# The 19th R&D Meeting

March 4, 2022
Sysmex Corporation

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

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

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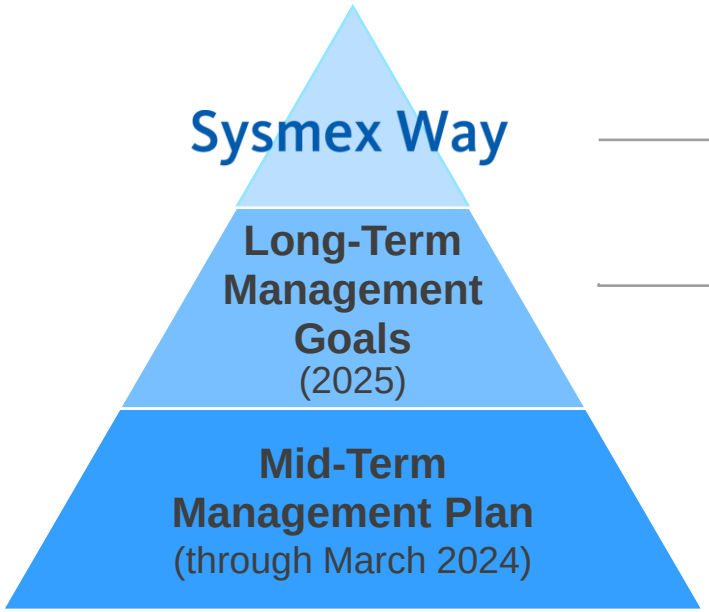
# Opening Presentation

Hisashi Ietsugu
Chairman and CEO

# Sysmex's Long-Term Management Goals




**Mission**

Shaping the advancement of healthcare.

**Value**

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

**Mind**

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

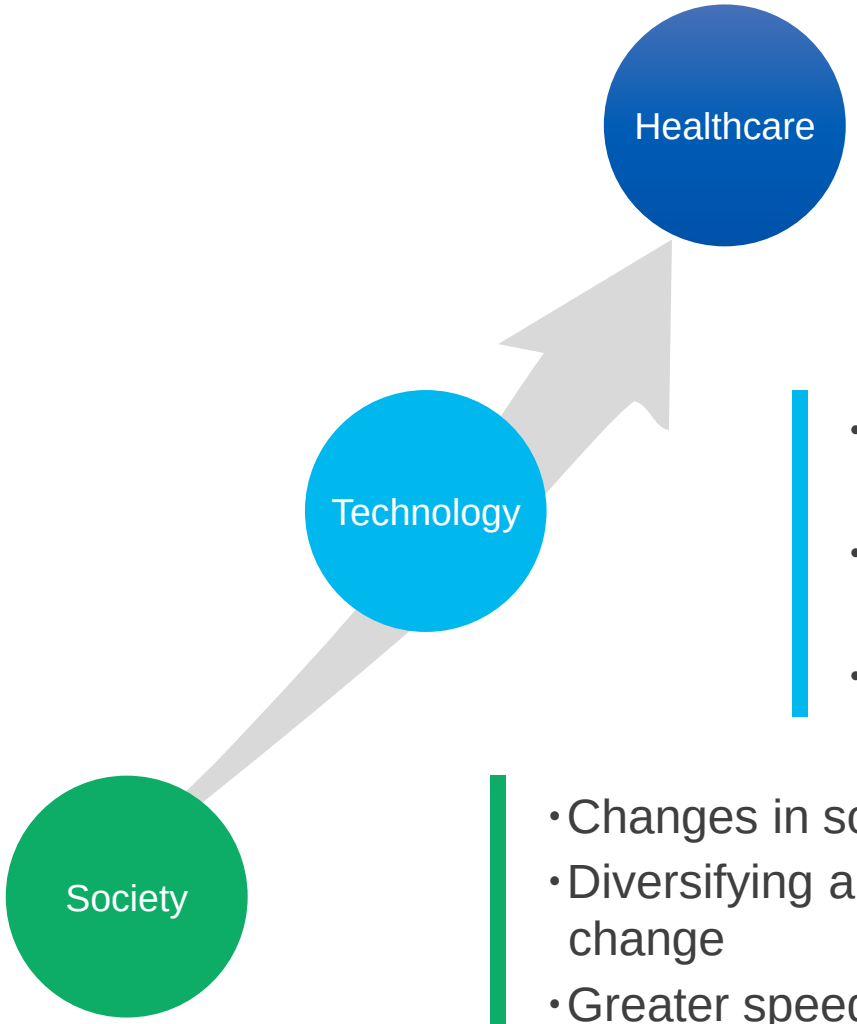
## Long-Term Vision

Unique & Advanced Healthcare Testing Company

## Positioning Targets

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

# Changes in the External Environment

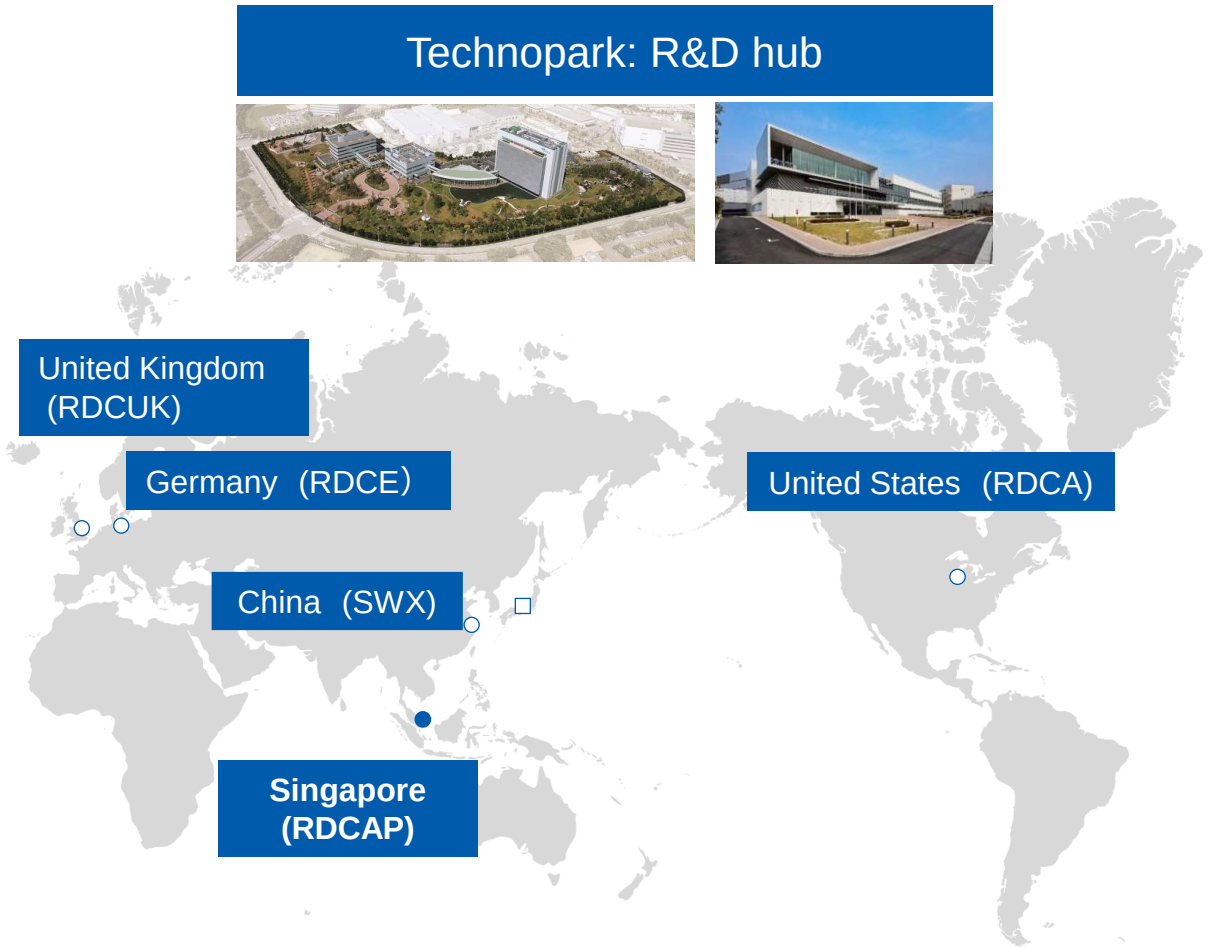



- Changes in healthcare policy (from reducing healthcare costs to strengthening healthcare infrastructure and improving access)
- Self-medication, digitalization (online medicine, treatment apps)
- Progress of personalized medicine (cancer, dementia)

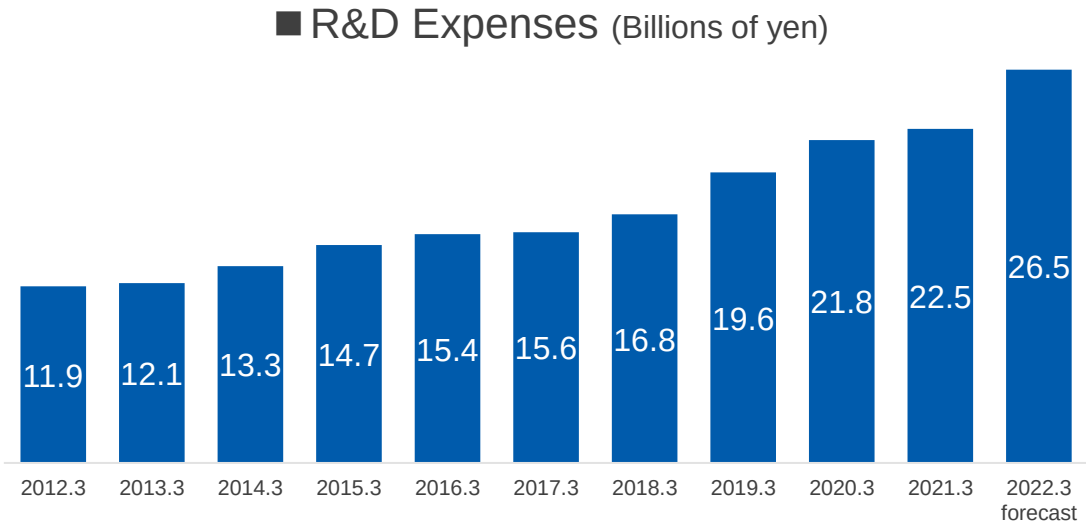
- Market penetration of PCR tests, and early commercialization of innovative technologies such as mRNA vaccines
- Social implementation of digital tools (digitalization, AI, virtual and augmented reality)
- Technological innovation toward zero carbon (clean energy, power saving)

- Changes in social behavior during and after the COVID-19 pandemic
- Diversifying and increasing social demands, such as SDGs and responses to climate change
- Greater speed and flexibility being required as uncertainty increases

# Establishing a Global R&D System



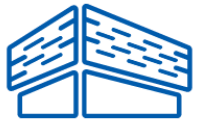

1993 Japan (Techno Center (presently Technopark))
2006 Germany (RDCE)
2009 China (SWX)
2013 United States (RDCA)
2019 Japan (Technopark East Site (bio reagents base))
2020 United Kingdom (RDCUK)
**2022 Singapore (RDCAP)** *Plans
**Digitalization, response to local needs, etc.**



# Sysmex's Value Creation

## Principal management resources

R&D capabilities



Production system

Global sales and service structure

Diverse human resources

## Technology platforms

**Cell measurement**

**Protein measurement**

**Gene measurement**

## Provision of products, services and quality

**Instruments**

**Specialized reagents**

**IT, software**

**Quality control**

## Shaping the advancement of healthcare

**DX**

(Digital transformation)

- Caresphere
- Digital medicine

**Diagnosis + disease management**

- Personalized medicine (Cancer, Dementia)

**Taking on challenges in new domains**

- Regenerative cell medicine
- Medical robotics

## Resolve social issues, achieve sustainable growth

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# R&D Initiatives under the Mid-Term Management Plan

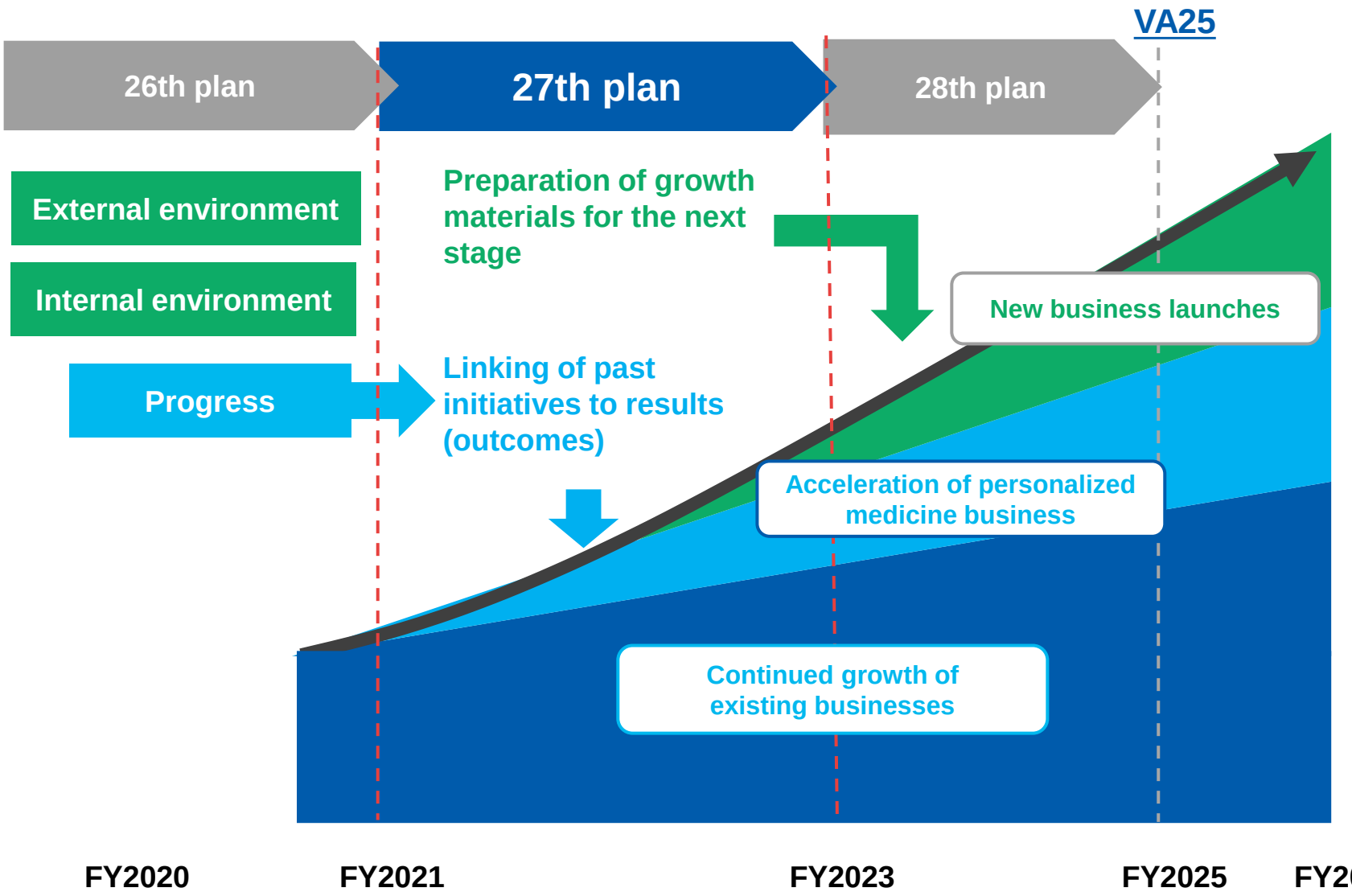
## (Fiscal Years Ending March 31, 2022 to 2024)

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

(1) R&D Initiatives under the Mid-Term Management Plan

(2) Initiatives Targeting Digital Medicine

# Overview of the Mid-Term Management Plan




## Key Actions

1. Accelerate the introduction of new products aimed at improving growth and profitability, and promote emerging market strategies
2. Achieve high growth through proactive investment in key fields (hemostasis, immunochemistry and life science)
3. Introduce new business to achieve dynamic growth (the MR business and further technology and business developments)
4. Promote digitalization in the Group and achieve DX to create customer value
5. Enrich the talent portfolio, which contributes to strategy execution, and create an attractive organizational climate that leverages diverse talent
6. Formulate a vision and roll out measures to reinforce and implement sustainability management

# Linking of Past Initiatives to Results (Outcomes)

## Major R&D Initiatives during the Mid-Term Management Plan

- **Hematology:** Develop next-generation hematology system (XR-9000)
  Develop products for emerging markets
- **Urinalysis:** Develop technology for next-generation UN-Series and develop rapid drug susceptibility testing technology
- **Hemostasis:** Conduct regulatory registration of CN-Series
- **Immunochemistry:** Develop reagents to expand parameters
  Develop unique parameters (Alzheimer's disease, HDL)
- **Life science:** Development of products related to personalized medicine (NGS-based, PCR-based, liquid biopsy)
- **Infectious diseases:** Testing related to COVID-19

# Launch of New Businesses Leading to the Next Stage

## Initiatives for new business development

- **Medical robotics business:**

  Adding functions and increasing the line-up of device for “hinotori,” a robotic assisted surgery system
  Technological developments targeting the surgical field (MINS, “Surgery + Testing”)

- **Regenerative and cellular medicine:**

  Established the quality control scheme using testing technology
  Automation of manufacturing processes using robotics technologies

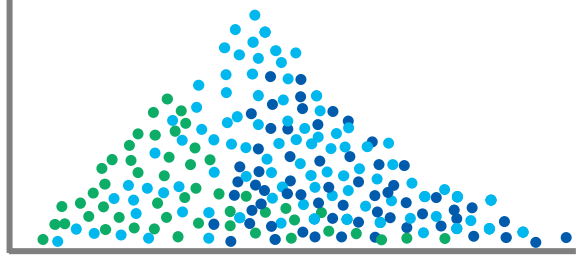
- **Digital medicine:**

# Initiatives Targeting Digital Medicine

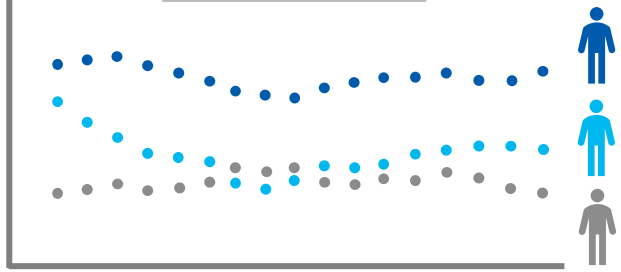
# How to Utilize Testing Data?

| | Population Health | | Personalized Health |
|---|---|---|---|
| Data type | Anonymized large-scale data (statistical values) | | Individual time-series data |
| Targets | All, including healthy people | | Patients who have transitioned from acute to chronic care |
| Main objectives | ✓ Support for diagnosis<br>✓ Prevention<br>・Prevention of disease (health promotion)<br>✓ Epidemiological studies | DX Current medicine DX | ✓ Treatment (digital medicine)<br>✓ Early detection of recurrence<br>✓ Prevention of serious illness |
| Target patients | People who have chronic diseases or are pre-symptomatic | | Patients who need chronic care |

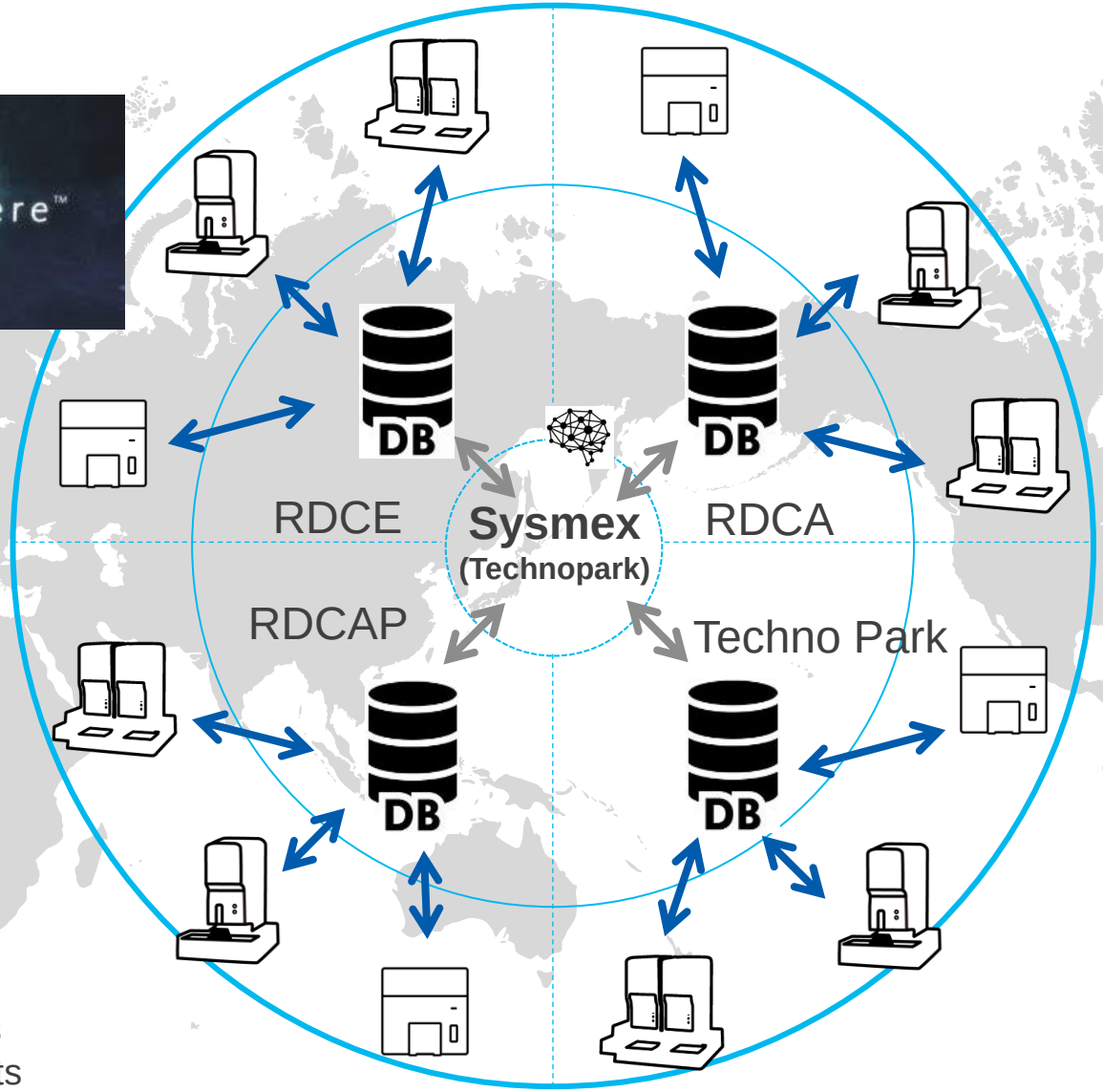
Big data



Big data



# Population Health


Laboratory support

Diagnostic support

Epidemiological studies

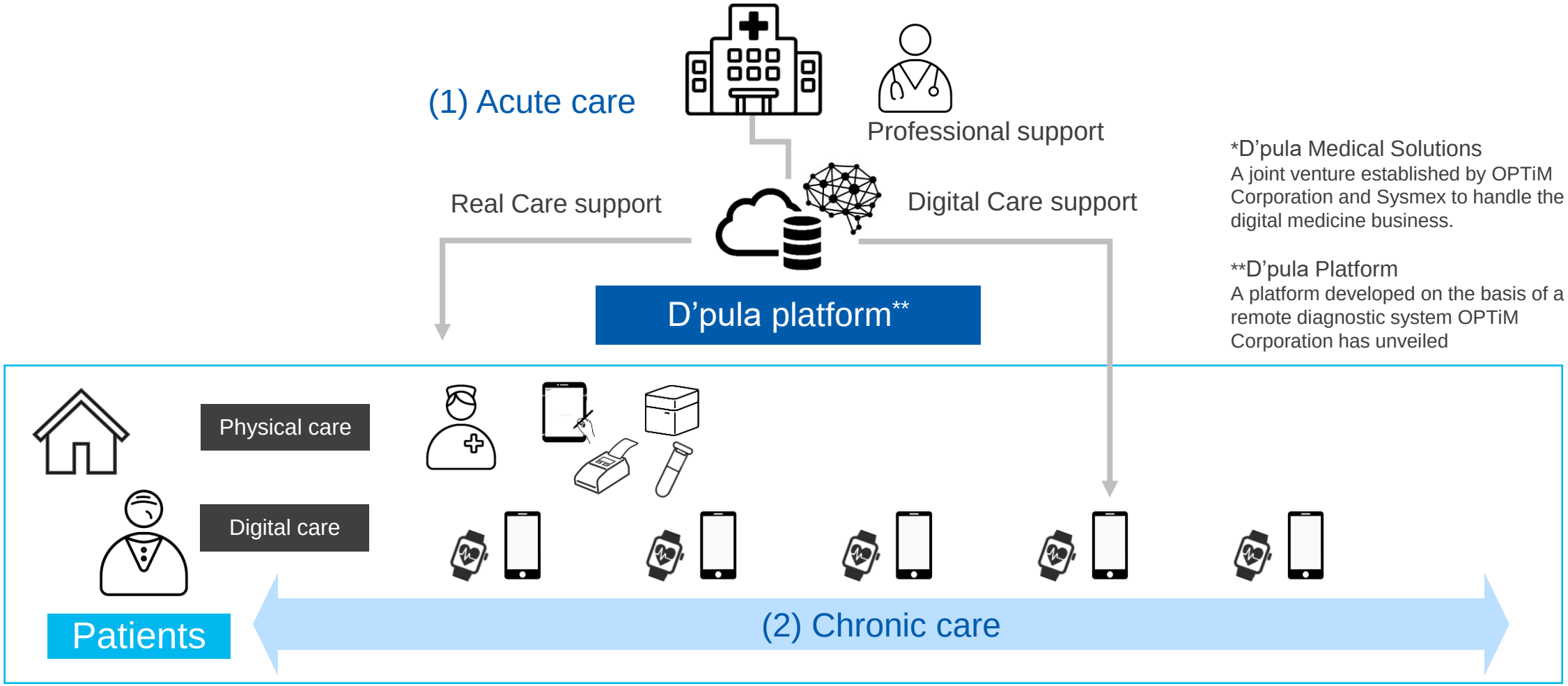
Cohort studies

Anonymized data

Sharing of analysis methods and results

# D'Pula*'s Offerings for Digital Medicine

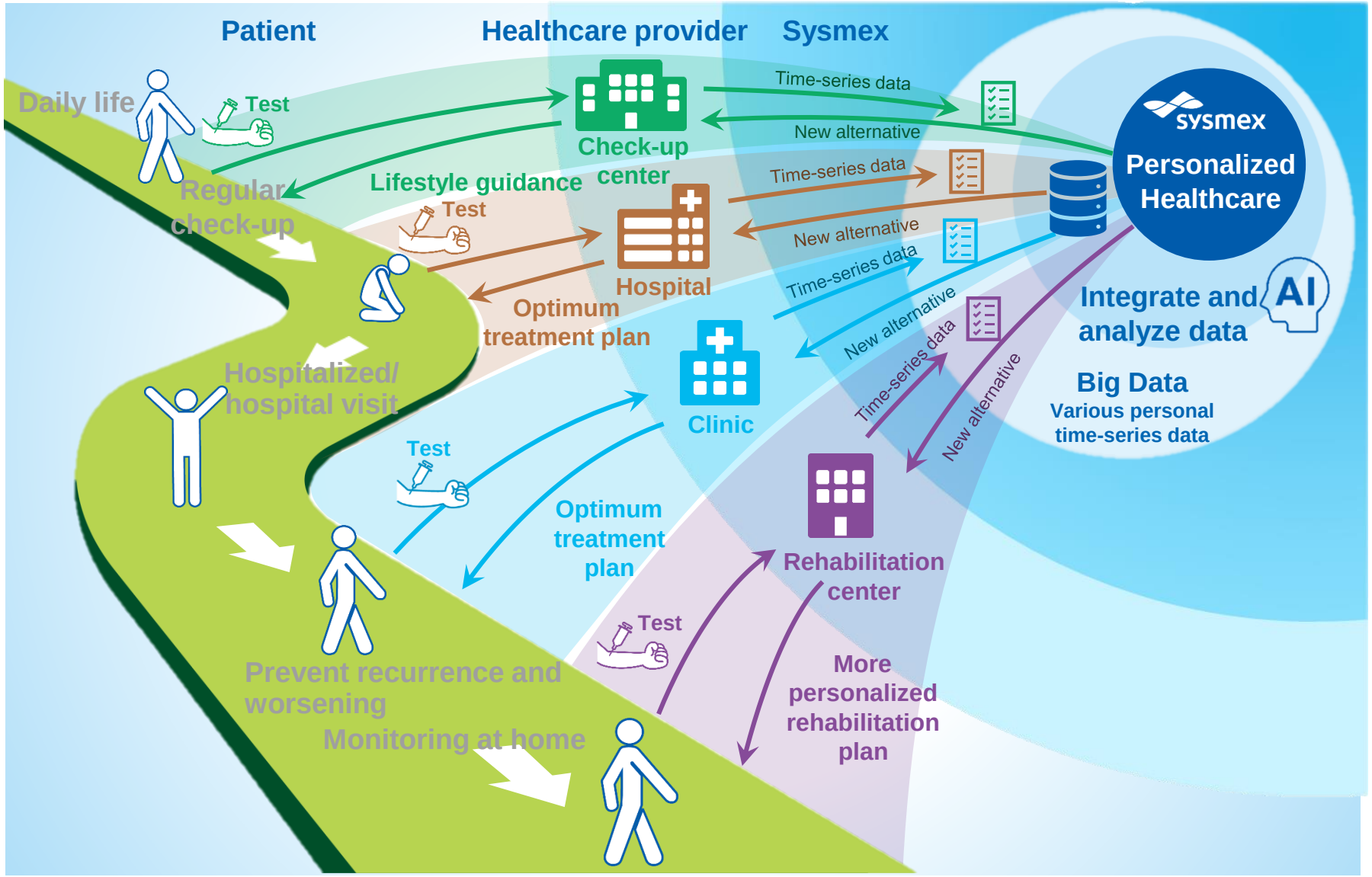
**Connect the actions and series of processes of healthcare professionals and patients in digital and real life.**




*D'pula Medical Solutions
A joint venture established by OPTiM Corporation and Sysmex to handle the digital medicine business.

**D'pula Platform
A platform developed on the basis of a remote diagnostic system OPTiM Corporation has unveiled

# （Appendix） Patient journey



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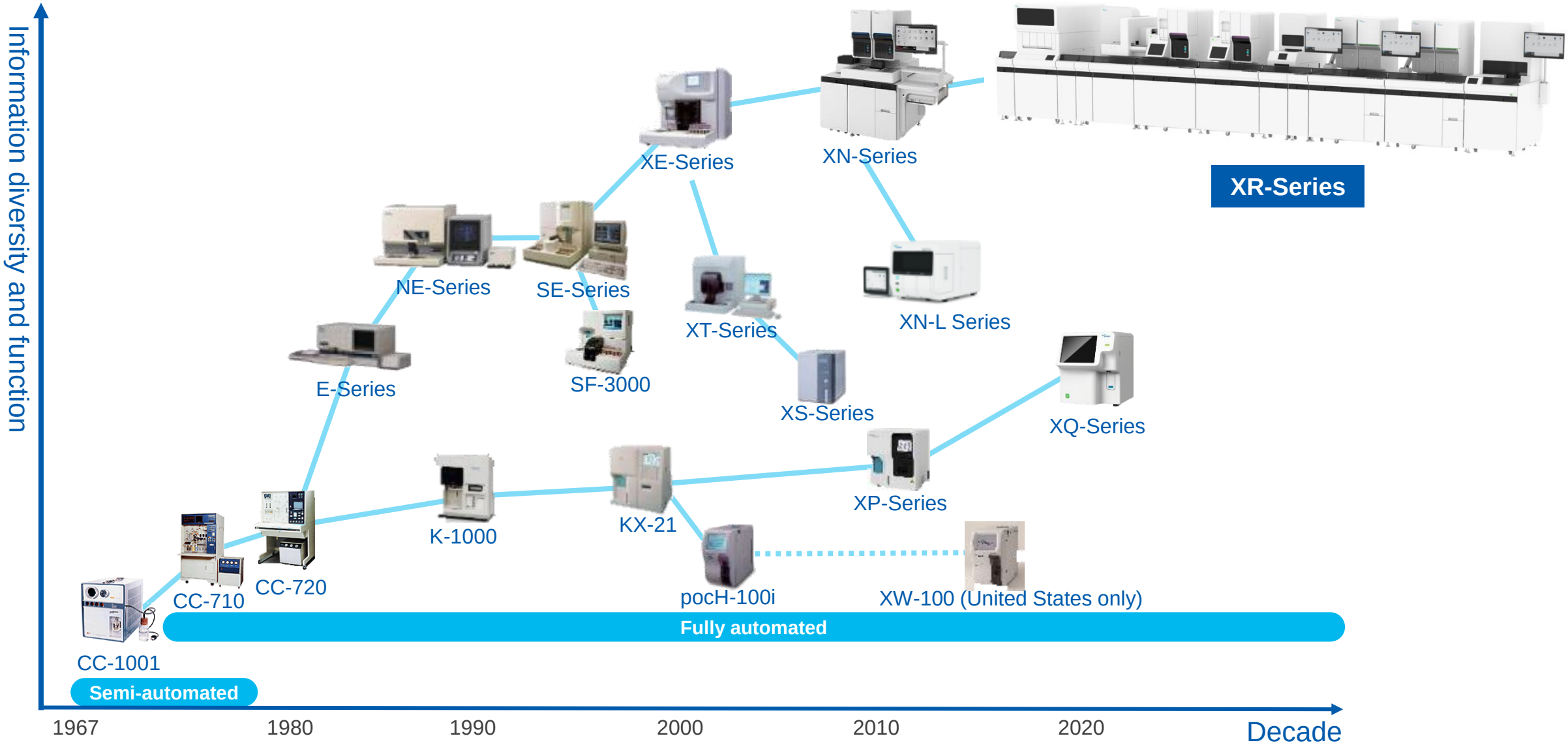
# Creation of New Laboratory Testing Value Based on Hematology

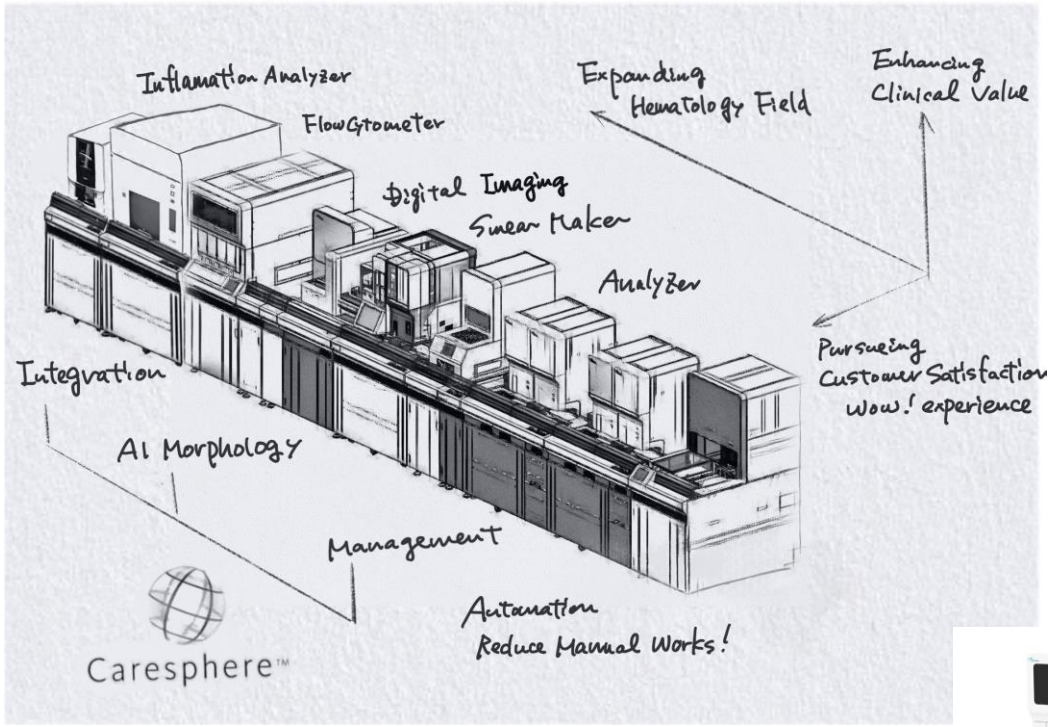
Takaaki Nagai
Executive Officer
Executive Vice President of
System Engineering Div.

# History of Hematology Instruments



# Next-Generation Hematology Product Concepts

## Shown at the 18th R&D Meeting




The first phase is to systematize the XR Series.

# The XR-Series Value Proposition

**“Providing more valuable test results and realize laboratory environment where customer can focus on specialized work utilizing those results”**

## 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.

## CLINICAL VALUE

Lighting the shortest route to diagnosis by utilizing test results

Provide test results which are valuable for patients and clinicians by both defense and offense approach.

## MANAGERIAL VALUE

Delivering best quality assurance to improve role and reliability of laboratory

Support smooth acquisition and operation of ISO by improving efficiency in document maintenance before and after acquiring ISO, as well as contribute to hospital management by improving laboratory operation efficiency.

# XR-Series Product Lineup

## Taking forward the modular concept from the XN-Series

XR-1000

(hematology analyzer)

XR-1500

(hematology analyzer + slide preparation unit)

XR-2000

(hematology analyzer)

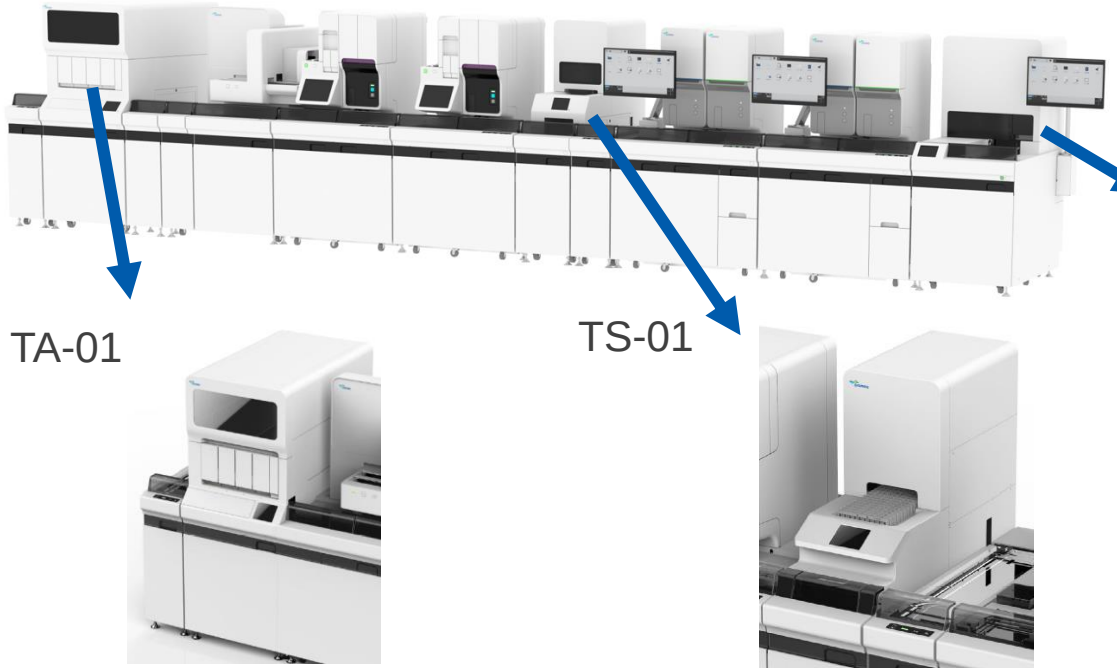
XR-3000

(hematology analyzer + slide preparation unit )

XR-9000

# Contains World's First Scheduling Function, Automated Startup and Shutdown, Automated Quality Control

**OPERATIONAL VALUE: Touch-free concept:** Aiming to create a testing system that requires no manipulation during testing




Sample storage unit **(more compact)**
- ✓ Functions:
  - ➢ Compact module for storage of blood collection tubes
  - ➢ Stores finished blood collection tubes in order of measurement and reception number
  - ➢ Sample pickup function available.

Sample sorting unit **(more compact)**
- ✓ Functions:
  - ➢ Compact module for sorting blood collection tubes

## Plan to launch in Q2 FY2022

BT-50: Bar code terminal **(a world's first scheduling function)**
- ✓ Functions:
  - ➢ Automated startup and quality control
  - ➢ Automated cleaning and shutdown also possible
  - ➢ Read bar code label on blood collection tube and confirm the tube's arrival

Market requirements, customer issues (distributor in Europe)
- ✓ QC measurements require effort and time. QC handling and mixing is operator-dependent, and malfunctions can occur in the event of bad mixing, cooling, or warming.

**Reduced footprint and environmental impact**

Size: Width reduced by 15%
Power consumption: down by 40%
(Compared with current XN Series)

# Bar Code Terminal (BT-50)　Touch-Free Concept

## World's first* hematology system equipped with this technology

**On-board scheduler** *World's first
Automation of wake-up (equipment power up), quality control, and cleaning

**Flexible automated shutdown**
Shutdown of individually selected instruments

**Quality Control blood temperature adjustment**
Keeps control blood (XN CHECK) cold and adjusts temperature for optimal measurement

**Dedicated agitation for quality control blood**
High quality precision control with optimal agitation for control blood

**Management of consumables**
Management of control blood, cell clean auto, etc.

**Displays "today's schedule"**
Batch display of equipment operation schedule and information about consumables

**New design**
Silent Design provides a unifying feeling across the entire system

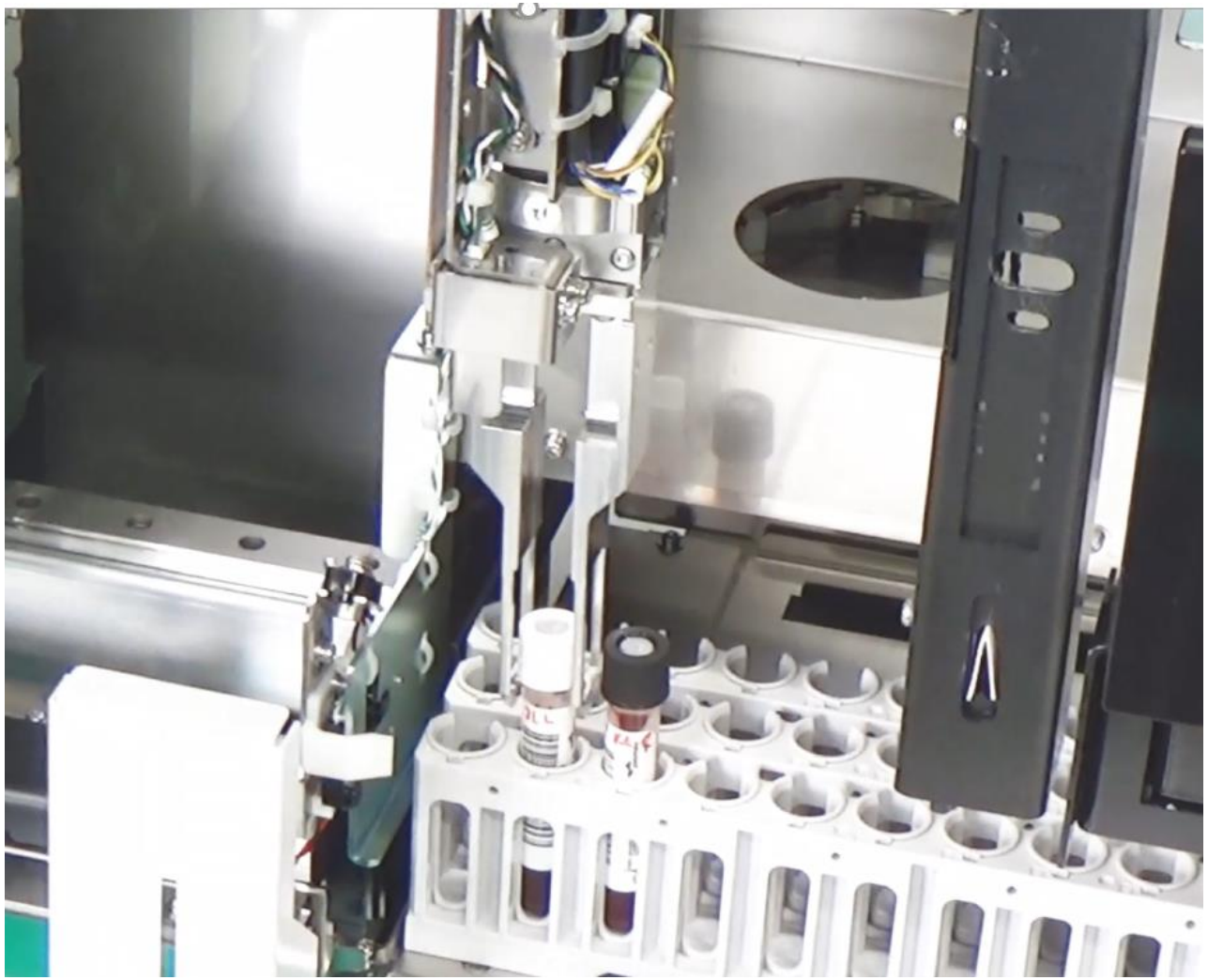
**Core functions**
"Blood collection tube barcode label reading function"
"Blood collection tube arrival confirmation function"

Complete preparations for measurement without touching the instrument

Automatic cleaning and shutdown after testing

High-end quality control without manual operation

# Bar Code Terminal (BT-50)　Touch-Free Concept



# Scheduler Function

In the past, testing startup, quality control and cleaning were all performed manually. The scheduler function uses ICT to automate these tasks.

**Wake-Up**
Wake-on-LAN technology allows the BT-50 to send a signal to the entire system to start it up.

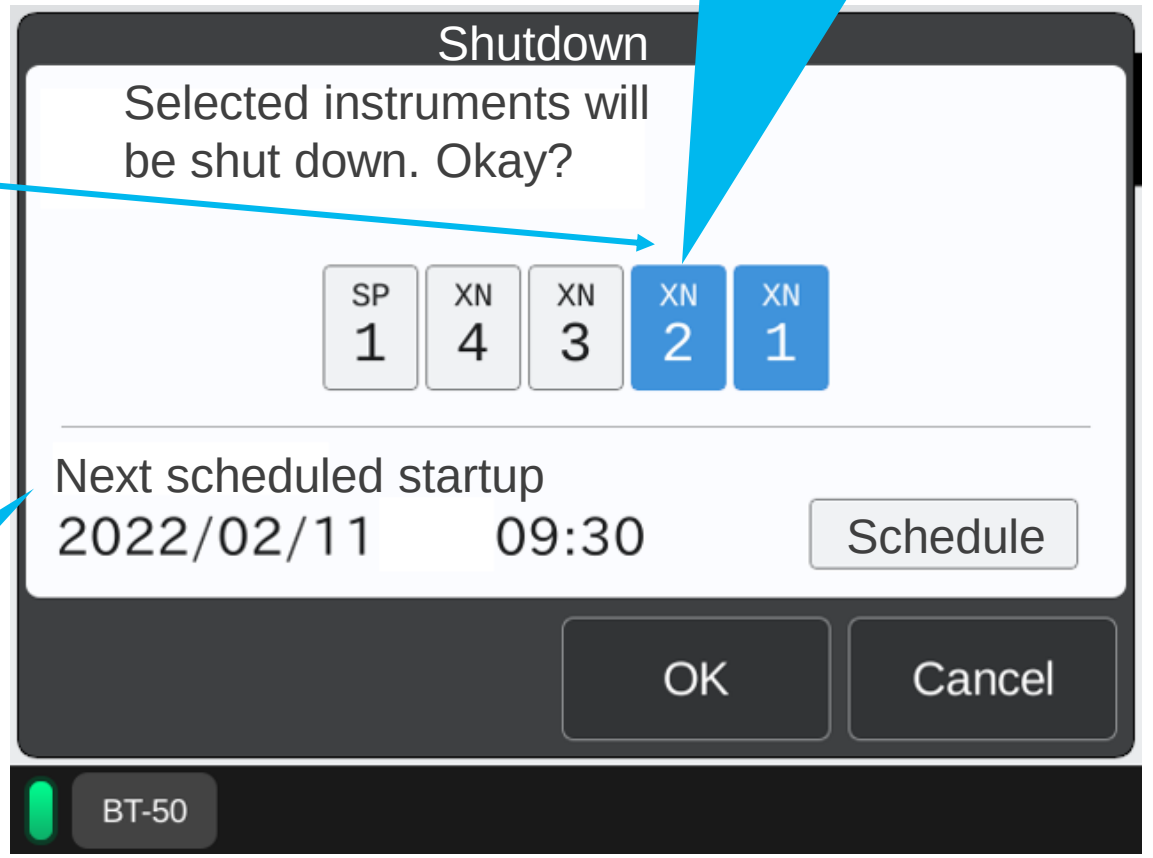
**Quality Control**
The cooled control blood is returned to room temperature and transported to the analyzer for automated quality control.

**Clean**
The cleaning agent (Cell Clean Auto) is transported to the analysis equipment for automatic cleaning.


- ✓ Detailed information about the date and time of operations can be registered in line with laboratory operations.
- ✓ Operations commence automatically at the registered time and date.

# Flexible Automatic Shutdown

At night, when fewer tests are performed, individually selected instruments can be shut down automatically to save power.




Information about the next startup date and time can be checked.

# Using AI Technology in Hematology

## AI-based diagnostic support enables laboratory technologists to perform their work with automated systems

**Measurement**

**XR-Series**
multiparameter automated hematology analyzer

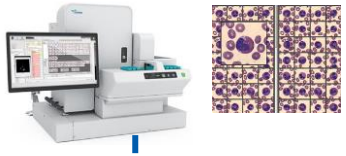
If positive
Assumed to be 30–50% of all samples

**Slide preparation**

**SP-50**
slide preparation unit

**Blood image analysis**

**DI-60**
Digital cell morphology analyzer



If negative

If negative

**If positive** (Assumed to be 10–15% of all samples)

**AI analysis**

**AI image analysis technology**
**Few seconds/patient**


Cell counting/abnormality detection

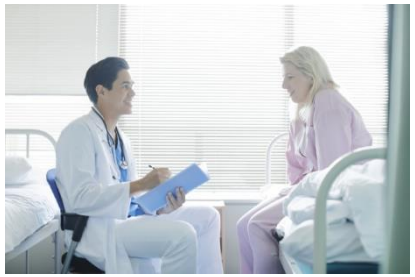
**Reporting**

**Caresphere™ LWS**
laboratory information system

- Forecast disease
- Assume additional tests
- Create comments on sample

Reporting

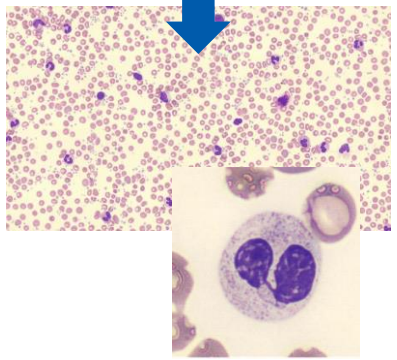
**Clinic diagnosis**



- ✓ Display diagnostic support information on cell classification and cell morphology using AI analysis
- ✓ Reduce missed items through visual inspection
- ✓ Anticipated for use in remote areas where there are few laboratory technologists specializing in blood diseases

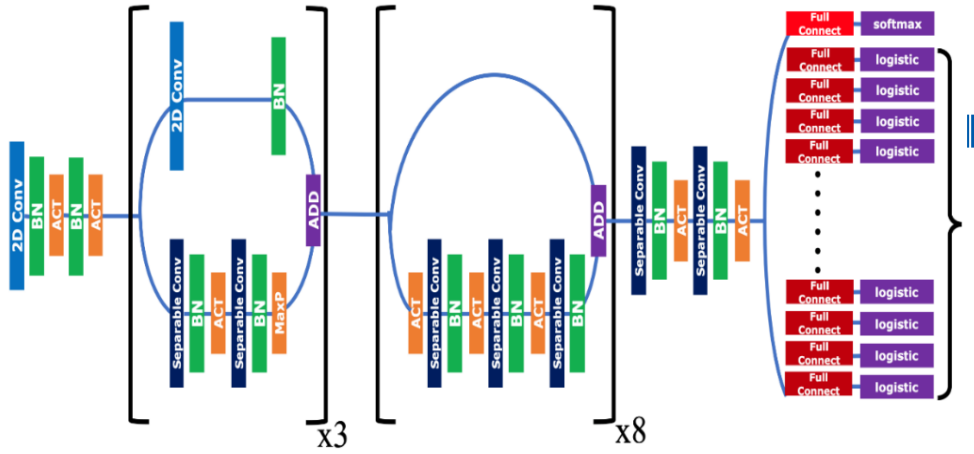
# Using AI Technology in Hematology

## Development of an automated blood image analysis system based on CNNs*



**Digitalization of cell images**

Training with 700,000 cell images




Differentiation of 17 classes of cells

Existence/ non-existence of 19 categories of morphological abnormality

*Convolutional neural networks

# Using AI Technology in Hematology

## Achieved much better performance than the existing system (DI-60) at differentiating cell type

| | Conventionally | | AI | |
|---|---|---|---|---|
| Cell type | DI-60 | | CNN-based digital morphology analysis system | |
| | Sensitivity | Specificity | Sensitivity | Specificity |
| Segmented neutrophil | 92% | 91% | 98% | 98% |
| Band neutrophil | 27% | 99% | 98% | 97% |
| Metamyelocyte | 19% | 100% | 94% | 96% |
| Myelocyte | 59% | 100% | 98% | 97% |
| Promyelocyte | 76% | 99% | 99% | 98% |
| Blast | 80% | 99% | 97% | 99% |
| Lymphocyte | 82% | 94% | 99% | 97% |
| Variant lymphocyte | 0% | 100% | 95% | 98% |
| Monocyte | 88% | 99% | 100% | 99% |
| Eosinophil | 72% | 100% | 100% | 100% |
| Basophil | 91% | 99% | 99% | 100% |
| Large platelet | 98% | 99% | 100% | 99% |
| Megakaryocyte | 0% | 100% | 94% | 100% |
| Platelet aggregation | 0% | 100% | 96% | 99% |
| Erythroblast | 92% | 100% | 100% | 99% |
| Smudge | 78% | 97% | 95% | 98% |
| Artifact | 62% | 99% | 99% | 99% |

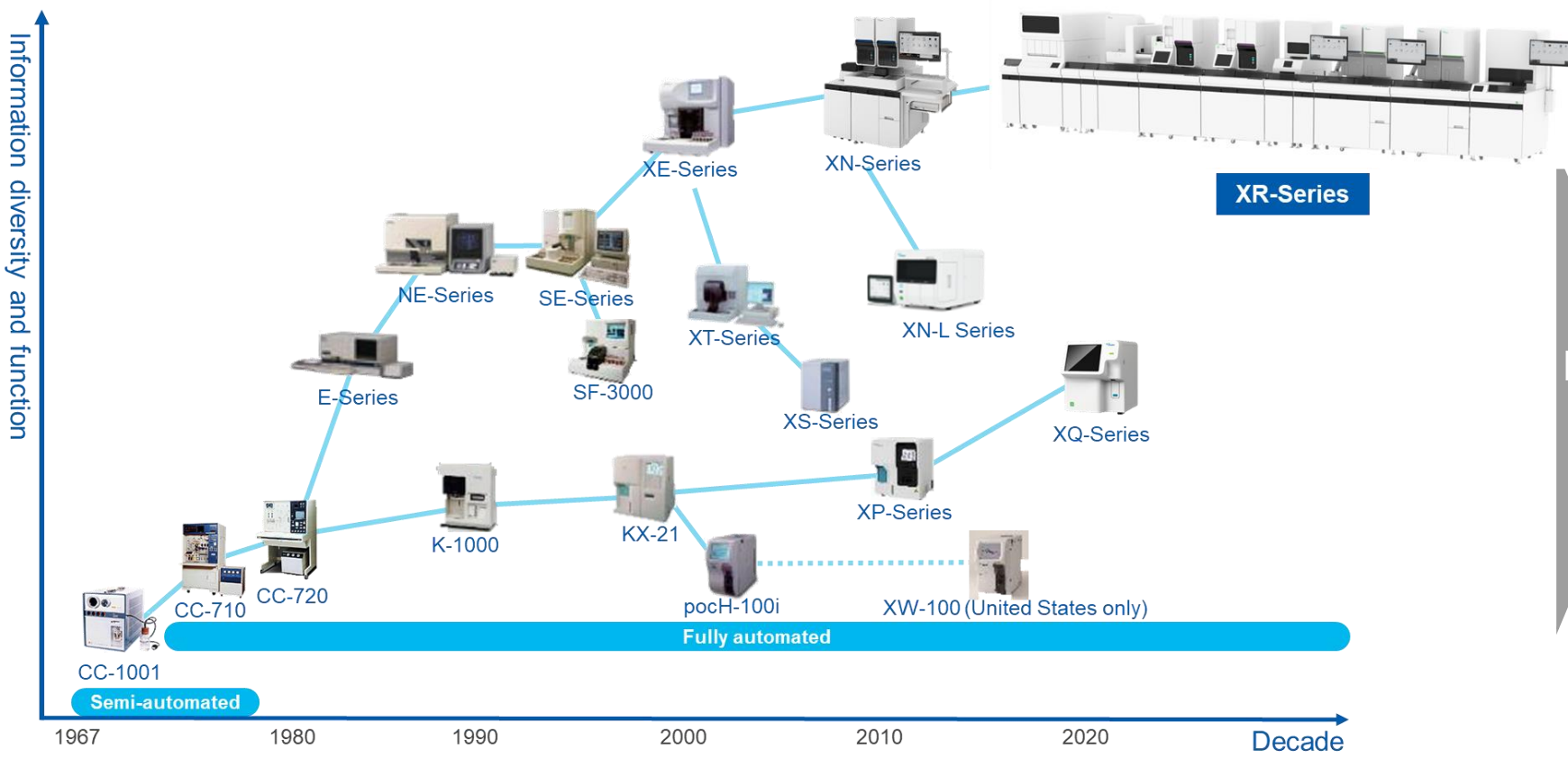
CNN, convolutional neural networks

References: Artificial intelligence (AI) and blood disorders
“Development of a Blood Image Analysis System Using Convolutional Neural Network Technology”

- ✓ Started multi-center performance evaluation for commercialization, including detection of abnormal morphology
- ✓ Aiming to conclude development in FY2022

# Toward Further Advances in Hematology

## Combine technologies cultivated as a leading company with advanced technologies (ICT, AI) to move to the next stage.




ICT, AI

- Increased diagnostic precision (Suggestions to clinician)
- Reduced patient burden (Shorter wait times, etc.)
- More productive laboratory operations
- Realization of medical collaboration (Standardization of testing data)
- Environmentally responsive (Power-saving, more compact)

4

# Creation of Clinical Value Using Cancer Genetic Testing Technology

Reiko Watanabe
Executive Officer
Executive Vice President of
Medical Affairs Div.

# Initiatives in the Life Science Field (Technologies Map)

Technologies we will explain today

sysmex

Real-world data

**2022** OSNA™ TTL digital indicator

Prediction model

Multiple-factor analysis

Circulating tumor DNA (ctDNA)

**2021** Plasma-Safe-SeqS (PSS)

**2019** OncoBEAM™ RAS CRC kit (two genes)

Recurrence monitoring and selection of treatment

Highly sensitive liquid biopsy (dPCR, NGS)

Genome DNA

Inherited retinal dystrophy (IRD) panel system
(82 genes)

Lymph node

DX

**From 2008**

OSNA™ method for diagnosing cancer lymph node metastasis
(breast, colon, stomach, lung, cervical (application in progress))

Sentinel lymph node metastasis test
Interaoperative decision on lymph node dissection

Tumor tissue

**2021** AmoyDx® lung cancer multigene PCR panel (five genes)

**2017** AmoyDx® ROS1 fusion gene detection kit

Gene testing of malignant tumor tissue
Selection of molecularly targeted therapy (CDx)

OncoGuide™ NET

OncoGuide™ portal

**2019** OncoGuide™ NCC Oncopanel System
(124 genes)

Expert panel support system

Genome profiling

Single markers (RT-PCR, LAMP, dPCR)

Multi-markers (RT-PCR, NGS)

Cancer

Hereditary disease

# Positioning of Genome Profiling in Decisions on Therapeutic Drugs

## Prioritize testing with a high decision rate

**Gene testing of malignant tumor tissue (multi-marker / *CDx*)**

***AmoyDx* lung cancer multigene PCR panel (five genes)**

***Plasma-Safe-SeqS (PSS)* breast and colon cancer***
***OncoBEAM RAS CRC***

**Decision rate: 30 - 80%**

*unapproved item

In case molecularly targeted therapy cannot be identified

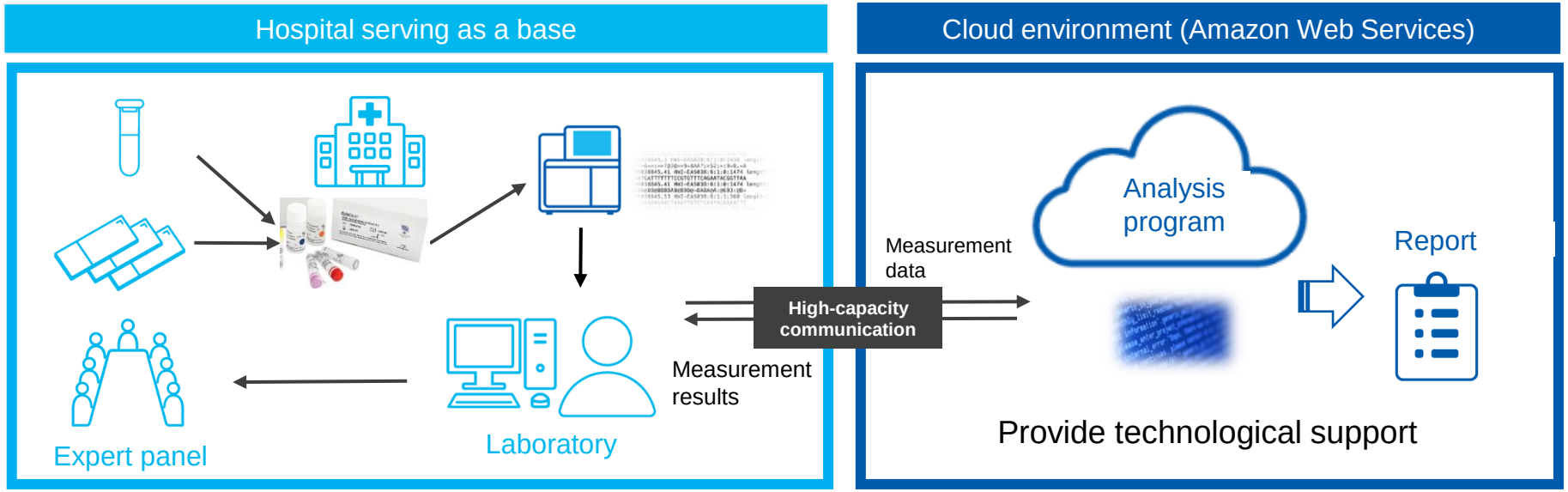
**Genome profiling (across organs)**

***OncoGuide NCC* Oncopanel System**

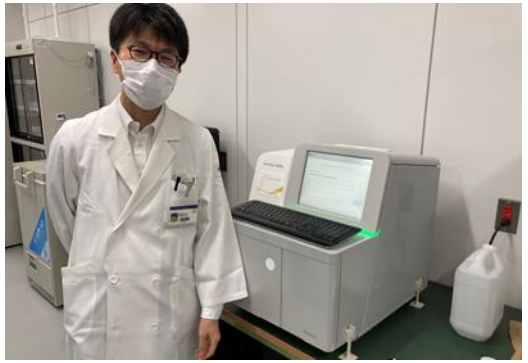
**Decision rate: 35 - 40% (after expert panel)**

# OncoGuide NCC Oncopanel, In-Hospital Genome Testing

- Next-generation sequencers operated in hospitals' clinical laboratories
- Realization of a system for transferring large amounts of data from the hospital to the cloud with guaranteed security
- Operation of analysis programs in a cloud environment




"Our in-hospital laboratory for complete gene testing helps promote genomic medicine and contributes to HR development."



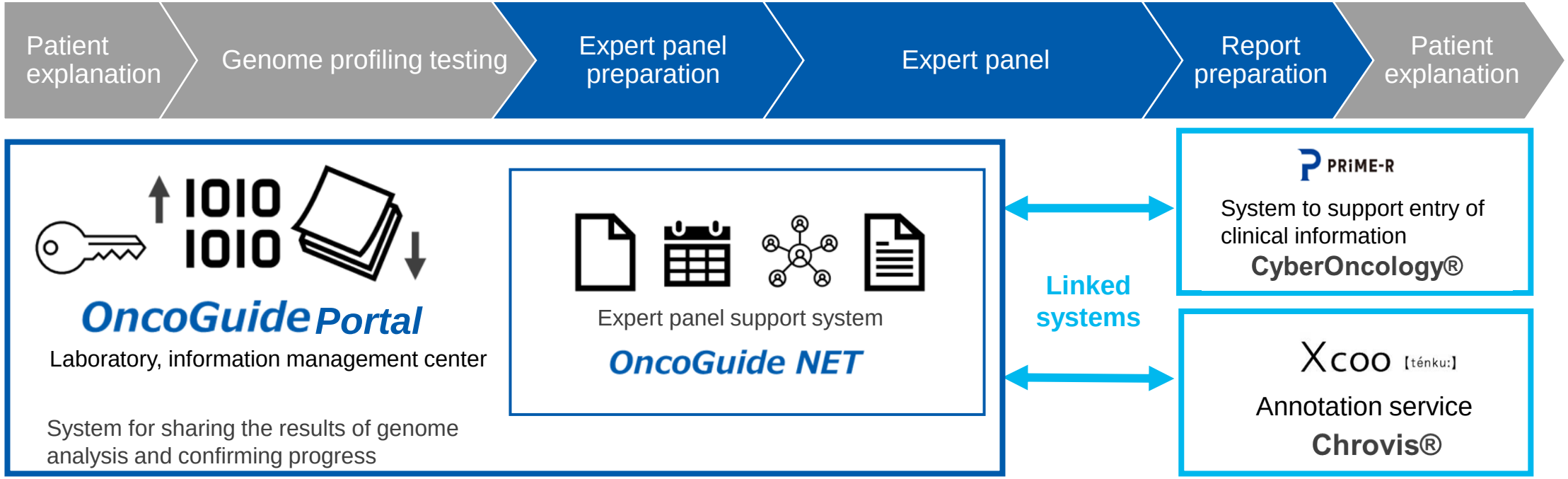
Dr. Kousuke Watanabe
Department of Clinical Laboratory
The University of Tokyo Hospital

The ability to handle complete gene profiling within the hospital promotes genomic medicine at those facilities.

# OncoGuide NET

- Burden on medical facilities (doctors) that provide genomic medicine
  - Handling secured information and large data volumes
  - Expert panel operation

    Preparation of case summaries, schedule coordination, report writing, search for candidate drugs and clinical trials, inter-hospital collaboration, etc.




**Smart operation of expert panels by linking with various companies' services**

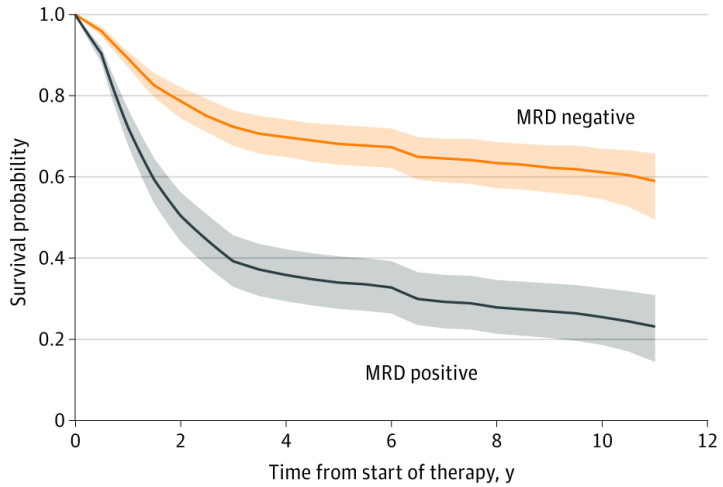
# Highly Sensitive Liquid Biopsy: Plasma-Safe-SeqS (PSS)

## AML-MRD-SEQ (20 on-board genes)

**Helps to improve prognosis by diagnosing recurrence and selecting molecularly targeted therapeutic drugs**

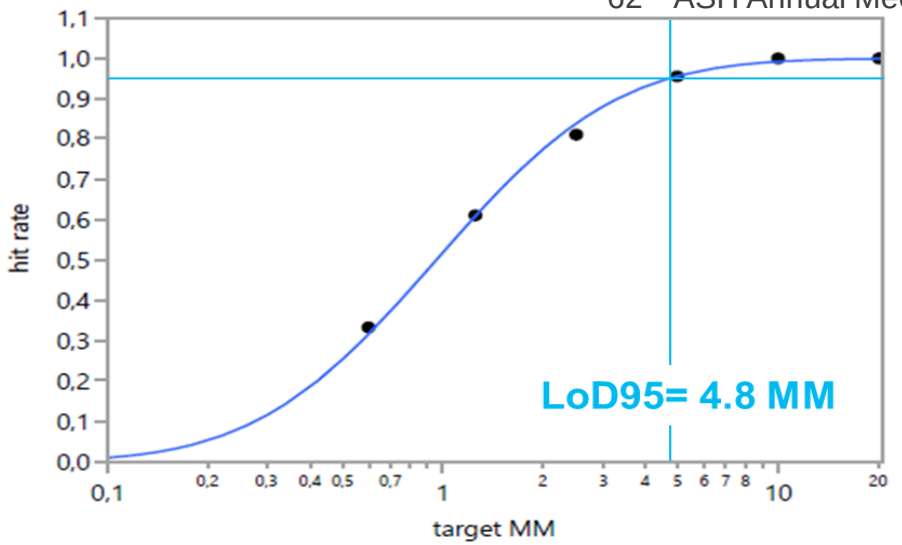
Early detection of minimal residual disease (MRD) and detection of markers for molecularly targeted therapy

A Overall survival https://jamanetwork.com/journals/jamaoncology/fullarticle/2771199




Assumed five-year survival rates:
34% for MRD positive / 68% for MRD negative

62nd ASH Annual Meeting 2020




Sensitivity: 0.025%
(VS Vestigial Method 50-100x High Sensitivity)

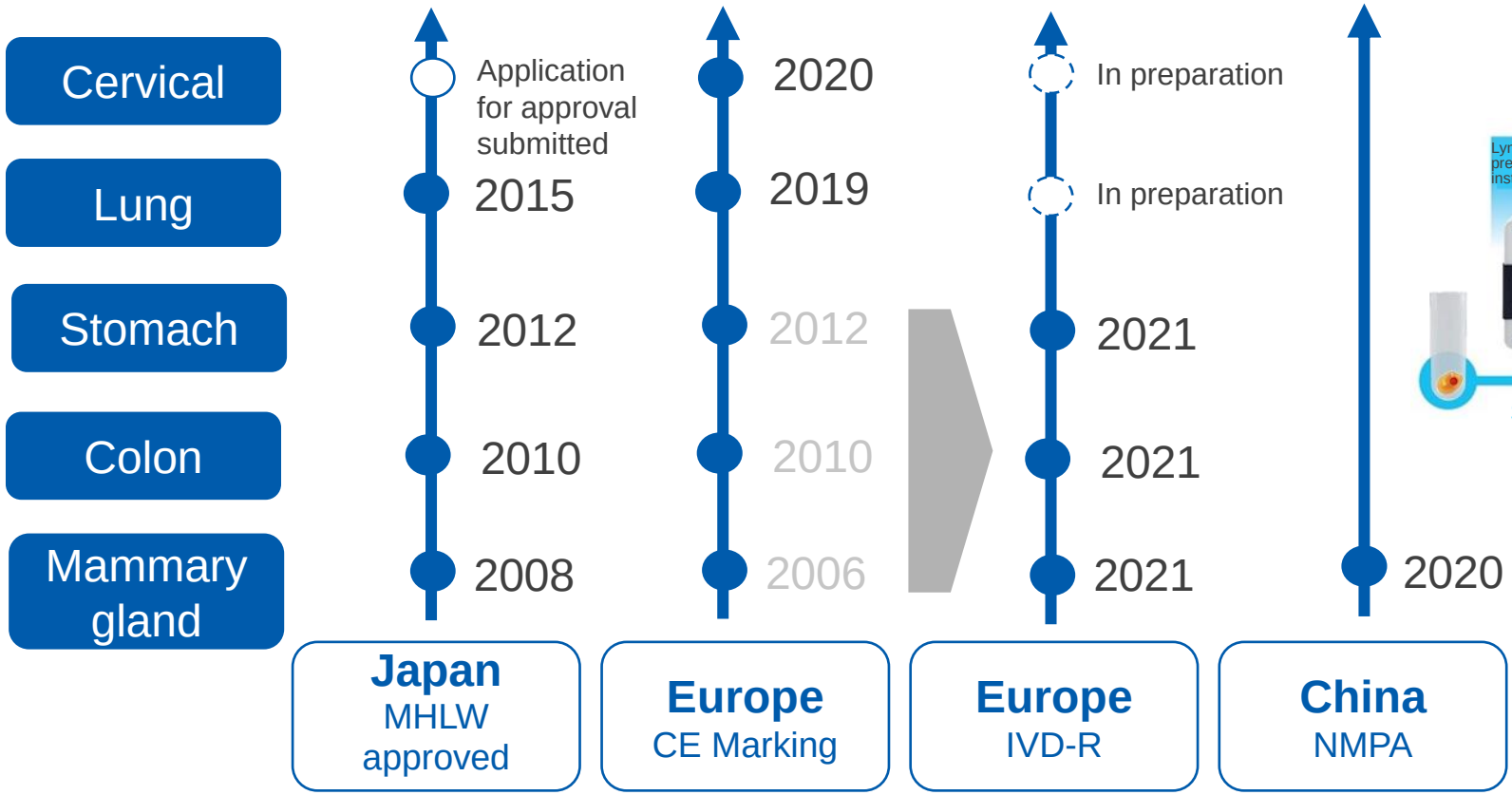
- Launched CLIA assay service for pharmaceutical clinical trials (October 2021)
- Participation in NIH Biomarker Consortium's AML-MRD project (February 2022)

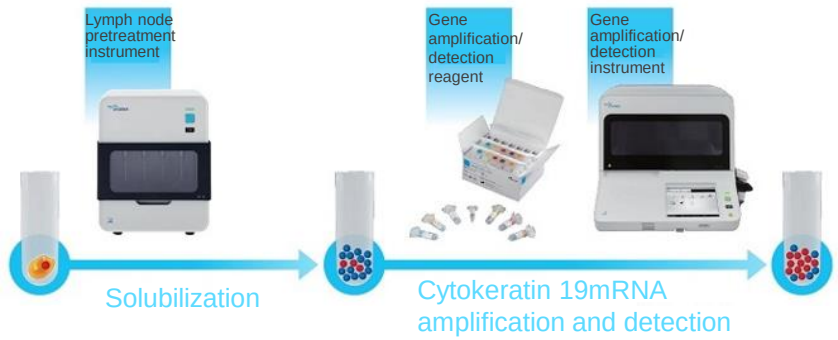
https://fnih.org/news/announcements/fnih-biomarkers-consortium-project-will-establish-new-methods-detecting-disease

# OSNA Method for Diagnosing Cancer Lymph Node Metastasis

## Increasing applicability to different types of cancer, expansion centered on Japan and Europe

- Total units installed globally: approx. 400 (FY2021)
- Track record: 500,000 patients tested




RD-100i, RD-200, RD-210

# Breast Cancer:
# OSNA TTL Clinical Efficacy Study of Digital Indicator

## Japanese Association for Theranostics (Doctor-led research group)


- More than 70 members (60 participating institutions)
- Building database (Lynolog) with more than 10,000 cases (as of 2021)
- Developing OSNA TTL (digital indicator) for total CK19mRNA volume on the positive sentinel lymph node

**Example:**

| Sentinel LN-1 | Sentinel LN-2 | Sentinel LN-3 |
|---|---|---|
| 500 copies | + 9,500 copies | Negative |

→ **Lymph node metastasis: two positives (N1)**

→ **OSNA TTL 10,000 copies**

## A prediction model of lymph node metastasis probability and postoperative treatment effect using digital indicators

- During surgery, surgeon checks the probability of metastasis to axillary lymph nodes
- Estimates the effect of postoperative drug therapy (calculates the five-year metastasis-free survival rate)

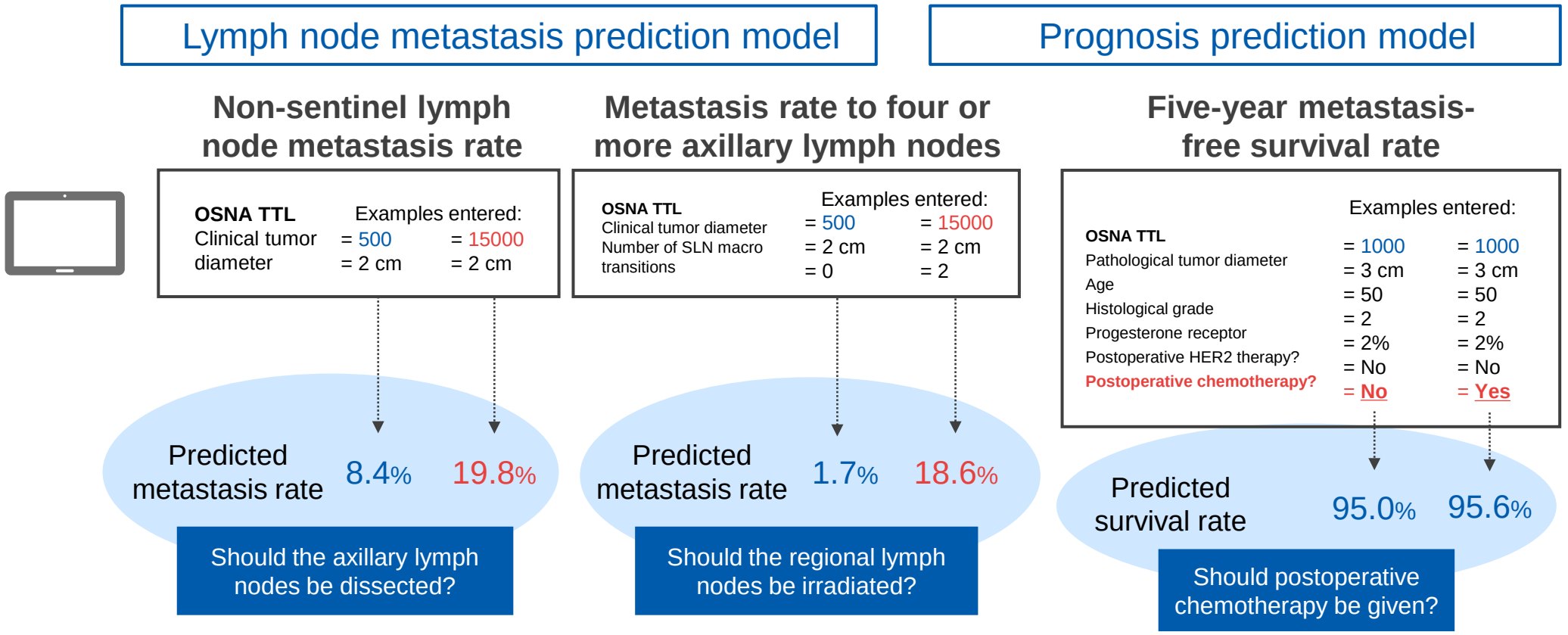
**Accumulate clinical information and OSNA test results to build a prediction model**

# Proposal of Prediction Model for Lymph Node Metastasis and Postoperative Therapeutic Result

## Use of prediction models to further promote personalized medicine

### Lymph node metastasis prediction model

### Prognosis prediction model




**Three prediction models will soon be available on the Japanese Association for Theranostics website.**

https://www.theranostics.jp/

5

# Initiatives for the Realization of Personalized Medicine

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

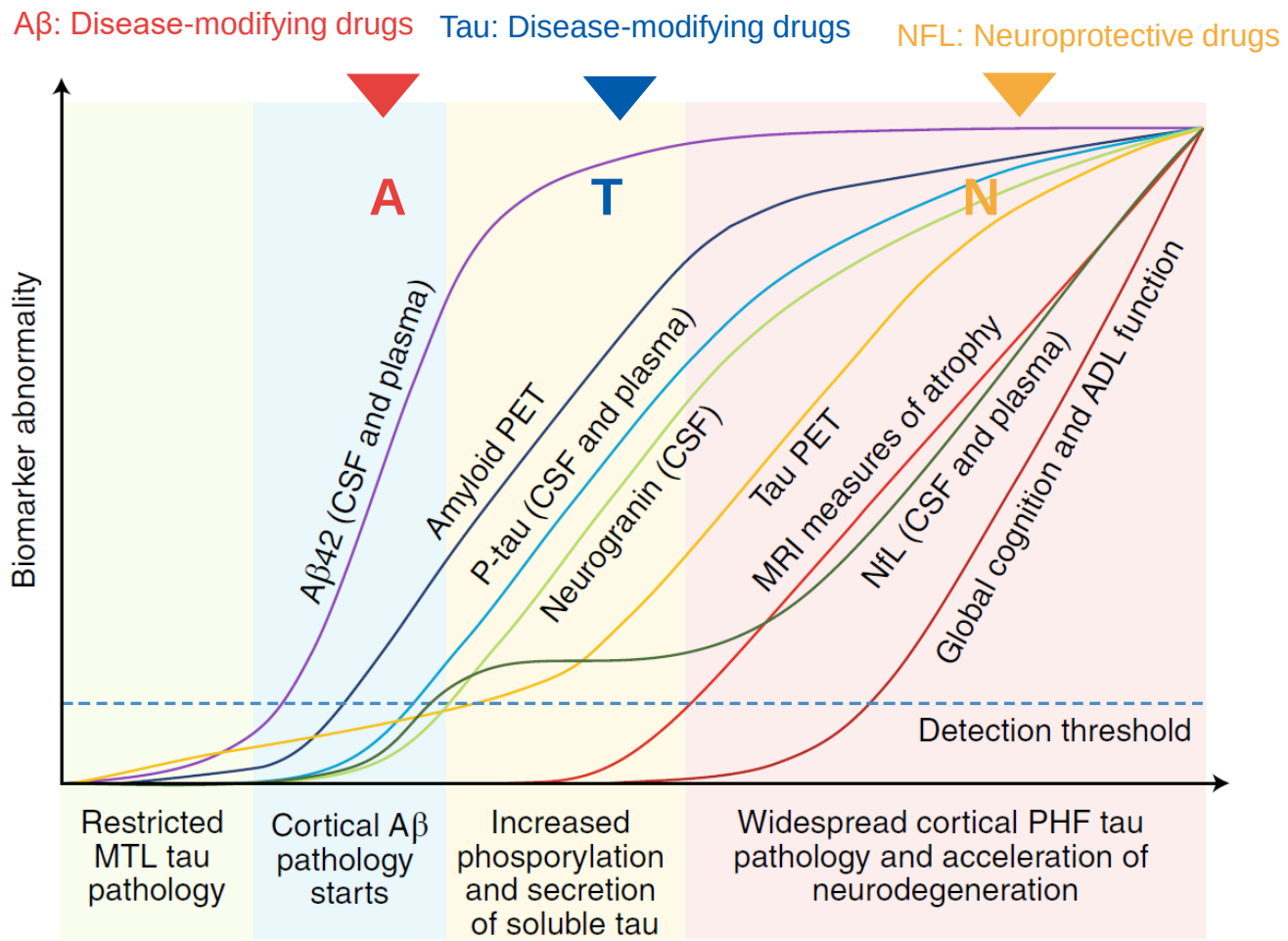
(1) Initiatives Targeting Alzheimer's Disease

(2) Initiatives for Cardiovascular Disease (Development of Technology to Measure HDL Function)

# Initiatives Targeting Alzheimer's Disease

# Multiparameterization of Dementia Diagnosis with Dementia Research and Drug Development

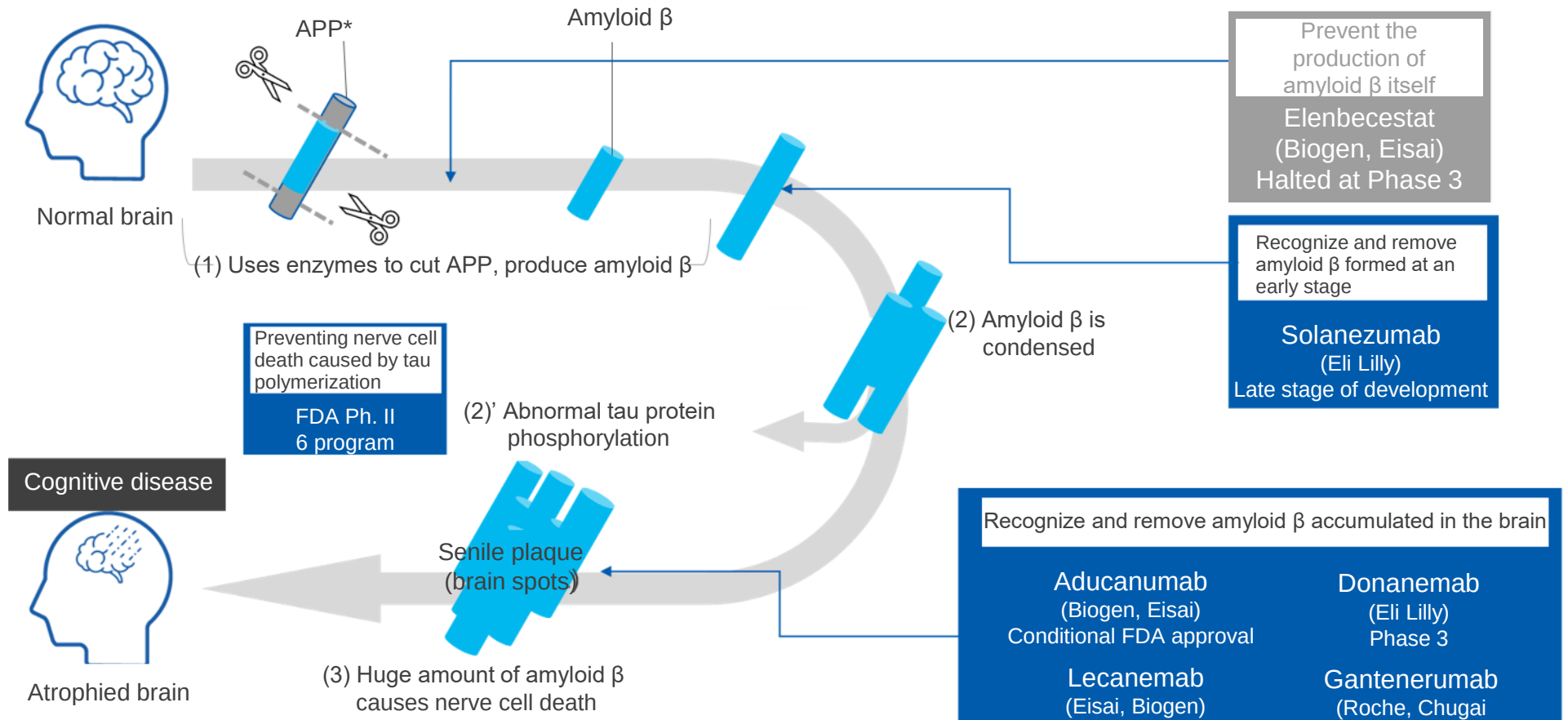
The development of drugs targeting the substances that cause Alzheimer's disease is underway. It can be to classify the stage of dementia and select appropriate therapeutic drugs by testing multiple biomarkers over time.




Cited from O. Hansson Nat. Med.27, 954-963 (2021)

# Accelerating the Development of Therapeutic Drugs Based on the Amyloid Hypothesis and New Challenges

## Alzheimer's disease: Structural and quantitative measurements of amyloid β are important.




*APP: Amyloid β precursor protein (normally involved in nerve growth and repair)

# Technology for Diagnosing Alzheimer's Disease: The Spread of Blood Biomarkers

**Blood (plasma): Aβ42, Aβ40, Aβ composite, p-Tau181**
- Mass spectrometry systems: C2N*, Shimadzu
- Fully automated immunoassay systems: Roche*, **Sysmex (HISCL)**

*Research stage

**Sensitivity/specificity, quantitative**

**Low level of invasiveness, simple, standardized**

**Intrusive, simple**

**Image analysis**
- Amyloid PET: Siemens, GE, Hitachi (imaging agent: Fujifilm Toyama Chemical)
- Tau PET: Siemens, GE, Hitachi (imaging agent: Avid Radiopharmaceuticals)

**Video analysis**
- Eye movement: Optina
- Change in facial expression: FRONTEO

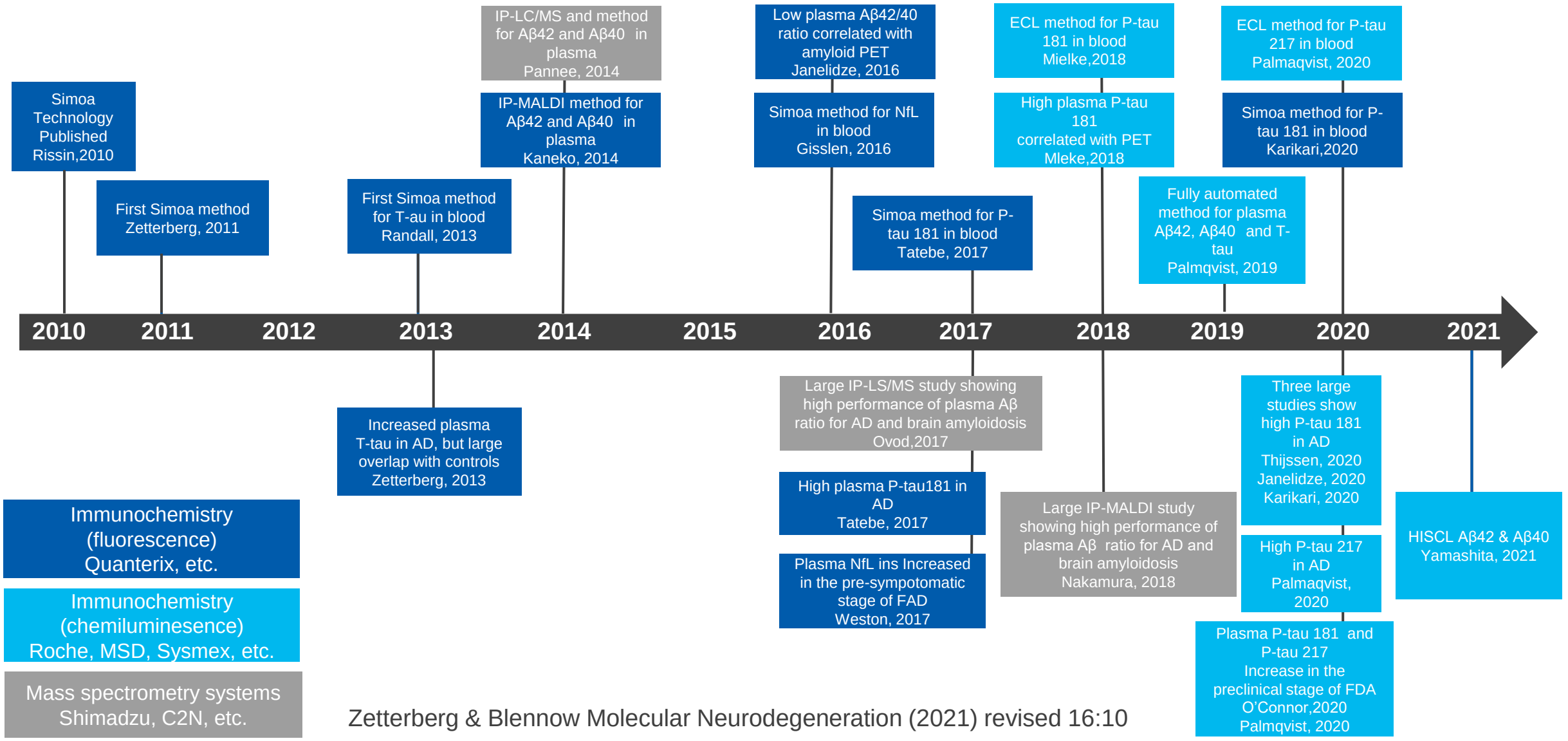
**Intrusive, simple**

**Cerebrospinal fluid (CSF):** Aβ42, Aβ40, p-Tau181
- Fully automated immunoassay systems: Roche, Fujirebio

**Quantitative, objective**

**Language, cognition functions**
- Hasegawa dementia scale
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale

# History of Blood BM Measurement Technology for Alzheimer's Disease




Zetterberg & Blennow Molecular Neurodegeneration (2021) revised 16:10

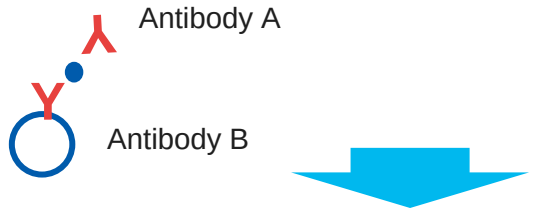
# Functions and HISCL™ Series Technology Characteristics

| Company or University | Sample types | Measurement principle/marker | AUROC | Sensitivity | Specificity |
|---|---|---|---|---|---|
| Shimadzu*1 | Blood | Mass spectrometry Aβ40, 42, APP669-711 combination | 0.91 | 0.86 | 0.82 |
| University of Washington*1 | Blood | Mass spectrometry Aβ42/40 comparison | 0.88 | 0.88 | 0.76 |
| C2N Diagnostic*1 | Blood | Mass spectrometry Aβ42/40 comparison | 0.81 | - | - |
| Roche*1 | Blood | Immunoassay Aβ42/40 comparison | 0.77 | 0.75 | 0.72 |
| Fujirebio*1 | Cerebro-spinal fluid | Immunoassay Aβ42/40 comparison | 0.86 | 0.82 | 0.82 |
| **Sysmex*2** (under development) | **Blood** | **Immunoassay Aβ42/40 comparison** | **0.92** | **0.95** | **0.78** |

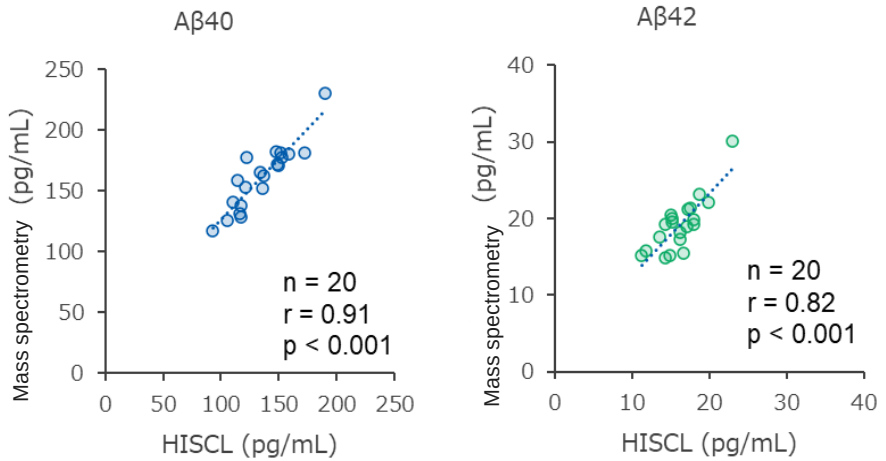
*1:Cited from published papers *2:data checked internally

## HISCL™ Series Technology Characteristics

- **Unique antibody combinations**
- **Fully automated**




**Establishment of specific measurement targets (confirmation using mass spectrometry)**




**High measurement precision**

| | measurement precision (%) |
|---|---|
| Aβ40 | < 4.6 |
| Aβ42 | < 5.3 |

# Apply to HISCL Series : Blood-Based Liquid Biopsy

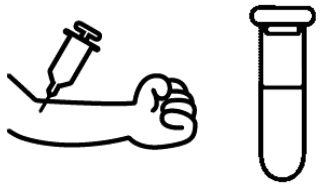
**Blood testing: Monitoring by frequent measurement**
**Easy to add parameters: Development of multiple markers**

## Image-based screening

MRI, PET, CT

## Spinal fluid test

## Blood testing



- **Standardization, simplification (fully automatic measurement)**
- High throughput
- **Quantitative**
- **Multi-marker analysis**

Measurement parameters

| Infectious diseases | Thyroid | Tumor marker | Central nervous system marker |
|---|---|---|---|
| HBsAg | TSH | AFP | **Aβ40** |
| HBsAb | FT4 | CEA | **Aβ42** |
| HBeAg | FT3 | PSA | |
| HBeAb | | CA19-9 | |
| HBcAb | | CA125 | |
| HBcIgM | | CA15-3 | |
| HCVAb | **Coagulation molecular marker** | ProGRP | |
| HCVGr | TAT | PIVKA-II | |
| HIV Ag+Ab | PIC | | |
| HTLV-1 Ab | TM | | |
| TPAb | tPAI・C | | |

# Reference: Characteristic Changes in CSF Biomarkers (Aβ42, t-tau, p-tau)

## Differential diagnostic biomarkers for central nervous system disease categories with similar symptoms

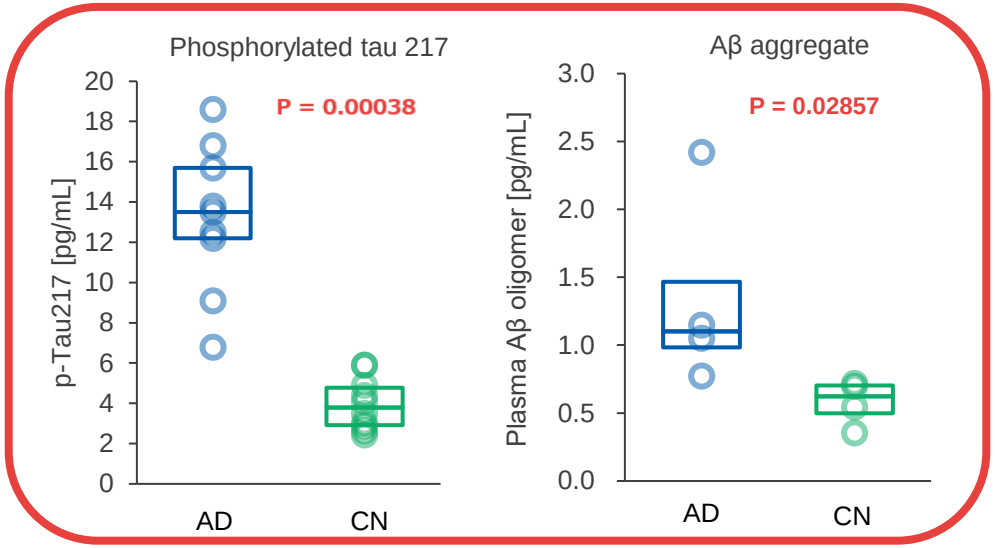
| Disease | Aβ42 | t-tau | p-tau181 |
|---|---|---|---|
| Alzheimer's disease | ↓/↓↓* | ↑ | ↑ |
| Acute-stage cerebral infarction | ― | ↑-↑↑ | ― |
| Alcohol-related dementia | ― | ― | ― |
| Creutzfeldt-Jakob disease | ↓ | ↑↑↑ | ― |
| Depression | ― | ― | ― |
| Lateral anterior cephalalgia | ↓ | ↑ | ― |
| Lewy body dementia | ―/↓* | ↑ | ↑ |
| Inflammation of the central nervous system | ↓ | ― | ― |
| Normal aging | ― | ― | ― |
| Parkinson's disease | ― | ― | ― |
| Vascular dementia | ↓-↓↓ | ↑ | ― |

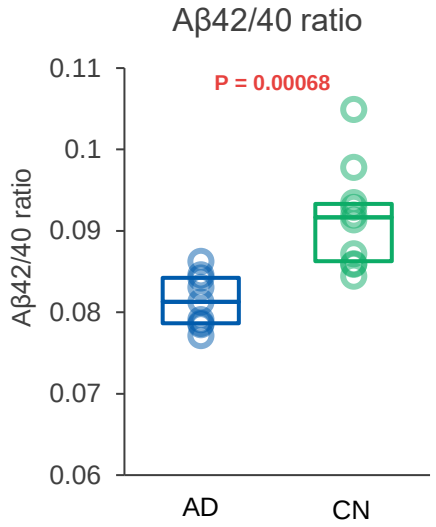
―: No change, ↑: Increase, ↓: Decrease (Humpel et al., Trends Biotechnol 1 26 2011, revised, *Steenoven et al., Alzheimers Res Ther 11 83 2019)

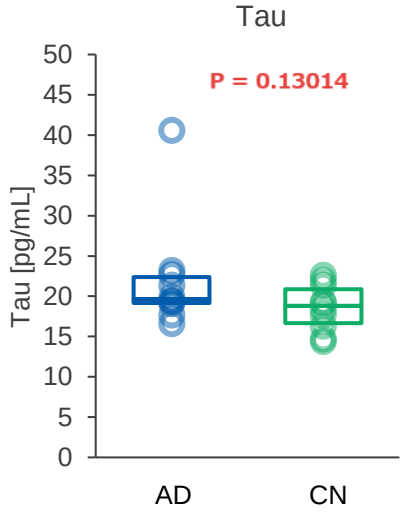
# Blood Biomarker Panel Parameters: Review Status

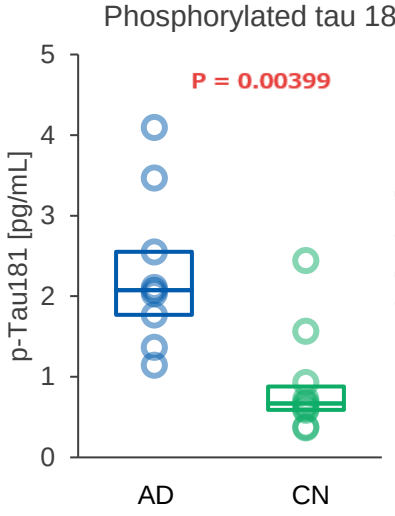
## Construction of BM (P-tau 217, Aβ polymers, etc.) panelized reagents based on the latest knowledge

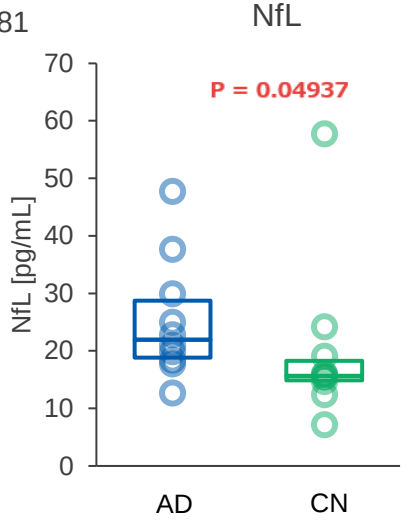
●: Alzheimer's disease
●: Normal cognition



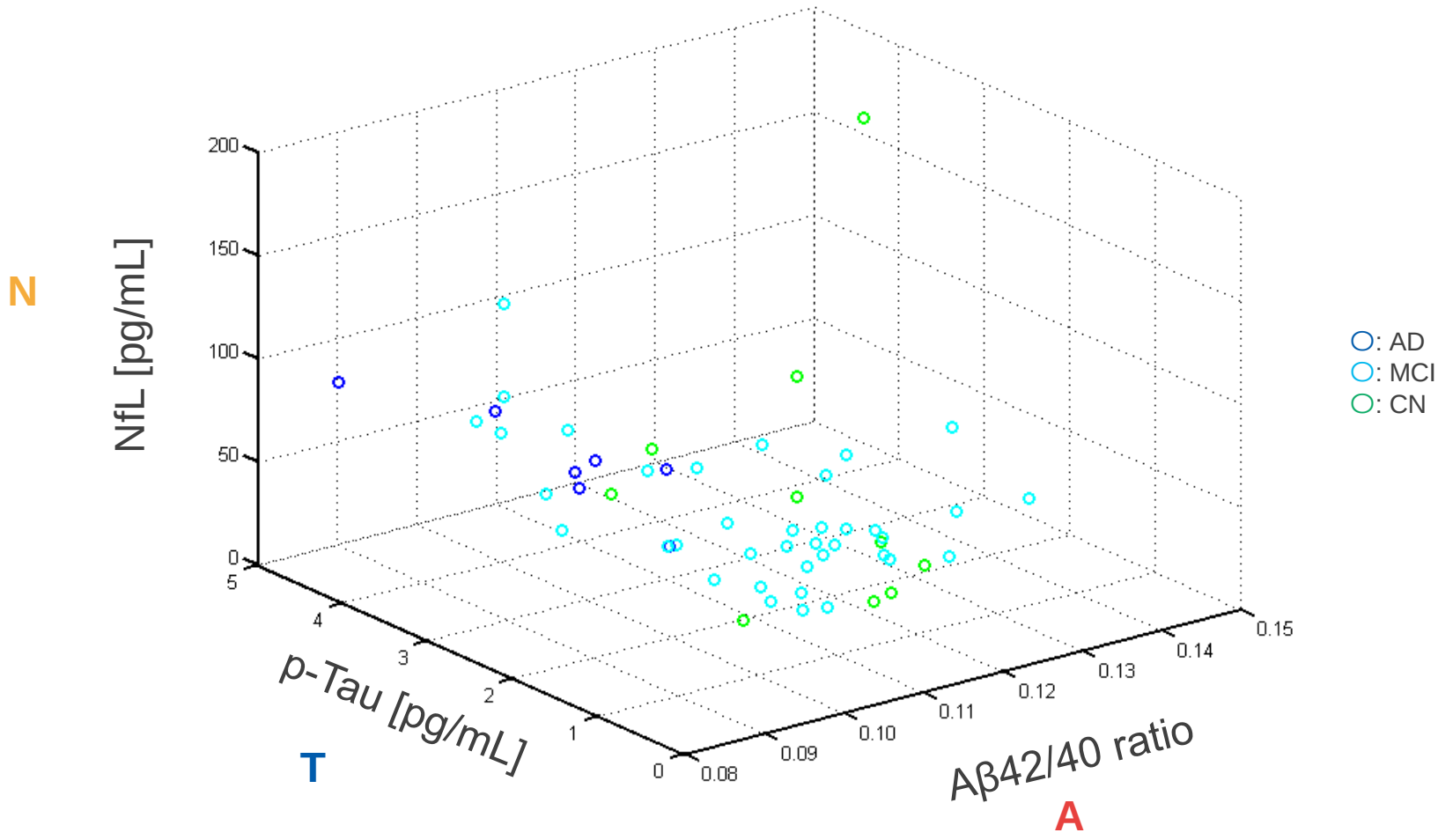




*data checked internally

# Use of Blood Marker Panels to Classify Dementia Progression: Review Status

## The Possibility of Classifying the Progression of Dementia by Quantitative BM Measurement




*data checked internally

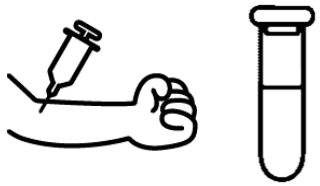
# Use of Blood Marker Panels to Classify Dementia Progression: Review Status

Projection only

# Sysmex's Initiatives

Along with efforts to get disease-modifying drugs approved, we are building testing systems in these regions. Regulatory application (Japan) and the BDD application (United States) have been completed, as well as preparing for LDT (United States).

## Blood testing



System advantages
- Automated medical testing systems
- Quantitative/rapid

Clinical research advantages
- Low level of invasiveness (frequency)
- Multi-marker

(Therapeutic target molecules, etc.)

**Moving to the stage of establishing value through market co-creation and awareness activities**

Screening/ patient stratification

Selection of treatment and prevention methods

Applied for approval in Japan (12/28)
**"Assay Kit That Assists in Identification of Amyloid Beta (Aβ) Accumulation in the Brain"**

Started preparing for regulatory filing in the United States (BDD application completed)

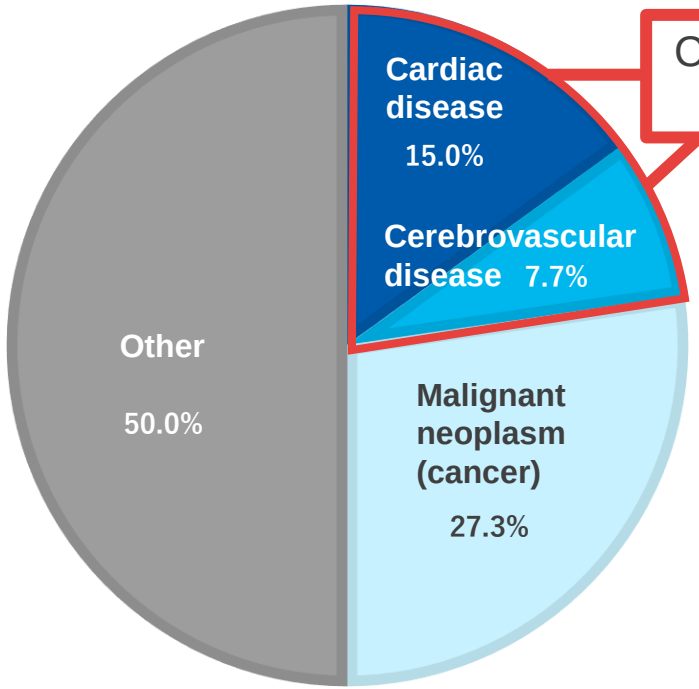
Lab assay service (LDT) to be launched in the United States (FY2022)
- Large commercial labs, etc.
- Sysmex Inostics Inc.

# Initiatives for Cardiovascular Disease

## (Development of Technology to Measure HDL Function)

# Current Status of Cardiovascular Disease

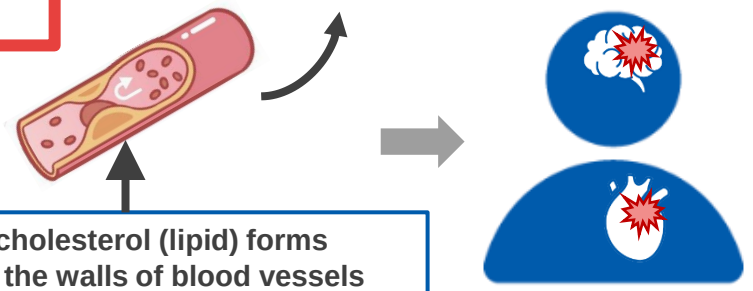
**Cardiovascular disease, the second leading cause of death after cancer, is mainly caused by arteriosclerosis, and lipid management is important to prevent its onset and progression.**




Cardiovascular disease

Overview of the Annual Report on Monthly Demographic Statistics 2018 (Approximations) (partially revised)

**(Good) HDL collects this cholesterol and sends it to the liver**



**LDL (bad) cholesterol (lipid) forms clumps on the walls of blood vessels and narrows the inside of the arteries.**

Cerebrovascular disease (cerebral infarction)

Cardiac disease (myocardial infarction)

Lipid control parameters

- LDL-C
- Non-HDL-C
- TG
- HDL-C

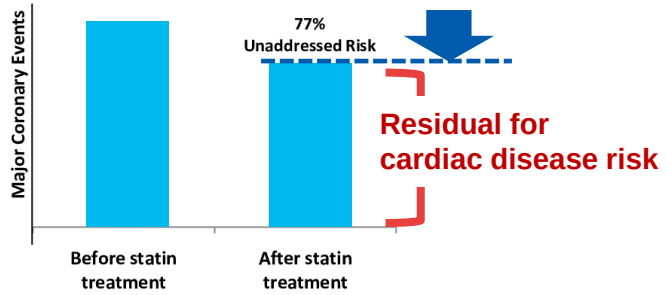
**Treatment is focused on controlling LDL-C levels, but the risk of developing the disease is not sufficiently controlled.**

## Treatment Methods

Therapies focus on lowering LDL-C

- HMG-CoA reductase inhibitors
- Small intestinal cholesterol transporter inhibitors
- PCSK9 inhibitors
- MTP inhibitors, etc.

## Effectiveness in LDL-C lowering therapy

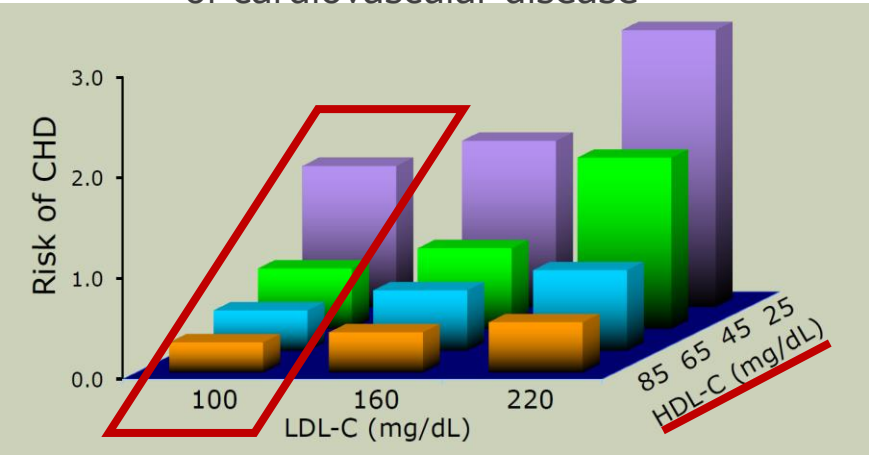



Lancet. 2005;366:1267-1278. (partially revised)

# Current Status of Therapeutic Drugs and Test Targeting HDL

**HDL-C is an indicator of heart disease risk, but HDL-C-increasing drugs failed to show the expected effect and were discontinued. Drugs and tests targeting HDL Function are under development.**

low HDL-C are associated with a high risk of cardiovascular disease




Gordon T et al. Am J Med 1977;62:707-714. (partially revised)

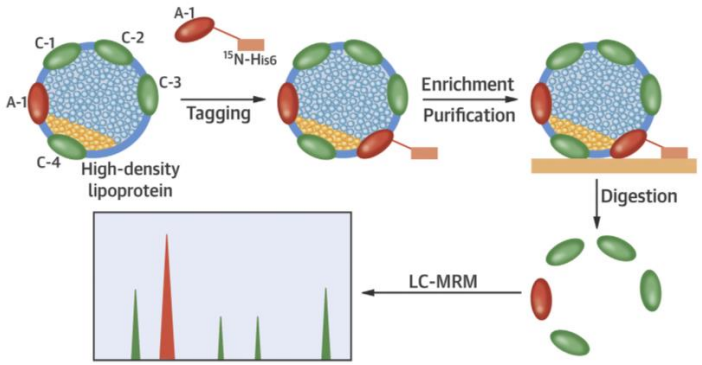
Drugs to increase HDL-C do not reduce risk of cardiac disease, so development has been halted.

| Drug | Mechanism of action | Screening status | Note on effects |
|---|---|---|---|
| Torcetrapib | CETP inhibition | Development halted | **Quantitative improvement** HDL-C increased around 30–60% |
| Dalcetrapib | | | |
| Evacetrapib | | | |
| Anacetrapib | | | |
| CSL-112 | Reconstructed HDL | Phase III (~2023) | **Qualitative improvement** (Approximately 3-fold increase in function) |

## Examples of clinical applications of HDL function tests

HDL*fx* Test (Cleveland Heart Lab (Quest))

- Measurement target: Five HDL constituent proteins
- Measurement principle: Mass spectrometry
- Clinical application: Assess risk of cardiac disease (coronary artery disease)
  Note: From 2020, provided as LDT in the United States by Quest

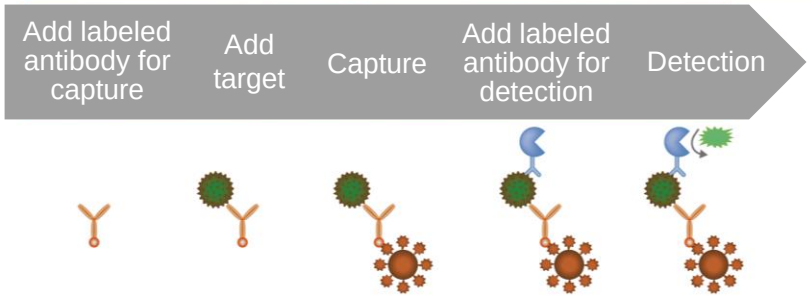


# Sysmex's Initiatives: HI-1000

(An Instrument for Research Use Incorporating Highly Sensitive Technology, the iCT Method)

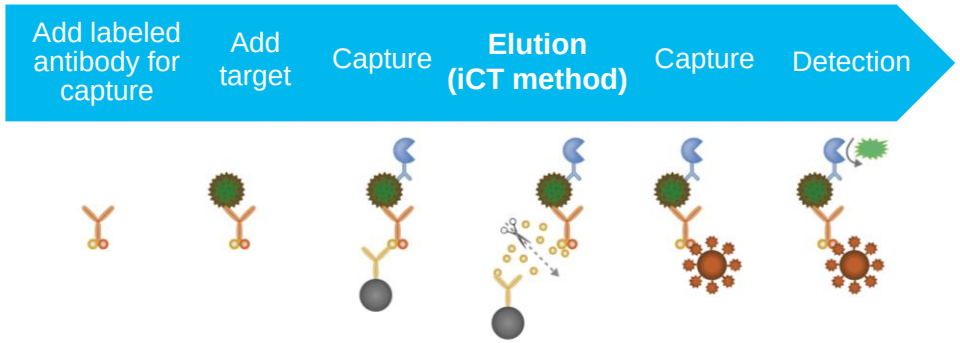
## Flexible, highly sensitive and automatic measurement possible using the HI-1000

**Typical Immunoassay**



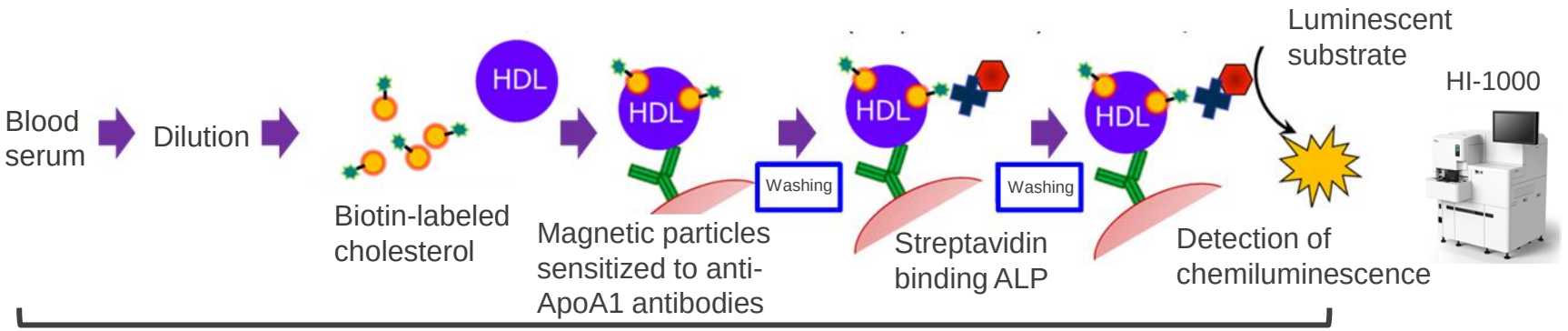

HI-1000

**Immunoassay incorporating the iCT (immune complex transfer) step***




*Pretreatment step can also be added

## Establish a measurement system for HDL function (cholesterol uptake capacity, or CUC)






HI-1000

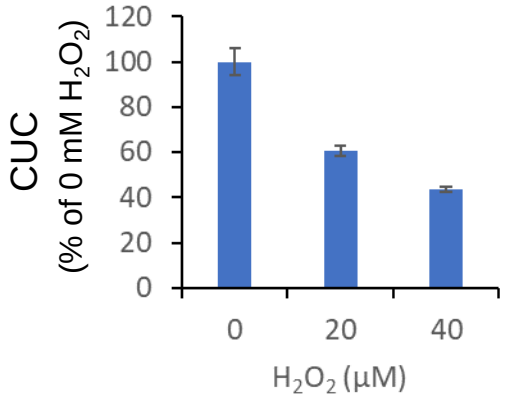
### Characteristics

- Fully automated measurement
- Throughput: 17 minutes/test (up to 33 tests/hour)
- Measurement precision: <10% (range of variability)

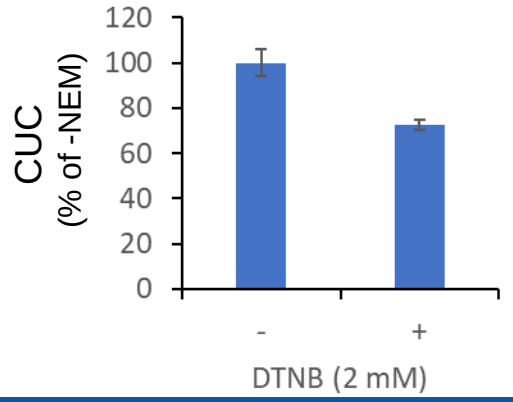
# Validation of HDL Function Using Fully Automated Measurement Method (CUC Method)

## The CUC method can detect variations in HDL(Reproduction of Physiology Function)

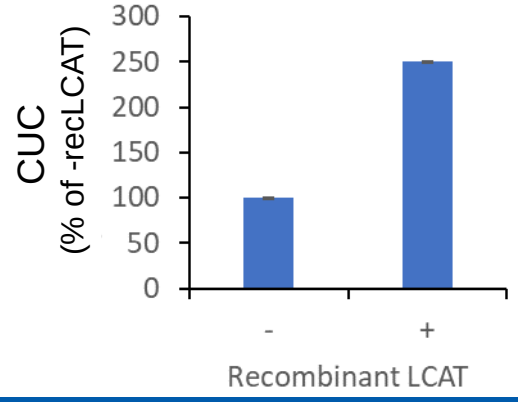
Functional decline due to oxidation




Suppression of function due to inhibitors




Enhancement of function due to addition of activating factors




*data checked internally

## Confirmed that trans fatty acids, which increase cardiovascular disease risk, are associated in the HDL Function Understanding some of the mechanisms that define HDL Function may lead to the development of new therapies

*nutrients* MDPI

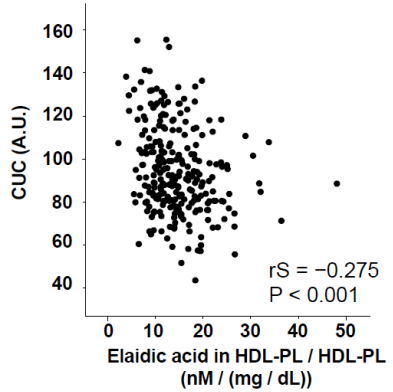
*Article*

**Effects of Elaidic Acid on HDL Cholesterol Uptake Capacity**

Takuya Iino [1,2], Ryuji Toh [3,*], Manabu Nagao [3], Masakazu Shinohara [4,5], Amane Harada [2], Katsuhiro Murakami [2], Yasuhiro Irino [2], Makoto Nishimori [1], Sachiko Yoshikawa [1], Yutaro Seto [1], Tatsuro Ishida [1] and Ken-ichi Hirata [1,3]

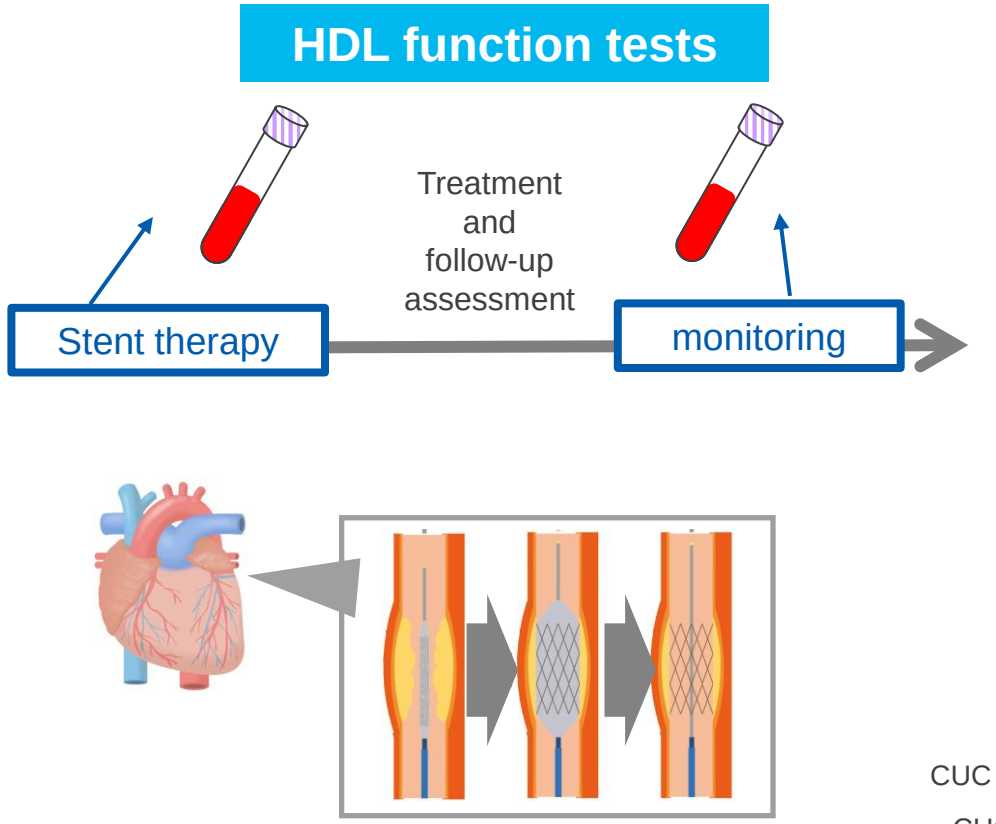
Nutrients. 2021;13(9):3112.

HDL with higher trans fatty acid content tends to have lower function.

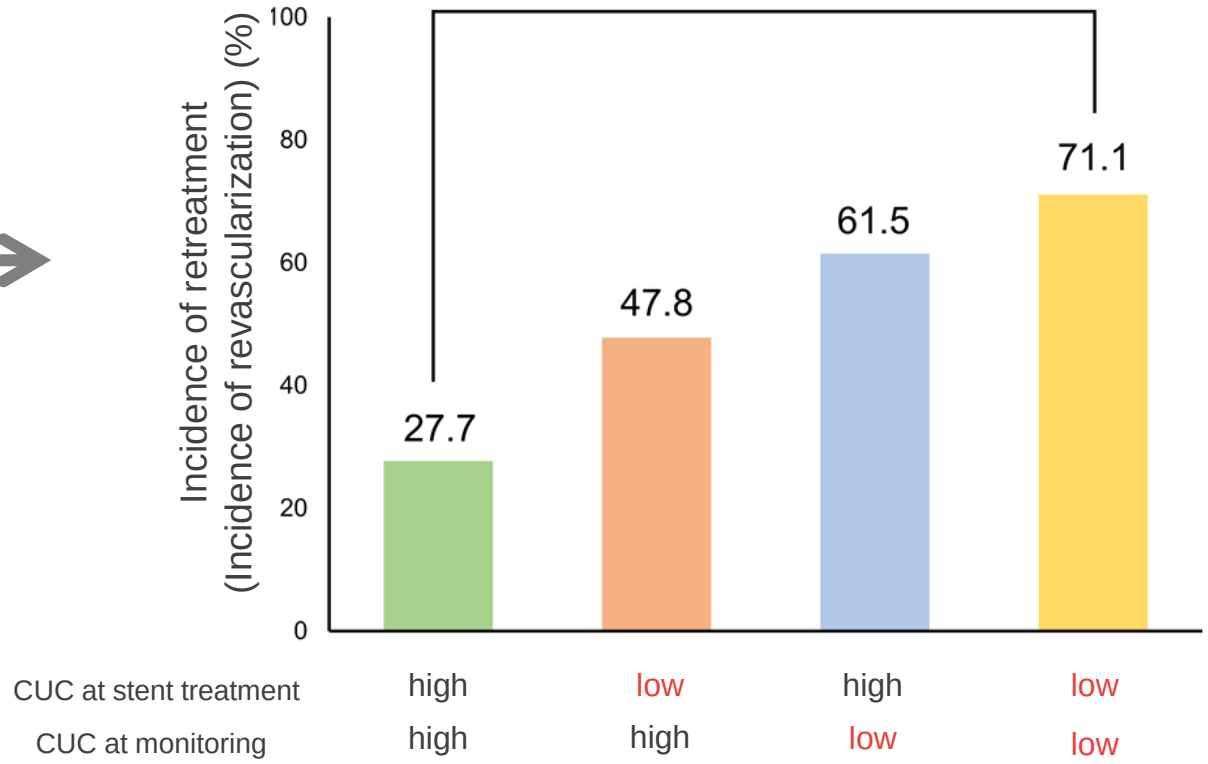


# Verification of Clinical Utility for HDL Function Tests (CUC Method)

## Confirmed the Possibility of Providing a Simple Test for Follow-up After Cardiac Catheterization.




Odds ratio: 6.06, 95% confidence interval: 2.44-15.1, p < 0.001 n=128



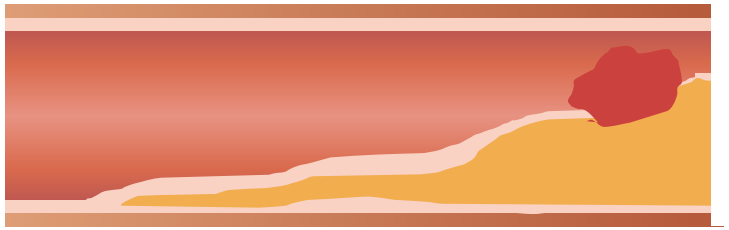

The group of patients with low CUC values at the time of treatment and monitoring were at a higher risk of retreatment than the group with high CUC values at both time points.

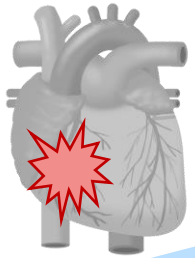
Atherosclerosis. 2022 Jan 24

# Future Directions: Expansion of Biomarkers Related to Cardiovascular Diseases

**Promoting research and development of novel biomarkers for the total management of cardiovascular diseases**

Metabolic abnormality → Arteriosclerosis → Angina pectoris → Myocardial infarction → Pathological remodeling / Myocardial fibrosis → Heart failure





Risk assessment of disease onset, early intervention | Disease identification | Malignancy assessment | Therapeutic drug selection

| | Risk assessment of disease onset, early intervention | Disease identification | Malignancy assessment | Therapeutic drug selection |
|---|---|---|---|---|
| **Blood testing** | Lipid markers<br>**HDL function***<br>T-Cho、LDL-C、HDL-C、TG<br>Vascular calcification markers<br>(feasibility study)*<br>Coagulation molecular markers<br>TAT、PIC、TIM、tPAI・C | Myocardiopathy marker<br>cMyC*<br>Troponin<br>CK-MB | Fibrosis Marker<br>M2BPGi*<br>Myocardium stress marker<br>NT-proBNP | Cardiac amyloidosis markers<br>(feasibility study)* |
| ***In vivo* testing** | Vascular endothelial function test<br>Blood pressure pulse wave test<br>Ultrasound scan (vascular echo) | CT<br>Electrocardiogram<br>Catheter examination (coronary angiogram) | MRI | Ultrasound scan (echocardiogram) |

* R&D parameters

# Glossary

# Glossary

| | |
|---|---|
| AML | “Acute myeloid leukemia.” |
| Amyloid-β | 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. |
| Annotation | In the field of AI, the creation of teaching data (correct answers, labels) to train machine-learning models. |
| APP | An acronym for “amyloid β precursor protein,” APP normally plays an important role in nerve growth and repair. (When cleaved by α secretase, APP is harmless, but when cleaved by β or γ secretase, APP produces amyloid βprotein, which is toxic to nerve cells.) |
| BDD | “Breakthrough Device designation” is a system established by the U.S. Food & Drug Administration to promote the development and review of devices that have the potential to show greater therapeutic or diagnostic efficacy than existing devices for serious diseases, and to deliver new devices to patients more quickly. |
| Cancer genome profiling | Analysis of information about genes significant to cancer diagnostics by looking at mutations, amplifications, and fusion of multiple genes in cancer tissue. |
| Cardiac amyloidosis | A disease in which abnormal proteins called amyloids are deposited in the heart, causing abnormal heart function, arrhythmia and heart failure. |
| Caresphere | Caresphere utilizes IoT and the cloud to establish a platform for the real time linking and analysis of a variety of information managed using testing instruments and clinical laboratory information systems. It is a new network solution that provides support for increasing the operational efficiency of professionals involved in testing and healthcare, enhancing quality and raising patient satisfaction. |
| CLIA | Laboratories with U.S. CLIA (Clinical Laboratory Improvement Amendment) certification are required to undergo periodic inspections to ensure quality maintenance, and having such registration indicates that a lab meets world-class technology standards for quality assurance and sufficient reliability in genetic analysis. |
| cMyC | A myocardial-specific protein that is released more rapidly after acute myocardial infarction. |
| ctDNA | Cancer derived DNA circulating in the blood. A focus of growing attention as a non invasive cancer biomarker for testing using liquid biopsy. |
| CUC | An acronym for “cholesterol uptake capacity,” CUC means the ability of HDL to take up cholesterol. |

# Glossary

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| Disease-modifying drug | Drugs that inhibit the recurrence rate or slow the progression of disease by focusing on the molecular pathology of the disease. |
| Drug susceptibility test | A test to determine the efficacy of various antimicrobial drugs against pathogenic bacteria in a sample. |
| 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. |
| HDL | An acronym for “high-density lipoprotein,” HDL has the role of collecting excess cholesterol in the vessel wall and returning it to the liver. |
| IRD | Inherited Retinal Disease. Hereditary diseases characterized by abnormalities in the photoreceptor cells or epithelial cells that adhere to the retina. |
| IVD | Acronym for “in vitro diagnostics.” Refers to in vitro diagnostic pharmaceuticals and products that have received regulatory approval. |
| LDT | Acronym for “laboratory developed test.” LDTs, often testing methods that have not received regulatory approval, include highly sophisticated and complex gene testing that can only be performed in specific clinical testing labs. |
| Liquid biopsy | This is a general name for technology using blood or body fluid samples for diagnosis and the prediction of treatment impacts rather than through the conventional practice of tissue biopsy, in which diagnosis is performed on diseased tissue that has been collected. Liquid biopsy is less invasive than tissue biopsy, but more highly sensitive detection technologies are required. |
| MRD | An acronym for “minimal residual disease,” MRD means the small number of cancer cells that remain in the body during and after treatment and that may eventually cause the disease to recur. |
| NCC | An acronym for “National Cancer Center Japan.” |
| NGS | Acronym for “next-generation sequencer.” May also refer to a next-generation sequencer, an instrument for reading gene base sequences at high speed. |

# Glossary

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| Patient journey | The process from the time when the patient is healthy to the time after the illness, including examination, diagnosis, treatment, prevention of recurrence and severity of illness, and end of life. |
| Personalized medicine | This type of medicine goes beyond the conventional practice of providing selected predetermined or uniform treatment for a given disease. Instead, the selection of treatment is optimized for individual patient characteristics, based on gene and other testing data. |
| Population health | Medical measures aimed at efficiently improving the health of an entire population having common elements （region, race, illness, etc.). |
| 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. |
| Primary care | The initial care provided at clinics or other locations when a patient first falls ill. |
| PSS | Acronym for "Plasma Safe Sequencing." This pretreatment technology is used to discern between gene mutations and read errors by attaching tags to genes to be amplified. |
| RAS | One of the gene that is known to cause cancer when it mutates. |
| RWD | An acronym for "real-world data," RWD is a generic term for medical data obtained in daily clinical practice, such as data from electronic medical records, medical checkups and wearable devices. |
| Self-medication | Taking responsibility for your own health and examine and treat minor physical ailments on your own. |
| Sentinel lymph node | A lymph node that cancer cells reach first. |
| Tau | A microtubule associated protein that exists in central nerve cells. Along with senile plaque, inordinately phosphorylated deposits of tau protein (neurofibrillary tangle) can be observed in the brains of patients with Alzheimer's disease. |
| TTL | An acronym for "total tumor load," TTL is the total number of CK19 mRNA copies from OSNA in sentinel lymph node. |
| Wake-on-LAN technology | A function that allows a computer connected to a communication network to be remotely powered up from another computer. |

# Lighting the way with diagnostics