare awareness | Acceleration of digital technologies | New treatment modalities |
|---|---|---|

**Increase in new entrants**
**Response to increasingly diverse medical services**

**Expansion of digital healthcare**
**Development of products and services**
**Response to increasing speed**

**Response to increasingly sophisticated treatment**

- ✓ **Shift from treatment to prevention**
- ✓ Self-medication
- ✓ Healthcare education
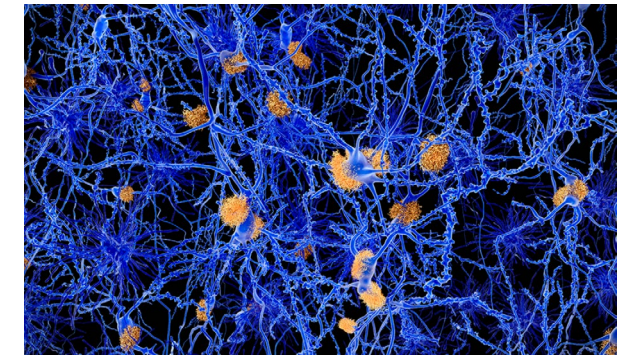- ✓ Increasingly diverse medical services

- ✓ **Rapid industrial utilization of AI and its application in the medical industry**
- ✓ Full-scale development of remote medical care
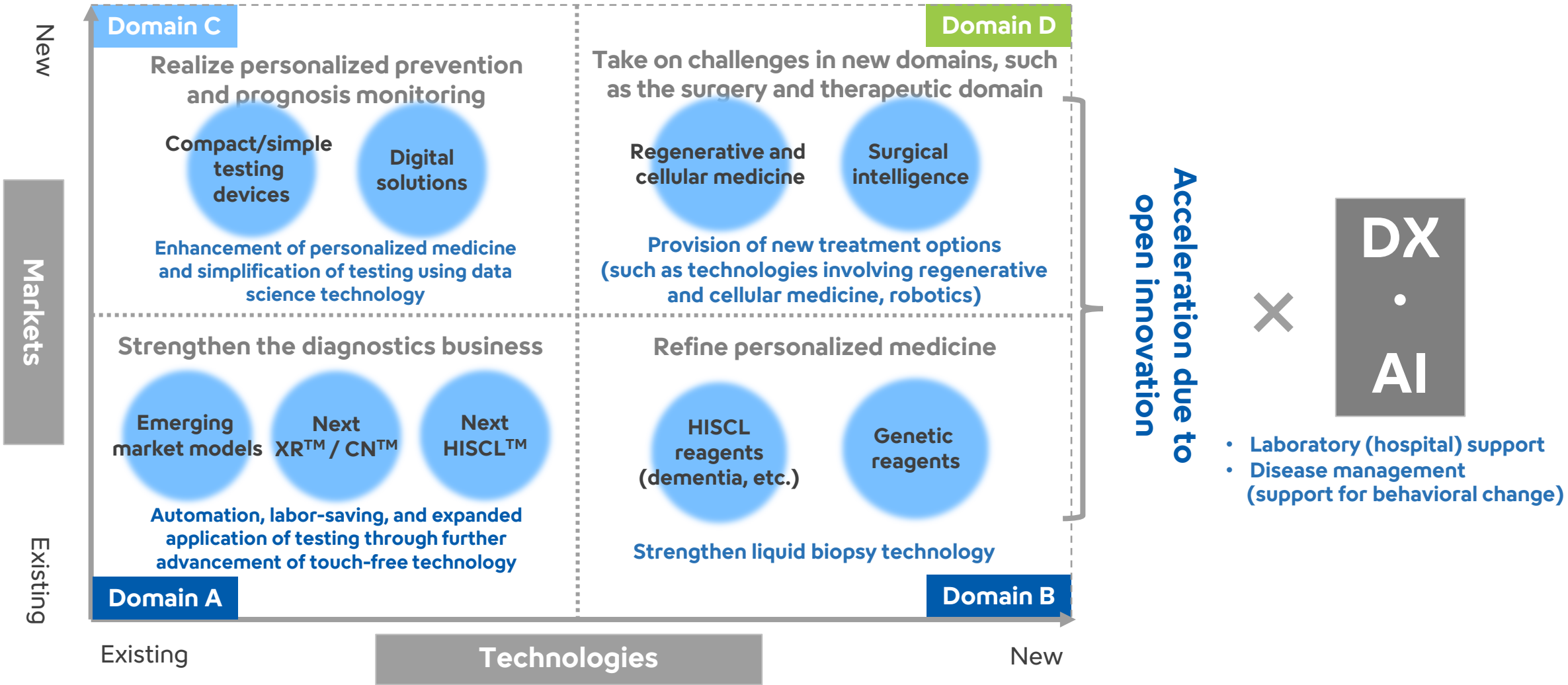- ✓ **Faster product development and analytical performance using digital technology**

- ✓ New treatments for Alzheimer's disease
- ✓ Practical application of regenerative cell medicine
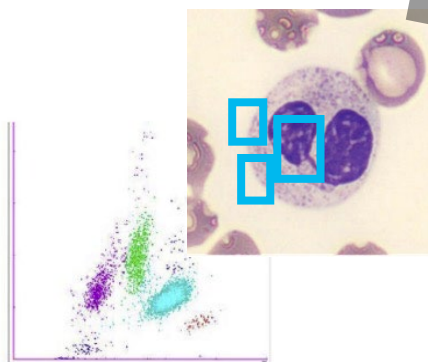- ✓ Application of gene editing technology

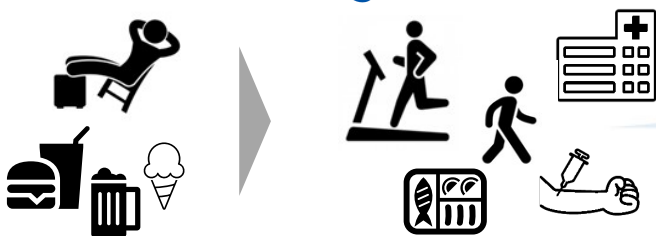# Product Development and R&D Initiatives in the Innovation Stream

**sysmex**

**Markets**

New

Existing

**Domain C**

Realize personalized prevention and prognosis monitoring

- Compact/simple testing devices
- Digital solutions

Enhancement of personalized medicine and simplification of testing using data science technology

**Domain D**

Take on challenges in new domains, such as the surgery and therapeutic domain

- Regenerative and cellular medicine
- Surgical intelligence

Provision of new treatment options (such as technologies involving regenerative and cellular medicine, robotics)

Strengthen the diagnostics business

- Emerging market models
- Next XR™ / CN™
- Next HISCL™

Automation, labor-saving, and expanded application of testing through further advancement of touch-free technology

**Domain A**

Refine personalized medicine

- HISCL reagents (dementia, etc.)
- Genetic reagents

Strengthen liquid biopsy technology

**Domain B**

**Technologies**

Existing          New

**Acceleration due to open innovation**

**×**

**DX · AI**

- Laboratory (hospital) support
- Disease management (support for behavioral change)

# AI Utilization in the Healthcare Journey

◆**Testing AI:**
**Disease prediction,**
**diagnostic support**

**Healthcare journey**

◆**Laboratory (hospital) support AI:**
**Improving the efficiency of**
**testing and medical operations**

Prognosis

Efficacy
evaluation

Treatment

Detailed
follow-ups

Medical
checkups

Support for the creation of
documents using LLMs,
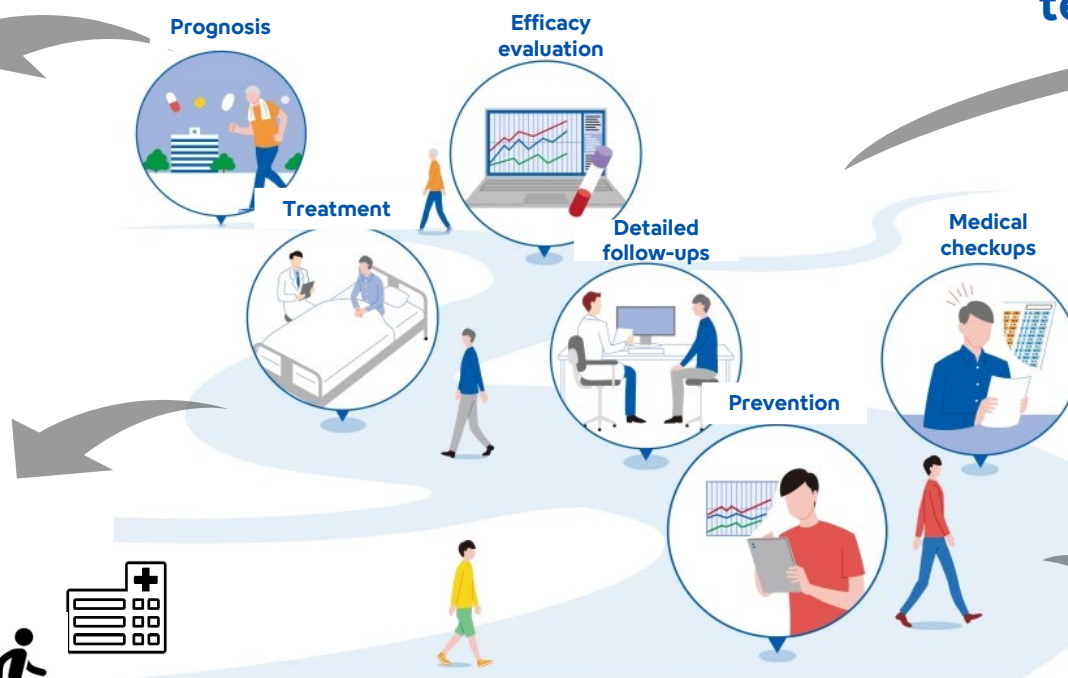custom AI, etc.

Prevention

**Support for**
**behavioral change**

◆**Acceleration of R&D**

- Motivation for daily health management
- Advice and education for individual patients
- Recommendations for necessary tests, etc.

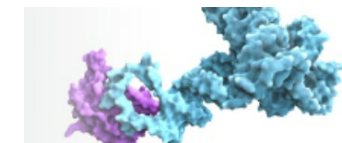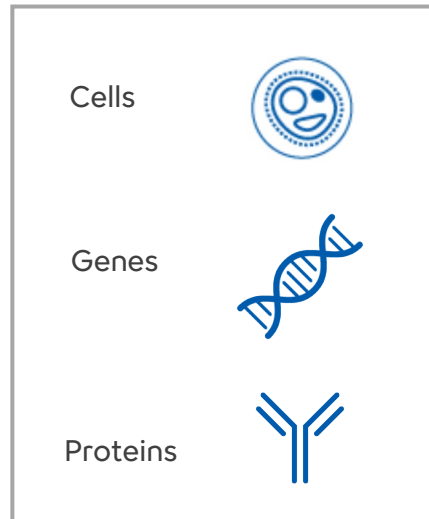# Strengthening Sysmex's Liquid Biopsy Technology

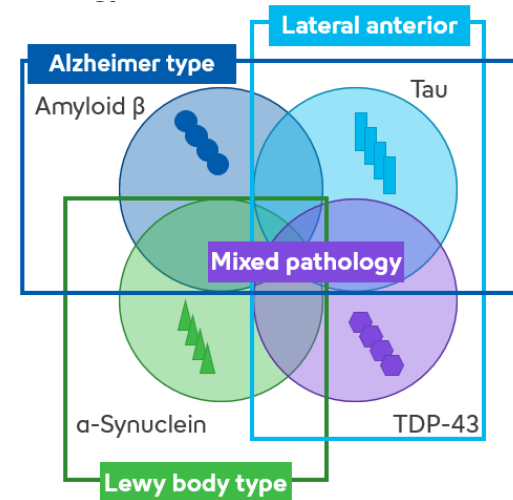## Reinforcing measurement technology

Blood component information
(liquid biopsy)

Cells

Genes

Proteins

- ✓ Ultrasensitive determination
- ✓ Multiparameter shift
- ✓ Functional measurement
- ✓ Structural stability measurement
- ✓ Activity measurement

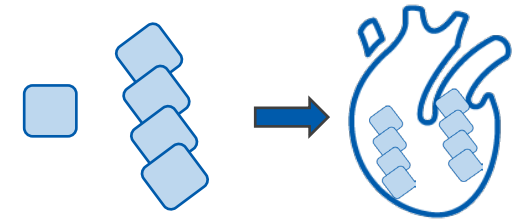## Expanding target diseases and into early diagnosis and prevention areas

Lateral anterior

Alzheimer type

Amyloid β

Tau

Mixed pathology

α-Synuclein

TDP-43

Lewy body type

Denaturation, agglutination

Tissue deposition

**Alzheimer disease**
Diagnosing the status of amyloid-β stored in the brain

↓

Differentiation of dementia

↓

Stratification of central nervous system diseases

Diseases caused by accumulation of aberrantly aggregated proteins in organs (amyloidosis)

↓

Risk assessment of thrombosis, heart failure, etc.

Blue: Covered today

# Strengthening R&D Functions

**sysmex**

By restructuring our global R&D system in collaboration with key opinion leaders, members of academia, and startup companies, we are responding promptly to changes in the environment surrounding health tech, medical services, and treatment.

✓ **Collaboration with affiliated companies**

✓ **Development of dementia-related parameters**

**RDCUK (UK)**

**RDCE (Germany)**

**Technopark (Japan)**

**RDCA (US)**

✓ **Clinical evaluation and development with testing centers**

**RDCAP (Singapore)**

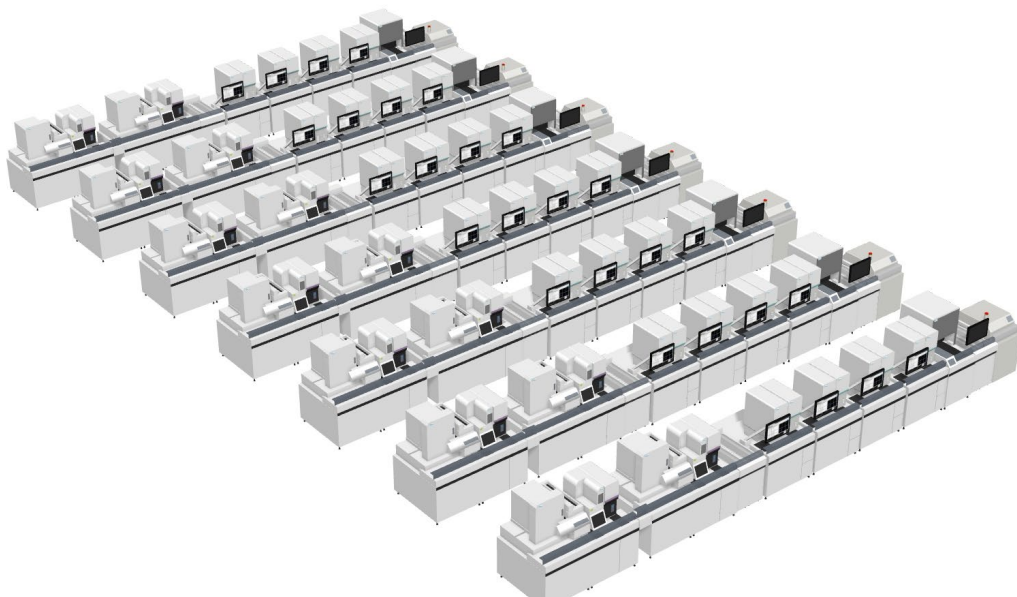✓ **AI development with academia**

🔬 **Clinical evaluation and development with testing centers**

**25** locations in **9** countries

# Promoting the Evolution of Hematology Systems

We are moving forward with the touch-free concept, improving workflow and enhancing work efficiency by reducing the number of manual processes.

## Pre-testing management

TA-01 sample storage unit

TS-01 sample sorting unit

BT-50 barcode terminal

- ✓ Sample storage and sorting
- ✓ Scheduler function
- ✓ (instrument startup/shutdown, cleaning)
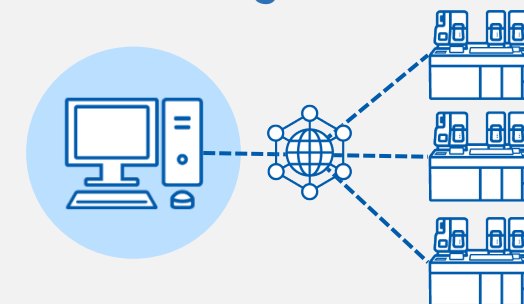- ✓ Automated quality control

## Reagent management during testing

RM-10 reagent supply unit

- ✓ No need to change reagents during testing

## Instrument management

- ✓ Visualization of instrument status

# R&D Topics

# System for Rapid Detection of Antimicrobial Susceptibility Wins One of the UK's Biggest Science Prizes

We employed proprietary microfluidic technology to create the PA-100 AST System, which achieves rapid testing for antimicrobial susceptibility.
The system is expected to transform the flow of diagnostics for urinary tract infections and advance measures to counter antimicrobial resistance. We have begun selling the system in Europe.

PA-100 AST System
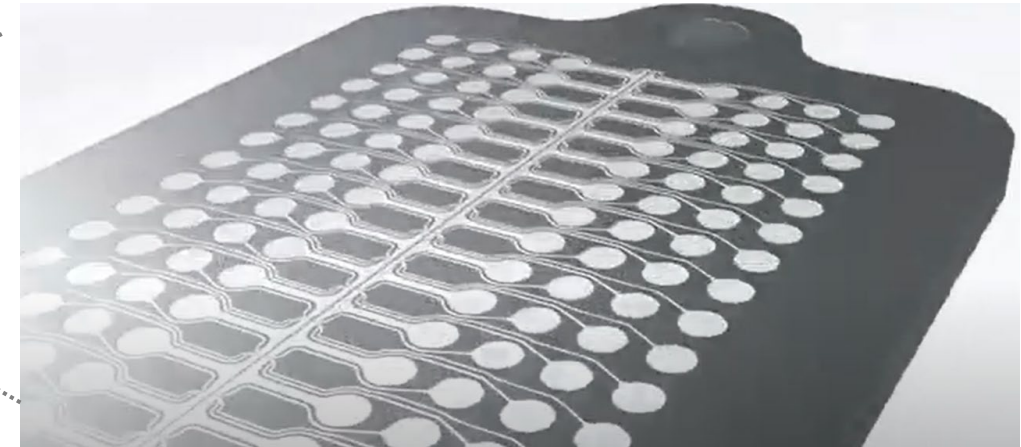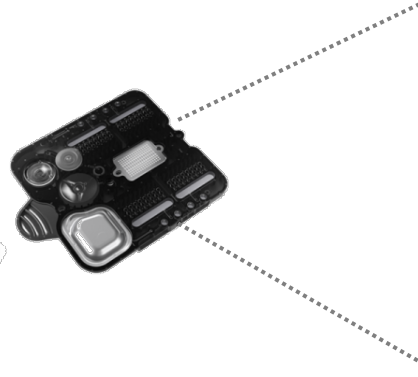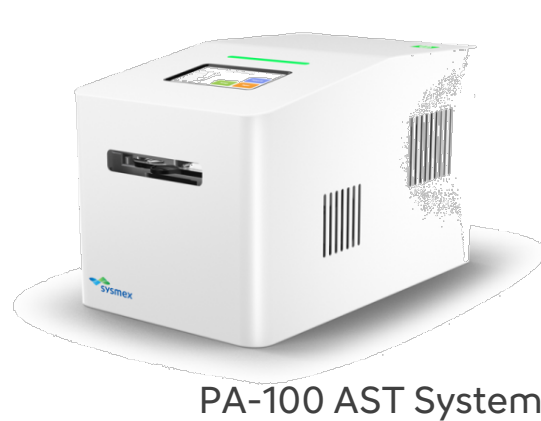
✓ Compared to conventional microbiology labs where tests take several days, this system allows the presence of bacteria to be determined in 15 minutes and the effectiveness of antibiotics in 30 minutes.
✓ Operation is simple and not require specialized knowledge.
✓ The system earned us one of the UK's biggest science prizes, the "Longitude Prize on AMR." Selected as the only winner from over 250 entries since the prize's establishment in 2014, this innovative technology contributes to transforming the diagnostic flow for bacterial infections and addressing antimicrobial resistance.

Cited from https://www.sysmex.co.jp/news/2024/240613.html, Sysmex Astrego AB - Longitude Prize

# Initiatives to Realize a Resource-Circulating Value Chain

**We became the first company in the industry to adopt the horizontal recycling of containers for reagents. We have established a process to collect used containers and produce contaminant-free recycled resin.**



**HISCL line washer concentrate**

**Used containers**

**Grinder**

**Recycled raw materials**
(Jointly developed with ZACROS Corporation)
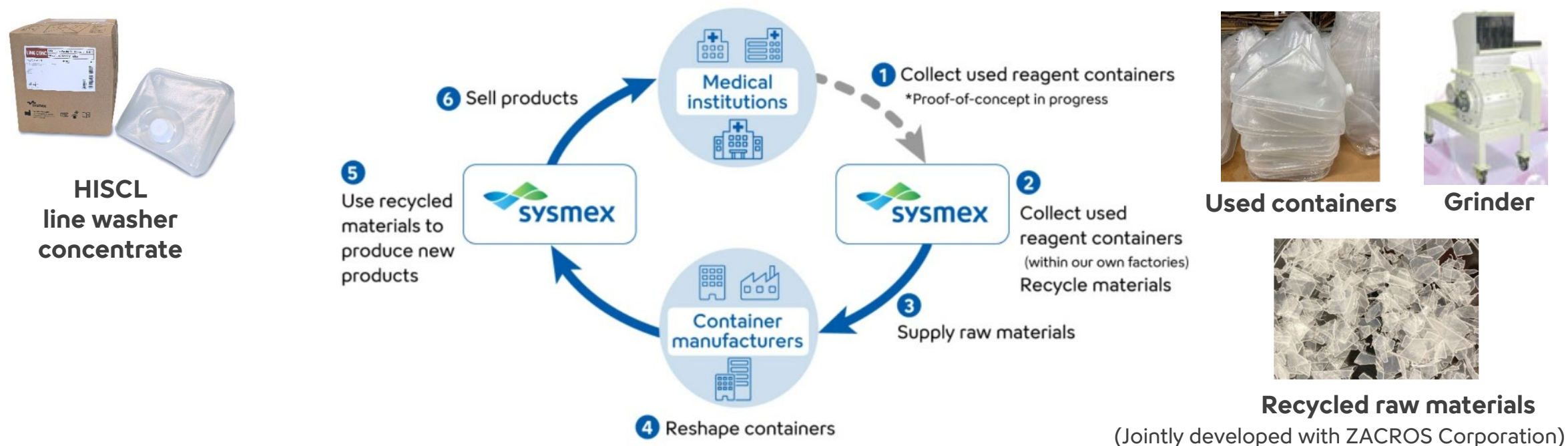
**This process reduces the consumption of virgin resin by approximately 30% and decreases $CO_2$ emissions by around 15 tons per year. We plan to expand the range of applicable products.**

https://www.sysmex.co.jp/news/2024/241223.html

# Product Development and R&D Initiatives in the Innovation Stream

**sysmex**

**Covered today**

Markets

New ↑

**Domain C**

Realize personalized prevention and prognosis monitoring

Compact/simple testing devices

Digital solutions

Enhancement of personalized medicine and simplification of testing using data science technology

**Domain D**

Take on challenges in new domains, such as the surgery and therapeutic domain

Regenerative and cellular medicine

Surgical intelligence

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Strengthen the diagnostics business

Emerging market models

Next XR™ / CN™

Next HISCL™

Automation, labor-saving, and expanded application of testing through further advancement of touch-free technology

Refine personalized medicine

HISCL reagents (dementia, etc.)

Genetic reagents

Strengthen liquid biopsy technology

**Domain A**

Existing ↓

**Domain B**

Existing ← Technologies → New

Acceleration due to open innovation

DX · AI

×

Laboratory (hospital) support
Disease management (support for behavioral change)

# Themes Covered Today

**2. Medical DX Utilizing AI**

Shigeki Iwanaga
Executive Vice President of
Technology Strategy

**3. Deepening of Liquid Biopsy Technology**

Toshiyuki Sato
Executive Vice President of
Central Research Laboratories

**4. Initiatives in Regenerative Cell Medicine**

Kenji Tsujimoto
Executive Vice President of
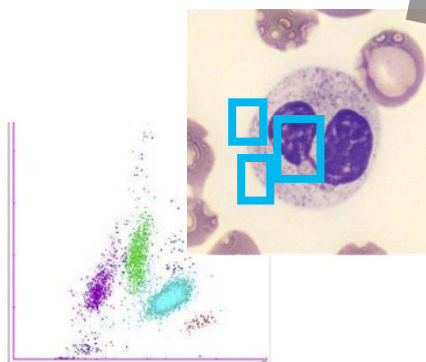Next Generation Medical Business
Development

# 2 Medical DX Utilizing AI

Shigeki Iwanaga
Executive Vice President of
Technology Strategy

# AI Utilization in the Healthcare Journey

**◆Testing AI:**
**Disease prediction,**
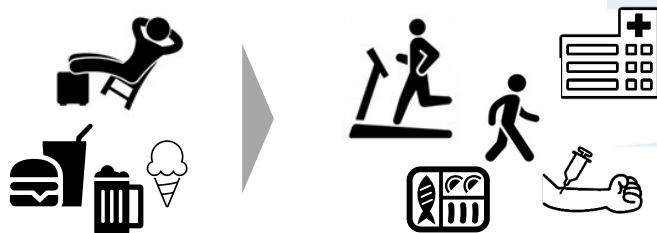**diagnostic support**

**Healthcare journey**

**◆Laboratory (hospital) support AI:**
**Improving the efficiency of**
**testing and medical operations**

Prognosis

Efficacy evaluation

Treatment

Detailed follow-ups

Medical checkups

Prevention

Support for the creation of documents using LLMs, custom AI, etc.

**Support for behavioral change**

**◆Acceleration of R&D**

- Motivation for daily health management
- Advice and education for individual patients
- Recommendations for necessary tests, etc.
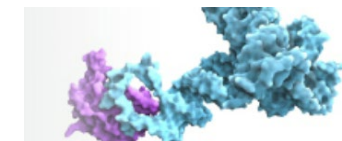
# Development of Sysmex AI

1. Features of Sysmex AI
2. Laboratory (Hospital) Support
3. Disease Management (Support for Behavioral Change)

# 1. Features of Sysmex AI



- **Possesses specialized knowledge in testing and diagnosis**
  - ✓ Knowledge of laboratory medicine
  - ✓ Large-scale receipt data and academic/testing data owned by Sysmex

- **Recommends tests to improve risk estimation accuracy**
  - ✓ Research parameters from Sysmex products
  - ✓ Utilization of Sysmex's proprietary biomarkers

- **On-premises LLM support tailored to clinical settings**
  - ✓ Secure AI that can operate without the need for an external internet connection

# 2. Laboratory (Hospital) Support

**We are working to improve the efficiency of hospital and laboratory operations through the use of AI, reducing the workload of healthcare professionals. Our AI operates in a secure environment using the expertise of testing specialists.**

## AI Laboratory support

- ✓ Provides high-accuracy risk prediction
- ✓ Offers specialized explanations for doctors and nurses
- ✓ Identifies causes of abnormal values and clinical explanations
- ✓ Avoids misdiagnosis and oversight
- ✓ Suggests additional tests
- ✓ Uses AI to improve accuracy

- ✓ Possesses specialized knowledge in testing
- ✓ Predicts the number of test orders
- ✓ Laboratory support
  - ・Confirms test purposes
  - ・Provides ISO operation support
- ✓ Technician training
  - ・Explains usage procedures
  - ・Has database of case studies
  - ・Contains educational programs
- ✓ Operates on-premises
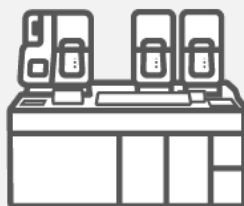
Lab technologists

## AI Hospital support

- ✓ Helps with document preparation
  - ・Medical record entry/information transmission
- ✓ Supports patient interviews/explanations to patients
- ✓ Provides scheduling for healthcare professionals
- ✓ Helps with hospital coordination

Doctors    Management

# 2. Laboratory (Hospital) Support: Examples of Research Parameters Utilized

**AI enables us to identify and differentiate previously difficult-to-diagnose diseases through multivariate analysis of blood cell counts and integration of specimen measurement information.**

XR-1000 multiparameter automated hematology analyzer

CN-3500/CN-6500 automated blood coagulation analyzer

Disease A

Disease B

Disease C

.
.
.
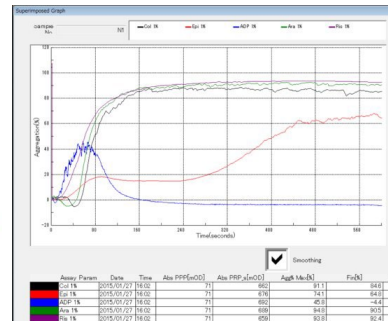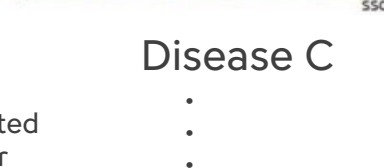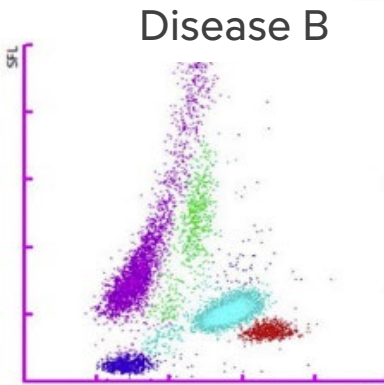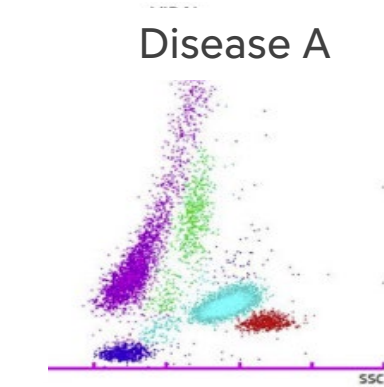
**AI Algorithm**

**Classification of diseases through reanalysis of measurement data**

Disease A

Disease B

Disease C

**Features** (parameters)

| RBC/PLT Reportable | WBC Reportable | WBC Research | WBC Sensitivity |
|---|---|---|---|
| RBC | WBC | TNC | NE-SSC |
| HGB | NEUT# | (WBC-N) | NE-SFL |
| HCT | LYMPH# | (TNC-N) | LY-X |
| MCV | MONO# | (BA-N#) | LY-Y |
| MCH | EO# | (BA-N%) | MO-X |
| MCHC | BASO# | (WBC-D) | MO-Y |
| PLT | NEUT% | (TNC-D) | NE-WX |
| RDW-SD | LYMPH% | NEUT#& | NE-WY |
| RDW-CV | MONO% | NEUT%& | LY-WX |
| NRBC# | EO% | LYMP#& | LY-WY |
| NRBC% | BASO% | LYMP%& | MO-WX |
| (PLT-I) | IG# | HFLC# | MO-WY |
| MicroR | IG% | HFLC% | NEUT-RI |
| MacroR | Q-Flag[LS] | (BA-D#) | NEUT-GI |
| R-MFV | Q-Flag[At-Ly] | (BA-D%) | |
| P-MFV | | | |
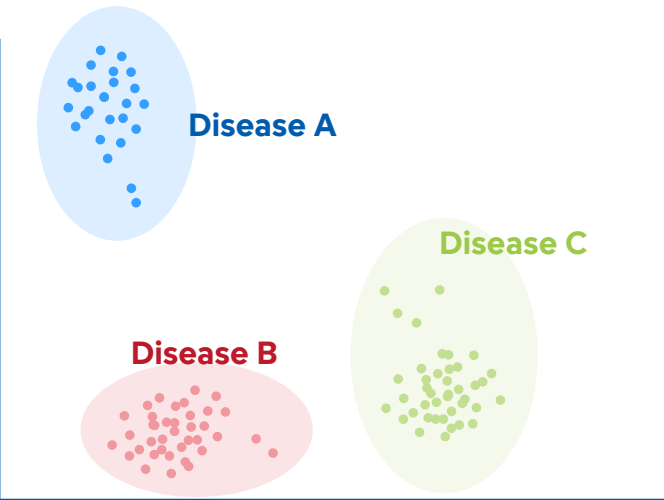
We are utilizing digital data and proprietary AI to promote medical schemes and individual behavior change.

# **P**redictive, **P**reventive, **P**ersonalized, **P**articipatory

Detection of onset ➡ **Prediction** of onset

Treatment of disease ➡ **Pre-disease** care and **prevention**

Standardized treatment ➡ **Personalized** medicine

Healthcare professional-centered ➡ **Active** individual **involvement**

**Medical checkups, detailed follow-ups** ➕ **Value provision through digital and AI**
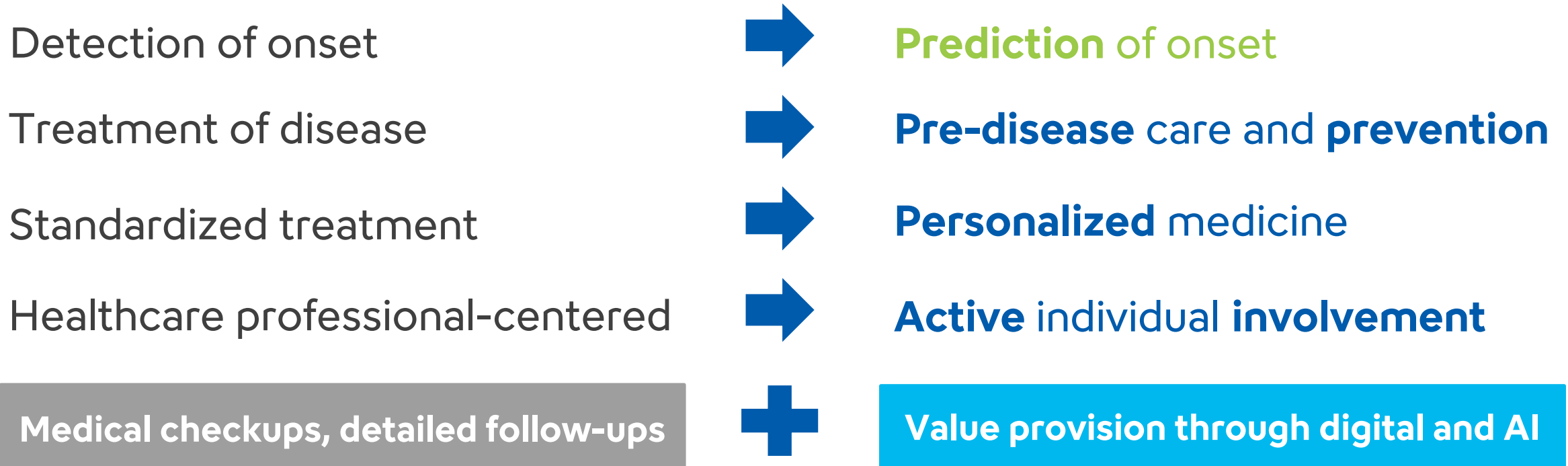
# 3. Support for Behavioral Change:
## Challenges in Disease Risk Prediction Using AI

**Current**

| Healthcare database | Machine learning | Prediction model | Risk of onset | |
|---|---|---|---|---|
|  | **AI** |  | 85%  10%  40% | Health guidance  Lifestyle improvement |

Disease risk prediction using general AI
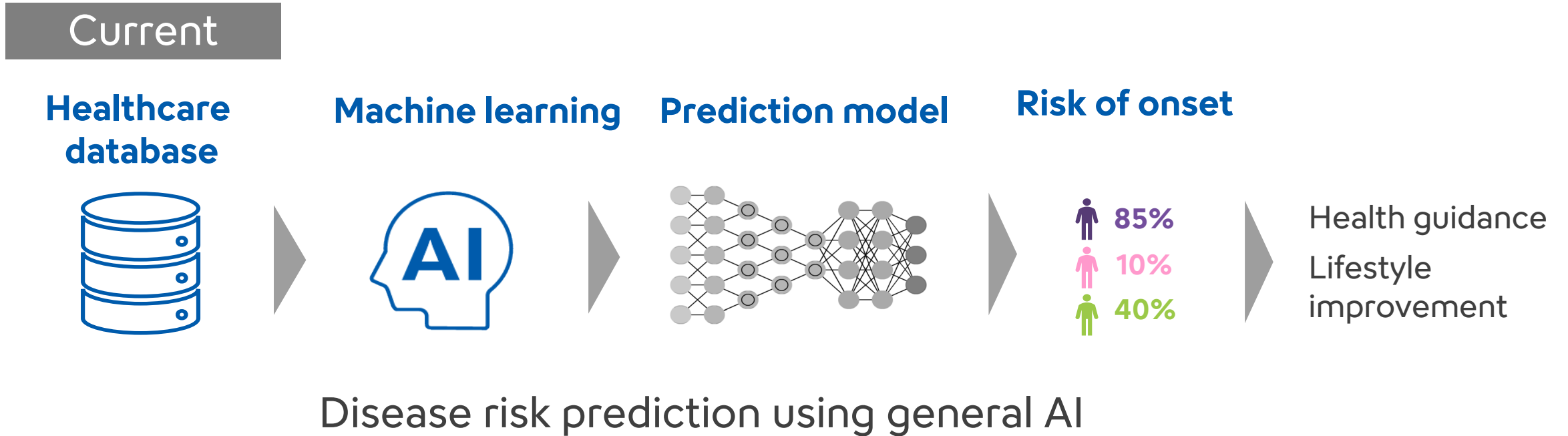
**Challenges**

✓ **Individual circumstances are not reflected.**

✓ **Accuracy of the prediction model**

✓ **Explainability**
(Reasons for the results are unclear.)

# 3. Support for Behavioral Change: Realization through Sysmex AI

By utilizing markers that reflect individual lifestyles and large-scale data, Sysmex AI facilitates highly accurate personalized disease risk prediction and supports behavioral change.

Sysmex AI

- Possesses specialized knowledge in testing and diagnosis
- Recommends tests to improve risk estimation accuracy
- Provides on-premises LLM support tailored to clinical settings

✓ High-accuracy prediction through quality control and measurement data
✓ Global data integration

**+ Bigdata Utilization**
**(PHR, HER, etc.)**

- Personalized feedback for each individual patients

✓ Proprietary biomarkers that reflect lifestyle habits
✓ Digital applications that reach individuals

**Fostering behavioral change**
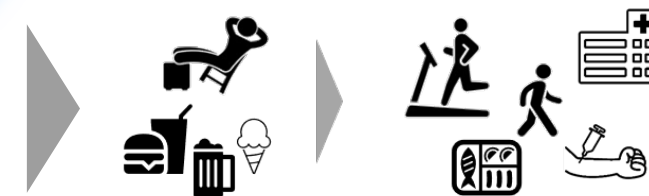
- Motivation for daily health management
- Advice and education for individual patients
- Recommendations for necessary tests, etc.

**3**

# Deepening of Liquid Biopsy Technology

Toshiyuki Sato
Executive Vice President of
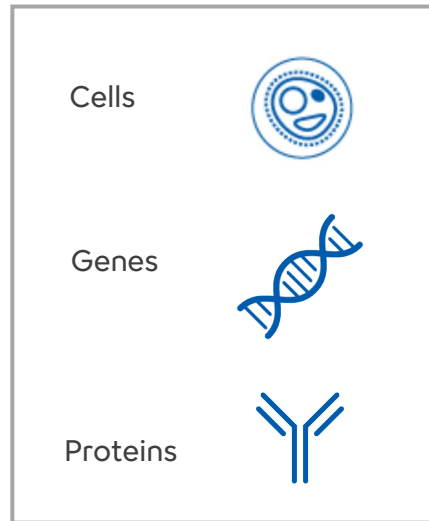Central Research Laboratories

# Strengthening Sysmex's Liquid Biopsy Technology

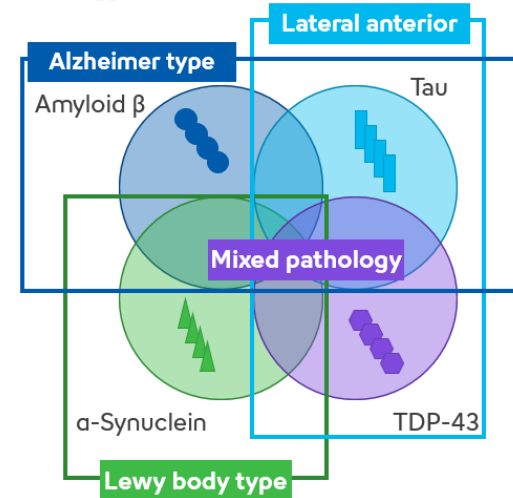sysmex

## Reinforcing measurement technology



**Blood component information**
**(liquid biopsy)**

Cells

Genes

Proteins

✓ Ultrasensitive determination
✓ Multiparameter shift
✓ Functional measurement
✓ Structural stability measurement
✓ Activity measurement

## Expanding target diseases and into early diagnosis and prevention areas



**Alzheimer type**
Amyloid β

**Lateral anterior**
Tau

**Mixed pathology**

α-Synuclein

TDP-43

**Lewy body type**
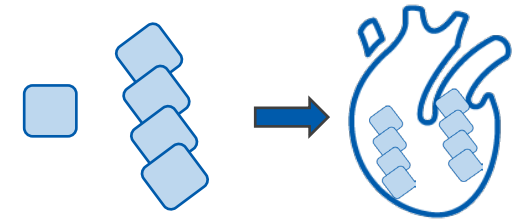
**Alzheimer disease**
Diagnosing the status of amyloid-β stored in the brain

↓

Differentiation of dementia

↓

Stratification of central nervous system diseases

Denaturation, agglutination

Tissue deposition



**Diseases caused by accumulation of aberrantly aggregated proteins in organs (amyloidosis)**

↓

Risk assessment of thrombosis, heart failure, etc.

Blue: Covered today

# Developing Amyloid-β Testing Reagents

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

| | 🇬🇧 | 🇨🇳 | 🇯🇵 | 🇺🇸 |
|---|---|---|---|---|
| Therapeutic drug (Lecanemab) | Approved in the UK | Approved | Approved | Approved |
| IVD reagent (Aβ42/40, Sysmex) | IVDD declared | Under consideration (Hong Kong and Macau) | Pharmaceutical approval | Application in preparation (LDT in progress) |
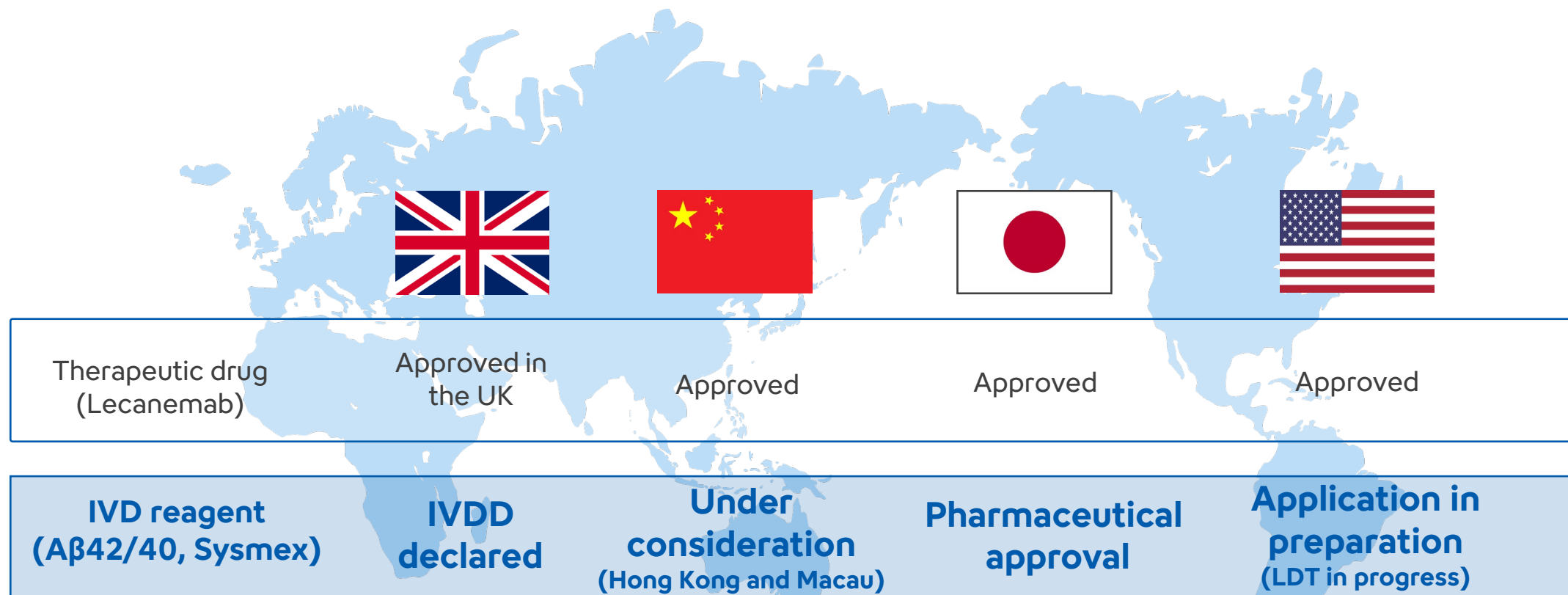
**We are also promoting market introduction in EU, Asian and Middle Eastern countries.**

# Testing Reagents to Determine the Risk of Drug Side Effects (ApoE Gene)

sysmex

Regarding the diagnostic reagent for predicting the risk of side effects when administering anti-Aβ antibody drugs, we have completed an application for manufacturing and marketing approval in Japan (September 2024).

## APOE genotype: association with the incidence of side effects from Lecanemab
ε2/2, 2/3, 3/3, 2/4, 3/4, 4/4 types exist

| APOE ε4 | Risk of side effects | |
|---|---|---|
| | Brain edema | Brain hemorrhage |
| Non-carrier type | 5.4 % | 11.9 % |
| Heterotype | 10.9 % | 14.0 % |
| Homotype (high risk) | 32.6 % | 39.0 % |

## Confirmed 100% accuracy rate of the diagnostic reagent

| APOE Genotyping test results | | <Reference method> Sanger sequencing method(Niigata Univ.& Sysmex) /PCR method(Niigata Univ.) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2/2 | 2/3 | 2/4 | 3/3 | 3/4 | 4/4 |
| <Testing method> Sysmex-developed product (PCR method) | 2/2 | 15 | 0 | 0 | 0 | 0 | 0 |
| | 2/3 | 0 | 15 | 0 | 0 | 0 | 0 |
| | 2/4 | 0 | 0 | 15 | 0 | 0 | 0 |
| | 3/3 | 0 | 0 | 0 | 15 | 0 | 0 |
| | 3/4 | 0 | 0 | 0 | 0 | 15 | 0 |
| | 4/4 | 0 | 0 | 0 | 0 | 0 | 15 |

https://www.sysmex.co.jp/news/2024/240917.html

Citation: van Dyck CH., et al. Lecanemab in early Alzheimer's disease. New Engl J Med. 388, 9-21 (2023)

# Trends in the Development of Disease-Modifying Drugs for Alzheimer's Disease

## Approval of Donanemab

✓ Approval of Lecanemab was followed by Donanemab, which is now in clinical use.
✓ Patients with mild cognitive impairment or early Alzheimer's disease require confirmation of amyloid pathology.

| Therapeutic agent | Development company | Approval status |
|---|---|---|
| Aducanumab (ADUHELM™) | Biogen, Eisai | US |
| Lecanemab (LEQEMBI™) | Eisai, Biogen | Japan, the US, China and the UK |
| Donanemab (KISUNLA™) | Eli Lilly | Japan and the US |

## Progress in the development of disease-modifying drugs

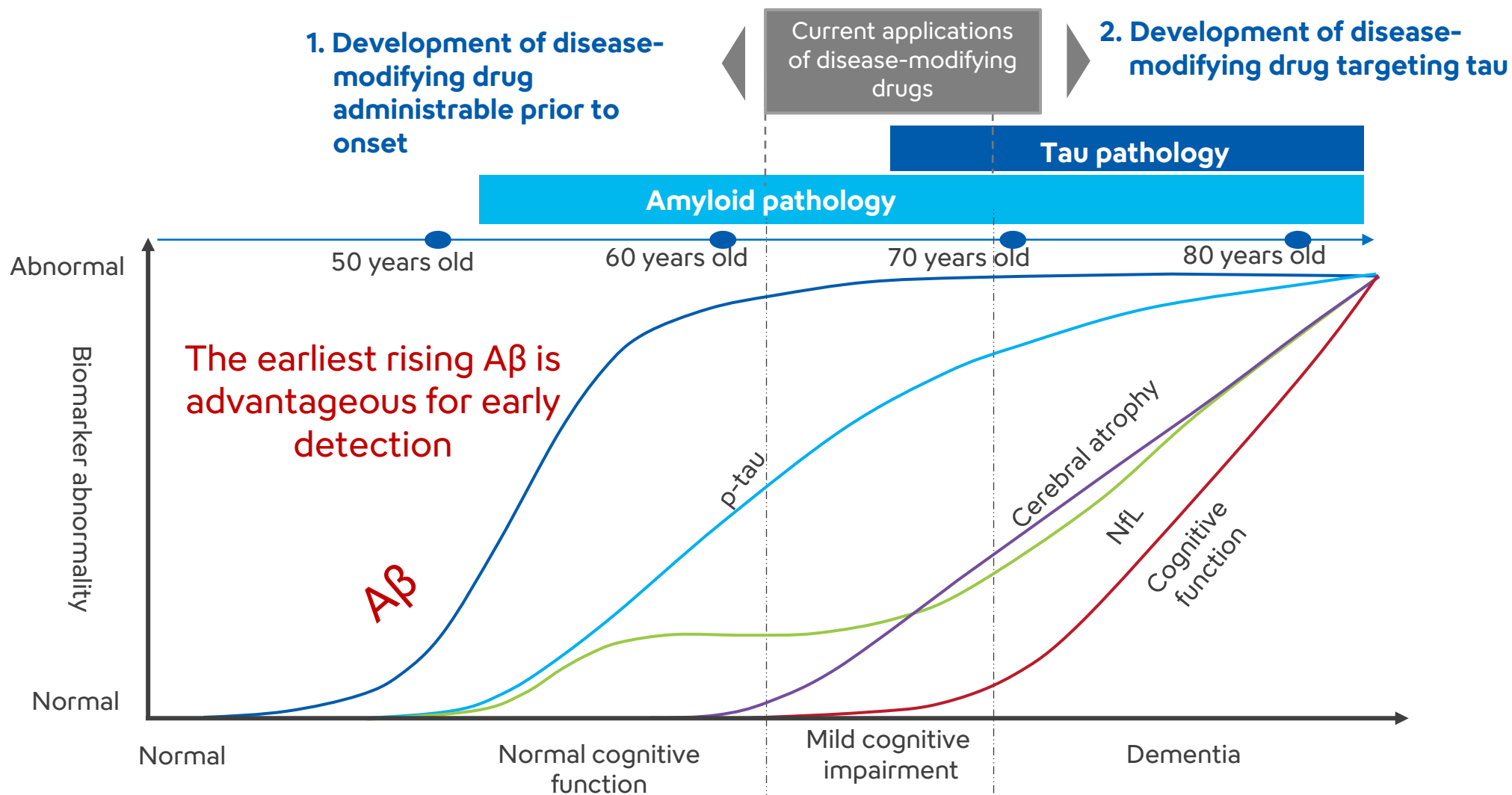### Studies are underway to apply drugs earlier (before disease onset).

✓ AHEAD3-45
✓ TRAILBLAZER-ALZ3

### Development of disease-modifying drugs for tau pathology is underway.

✓ E2814 (Eisai)
✓ BIB080 (Biogen)
✓ Bepranemab (Roche)
✓ JNJ-63733657 (Janssen)
✓ LY3372689 (Eli Lilly) etc.

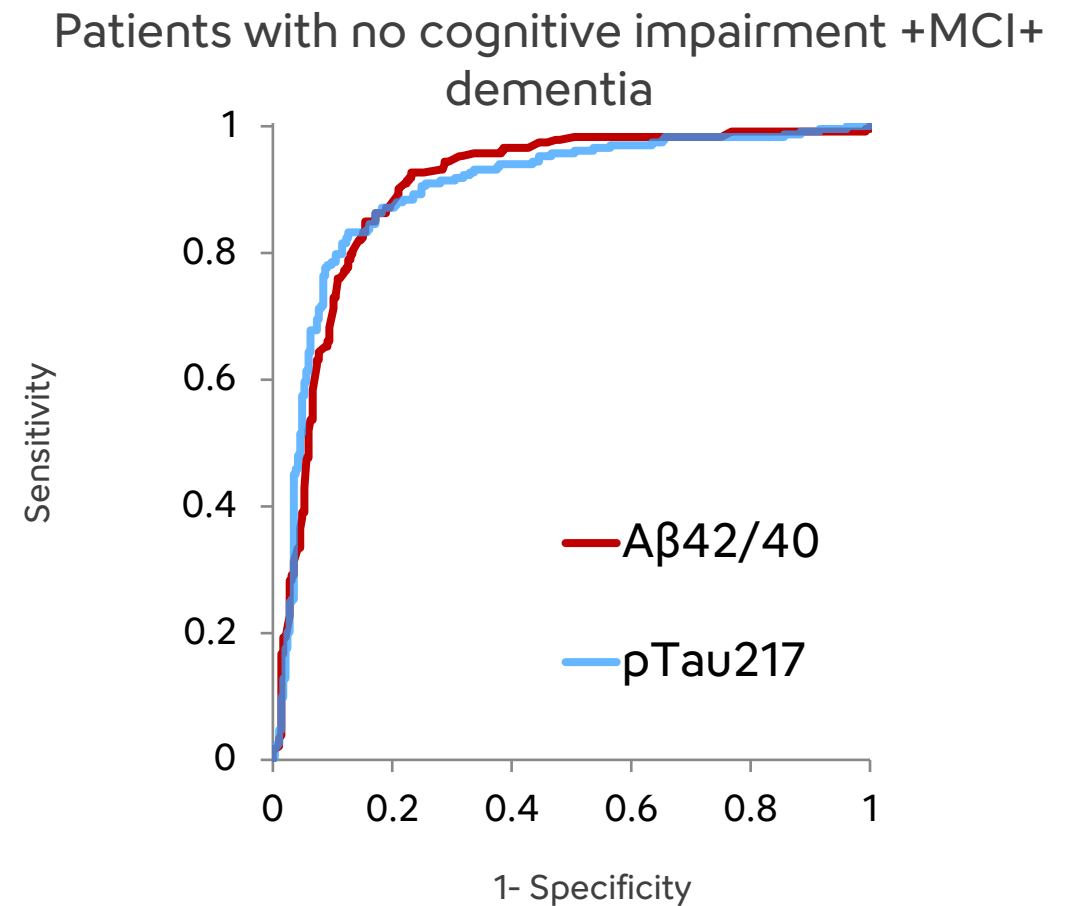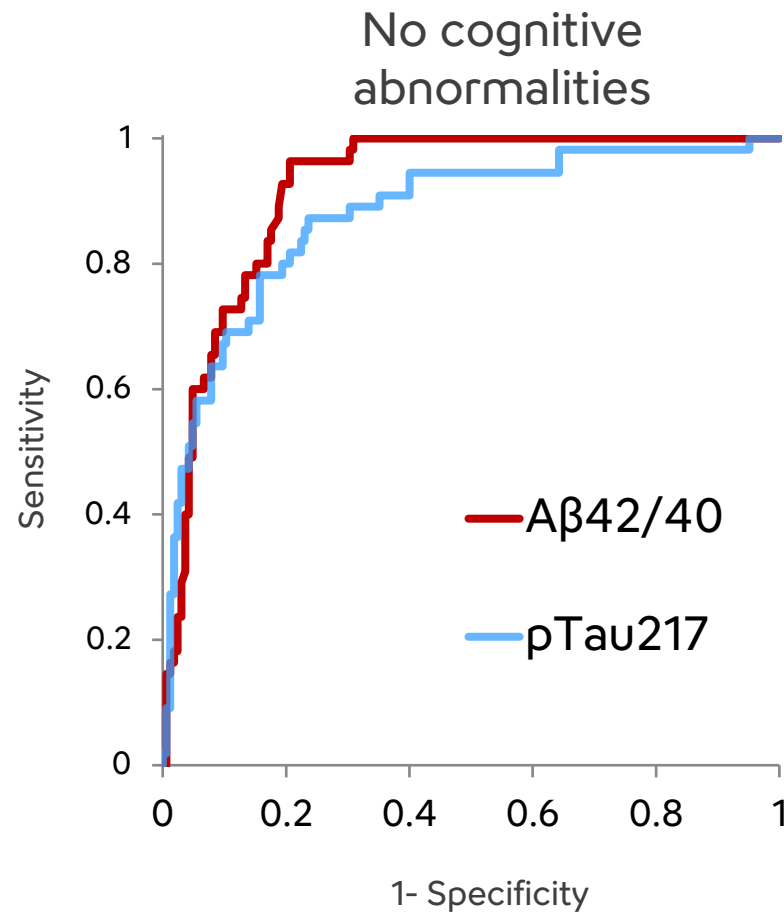Source: ClinicalTrials.gov, alzforum.org

# Development of Alzheimer Drugs and Required Tests

Biomarkers that can accurately determine the stage of disease are needed as drugs are developed.



1. Development of disease-modifying drug administrable prior to onset

Current applications of disease-modifying drugs

2. Development of disease-modifying drug targeting tau

Tau pathology

Amyloid pathology

50 years old    60 years old    70 years old    80 years old

Abnormal

Biomarker abnormality

The earliest rising Aβ is advantageous for early detection

Aβ

p-tau

Cerebral atrophy

NfL

Cognitive function

Normal

Normal    Normal cognitive function    Mild cognitive impairment    Dementia

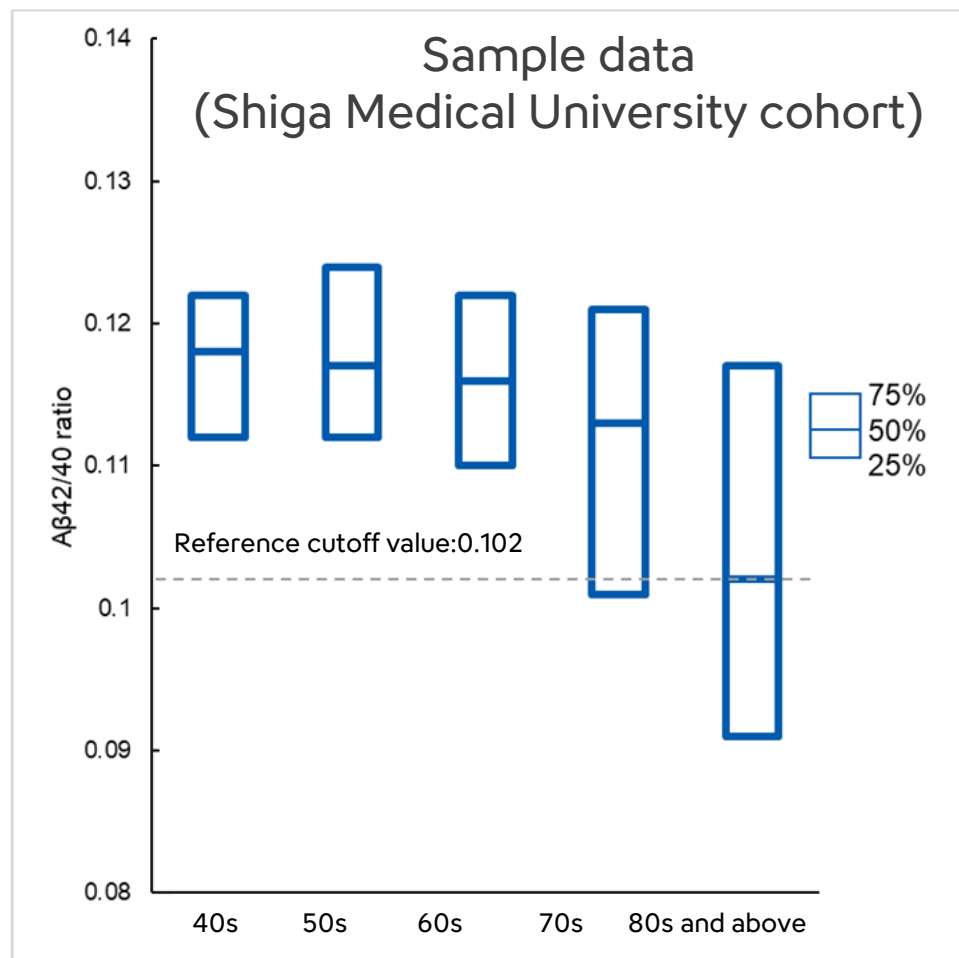# Performance Comparison of Aβ42/40
## (At the Stage with No Cognitive Abnormalities)

sysmex

Aβ42/40 method may be useful for the determination of medication in the stage with no cognitive abnormalities.



No cognitive abnormalities

Patients with no cognitive impairment +MCI+ dementia

Aβ42/40
pTau217

Aβ42/40
pTau217

Sensitivity

1- Specificity

Adapted from A Nakamura et al., Clinical Utility of Plasma Aβ42/40 and pTau217: 2- Relevance to Aβ and Tau Pathology, AAIC Advances: Modernizing Diagnosis, 2024

# Promotion of Real-World Data Acquisition for Aβ 42/40

We are promoting the evaluation of Aβ42/40 in the real world at multiple cohorts and facilities.



Sample data
(Shiga Medical University cohort)

Aβ42/40 ratio

Reference cutoff value:0.102

75%
50%
25%

40s    50s    60s    70s    80s and above

<Evaluation in cohorts>

✓ SESSAI, II, Woman (Shiga Medical University)
✓ Iwaki Health Checkup, Iki-iki Health Checkup (Hirosaki University)
✓ J-MINT prime TANBA (Kobe University) others

< Prospective real-world studies>

✓ Kobe University
✓ Tokyo Metropolitan Medical Center for Health and Longevity

Citation/Adaptation:  Kengo Ishiki et al., "Age dependency of blood-based biomarkers for AD measured by fully automated and highly specific immunoassays in general Japanese men: SESSA," International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders, 2024.
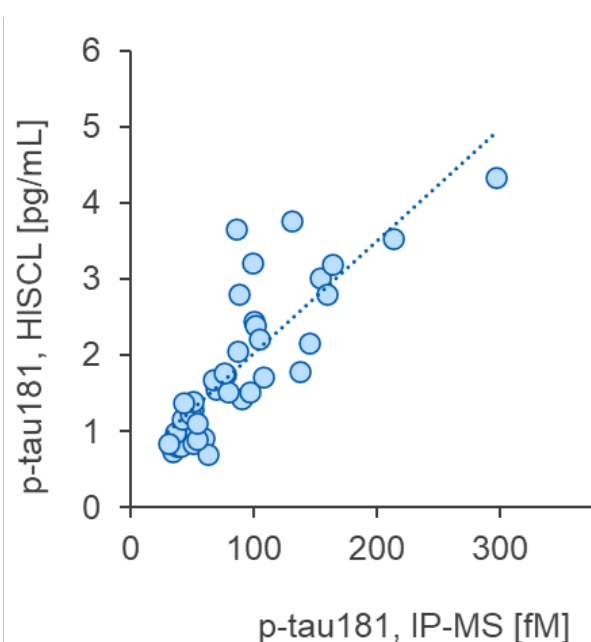
# Initiatives to Develop ρ-Tau Markers

We are developing an immunoassay system for tau markers with high correlation with mass spectrometry, in the aim of achieving high measurement performance, as with the development of Aβ reagents.

< Development Strategy >

Example of ρ-tau181
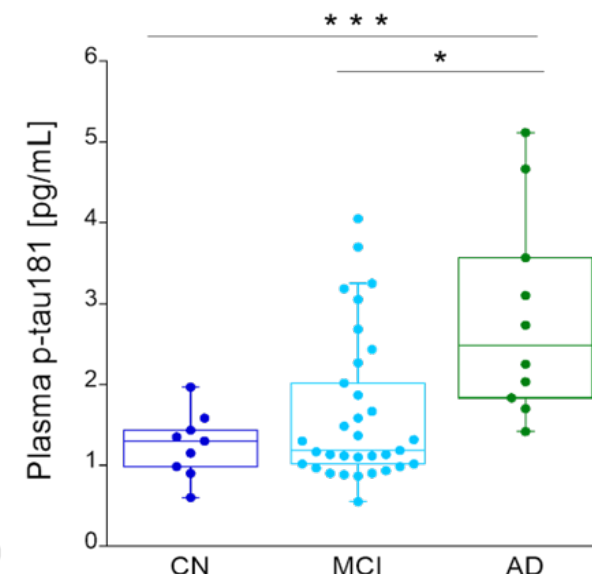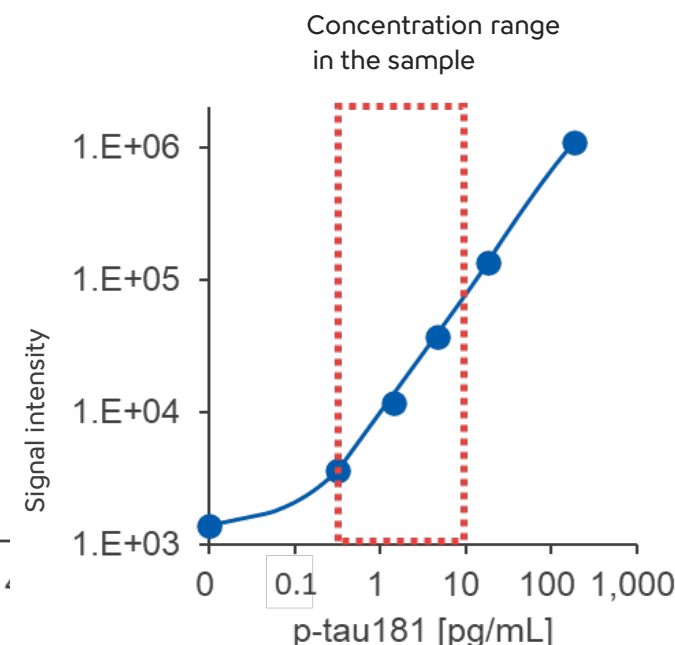
Phosphorylated tau has many analogues, as in the case of Aβ.

Development of the HISCL system with high correlation with the reference method mass spectrometry, similar to Aβ development

Performance verification in clinical samples



p-tau181, HISCL [pg/mL] vs p-tau181, IP-MS [fM]

Concentration range in the sample

Signal intensity vs p-tau181 [pg/mL]

Plasma p-tau181 [pg/mL] — CN, MCI, AD

Citation/Adaptation: Kengo Ishiki et al., "High correlation of plasma tau and p-tau181 levels measured by a fully automated immunoassay system and an immunoprecipitation mass spectrometry assay," International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders, 2024.
 Kazuya Matsumoto et al, "Correlations of ρ-tau217, ρ-tau181 and tau levels between CSF and plasma that are measured by fully automated immunoassay platform," Alzheimer's Association International Conference, 2023.

# Need for Diagnostics/Liquid Biopsy for New Therapeutics

Tau-targeted disease-modifying drugs are being developed.
There is no simple way to identify Tau accumulation in the brain

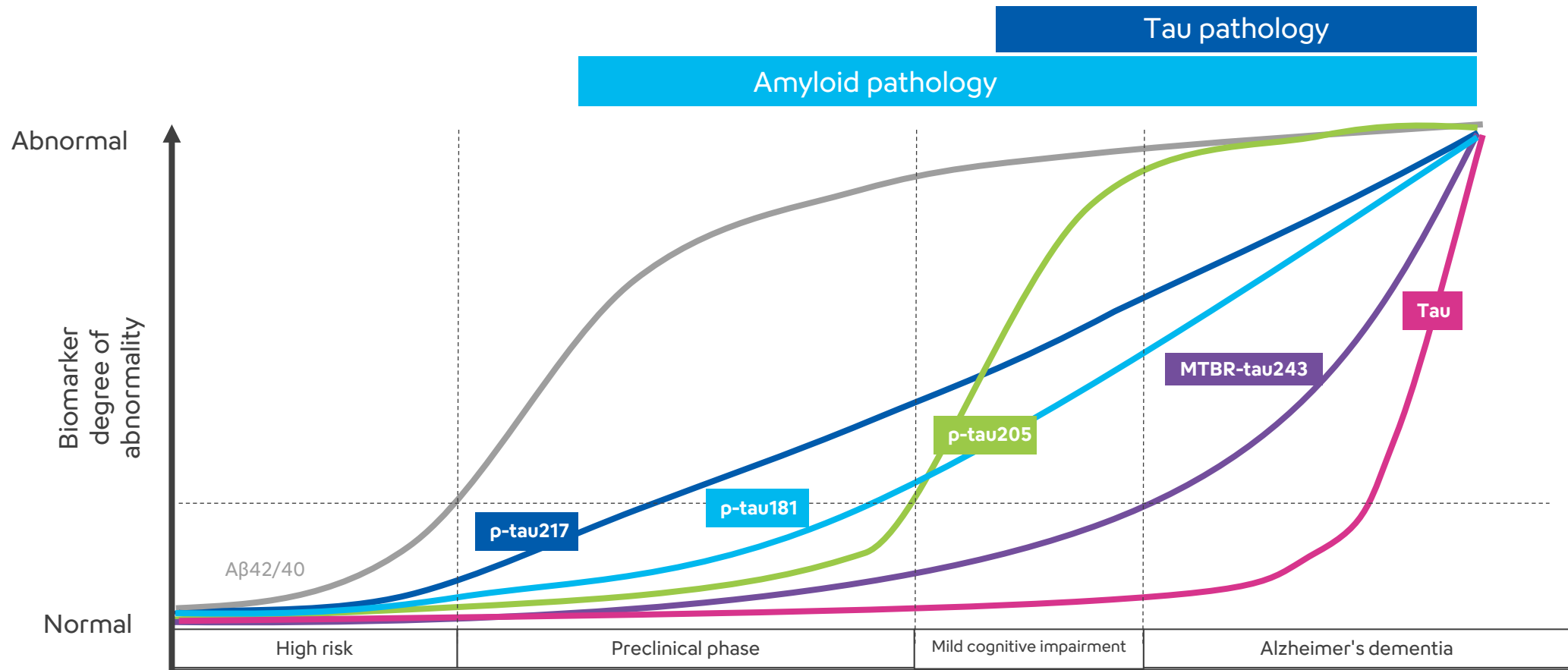TauPET is needed to determine the status of Tau accumulation



| Braak I | Braak II | Braak III | Braak IV | Braak V | Braak VI |
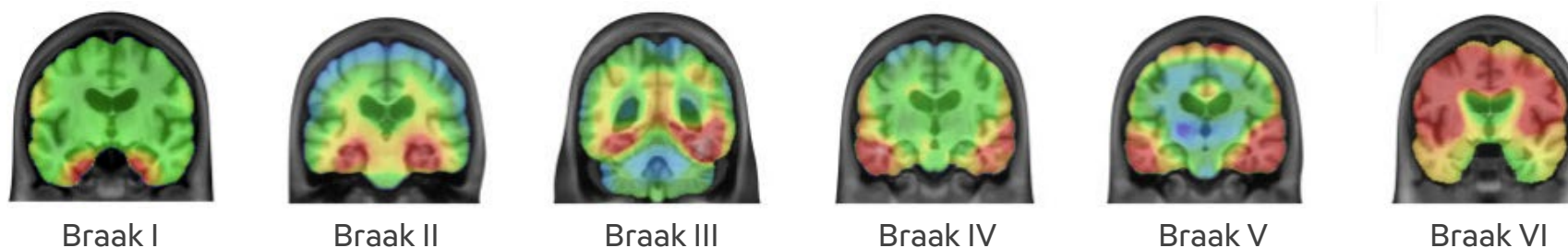
The latest clinical trial data on tau-targeted disease modification (E2814) (time course of PET images)



Week 0     60     108
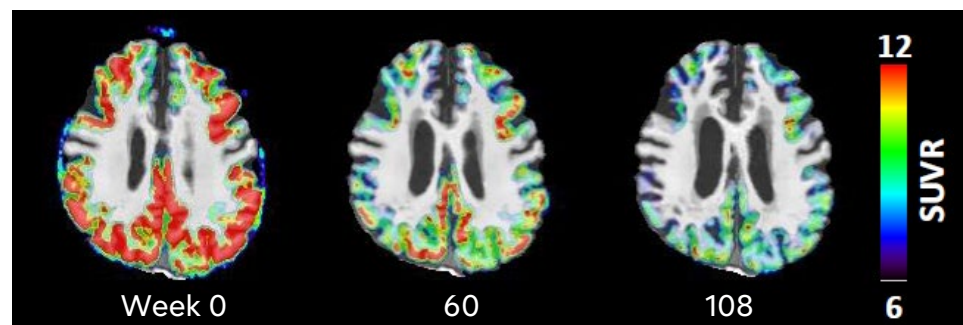
Citation/Adaptation:  Tharick A Pascoal  et al., "18F-MK-6240 PET for early and late detection of neurofibrillary tangles," Brain. 2020 Sep 1;143(9):2818-2830.
Kristin. R. Wildsmith et al., "Anti-Tau Therapeutic Antibody, E2814, Reduces Early and Late Tau Pathology Biomarkers in Patients with Dominantly-Inherited Alzheimer's Disease (DIAD),"
17th Clinical Trials on Alzheimer's Disease (CTAD), 2024

# Biomarkers for Understanding Tau Pathology

There are multiple markers that reflect tau pathology, and they may be used in combination for staging.



Citation/Adaptation: Gemma Salvadó et al., "Disease staging of Alzheimer's disease using a CSF-based biomarker model." Nat Aging. 2024 May;4(5):694-708.

# Development of Biomarkers for Patient Stratification to Aid Treatment

In order to accurately understand the state of the brain and lead to appropriate medication, we are developing multiple biomarkers in parallel.

### AA 2024 diagnosis and staging criteria

| Biomarker category | Cerebrospinal fluid and blood biomarker | Image biomarker |
|---|---|---|
| A | Aβ42 | Amyloid PET |
| T1 | p-tau217, 181, 231 | |
| T2 | MTBR-tau243, p-tau205, tau fragments | Tau PET |
| N | NfL | Anatomic MR, FDG-PET |
| I (Inflammation) | GFAP | |
| V (Vascular brain injury) | | Infraction on MR or CT, WMH |
| S (α-Synuclein) | α-Synuclein SAA* | |

\* Seed Amplification Assay    Blue: Under development

✓ Aβ42: Marketed
✓ p-Tau217: Scheduled to be launched in FY 2025 (for research)
✓ Other: Market evaluation scheduled as needed for research

Citation/Adaptation: Clifford R Jack Jr et al., "Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup" Alzheimers Dement. 2024 Jun 27;20(8):5143–5169.

# Expansion of Liquid Biopsy Technology Applications

# Efforts to Address Diseases Associated with Aging

**Efforts are underway to test for amyloidosis, which is of growing importance in an aging society.**

## About amyloidosis

Amyloidosis is a general term for diseases in which abnormal fibrous proteins called amyloids are deposited in various organs of the body and cause dysfunction.

1. Prevalence has increased in recent years as society ages (strong element of aging)

2. Difficult to diagnose using blood because it is deposited in tissues

3. Therapeutic drugs are under rapid development.

Precursor protein
(e.g., transthyretin)

Denaturation,
agglutination

Tissue
deposition

Tetramer
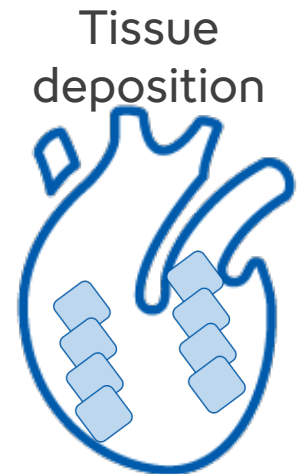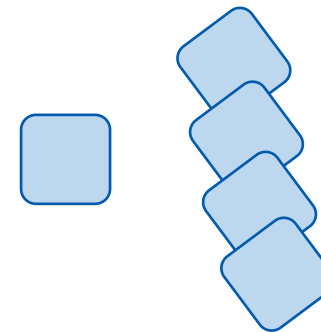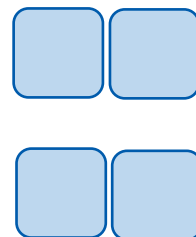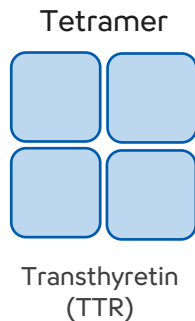
Transthyretin
(TTR)

# Approach to Cardiac Amyloidosis

sysmex

**As there are many potential patients with transthyretin cardiac amyloidosis, expectations for testing are high.**

**About transthyretin cardiac amyloidosis**

- This is a disease in which TTR amyloid, formed by aggregation of transthyretin (TTR), deposits in the heart, causing myocardial dysfunction.
- Although it is said to be latent in approximately 13 to 14% of patients with HFpEF *, many patients are undiagnosed [1, 2].

1. Prevalence has increased as society ages (strong element of aging)
   ->HFpEF * patients are estimated to number approximately 30 million worldwide (calculated from 3 and 4), and all patients are eligible for testing.

2. Difficult to diagnose by blood because it is deposited in tissues
   ->Confirmed diagnosis by tissue biopsy or radionuclide scanning, but challenges include invasiveness

3. Therapeutic drugs are under rapid development.
   ->Transthyretin stabilizer (Tafamidis/Pfizer) approved for treatment

* heart failure with preserved systolic function

1. Eur Heart J. 2015 Oct 7;36(38):2585-94.
2. ESC Heart Fail. 2023 Mar 27;10(3):1896–1906.
3. Eur J Heart Fail. 2020 Aug;22(8):1342-1356.
4. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

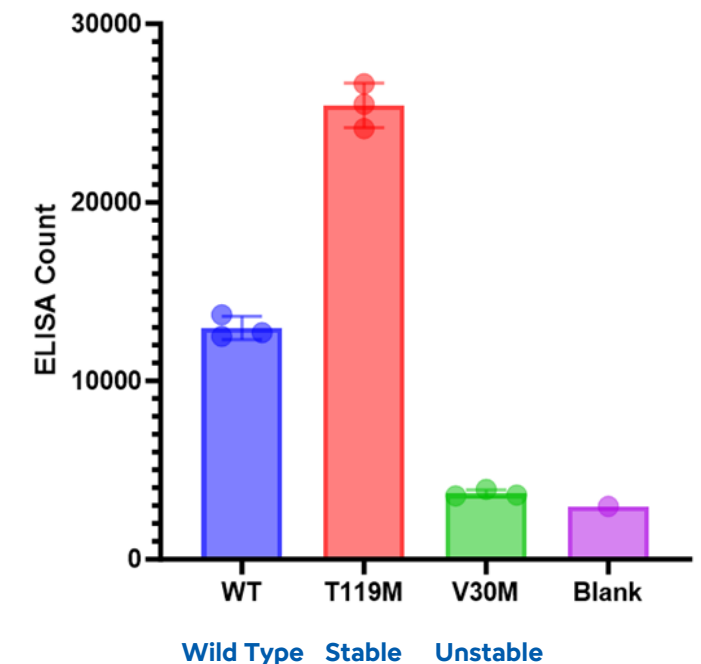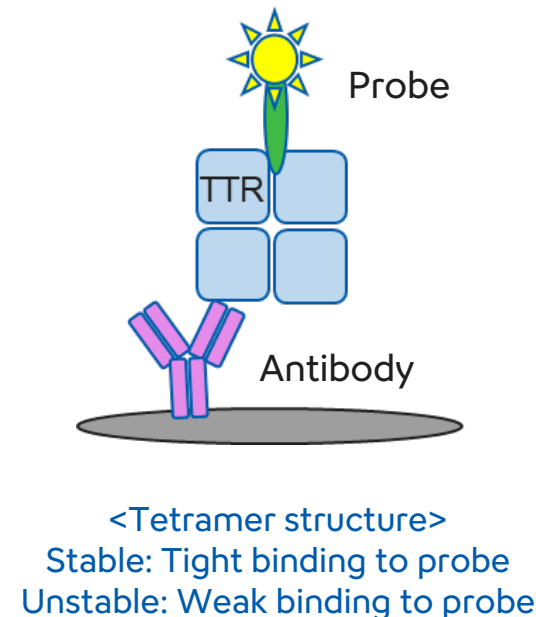# Development of New Test Method for Transthyretin-Type Cardiac Amyloidosis

The development of an amyloidosis test using HISCL is underway.
We have applied for a basic patent through joint research with Kobe University.

## Transthyretin (TTR) and its properties

Stable

Tetramer

Unstable

**Accumulates in the heart**
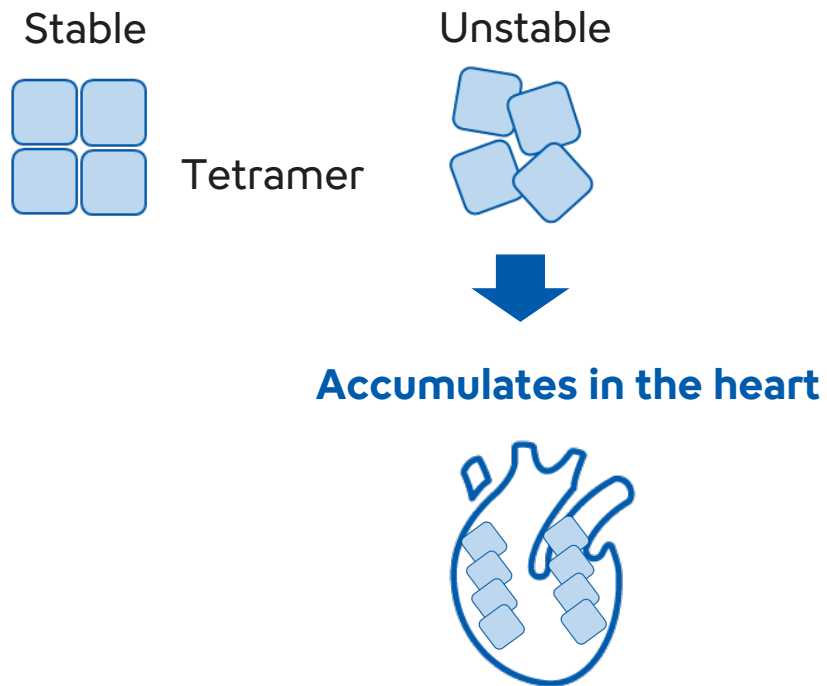
## Construction of measurement system using immune reaction

Interactions with TTR are evaluated by using probes that interact with the "pocket" formed in the tetrameric TTR according to the stability of the tetrameric structure.

Probe

TTR

Antibody

<Tetramer structure>
Stable: Tight binding to probe
Unstable: Weak binding to probe

ELISA Count

WT    T119M    V30M    Blank

Wild Type    Stable    Unstable

# Expanding Efforts to Address Amyloidosis-Related Diseases

**sysmex**

Through enhanced liquid biopsy technology and open innovation, we are establishing appropriate diagnostic techniques for a wide variety of amyloidosis diseases.

## Systemic amyloidosis:
Systemic amyloid deposits in multiple organs
- Transthyretin amyloidosis
  - Transthyretin-type cardiac amyloidosis
  - Carpal tunnel syndrome
- New amyloidosis
- AA amyloidosis, etc.

We have initiated joint research with Kumamoto University Amyloidosis Medical Center on new amyloidosis.

**+**

## Enhacement of liquid biopsy technologies

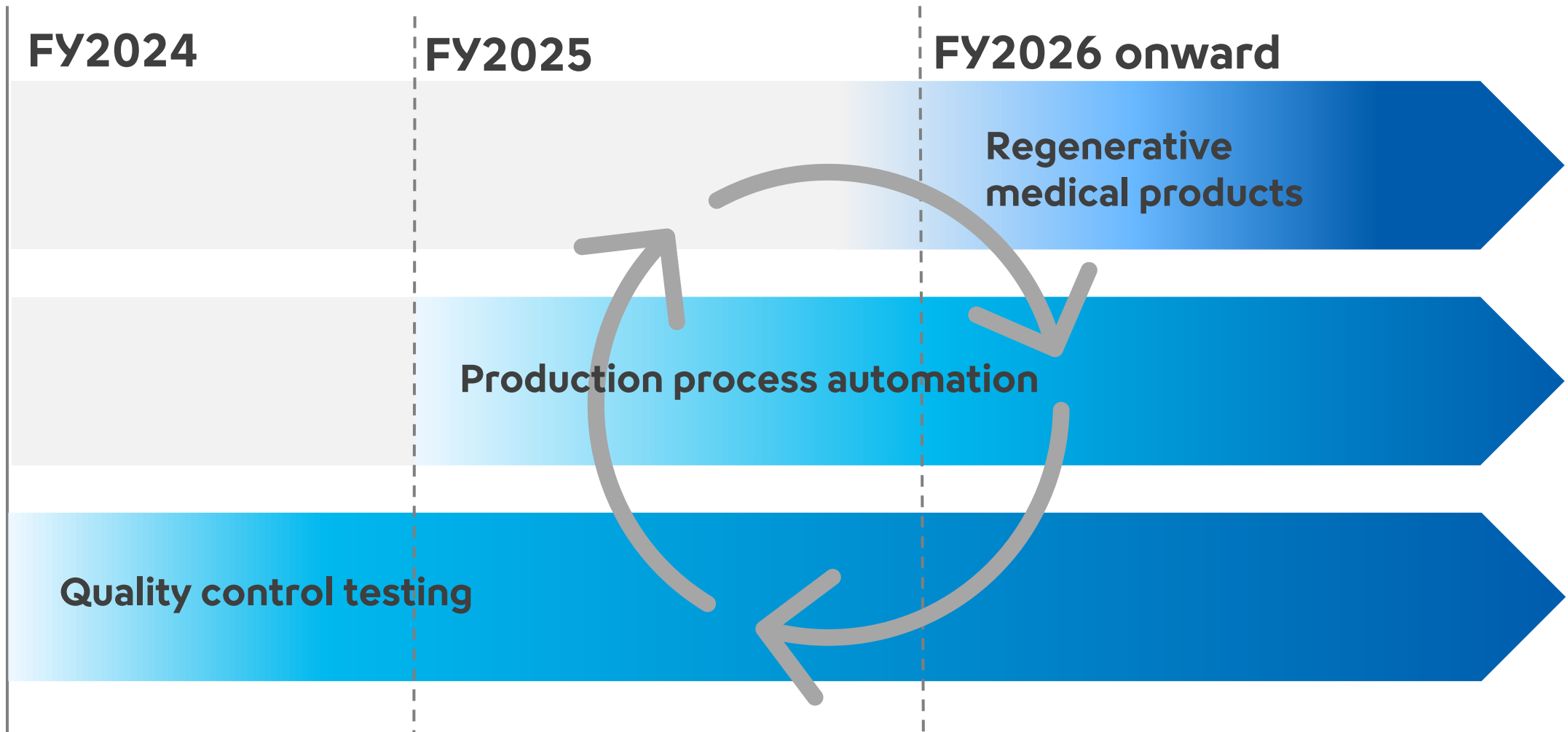We are enhancing and utilizing technologies such as ultra-sensitive quantification, multi-parameter analysis, functional measurement, structural stability measurement, and activity measurement.

## Localized amyloidosis:
Localized amyloid deposits in certain organs
- Cerebral amyloidosis
  - Alzheimer's disease
  - Prion diseases.... etc.
- Such as corneal amyloidosis

# Regenerative and Cellular Medicine Initiatives

# Roadmap for the Commercialization of Regenerative and Cellular Medicine

In addition to launching businesses that utilize our technologies at an early stage, we will strive to launch regenerative medical products.



FY2024 | FY2025 | FY2026 onward

Regenerative medical products

Production process automation

Quality control testing

# Regenerative Medicine Product Pipeline and State of Progress

sysmex

We are promoting the development of innovative regenerative medical products that offer new hope to patients.

| Cells | Target indication | Clinical value | Progress | Submission for regulatory approval (expected*) |
|---|---|---|---|---|
| Inducible inhibitory T-cells **AlliedCel** | Living donor (liver) transplants | Induction of immune tolerance in recipient T-cells | Investigator-initiated study underway | Around FY2026 |
| Cultured hematopoietic stem cells **AlliedCel** | Hematopoietic tumors | Restoration of hematopoietic function by cultured hematopoietic stem cells | Verification of the viability of expanded culture of hematopoietic stem cells underway using test animals | Around FY2030 |
| iPS cell-derived platelets **Mega karyon** | Thrombocytopenia | Restoration of hemostatic function with artificial platelets | Establishment of strains and manufacturing process (including automation) and search for indications | Around FY2029 |

*No change from last year's R&D meeting

# Changes in the Environment Surrounding Regenerative and Cellular Medicine

The importance of quality control and automation in regenerative and cellular medicine is growing.

## Issues

## Present to future

- Because the raw material consists of heterogeneous cells, quality control testing is considered important to ensure safety and functionality.

- Concerns have been raised regarding the safety of cell production and provision in private medical treatments under the Act on Securing Safety of Regenerative Medicine, and the importance of sterility testing has been reaffirmed.

▶ **Increased awareness of the need to ensure the safety of regenerative medicine, and the need for standardized quality control testing**

▶ **Standardization of quality control**

- The complex production process, which still relies heavily on human labor, drives up production costs.

- IoT adoption has not progressed, and data is not centrally managed.

▶ **METI and others have secured budgets to support production automation for regenerative and cellular medicine.**

▶ **Automation of production**

# Features of Sysmex's Quality Control Technology

**The technology has useful characteristics for research and manufacturing processes in regenerative and cellular medicine.**

**Simple, automated**

Simple and standardized measurement operations using a quality control platform developed with automation in mind

**High reproducibility and sensitivity**

Automation of the measurement process and proprietary reagent technology enable improved accuracy and higher sensitivity in cell and protein analysis within culture media

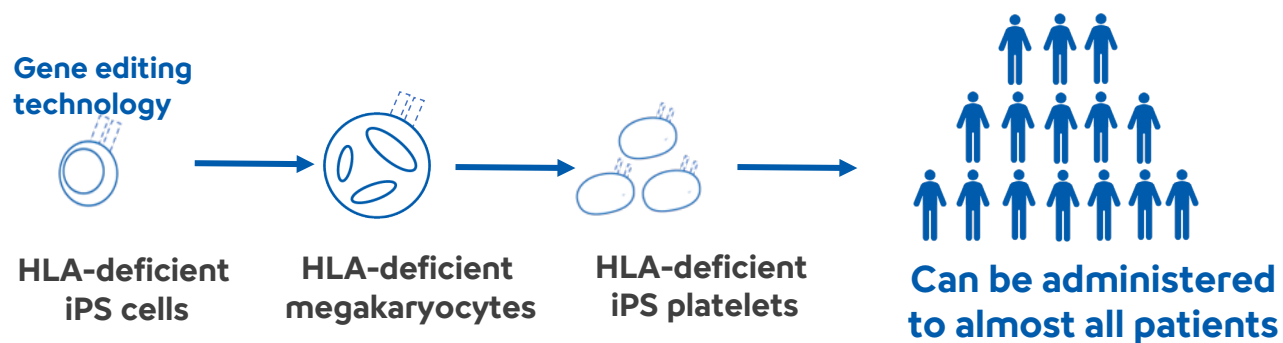**Quick and continuous measurement of multiple parameters**

Supports rapid and continuous measurement of large quantities of samples suitable for screening, as well as simultaneous measurement of multiple protein parameters

# iPS Cell-Derived Platelets

We are promoting the development of artificial platelets that could become a new constant in transfusion medicine.

## Characteristics of iPS cell-derived platelets

1. Transfusion possible regardless of patient's HLA type

2. Safety, without risk of infection or cancer

**Gene editing technology**

HLA-deficient iPS cells → HLA-deficient megakaryocytes → HLA-deficient iPS platelets →

**Can be administered to almost all patients**

## Applicability

Through presentations at the Japan Society of Transfusion Medicine and Cell Therapy and the Japanese Society for Regenerative Medicine, as well as through hearings with key opinion leaders, we are discovering the following potential applications.

1. Prophylactic administration for thrombocytopenia due to blood diseases

2. Platelet transfusions in standby/scheduled surgeries

# Standardization of Quality Control for iPS Cell-Derived Platelets

**sysmex**

We are promoting the application of our hematology technology to quality control testing.

## Production process for iPS cell-derived platelets

Human iPS cells → iPS cell-derived megakaryocytes → iPS cell-derived mature megakaryocytes → iPS cell-derived platelets
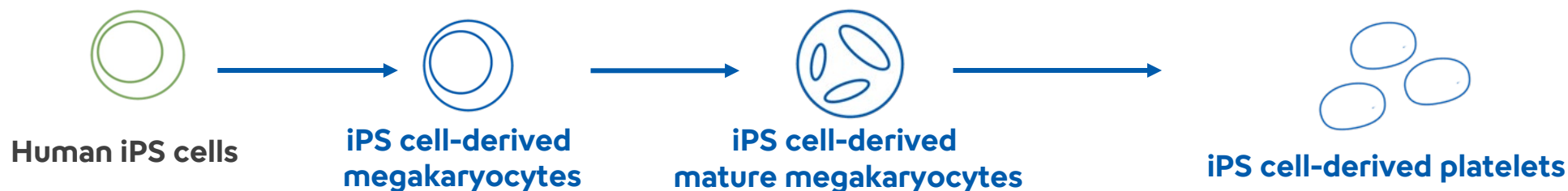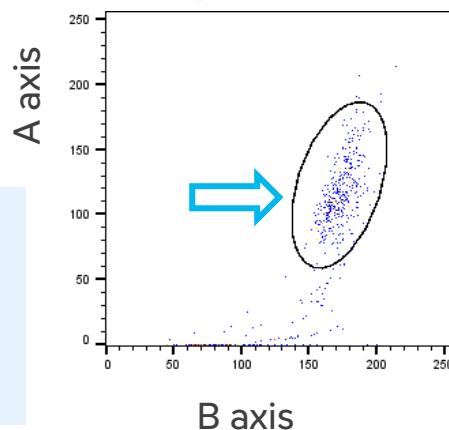
### Measurement

XR-1000 (XN-1000) multiparameter automated hematology analyzer

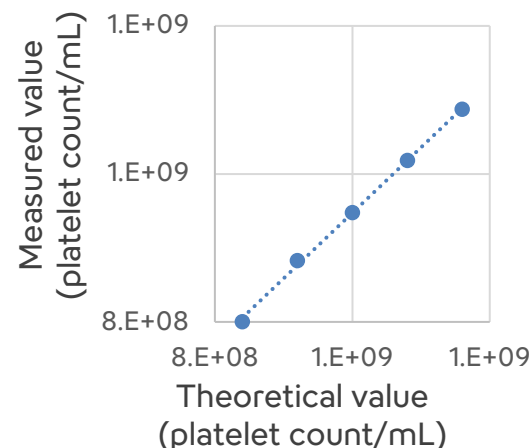**Rapid measurement of iPS megakaryocytes using Sysmex's proprietary staining technology and measurement optimization of the XR-1000**

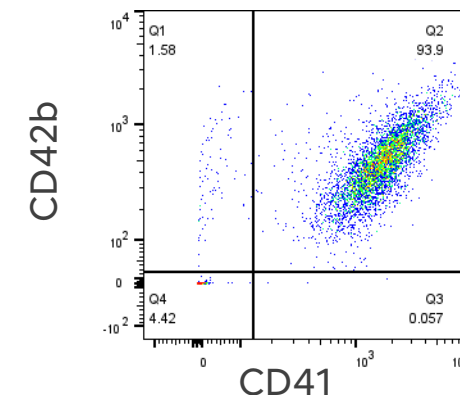**iPS cell-derived megakaryocytes**

A axis / B axis

**iPS cell-derived platelets**

Measured value (platelet count/mL) vs Theoretical value (platelet count/mL)

**Functional assessment**

XF-1600 Flow Cytometer

CD42b / CD41
Q1 1.58 | Q2 93.9
Q4 4.42 | Q3 0.057

# External Deployment of Our Quality Control Technology (HISCL) First Launch of a Product for Research Use

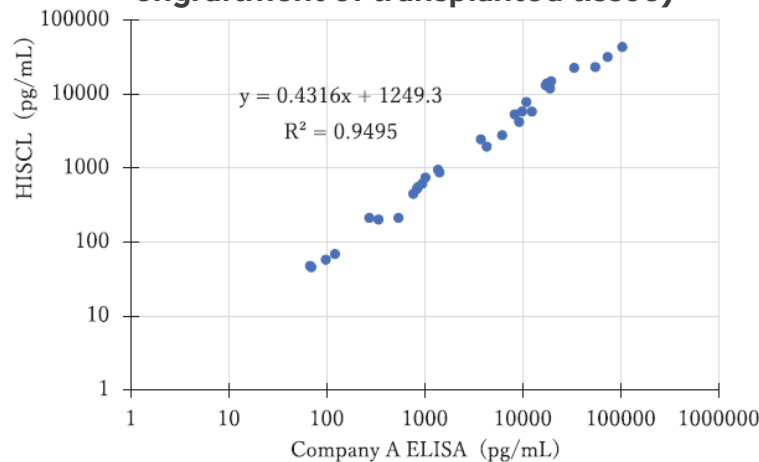**We are starting to launch HISCL™ VEGF reagents (for research) and HISCL™ PEDF reagents (for research).**
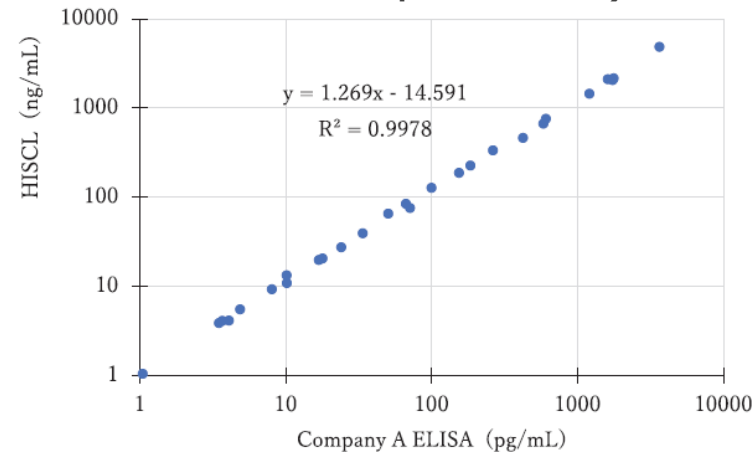
## Correlation with existing ELISA kits

### Features

### VEGF

**Vascular endothelial growth factor (Induction of blood vessels necessary for engraftment of transplanted tissue)**



$y = 0.4316x + 1249.3$
$R^2 = 0.9495$

X-axis: Company A ELISA (pg/mL)
Y-axis: HISCL (pg/mL)

### PEDF

**Pigmented epithelium-derived factor (Neuroprotection around transplanted tissue)**



$y = 1.269x - 14.591$
$R^2 = 0.9978$

X-axis: Company A ELISA (pg/mL)
Y-axis: HISCL (ng/mL)

- Significantly reduced measurement time with HISCL
- Wide dynamic range with highly sensitive detection
- Reduction of total cost for routing testing

We are also expanding the provision of *in vitro* diagnostic parameters (such as cardiac and diabetes markers) for use in cellular quality assessment (for research purposes).

Reference: The market for immunochemistry testing for us in manufacturing quality control for cell and gene therapies is reportedly likely to reach approximately $1.1 billion by 2033.

Source: BIS Research, "2023–2033 Cell and gene therapy manufacturing QC market - A global and regional analysis"

# External Deployment of Our Quality Control Technology (HISCL) Customer Feedback

| Customer | Theme | Reagents | User feedback |
|---|---|---|---|
| Masayo Takahashi, President and Representative Director, VCCT Inc. | Development of iPS cell-derived RPE cells for regenerative medicine for age-related macular degeneration | VEGF PEDF | • We have found a clue about reducing the workload by automation and stabilization of quality control. <br>• Sysmex's unique instruments excel at making testing more complete. |
| Shugo Toyama, Professor Fujita Medical Innovation Center Tokyo, Heartseed Inc. | Development of iPS cell-derived cardiomyocytes for regenerative medicine for heart failure | Cardiomyocyte endpoints | • The technology is suitable for screening and is useful in drug discovery research and disease pathogenesis. <br>• It has expanded my research because of its automation and fast results. |
| Hideki Endo, Specially Appointed Associate Professor Juntendo University Graduate School of Medicine | Development of pancreatic beta cells for regenerative medicine for type 1 diabetes | Items related to blood sugar control, such as insulin | • We can rapidly obtain measurement results for a huge number of samples, numbering in the hundreds. <br>• The technology contributes to advances in research and helps improve the work-life balance of researchers. |

Note: Taiwan, which is actively involved in regenerative and cellular medicine in the United States (the largest market for such medicine) and Asia, has also expressed interest in our quality control technology.

# External Deployment of Our Quality Control Technology (FCM)

## -New Possibilities in Sterility Testing-

**Our FCM may help ensure the safety of regenerative and cellular medicine.**

- Currently, most sterility testing is performed using PCR.
- PCR tests take a long time to produce results and are relatively expensive.

**As part of the AMED Research Project for Practical Application of Regenerative Medicine (FY 2021–2023), a joint study was conducted with Dr. Tobita and colleagues from Juntendo University to compare PCR and FCM methods for microbial testing in PRP\* therapy.**

## The possibility of using our FCM as a rapid microbiological testing method was suggested.

| | Detection limit (CFU/mL) | Identification of viable and dead bacteria | Time required | Consumables (/measurement) |
|---|---|---|---|---|
| **FCM** | $10^0-10^2$ | **Yes** | **30 min. or less** | **Good** |
| PCR | $10^0-10^1$ | No | Around 4 hrs. | Fair |
| Pharmacopeial sterility test | $10^0-10^2$ | Yes | 2 weeks | Good |
| Gram staining | $10^5-10^6$ | No | 30 min. or less | Very good |

FR-500 flow cyclometer for research

\* Platelet-rich plasma (PRP) therapy is a regenerative medical technique that involves treating patients using a cell-processed material derived from the plasma portion of venous blood, which is obtained through centrifugation and contains a high concentration of platelets. It is the most widely offered regenerative medical technology under the Act on Ensuring the Safety of Regenerative Medicine.
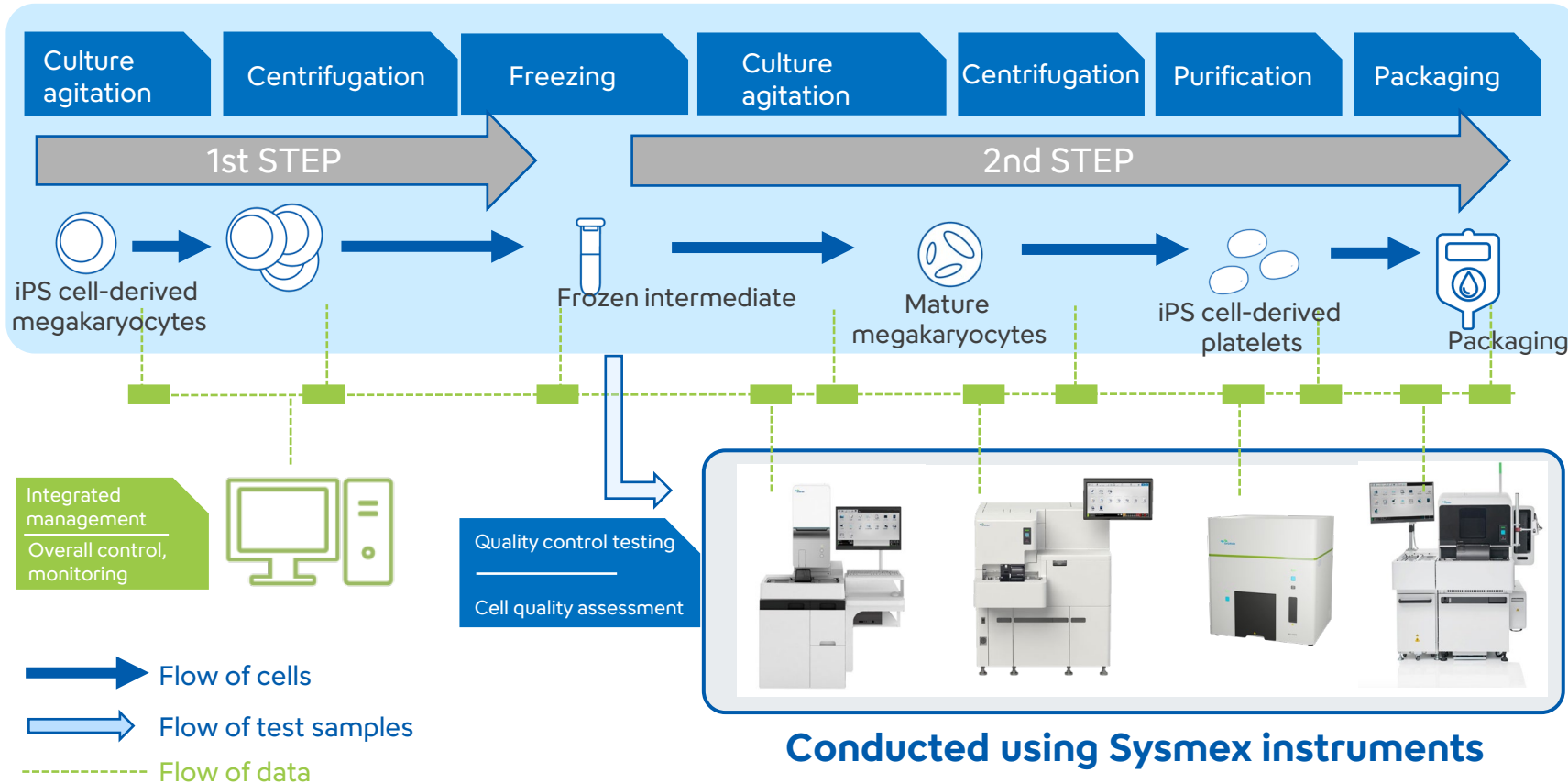
# Automating the Production Process for iPS Cell-Derived Platelets

**We have constructed a closed platelet production system with automatic process control and monitoring.**

## Production occurs in a continuous closed system, from expansion culture to formulation.

### Features

| Process Steps |
|---|
| Culture agitation → Centrifugation → Freezing → Culture agitation → Centrifugation → Purification → Packaging |

**1st STEP:** iPS cell-derived megakaryocytes → Frozen intermediate

**2nd STEP:** Mature megakaryocytes → iPS cell-derived platelets → Packaging

- iPS cell-derived megakaryocytes
- Frozen intermediate
- Mature megakaryocytes
- iPS cell-derived platelets
- Packaging

**Integrated management** — Overall control, monitoring

**Quality control testing** — Cell quality assessment

**Conducted using Sysmex instruments**

Legend:
- Flow of cells
- Flow of test samples
- Flow of data

Features:
- Production process: Built as a connected system based on our experience in the handling of hematopoietic cells
- Quality control: Uses an automated quality measurement platform
- Integrated control: Support for the digitalization of data, leveraging our data integration experience in clinical laboratories

1. **Lower production cost**
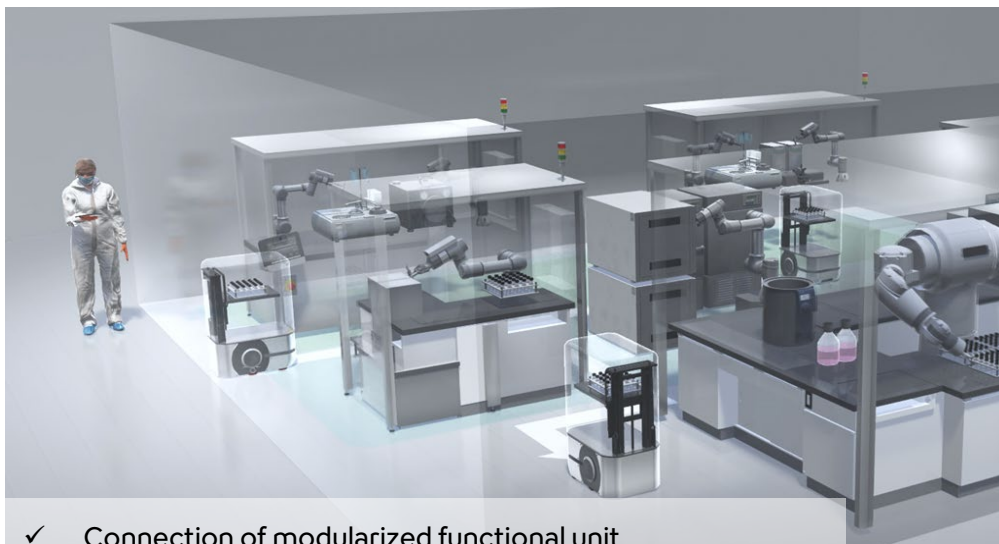2. **Stable quality**
3. **Data integrity**

# External Deployment of Our Automation Technologies

sysmex

**We are moving ahead with the automation of cell production, using our technology with strategic partners.**

## Initiatives with VC Cell Therapy

**Conceptual design of a system with linked functional modules**



- ✓ Connection of modularized functional unit
- ✓ Self-propelled transport systems that maintain cleanliness
- ✓ Deploy only the units needed at more locations

- **Completed conceptual design of functional modules**
- **Started discussing regulatory compliance for individual instruments**

## Initiatives with J-TEC

**Basic agreement to advance manufacturing capabilities in regenerative and cellular medicine**

J·TEC        sysmex

- ✓ Provider of platforms for autologous regenerative medicine
- ✓ Track record for the development and stable manufacturing of regenerative medical products
- ✓ Cell culture technology and process design capabilities

- ✓ Leading *in-vitro* diagnostics company
- ✓ Automation platform developed through clinical testing
- ✓ Systematization and digitization made possible by clinical testing
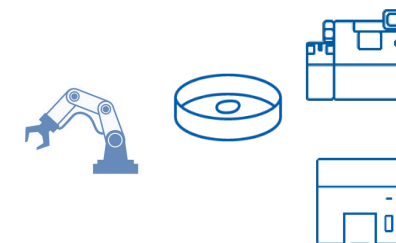
- **Addressing barriers to mechanization and automation in regenerative and cellular medicine production functions**
- **Contributing to the sustainability and development of Japan's regenerative medicine industry**

Reference: 24th Congress of the Japanese Society for Regenerative Medicine, Co-Sponsored Academic Seminar (March 21, 2025)
Title: Sysmex and J-TEC's vision for the development of the regenerative and cellular medicine industry

# Glossary

# Glossary

| | |
|---|---|
| Age-related macular degeneration | An eye disease primarily affecting the elderly, in which the macula—the central part of the retina—becomes damaged, leading to vision loss. |
| Amyloidosis | A disease in which abnormal proteins called amyloids accumulate in various organs of the body, leading to functional impairment. |
| 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. |
| Carpal tunnel syndrome | A condition caused by compression of the median nerve passing through the carpal tunnel, a narrow passage in the wrist. |
| Closed platelet | A type of platelet in which the open canalicular system (OCS) on its surface is in a closed state. |
| Cultured hematopoietic stem cells | Hematopoietic stem cells which expanded and cultured in-vitro in the presence of proprietary growth factors, compounds, etc. |
| 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. |
| HFpEF | Heart failure with preserved ejection fraction (HFpEF) is a type of heart failure in which the heart's ability to expand is impaired, but its function as a pump to send blood throughout the body is maintained. |
| 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. |

# Glossary

| | |
|---|---|
| Inducible inhibitory T-cells | T cells that suppress immune responses to specific antigens induced by antigens and anti-CD80 and anti-CD86 antibodies. |
| LLM | Large language model (LLM) refers to a large-scale language model that serves as the foundation for generative AI. |
| NfL | Neurofilament light chain (NfL) is a neuron-derived protein, which is used as a biomarker for cognitive function. |
| Pancreatic beta cells | A type of cell found in the islets of Langerhans in the pancreas, responsible for secreting insulin. |
| Prion disease | A group of neurodegenerative disorders caused by the accumulation of abnormal prion proteins in the brain. |
| Recipient T cells | T cells of a patient who receives a transplant operation. |
| 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. |
| 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. |
| Virgin resin | Newly manufactured plastic resin that does not contain recycled or reused materials. |

Together for a better
healthcare journey