The 20th R&D Meeting

March 3, 2023
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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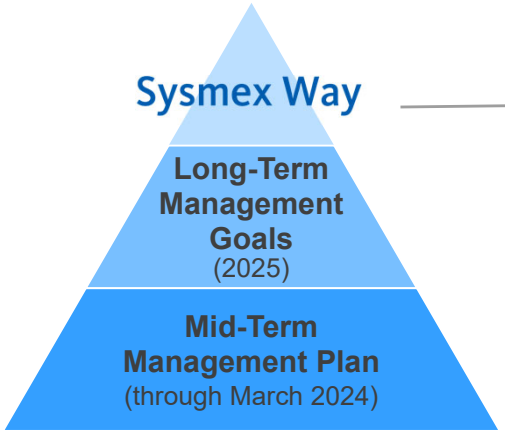
Opening Presentation

Hisashi Ietsugu
Chairman and CEO

Sysmex's Corporate Philosophy and the Source of Value Creation



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

Source of value creation

Technology platforms

- **Cell measurement**
- **Protein measurement**
- **Gene measurement**

Provision of products, services and quality

- **Instruments**
- **Specialized reagents**
- **IT / software**

+ **Quality control**

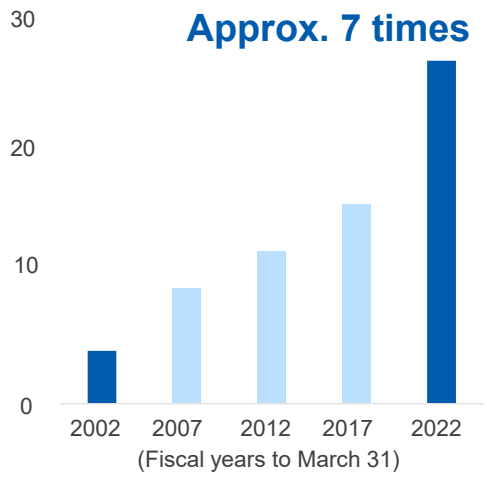
Changes in the Operating Environment and Initiatives over the Past 20 Years

	2000s	2010s	2020s
Healthcare	✓ Introduction of molecularly targeted therapeutic drugs ✓ From treatment to prevention (lifestyle diseases)	✓ Growing healthcare disparities among countries and regions due to increasingly sophisticated testing ✓ Further increases in medical expenses	✓ COVID-19 Pandemic ✓ Adoption of online medicine ✓ Optimization of medical expenses
Technology	✓ Sequencing of the human genome ✓ Rise of gene detection technology ✓ Electronic medical charges and other use of ITC in healthcare	✓ Rise of next-generation sequencers ✓ Leap forward in high-speed communication technology ✓ Advances in automation technology	✓ Realization of personalized diagnostics ✓ Implementation of liquid biopsy ✓ Implementation of remote and virtual technologies
Sysmex	✓ R&D expenses: Approx. ¥4.0 billion (FY2001 Results) ✓ Opening of Central Research Laboratories ✓ Opening of Technopark	✓ Liquid biopsy initiatives ✓ Expansion of unique testing (OSNA™, hepatic fibrosis markers, etc.) ✓ Reinforcement of IT products ✓ Strengthening of global development structure	✓ R&D expenses: Approx. ¥33.5 billion, (FY2022 Forecast) ✓ Global rollout of the XR™-Series ✓ Advances in unique tests (testing for Alzheimer's disease, etc.)

R&D Investment Trends

R&D Expenses

(Billions of yen)

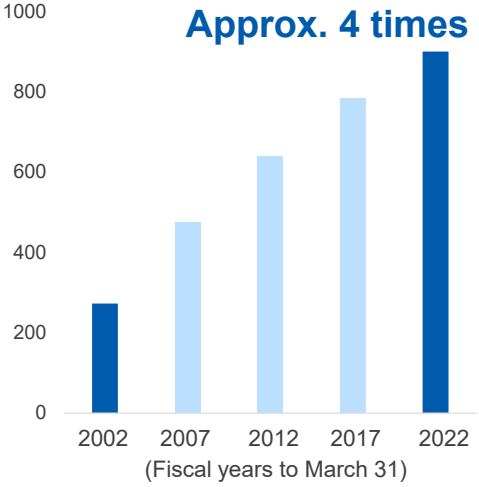


Total investment over the past 20 years: Approx. ¥300 billion

- Advances in the hematology field (XE-Series→XN™-Series→XR-Series)
- Expansion of the immunochemistry and life science fields

R&D Personnel*

(People)



Expansion to around 1,000 people over the past 20 years

- Acquisition and development of diverse specialized human resources to enhance competitiveness (mechanics, biology, software, etc.) *only S-Corp employees

R&D Locations

- 2000 Japan (Central Research Laboratories: R&D in liquid biopsy and digital medicine)
- 2006 Germany (RDCE: R&D in liquid biopsy)
- 2008 Japan (Technopark: R&D CoE hub)
- 2009 China (SWX: R&D base mainly in the immunochemistry field)
- 2013 United States (RDCA: R&D in immunochemistry)
- 2019 Japan (Bio-diagnostic reagent base: Development of raw materials and production technologies)
- 2020 United Kingdom (RDCUK: R&D in gene testing)
- 2022 Singapore (RDCAP: Digital medicine, researching regional testing needs)

Opening of bases in six countries in the past 20 years

- Ascertaining leading-edge technologies and customer needs globally

Sysmex's Objectives

Core Competencies

No. 1 share of the global market in hematology field

Global sales and service structure

R&D capabilities
(Instruments, Reagent, IT)

Production structure

Diverse human resources

Materiality and Contributing SDGs

Mission : Shaping the advancement of healthcare.

Diagnostics business

- Expansion of immunochemistry test parameters
- Further involvement in the hematology field (FCM)

Diagnosis + patient management

- Personalized medicine (cancer, dementia)
- Rare diseases (such as hereditary diseases)

Digital transformation

- Caresphere™
- Digital medicine

Challenges in new domains

- Regenerative medicine
- Medical robotics

Extend healthy lifespans

Improve accessibility to healthcare

Increasingly sophisticated healthcare

Optimization of medical expenses

2

R&D Initiatives under the Mid-Term Management Plan

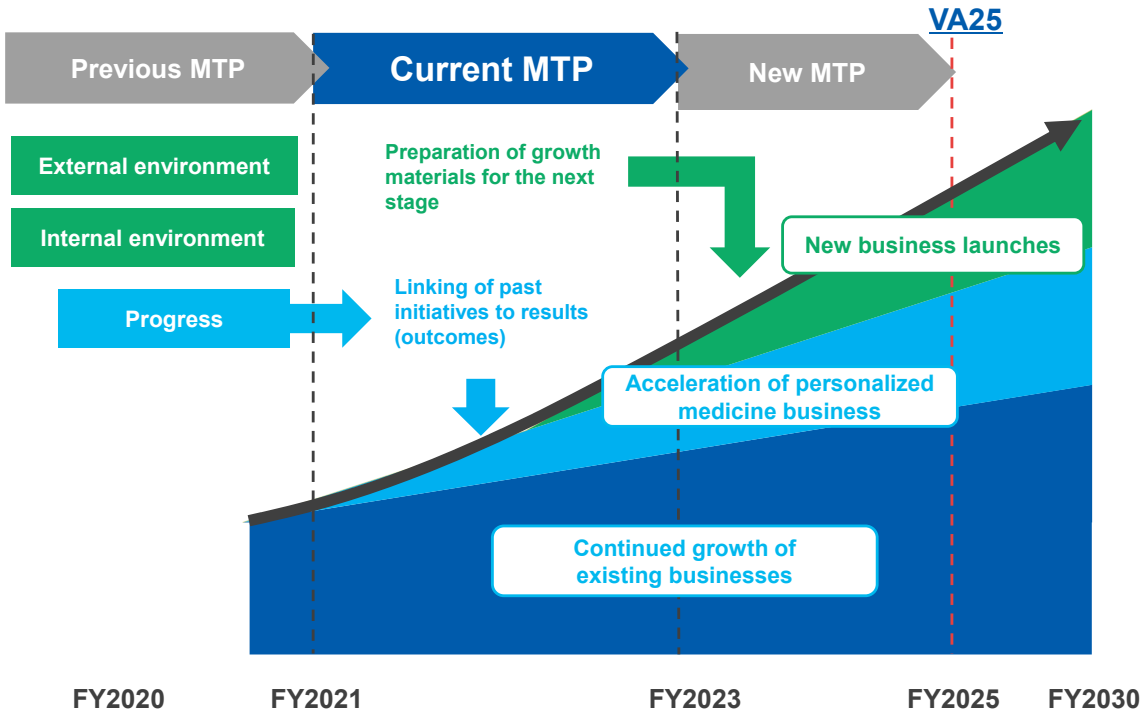
(Fiscal Years Ending March 31, 2022 to 2024)

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

(1) Initiatives Targeting Digital Medicine

(2) Initiatives Targeting Regenerative Cell Medicine

Overview of the Mid-Term Management Plan（MTP）



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

Preparation for the next stage

- ## Digital medicine

  Creating new businesses using testing data

- ## Regenerative and cellular medicine

  Entering the regenerative and cellular medicine business by utilizing cell testing and cell handling technology

(1) Initiatives Targeting Digital Medicine

Decentralization of Medical Functions

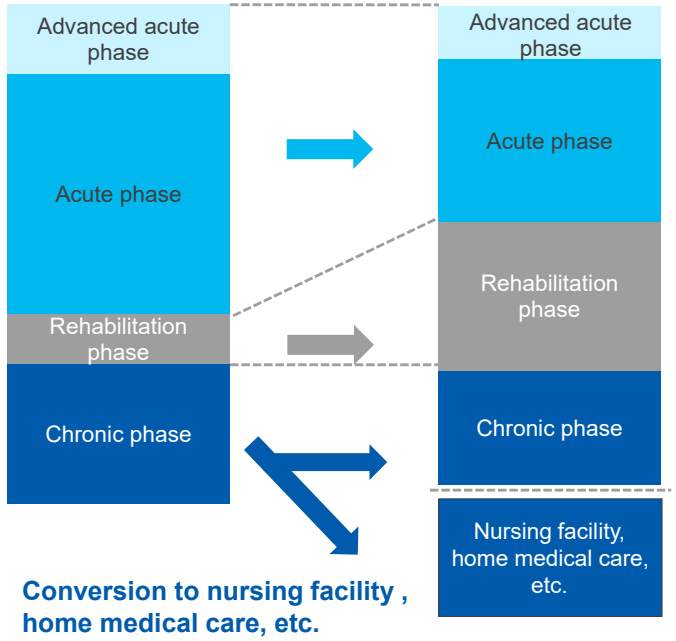
Progression of aging and soaring medical expenses in worldwide

To make effective use of limited medical resources

- Decentralization of medical functions
- Linkage of medical information
- Utilization of personal data

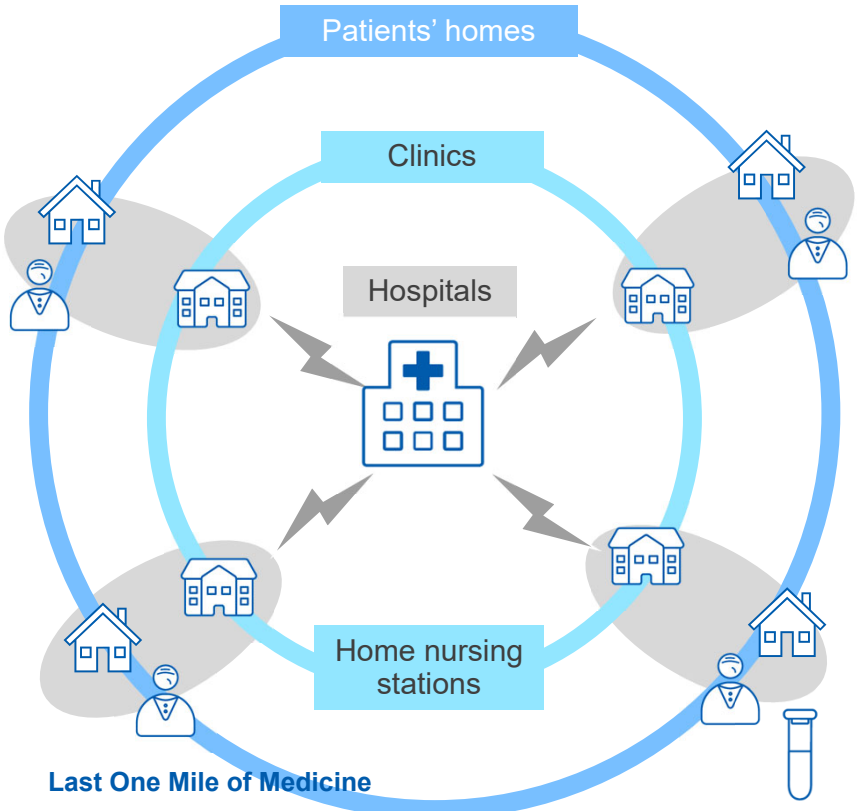
Digital formation of Medicine

Decentralization of medical functions



Conversion to nursing facility , home medical care, etc.

Regional Medical Liaison



Sysmex's initiatives

- **Decentralization of medical functions**

  Development of devices for testing at clinics and at home medical care

Compact Immunoassay System

Instrument & Cartridge for antimicrobial susceptibility testing (Sysmex Astrego AB)

- **Linkage of medical information**

  Digital platform for community collaboration

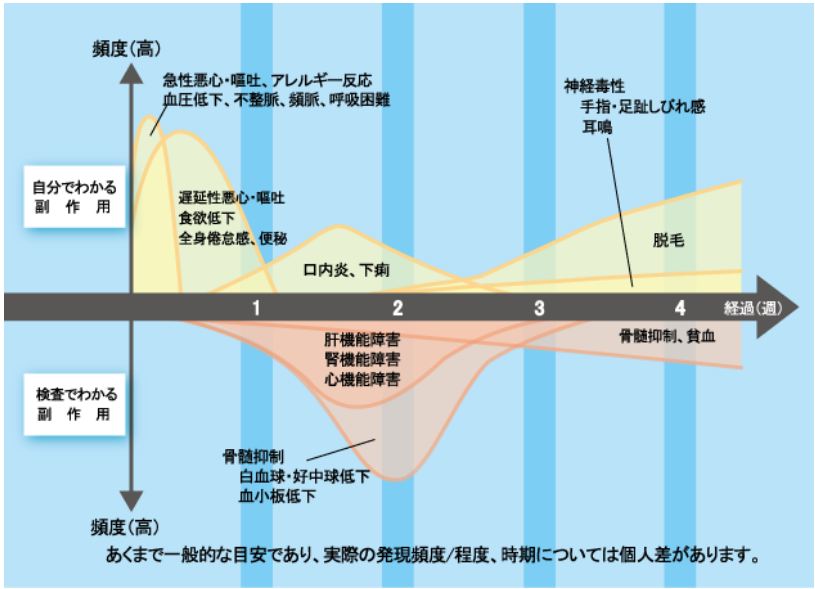
- **Utilization of personal data**

  Construction and analysis of test database (including genome information)

(Reference) What's Happening in Hospitals and Home Nursing (Anticancer Drug Care)

Comprehensive medical care, such as recovery prospects, side effects, and life planning, is necessary, but hospitals cannot ascertain the status of at-home patients and do not provide them with treatment information.

■ Side effects after administration of cancer drugs



Source: National Cancer Center Cancer Information Service
*Posting in Japanese only due to rights

■ Issues with hospital and community care

Outpatient hospitals

Patient concerns about daily side effects of anticancer drugs

- ✓ Inability to discuss the pain of side effects.
- ✓ Trouble explaining loss of appetite and persistent diarrhea.
- ✓ Inability to express concern about medical expenses.

Home nursing

Home nurses' concerns

- ✓ Don't know why the current treatment method was prescribed.
- ✓ Don't know if current symptoms are due to exacerbation of the disease or drug side effects

Introduction of D’PULA Medical Solutions

Established in June 2020 as a joint venture between Sysmex and OPTiM
with the aim of creating new digital health

sysmex × OPTiM

D’PULA Medical Solutions Corporation

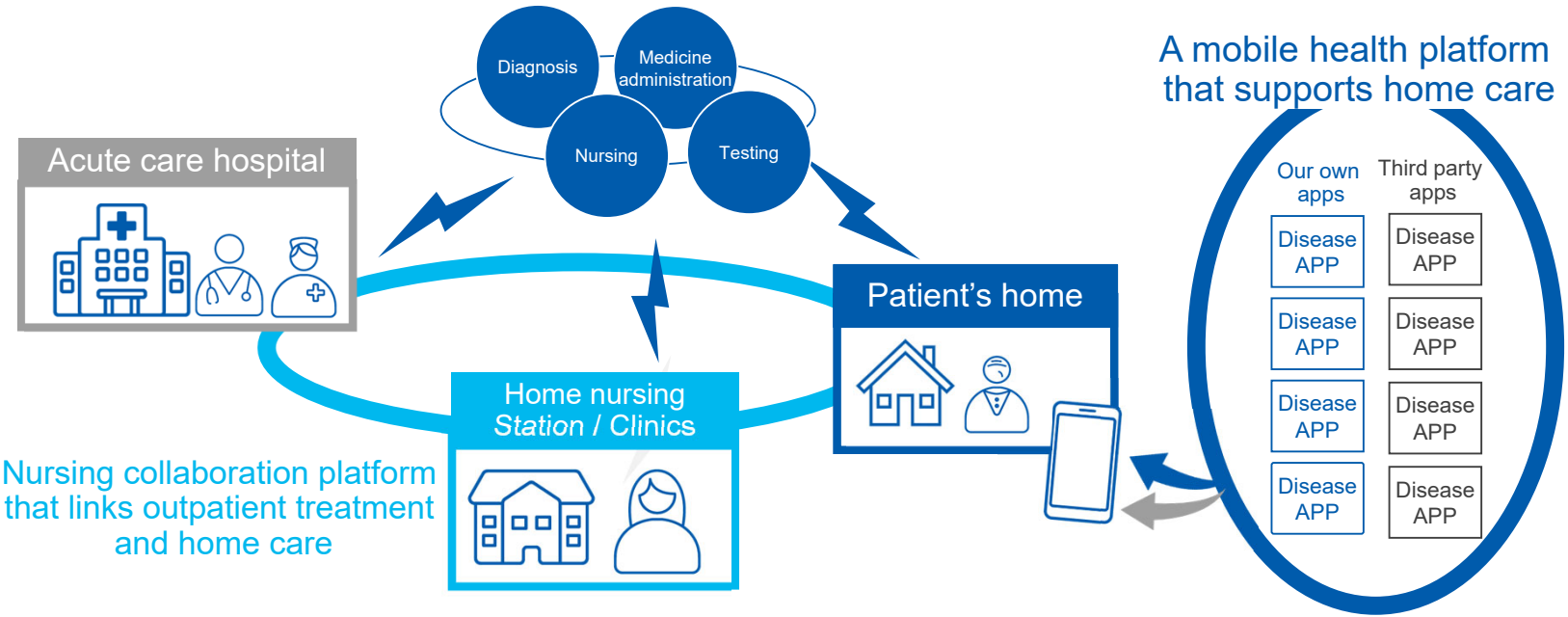
Corporation Philosophy

Connecting Lives, Connecting Healthcare

"D'PULA": Derived from the “D” in “Digital/Data” with the Greek word ” γέφυρα” (pronounced “gepura”) meaning “bridge”.
Through evolving digital technology, we will create a new dimension of medical care and link it through to the next generation.

D'PULA's Digital Platform

A digital platform that utilized D'PULA's AI, IoT, & ICT technologies and Sysmex's testing technology to achieve the triad of hospital treatment, home-visit nursing, and home care.



“kaleido TOUCH™”, a Nurse-to-Nurse Collaboration APP that Connects Hospitals and Homes

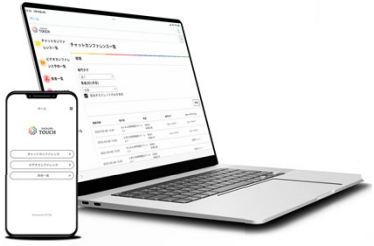
Hospital nurses

Test information

Medication status

Side effects

kaleido TOUCH™



Medical treatment information

Prescription information

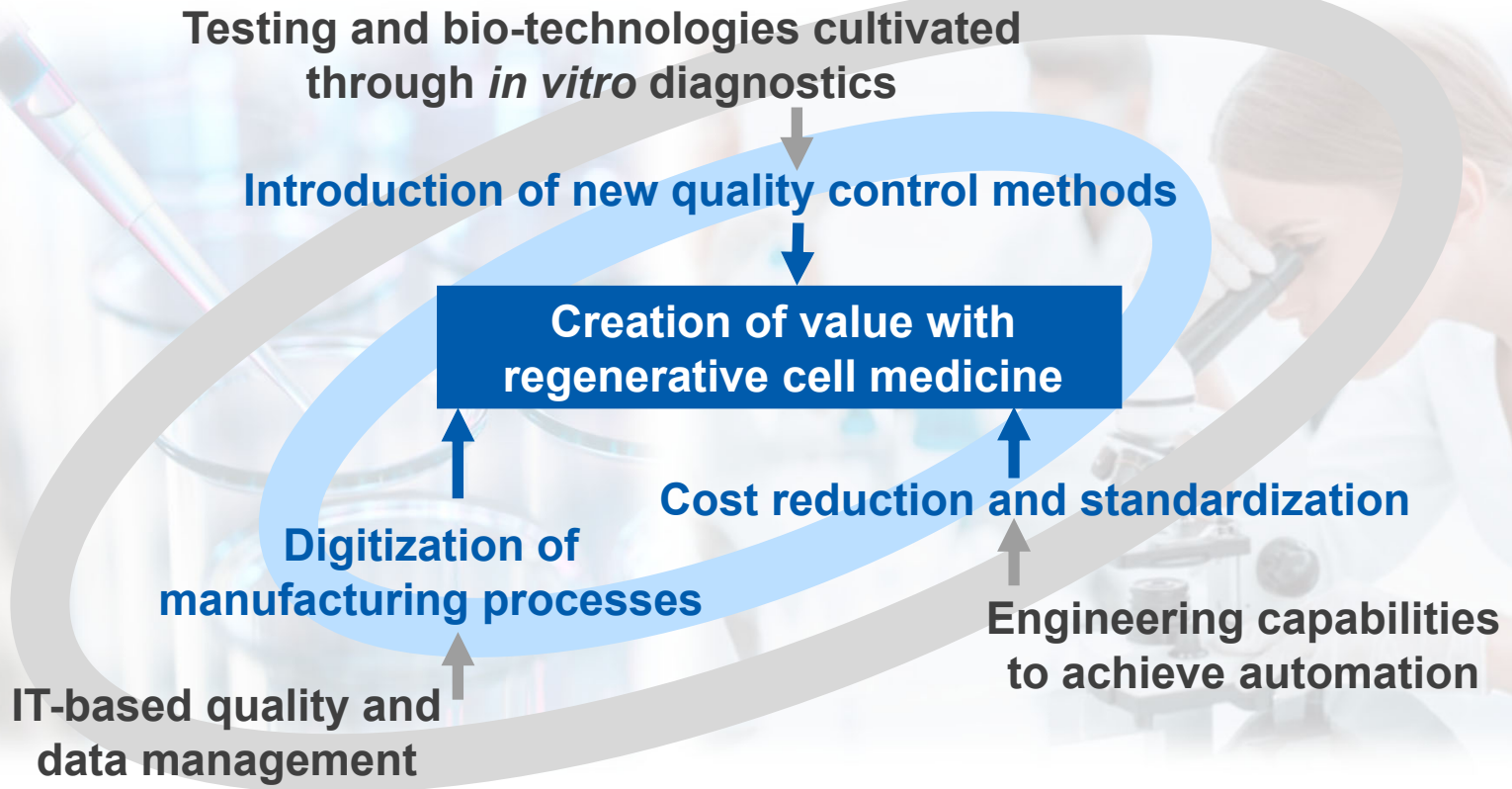
Treatment plans

Visiting nurse

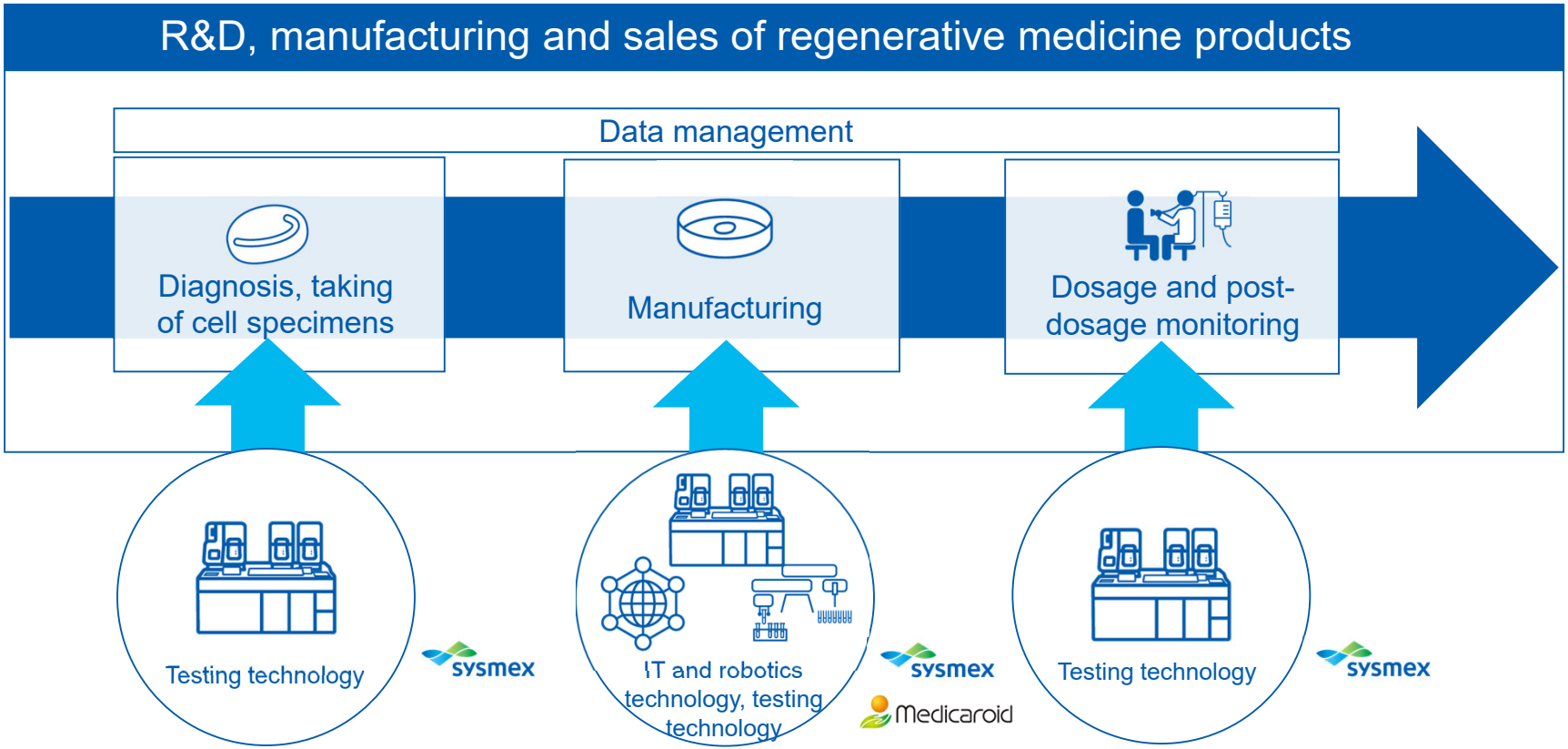
kaleido TOUCH is a trademark of D'PULA Medical Solutions Corporation.

(2) Initiatives Targeting Regenerative Cell Medicine

Deployment of Our Technologies in Regenerative Cell Medicine



Helping to Create Value across the Entire Value Chain for Regenerative Cell Medicine



Our Technologies and Value Provided

Our technologies will be used in all aspects of regenerative cell medicine.

Evaluation with sophisticated equipment at the medical device level (cell counting by absolute quantification)

More accurate measurement of blood cells

Automated protein assay using HISCL™ fully automated immunoassay systems

Achieving Fully automation of ELISA protein assay

Assessment of the amount of undifferentiated iPS cells using miRNA in culture medium

Non-destructive negative testing for iPS cell contamination

Immunological synapse study using molecular imaging FCM (MI-1000)

Pre-transplant compatibility testing for allogeneic transplants

Robotics technologies to achieve laboratory automation

Automation of cell production and quality inspection

Caresphere and other systems for data aggregation, management and analysis

Linkage of manufacturing data

Establishment of AlliedCel Corporation

AlliedCel

Establishment of a joint venture* aimed at R&D and the early-stage commercialization of regenerative medicine products

Unlocking the potential of cells using hematopoietic stem cell proliferation technology to provide new therapeutic opportunities

sysmex

Track record and expertise in quality inspection and IoT cultivated through the diagnostics and medical robotics businesses

JCR Pharmaceuticals

Expertise in the development, manufacture and sale of regenerative medicines
First sales in Japan of regenerative medicines from other families

*A 50:50 joint venture, established October 3, 2022. Each partner has dispatched one person with the right of representation.

Contribution to Hematopoietic Stem Cell Transplantation Implemented by AlliedCel

Target for FY2023: Define TPP* and start non-clinical trials by integrating the cell handling technologies of both companies.

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Blood cell/hematopoiesis stem cell analysis technology

AI/IoT data management

Lab automation

Cold chain technology

AlliedCel

Achievement of transplantation Treatment via hematopoietic stem cell expansion technology

JCR Pharmaceuticals

Cell amplification culture technology

Regenerative medicine product manufacturing expertise

Know-how of clinical development and regulatory affairs for regenerative medicine products

*TPP：Target Product Profile

Timeline in the Area of Regenerative Cell Therapy Business

Aim to become a Solution Provider of cell manufacturing by FY2025, and to launch regenerative medicine products by FY2030 using accelerated approval programs, through synergies of AlliedCel, Sysmex and Medicaroid.

Development of competitive regenerative medicine products

Creation of regenerative medicine and cell medicine

Innovative cell manufacturing using robotics and IT technology

Streamlining and information management of cell manufacturing

Quality control platform development and maintenance

Cell quality control, inspection

Creation of regenerative medicine products

Regenerative cell therapy solution provider

FY2023 **FY2025** **FY2030**

(Reference) Outline of JCR Pharmaceuticals Co., Ltd.

Providing patients with high-quality biopharmaceuticals and regenerative medicine products through an integrated system from research and development to production and sales.

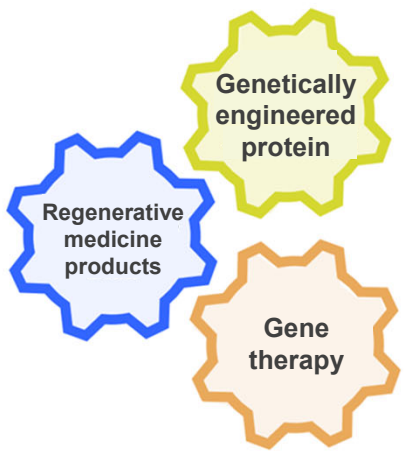
Company profile (as of March 31, 2022)

Company name	JCR Pharmaceuticals Co., Ltd.
Headquarters	3-19 Kasuga-cho, Ashiya, Hyogo Prefecture (Production research base in Nishi Ward, Kobe City)
Representative	Shin Ashida, Chairman and President
Founded	September 13, 1975
Paid-in Capital	JPY9,061.86 million
Employees	816 (consolidated) / 797 (parent)

Source: JCR Pharmaceuticals Co., Ltd. company profile

Focus areas

Biopharmaceuticals

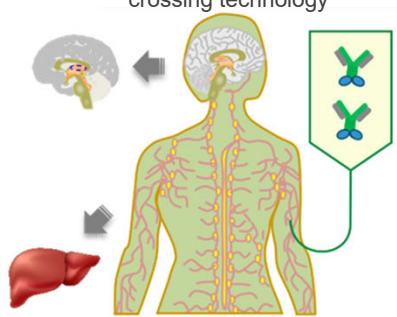


Proprietary biotechnology

Regenerative medicine products

Human (allogeneic) bone marrow-derived mesenchymal stem cells
TEMCELL® HS Injection

Blood-brain barrier crossing technology



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Creation of Testing Value in Key Domains in MTP

Tatsuya Ohashi
Executive Vice President,
Reagent Engineering Division

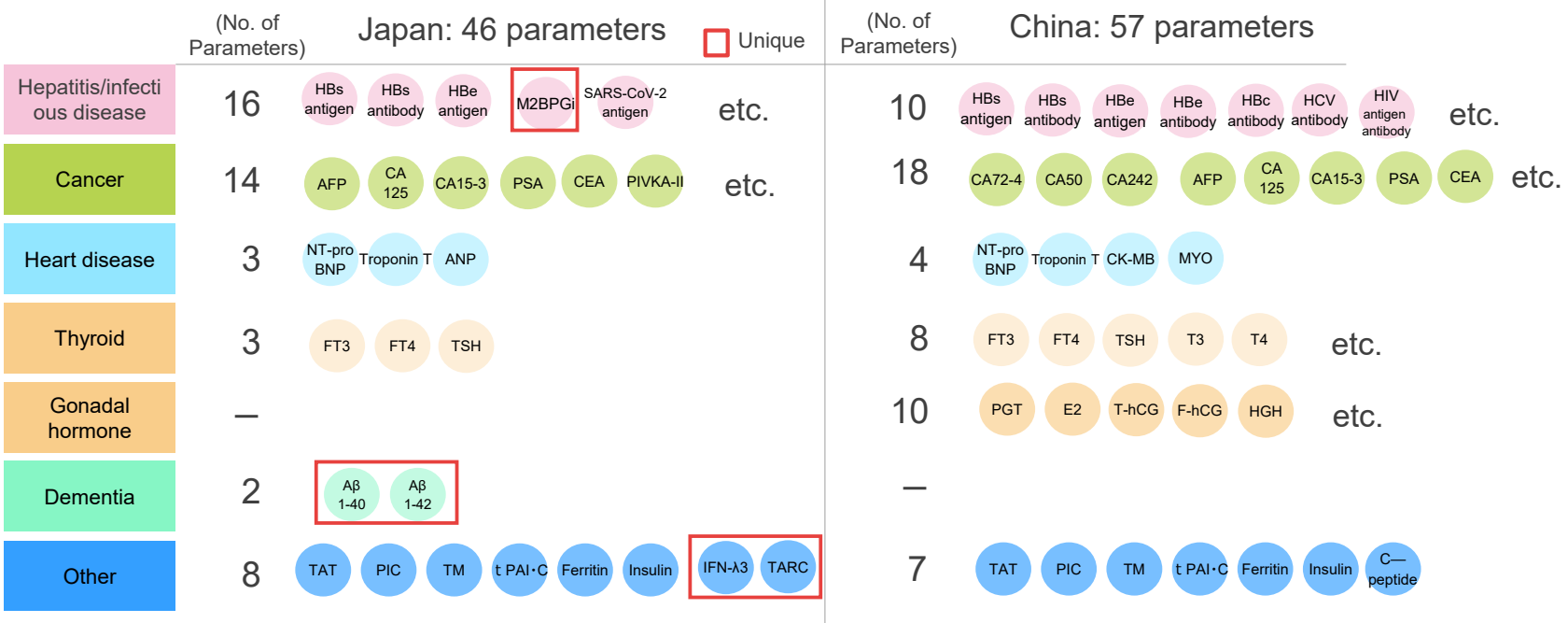
(1) Initiatives in the Immunochemistry Field

(2) Initiatives in the Life Science

(1)Initiatives in the Immunochemistry Field

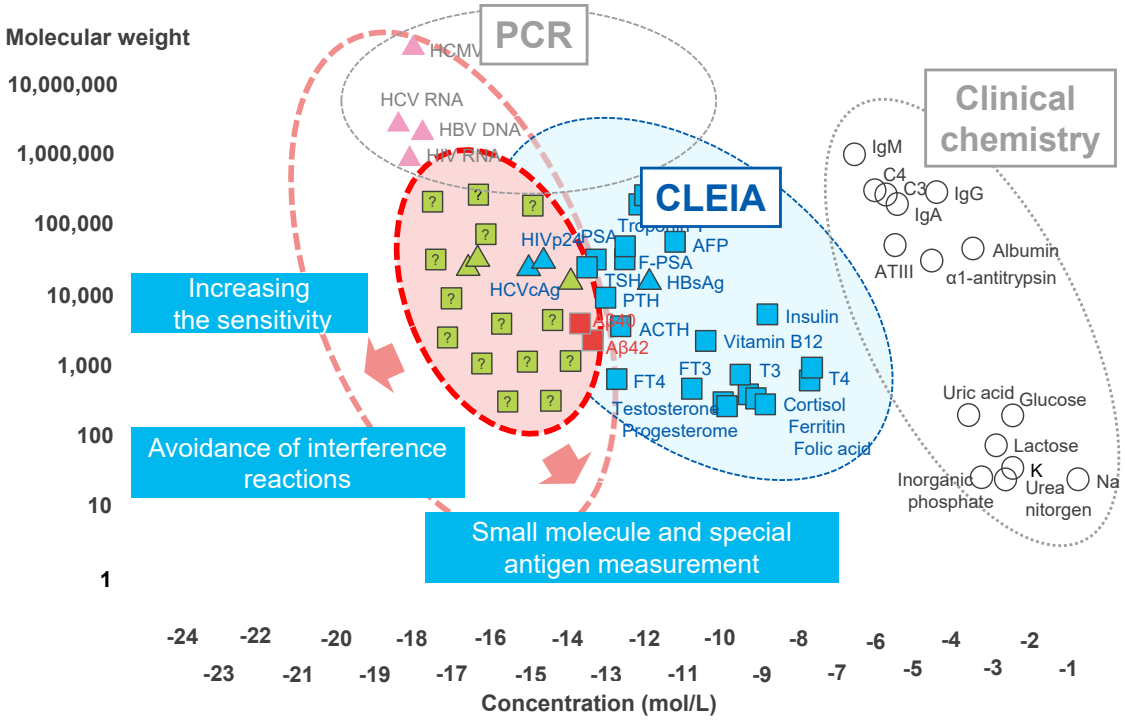
HISCL Reagent Portfolio Progress (Japan/China Region)

Japan: Demonstrating market presence with our own parameters such as M2BPGi™ and amyloid β
China: Improving market competitiveness by expanding product lineup with the utilization development bases in China and supporting panel testing.



Expanding the Strength of HISCL with Technology

Creating clinical value by increasing the sensitivity, small molecule and special antigen measurement, and avoidance of interference reactions



1. High sensitivity

- High affinity antibodies & noise reduction

2. Small molecule and special antigen measurement

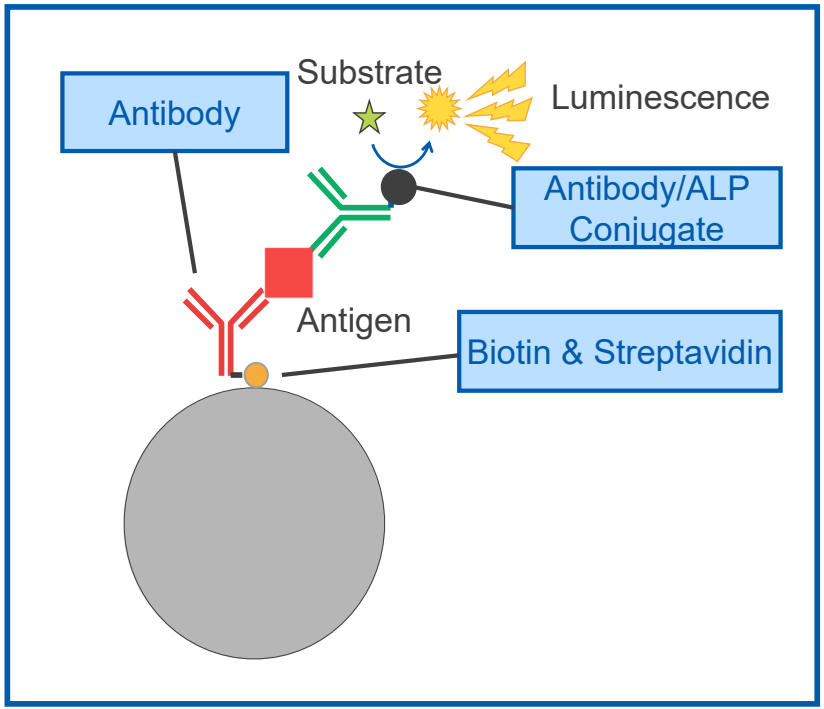
- Development and selection of antibodies that can recognize antigens with unstable structures

3. Avoidance of interference reactions

- Reduction of interference reactions leading to correct measurement results

Core Technology: Key Points for Improving Immunochemistry Reagent Performance

Immunochemistry reagent performance is determined by high-performance raw materials



Antibody

Antibodies with confirmed disease specificity in addition to basic performance

Antibody/ALP Conjugate

Increasing the sensitivity by using uniform molecules via genetic engineering

Biotin & Streptavidin

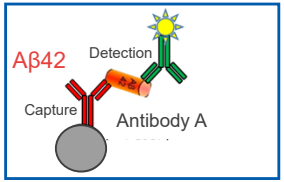
Avoiding interference by developing highly original new substances

Confirm Clinical Utility when Selecting Reagent Antibodies

Evaluation of clinical utility in addition to specificity and affinity as selection criteria for raw material antibodies

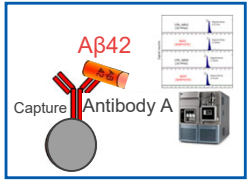
■ Confirmation of clinical specimen reactivity in amyloid beta 42 (Aβ42) antibodies

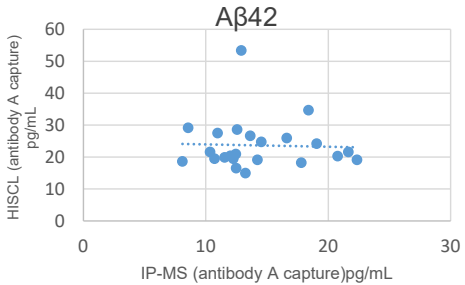
HISCL (antibody A capture)



VS

IP-MS (antibody A capture)





No correlation

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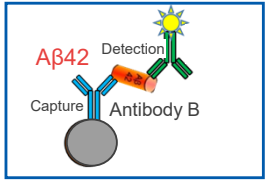
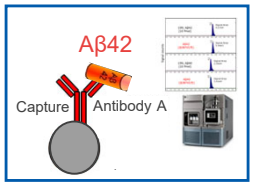
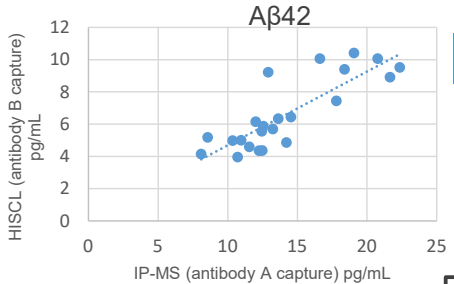
HISCL (antibody B capture)



VS

IP-MS (antibody A capture)





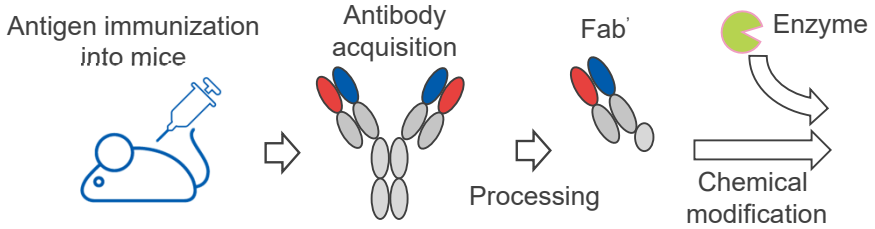
Correlation

Patent pending

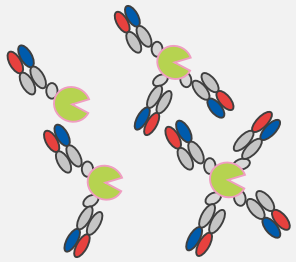
Reagent Development Using Antibody-Enzyme Fusion

Product application of antibody-enzyme fusion with uniformity and high activity

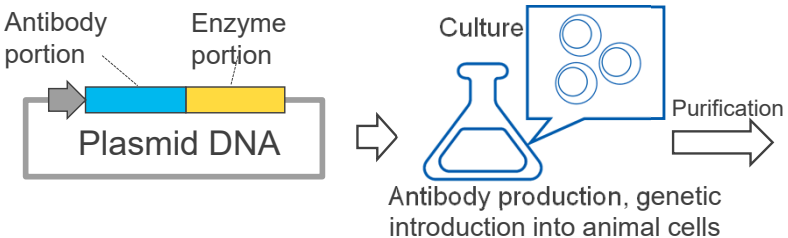
■ Existing reagent: Antibody labeling through chemical modification



Nonhomogeneous ratio of antibody to enzyme



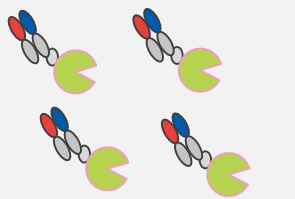
■ New reagent: Recombinant expression of antibody-enzyme fusions (developed at a bio-diagnostic technology center)



Patent pending

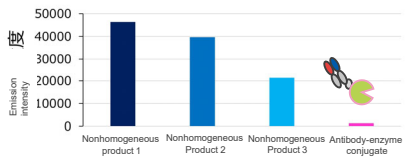
Practical use in COVID-19 antibody measurement reagent

Homogeneous ratio of antibody to enzyme

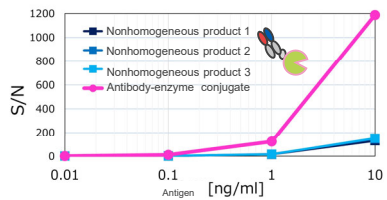


Antibody-enzyme fusion

Background



Reactivity



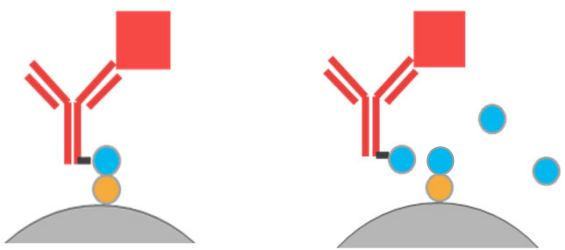
Optical Isomer Streptavidin/Biotin Method

Avoidance of interference reactions between completely new idea and technology

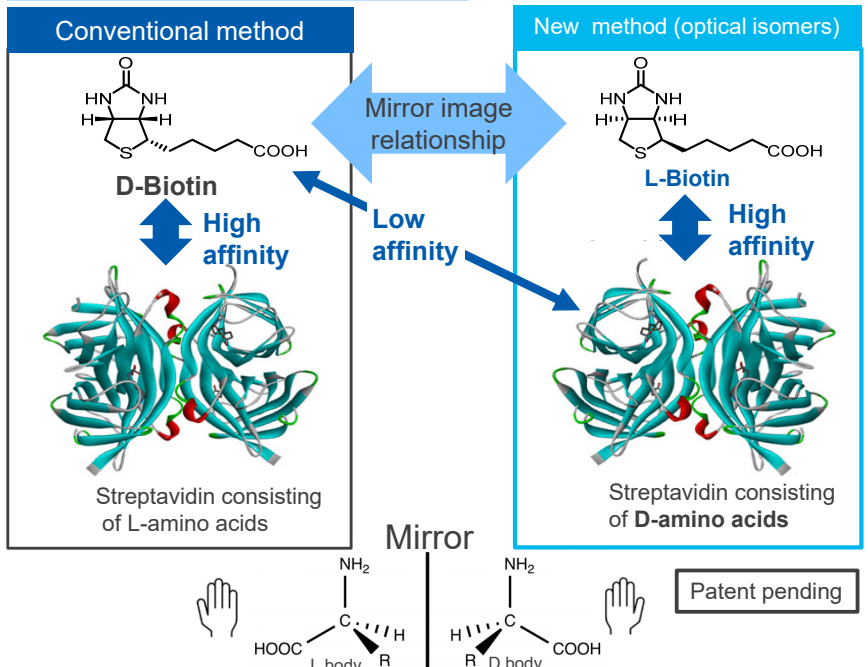
Challenge

Taking high-dose biotin supplements poses a rare risk of reduced accuracy if the subject's blood contains high concentrations of biotin.

Streptavidin Biotin



What are optical isomers?



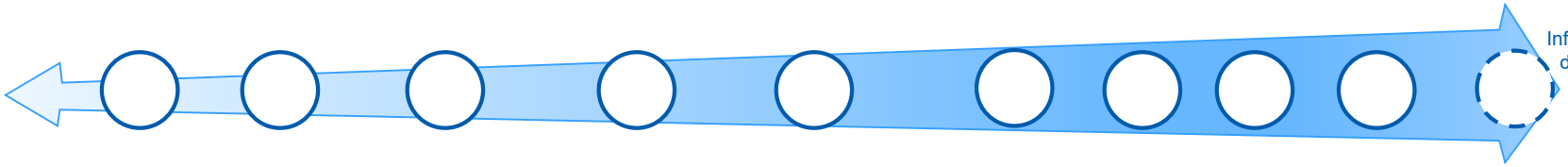
(2) Initiatives in the Life Science

- Highly Sensitive NGS Technology - Plasma Safe-SeqS
- Gene Panel Testing Technologies

Life Science
Main technologies Aimed at the Realization of Personalized Medicine

Expanding into personalized medicine by leveraging technology assets that cover a wide range of clinical needs, from rapid testing to comprehensive analysis

Rapid testing, few parameters	Highly sensitive, liquid biopsy	Comprehensive, genomic profile



OSNA | PCR | Multi-parameter PCR | BEAMing | Plasma Safe-SeqS | Micro array | NGS ～50 | NGS ～100 | NGS 100～ | Whole-Exome Whole-Genome

- Cancer
- Hereditary disease
- Infectious disease

- OSNA LYNOAMP™ CK19/CK19E (IVD)
  diagnosis of cancer lymph node metastasis
  Breast, colorectal, stomach, lung, gynecological, prostate (Europe)
- ROS1 fusion gene detection kit, lung cancer multigene PCR panel, SARS-CoV2 PCR kit (IVD)
- OncoBEAM™ RAS CRC kit (IVD)
  CDx for Colorectal Cancer-Related
- Plasma Safe-SeqS (IVD/RUO)
  CE-IVD/RUO kit
  CDx
  LDT assay
  Breast Cancer, Solid Cancer, Colorectal Cancer
- CytoSure SureSeq (RUO)
  Cancer-Related NGS panel
- Curebest 95GC (RUO)
  prognostic prediction
- Genetic Panel Testing System for Inherited Retinal Dystrophy (Applying)
- NCC Oncopanel System (IVD)

Future Clinical Deployment of Plasma Safe-SeqS (PSS), a Highly Sensitive Next-Generation Sequencing (NGS) Technology

Compatible with liquid biopsy with a technology that is about two orders of magnitude more sensitive than general NGS

Plasma
2–4mL

DNA extraction and quantification

Reagent kit

Library preparation
(UID PCR, Index PCR)

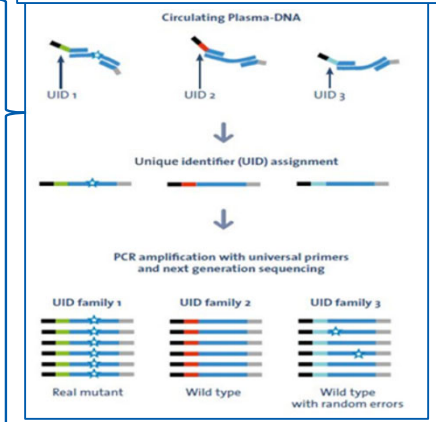
Sequencing

Next-Generation Sequencing(NGS)

Analysis program

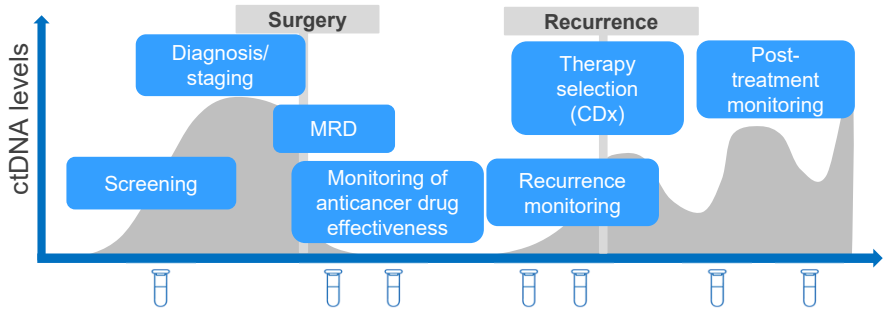
Analysis, reporting

Principals of Plasma Safe-SeqS method

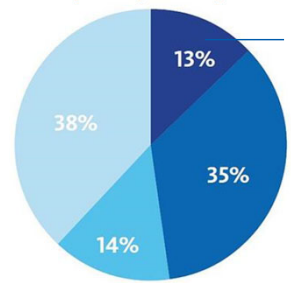


Highly sensitive NGS with a different sequence barcode (UID) added to each DNA molecule

High sensitivity is required to detect mutant allele frequencies below 0.1%.

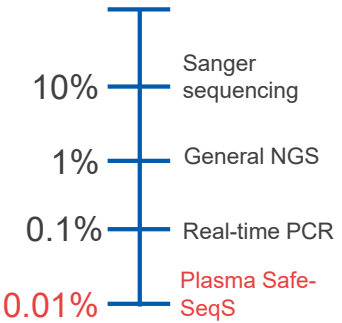


■ Colorectal Cancer RAS Mutation Allele Frequency in Liquid Biopsy



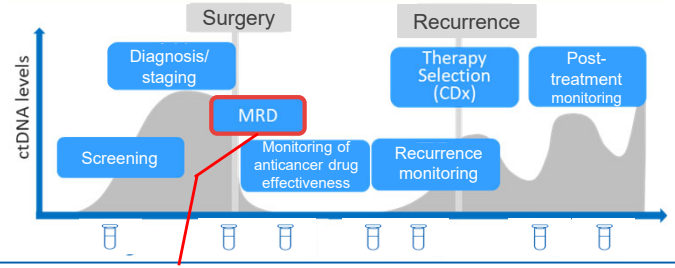
13% of cases had mutant allele frequency <0.1%

■ Detection sensitivity

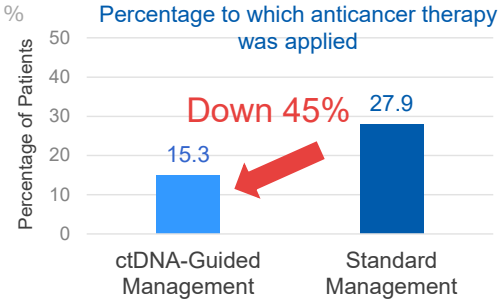


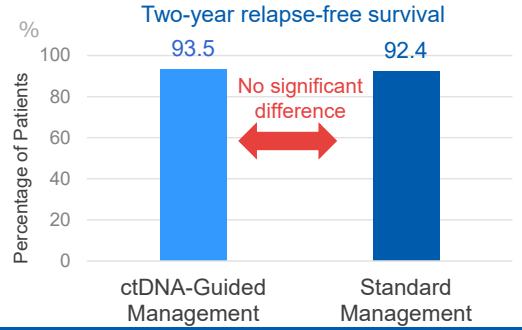
Future Clinical Deployment of Plasma Safe-SeqS (PSS), a Highly Sensitive Next-Generation Sequencing (NGS) Technology

Collecting evidence for microscopic residual lesion (MRD) detection and treatment selection to expand clinical applications of liquid biopsy



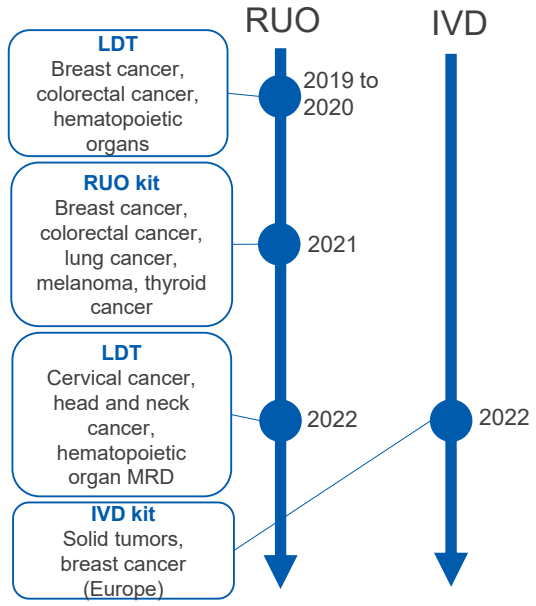
PSS Panel for MRD Detection of Colorectal Cancer (*N ENGLJ MED 386;24* and ASCO 2022, data partly modified)





Anticancer drugs based on ctDNA MRD detection suggests that anticancer drug treatment for appropriate patients can be realized

CE-IVDD/RUO kits for five cancer types, expanded to six types of LDT assays



Expansion to Genomic Medicine for the Inherited Retinal Dystrophy (IRD)

Personalized diagnostic to enable the best care for each IRD patient to improve their quality of life

Inherited retinal dystrophy (IRD)

- **Top cause of blindness** in Japan, **designated as an intractable disease**
- No fundamental cure exists
- **Advances being made with gene replacement therapy**

  Gene therapy has been approved in the United States and Europe, and clinical trials are underway in Japan.

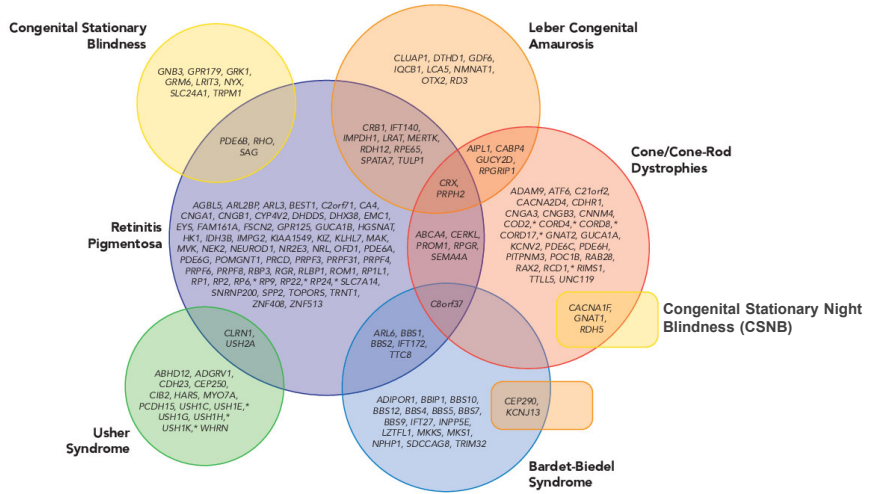
Field of vision of a normal person

Field of vision of an IRD patient

Resource; NIH National Eye Institute

Need for a multigene panel

- **Approximately 300 causative genes** have been reported, and each leads to different symptoms and severity
- **Identifying causative genes is important** for low vision care planning



Quoted from E.Pennesi ;Brave New World : GENE THERAPY FOR INHERITED RETINAL DISEASE

Genetic Panel Testing System for Inherited Retinal Dystrophy

sysmex

Utilize the Sysmex Group's gene panel testing assets to develop a gene panel testing system for inherited retinal dystrophy

Existing gene panel testing assets

Gene mutation analysis set (for cancer genomic profiling)

OncoGuide™
NCC Oncopanel System

ogt
A Sysmex Group Company

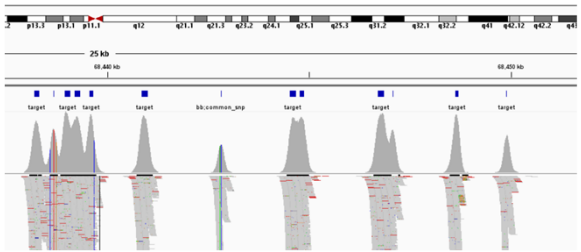
CytoSure
CytoSure array and NGS products for cytogenetics and rare disease

SureSeq
SureSeq NGS products for haematological cancer and solid tumours

riken genesis

Expert panel support system
OncoGuide™ NET

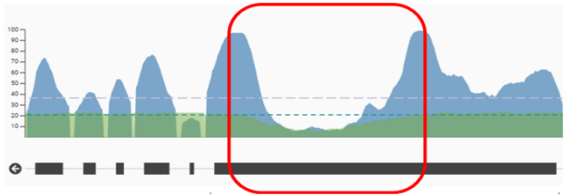
Panel system for inherited retinal dystrophy



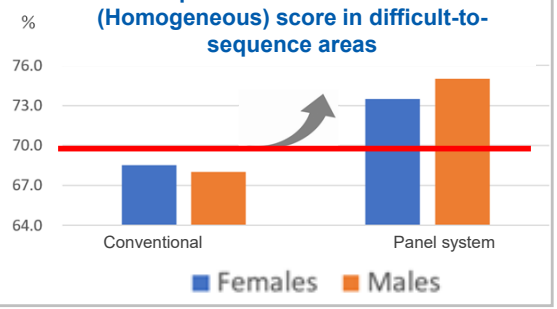
Extraction and mutation analysis of **about 80 genes** associated with disease

Achieve target values even in difficult-to-sequence regions by improving boosting and tiling of gene capture kits

difficult-to-sequence regions with whole-exon testing



Improvement of evenness (Homogeneous) score in difficult-to-sequence areas



4

Initiatives for Diagnosing Central Nervous System Diseases

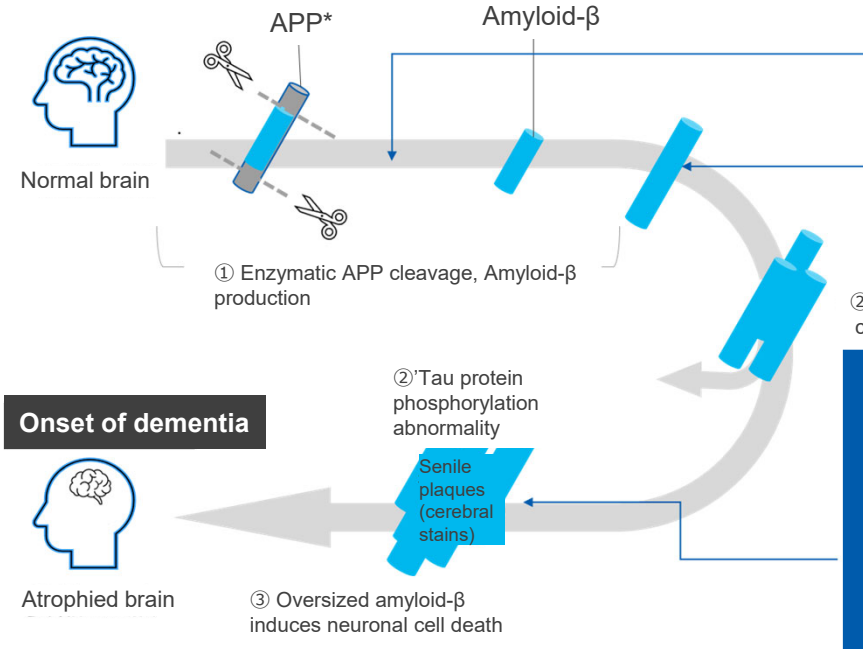
Tomokazu Yoshida
Member of the Managing Board and Senior Executive Officer
Managing Director

(1) Realization of Personalized Medicine of Dementia Treatment
(2) Initiatives Targeting Diagnosis Evolving Along with Progress in Therapeutic Research
(3) Further Undertakings for Central Nervous System Disease Using Liquid Biopsy

(1) Realization of Personalized Medicine of Dementia Treatment

External Environment: Progress in Alzheimer's Drug Development

Successful development of amyloid beta drugs for patients of Alzheimer's-caused mild cognitive impairment and mild dementia



Inhibiting the production of amyloid-β itself

Elenbecestat (Biogen, Eisai)
discontinued at Phase III

Identification and removal of amyloid-β at initial stage

Solanezumab (Eli Lilly)
Late-stage development

Identification and removal of cerebral amyloid-β deposits

Aducanumab
(Biogen, Eisai)
FDA accelerated approval (June 2022)

Lecanemab
(Eisai, Biogen)
FDA accelerated approval (Jan 2023)

Donanemab
(Ely Lilly) Phase III

Gantenerumab
(Roche, Chugai Pharma)
discontinued at Phase III

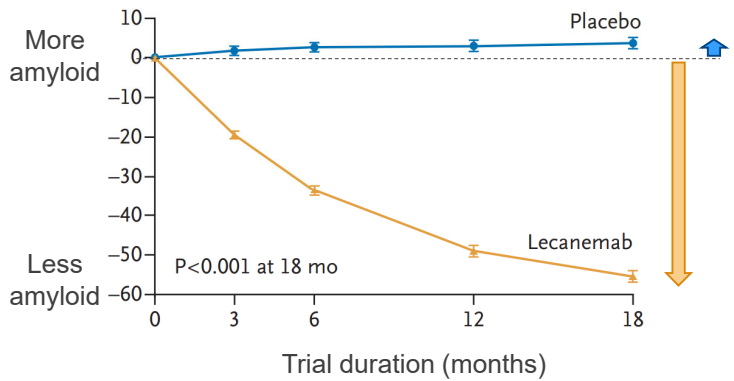
Administered to patients of Alzheimer's-caused mild cognitive disorder and dementia

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

External Environment:
Treatment Efficacy Shown in Disease-modifying Drugs Targeting Aβ

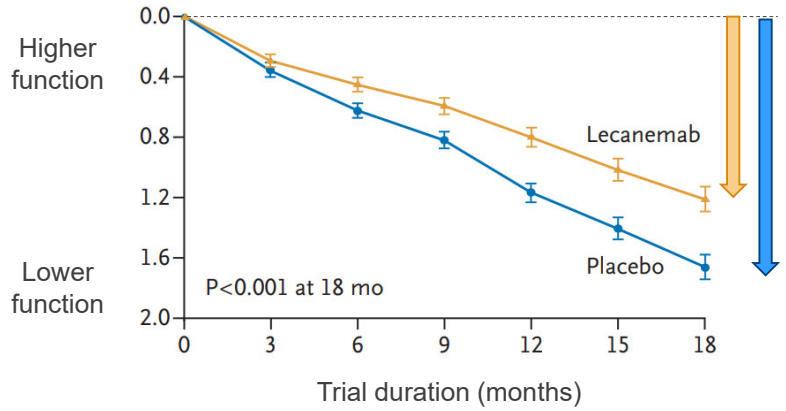
Early and accurate detection of the state of cerebral amyloid-β deposits is important for treatment

■ Relation between quantity of cerebral amyloid- β deposits and trial duration (Confirmed by amyloid PET)



No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

■ Relation between cognitive function and trial duration



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

C. H. van Dyck et al., N Engl Med 388;1 (2023)

External Environment: Cerebral Amyloid-β Testing Methods and Expansion into Blood Biomarkers (BM)

Blood (plasma): Aβ42, Aβ40, Aβ composite, p-Tau181, p-Tau217

- Mass spectrometry systems : C2N, Shimadzu Corporation
- Fully automated immunoassay systems : **Sysmex（HISCL）**、**Roche*** **FUJIREBIO***

*Research stage

Sensitivity, specificity, quantitativity

Minimal invasiveness, convenience, standardization

Minimal invasiveness, convenience

Imagery analysis
- Amyloid PET : Siemens, GE, Hitachi (imaging materials: FUJIFILM Toyama Chemical, etc.)
- Tau PET: Siemens, GE, Hitachi (imaging materials: Avid Radiopharmaceuticals)

Video analysis
- Eye movement : Optina
- Facial expression : FRONTEO

Minimal invasiveness, convenience

Cerebral spinal fluid (CSF) : Aβ42, Aβ40, p-Tau181
- Fully automated immunoassay systems : Roche, FUJIREBIO

Quantitativity, objectivity

Speech & cognitive function
- Hasegawa's Dementia Scale
- MMSE screening (Mini-Mental State Examination)
- Alzheimer's Disease Assessment Scale

Internal Environment: Sysmex's Initiatives

Aβ blood high sensitivity and quantitative measurement using HISCL-5000 fully automated immunoassay systems

Rapid testing

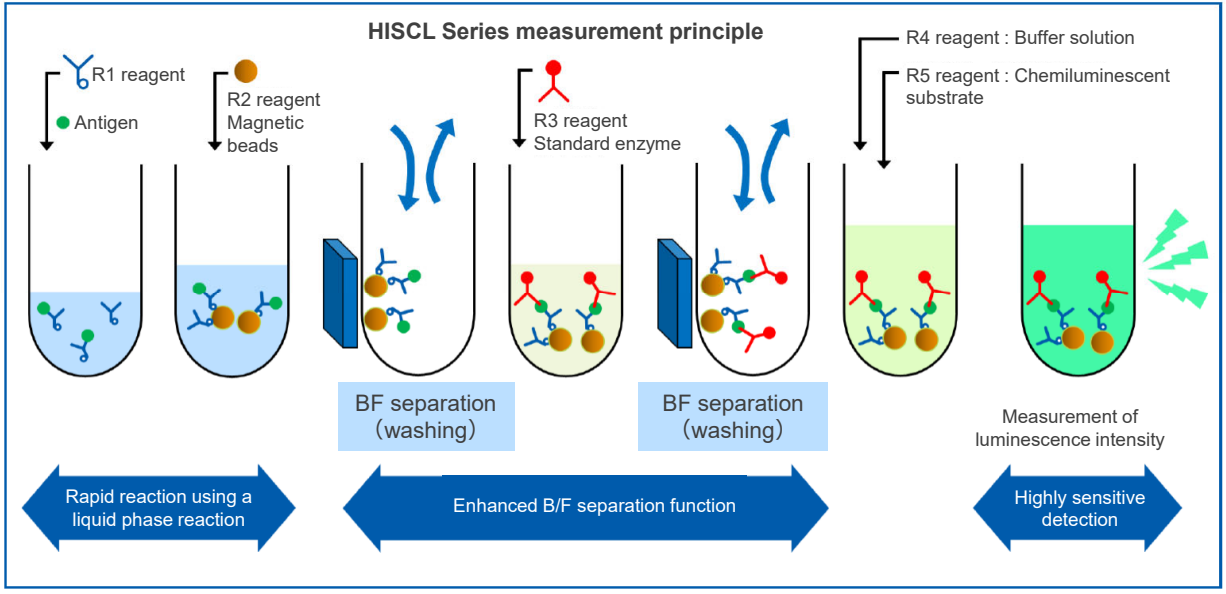
17min
per test

High processing capacity

Up to 200 tests
per hour

Small sample quantities

10-30μL
per test



Internal Environment:
Performance and HISCL Series Technological Features

Manufacturer or University	Specimen type	Measurement principle / markers	AUROC	Sensitivity	Specificity
Shimadzu Corporation*1	Blood	Mass spectrometry Aβ40, 42, $APP_{669-711}$ combination	0.91	0.86	0.82
Washington University*1	Blood	Mass spectrometry Aβ42/40 ratio	0.88	0.88	0.76
C2N Diagnostic*1	Blood	Mass spectrometry Aβ42/40 ratio	0.81	-	-
Roche*1	Blood	Immunoassay Aβ42/40 ratio	0.77	0.75	0.72
FUJIREBIO*1	CSF	Immunoassay Aβ42/40 ratio	0.86	0.82	0.82
Sysmex*2	**Blood**	**Immunoassay Aβ42/40 ratio**	**0.86**	**0.88**	**0.72**

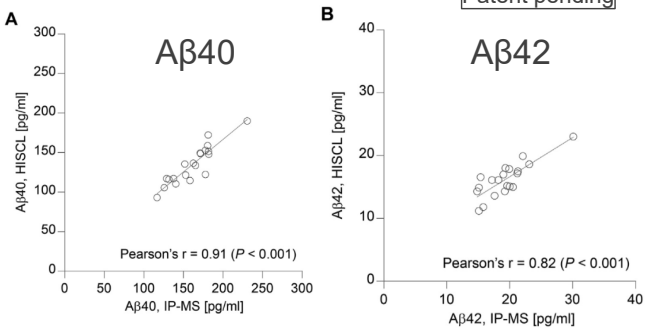
HISCL Series Technological Features

■ **Unique antibody combination**

■ **Fully automated**

■ **Establishment of specific measurement target (confirmed by mass spectrometry)** *3

Patent pending



■ **High measurement precision** *3

	Measurement precision(%)
Aβ40	< 4.6
Aβ42	< 5.3

*1 : quoted from published study *2 : study data (K. Yamashita et al, Alz Res Ther 14, 86 (2022)) , performance of amyloid PET (interpretation method) *3 : study data (K. Yamashita et al., BBRC 576 22-26(2021))

Internal Environment: Achievement of Dementia Diagnosis by Aβ measurement in blood

2022/12/19: HISCL Aβ40/42 reagent manufacturing approval

News

Press Release

Dec. 22, 2022

Sysmex Receives Manufacturing and Marketing Approval for an Assay Kit to Identify Amyloid Beta (Aβ) Accumulation in the Brain, a Cause of Alzheimer's Disease, Using a Small Amount of Blood

– Measurement of Plasma Aβ Using Automated Immunoassay System HISCL™-5000/HISCL™-800 –

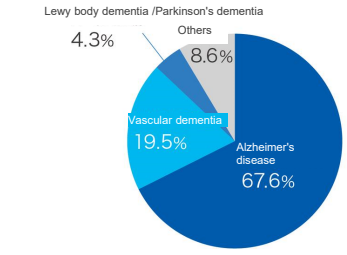
On December 19, 2022, Sysmex Corporation (HQ: Kobe, Japan; Chairman and CEO: Hisashi Ietsugu) received manufacturing and marketing approval in Japan for the HISCL β-Amyloid 1-42 Assay Kit and the HISCL β-Amyloid 1-40 Assay Kit (collectively, "the Product") as *in vitro* diagnostics to measure amyloid beta (Aβ) in the blood. The Product assists in identifying Aβ accumulation in the brain, which is a characteristic of Alzheimer's disease, by measuring Aβ levels in the blood using the company's automated immunoassay system HISCL-5000/HISCL-800 (the "HISCL-Series"). We will prepare for market introduction in Japan to give patients access to this minimally invasive and simple test as soon as possible.

Unprecedented experience in challenging research and product development process

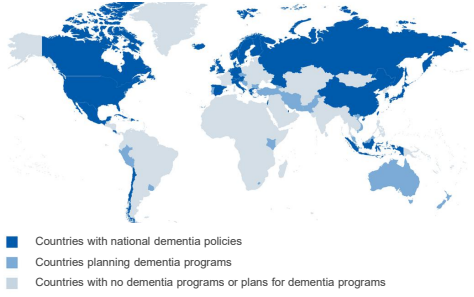
Contribution to progress in healthy life, and aging society

- By 2030, 20% of people over the age of 65 will have dementia
- Active development of dementia prevention and treatment globally

Percentage of dementia type



Status of national strategy development for dementia (as of April 2021)



Takashi Asada, et al.: Prevalence of dementia in urban areas and response to dementia's functional impairment. 2012 Health Labor and Welfare Science Research Grant (Comprehensive Research Project for Dementia Countermeasures) Comprehensive Research Report.
[https://mhlw-grants.niph.go.jp/system/files/2012/123021/201218011B/201218011B0001.pdf]

External Environment: Possibility of clinical implementation of dementia treatment (disease-modifying drug)

Eisai Submits Supplemental Biologics License Application to FDA for Traditional Approval of LEQEMBI™ (lecanemab-irmb) for the Treatment of Alzheimer's Disease

Submission for traditional approval follows FDA accelerated approval of LEQEMBI on the same day, *and is based on data from the confirmatory Phase 3 Clarity AD clinical trial*

TOKYO and CAMBRIDGE, Mass., January 6, 2023 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Christopher A. Viehbacher "Biogen") announced Eisai has submitted a supplemental Biologics License Application (sBLA) to the U.S. Food and Drug Administration (FDA) supporting the conversion of the Accelerated Approval of LEQEMBI™ (lecanemab-irmb) 100 mg/mL injection for intravenous use to a traditional approval. This sBLA is subject to validation of whether the FDA accepts the application for review. LEQEMBI is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble ("protofibrils")* and insoluble forms of amyloid beta (Aβ), approved under Accelerated Approval Pathway by the FDA on January 6, 2023, for the treatment of Alzheimer's Disease (AD). Treatment with LEQEMBI should only be initiated in patients with the mild cognitive impairment or mild dementia stage of disease and confirmed presence of Aβ pathology.

EISAI FILES MARKETING AUTHORIZATION APPLICATION FOR ANTI-AMYLOID-BETA PROTOFIBRIL ANTIBODY LECANEMAB FOR EARLY ALZHEIMER'S DISEASE IN JAPAN

TOKYO and CAMBRIDGE, Mass., January 16, 2023 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Christopher A. Viehbacher, "Biogen") announced today that Eisai has submitted a marketing authorization application for lecanemab (Brand Name in the U.S.: LEQEMBI™), an investigational anti-amyloid beta (Aβ) protofibril[1] antibody for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD dementia (collectively known as early AD) with confirmed presence of amyloid pathology in the brain to the Pharmaceuticals and Medical Devices Agency (PMDA).

This application is based on the results of the Phase III Clarity AD study and Phase IIb clinical study (Study 201), which demonstrated the lecanemab treatment showed a reduction of clinical decline in early AD. Prior to submitting this application, Eisai utilized the prior assessment consultation system of PMDA, with the aim of shortening the review period for lecanemab.

Resource: Eisai Co.,Ltd website

Global Status of Dementia Treatment and Diagnosis

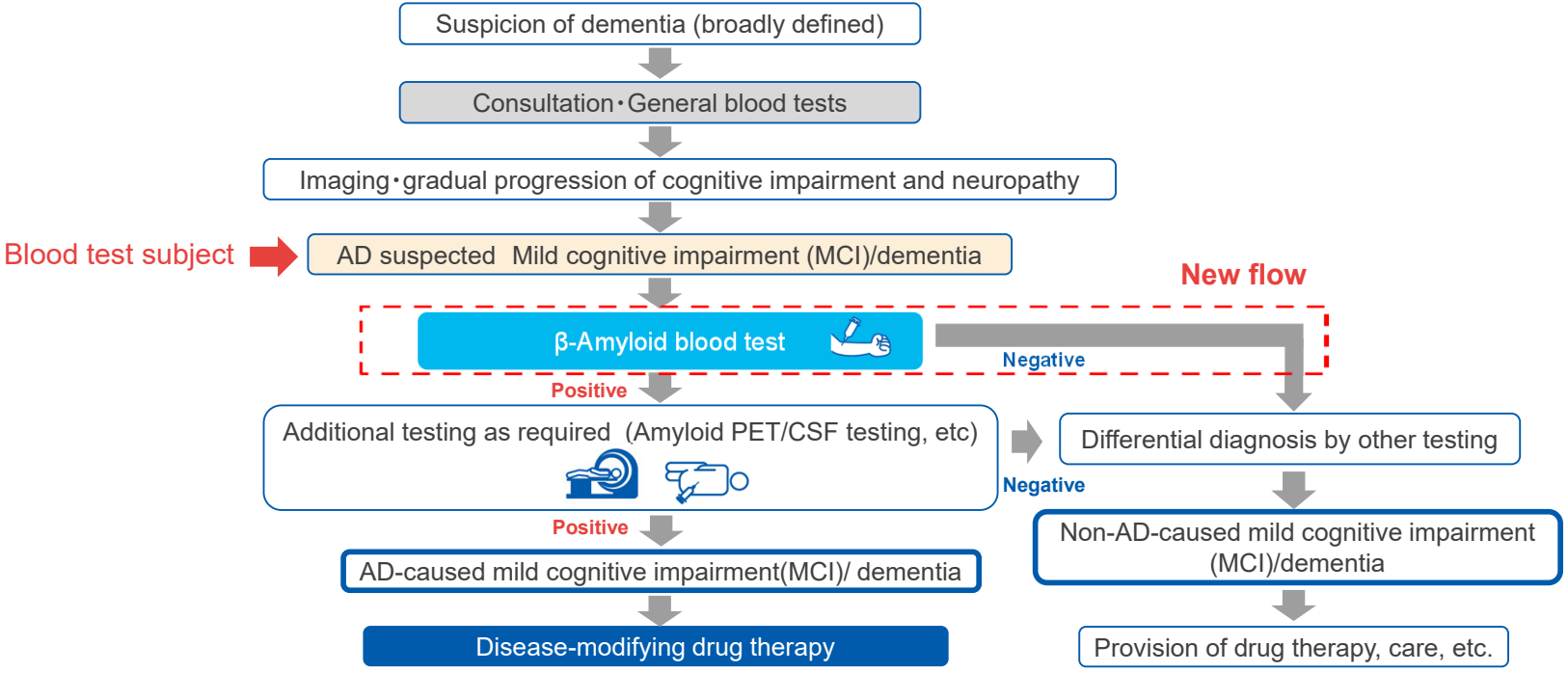
Regional deployment to provide blood testing conditions free of drug approval delays

Therapeutic drug	Under review	Designated for Priority review	Under review (Priority review items)	Accelerated approval (with conditions) Partial changes sought (under review)
IVD reagent (Sysmex)	IVDD declarations concluded* (FY2022Q1)	Under consideration	Pharmaceutical approval (FY2022 Q3)	Preparing for LDT (FY2023 Q1 tentative)

* Scheduled to complete IVDR declaration for related products in FY2023 Q3

Image of the Flow of Alzheimer's Disease (AD) Diagnosis Using Aβ Blood Test

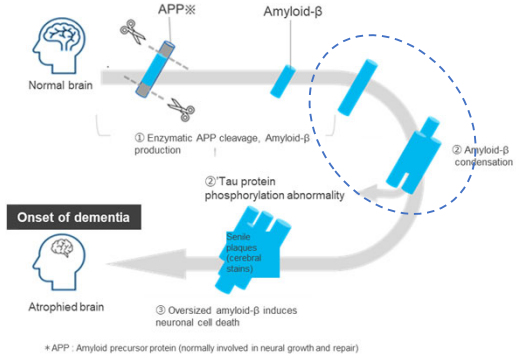
Prescreening for differential diagnosis of AD, non-AD patterns
Blood testing reduces physical burden and social cost, and enables chronological measurement



(2) Initiatives Targeting Diagnosis Evolving Along with Progress in Therapeutic Research

Trends in Drug Development Targeting Aβ

Progress in clinical research aimed at early treatment initiation (early administration), and clinical trials on drugs that act on amyloid-β, like lecanemab (they differ in recognition)



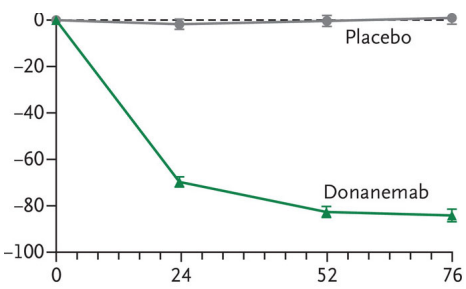
◆Clinical research regarding early administration of therapeutic drugs (preclinical) is progressing

-A4 study (Eli Lilly, 2014-)
-AHEAD study (Eisai, 2020-)
-Trailblazer 3 (Eli Lilly, 2022-)
-Skyline trial (Roche, Chugai, 2023-)
-DIAN-Trial Unit 3 (Wash U/Eisai)

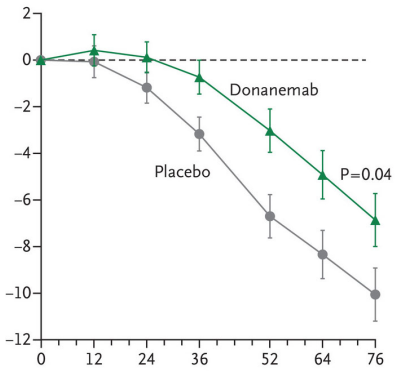
New tests that lead to patient stratification, drug selection & efficacy prediction, and monitoring are needed

■Clinical study of Aβ disease-modifying drugs to follow lecanemab (Eli Lilly: Donanemab)

Cerebral amyloid-β plaque level (amyloid PET)



Cognitive function



Quoted from M. A. Mintun et al., N Engl J Med. 384, 1691-1704 (2021)

Undertakings Utilizing Treatment Research

Devising a measurement system that enables detailed evaluation of Aβ aggregates (oligomers and protofibrils), which are targets of disease-modifying drugs

Single Molecule Fluorescence Microscope For Research Use

HM-1000

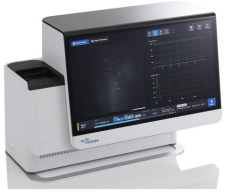
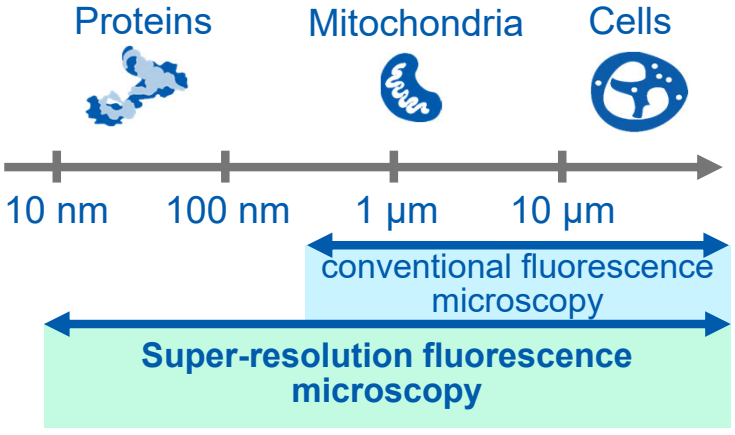
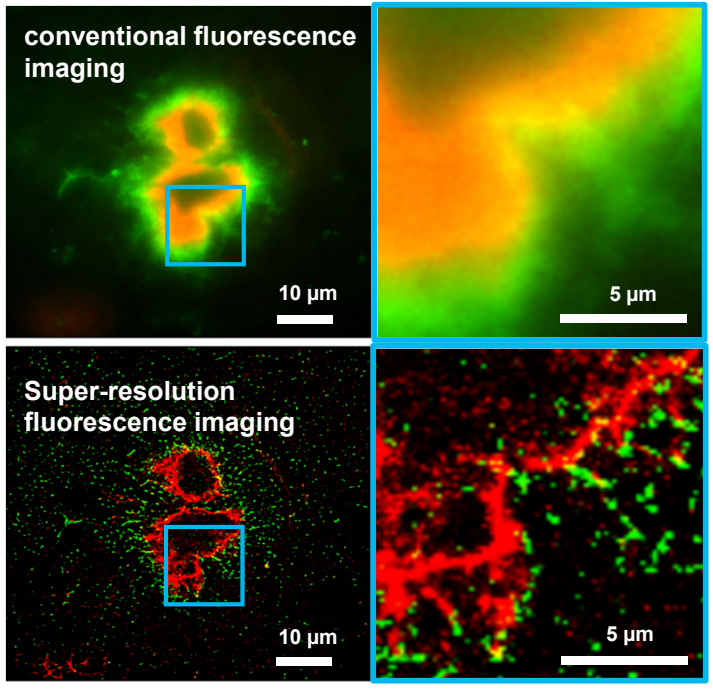


Image resolution (spatial resolution)

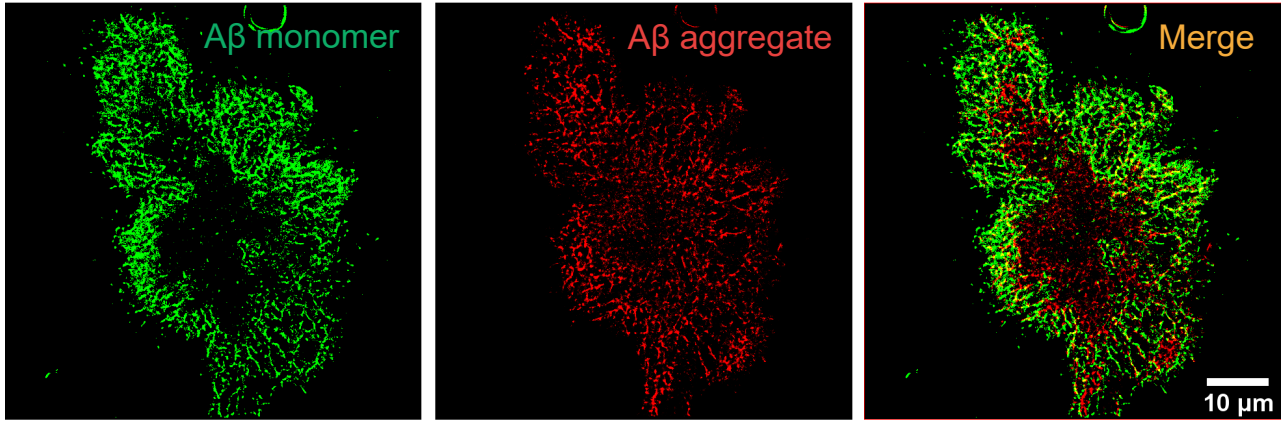


Fluorescence imaging of mouse brain section (Aβ monomer Aβ aggregate)



Visualization of Aβ Aggregate Distribution in Mouse Brain Amyloid Plaques

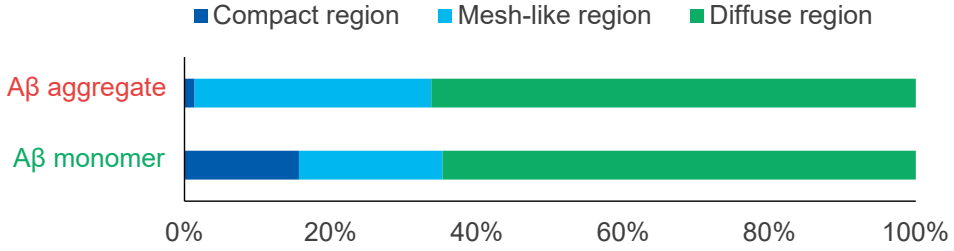
Difference in staining and aggregation density between Aβ monomers and Aβ aggregates confirmed. Enables detailed analysis of the characteristics of new therapeutic drugs for future approval



Compact region:
The unstained area in the center of the plaques.

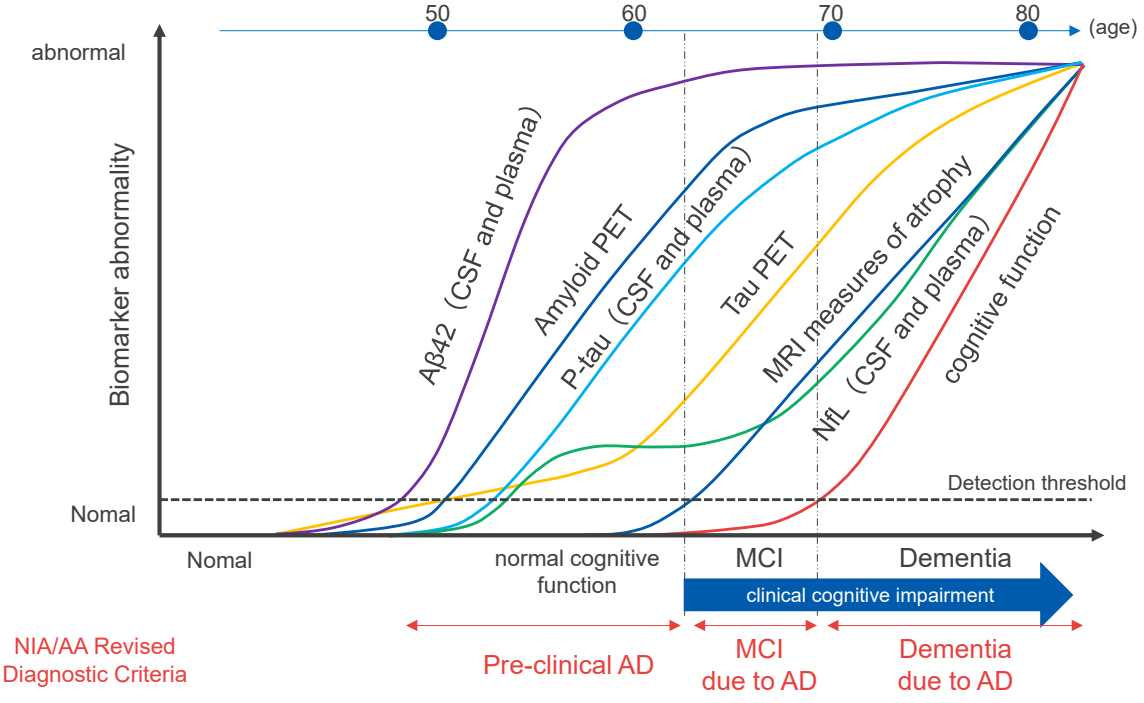
Mesh-like region:
The area formed by interweaving of individual Aβ fibrils.

Diffuse region:
The area other than above.

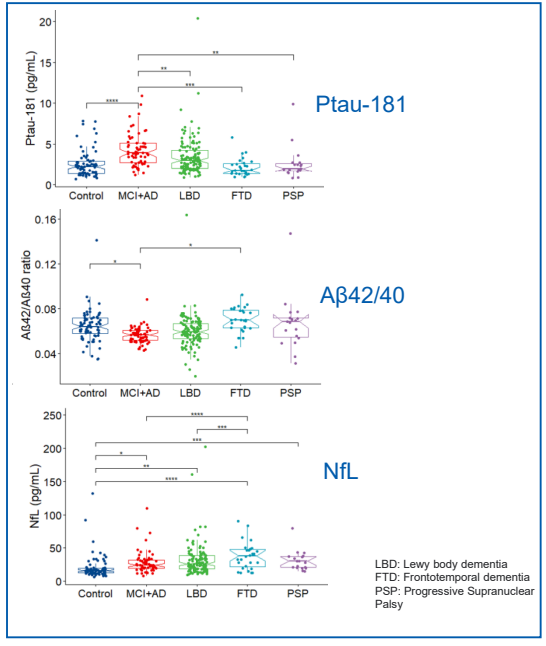


Undertakings Toward Patient Stratification; Diagnosis of disease progression

Biomarkers associated with Alzheimer's disease change in order of ATN in line with with disease progression
Understanding the status of individual biomarkers is important to understanding pathological status



Leading research
(J.Neurol Neurosurg Psychiatry (2022))

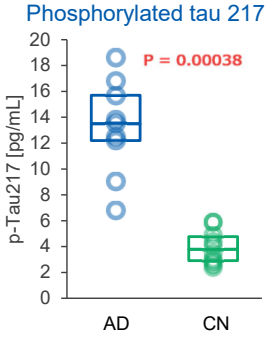


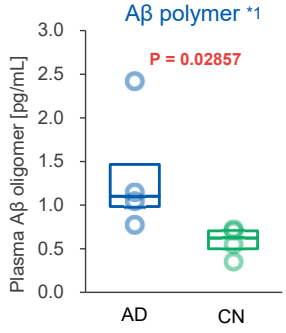
Modified from O. Hansson Nat. Med.27, 954-963 (2021), Tokuda Journal of the Society for Gerontological Dementia Vol21 No.4 2017

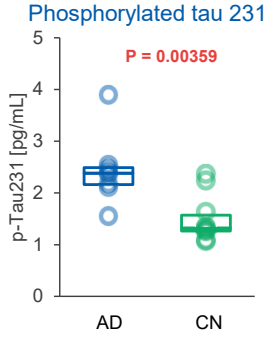
Expansion of Blood Biomarker Panel Items

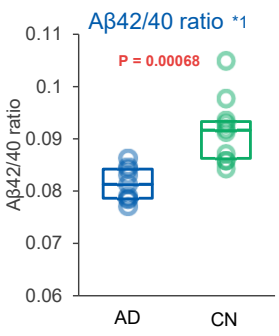
Construction of Biomarker panel reagents based on the latest findings

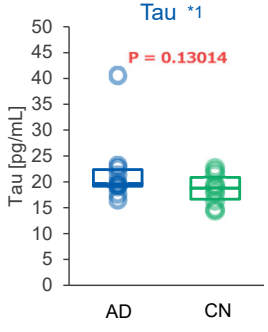
●: AD
●: Normal cognitive function (CN)

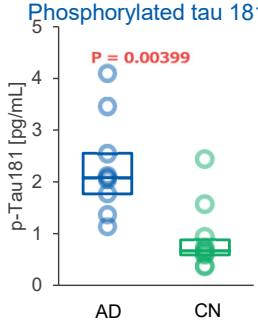


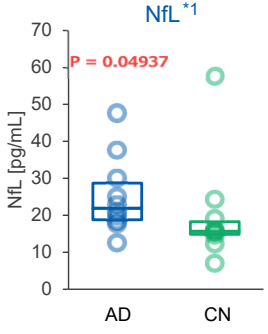








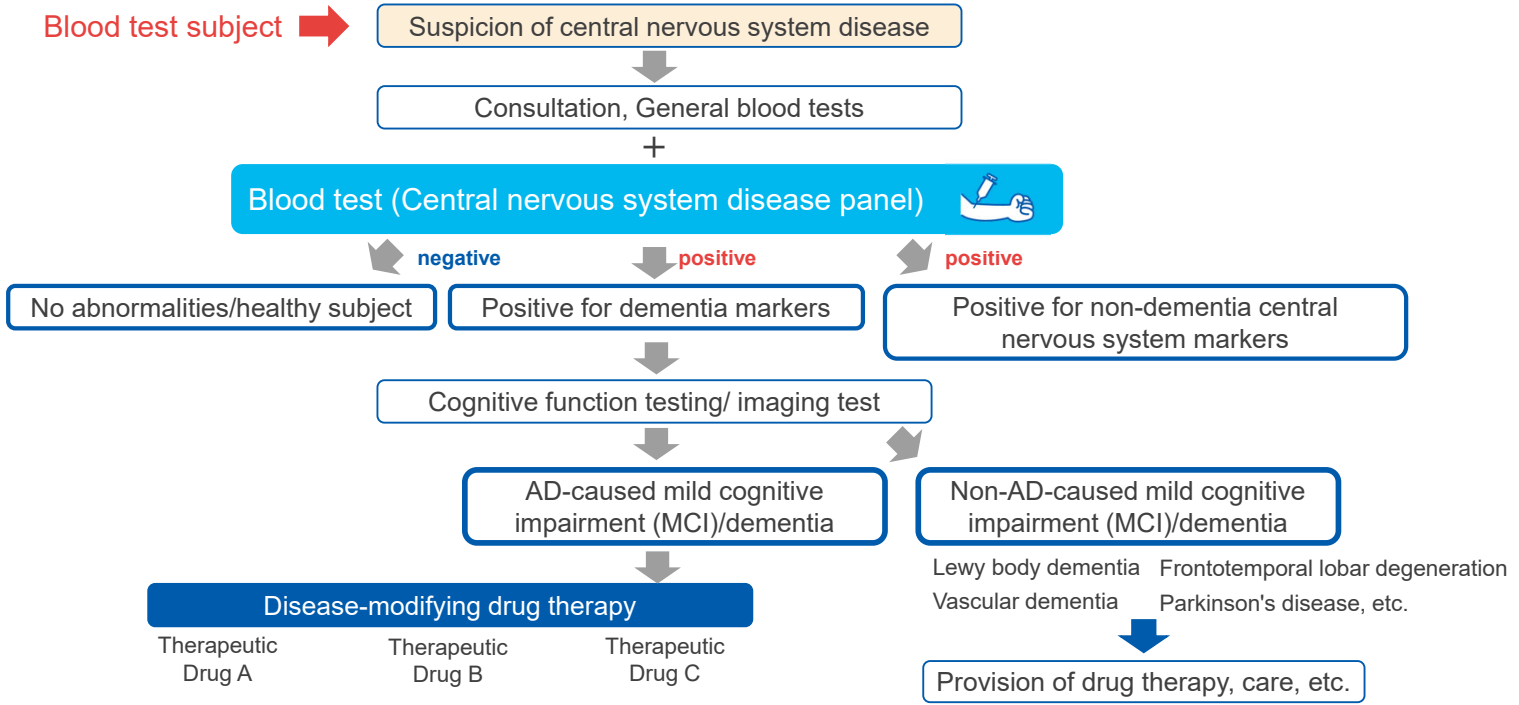




*1:data checked internally, *2:Phosphorylated tau 231 antibody provided by ADx Neurosciences, Fujirebio company

Undertakings to Achieve Personalized Medicine for Central Nervous System Diseases Including Dementia

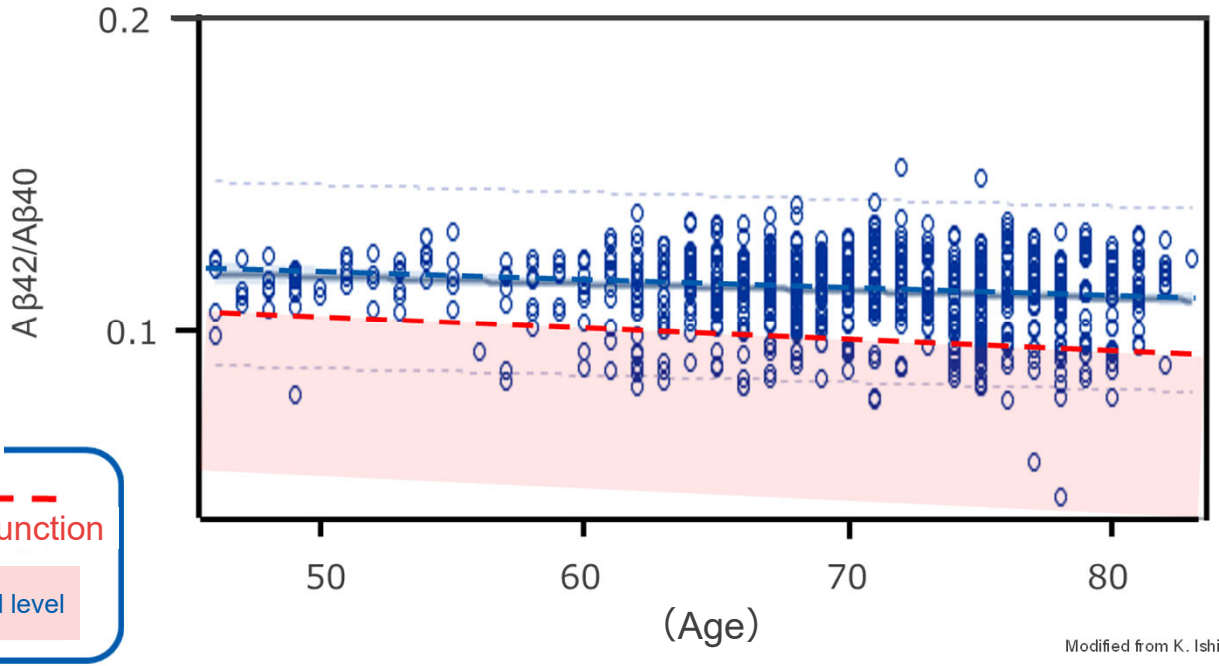
Differentiation of central nervous system diseases and selection of therapeutic drugs via blood testing



(3) Further Undertakings for Central Nervous System Disease Using Liquid Biopsy

Age-Associated Changes in Biomarkers; Understanding what Is Normal

Acquisition of data on changes in Aβ due to aging through cohort studies,
Acquisition of non-Aβ as well, and, verification of the potential for AD stratification from preclinical to MCI due to AD



Hypothesis

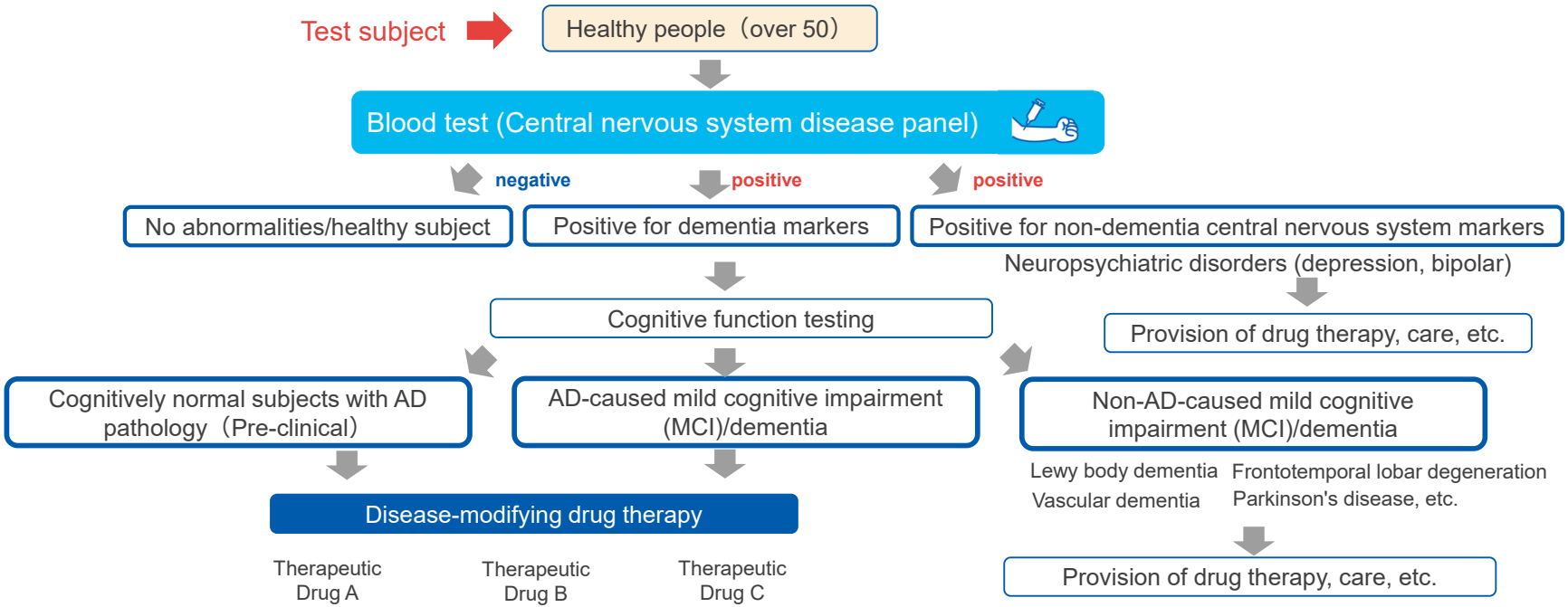
Cognitive dysfunction

Testing required level

Modified from K. Ishiki et al., CTAD (2022)

Undertaking the Challenge of Diagnosing Central Nervous System Diseases Using Liquid Biopsy

Achievement of a healthy society with reduced physical burden and social costs through the development of liquid biopsy technology



Glossary

Glossary

ALP label	A general term for complexes in which an ALP (Alkaline Phosphatase) enzyme that reacts with a chemiluminescent substrate is bound to an antibody or antigen.
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.
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 β protein, which is toxic to nerve cells.)
Background	Noise signal of a luminescence signal generated from non-specifically bound substances
Biotin & Streptavidin	Interacting substances used in immunological measurement technology. Biotin and streptavidin show extremely high affinity and bind very strongly.
CE-IVDD	IVD products that comply with the European IVD Directive and are CE marked
Chemical modification	Altering functions such as activity and reactivity by chemically changing specific functional groups contained in biopolymers such as proteins and DNA.
CSF	A general term for tests using cerebrospinal fluid. Indispensable test for diagnosing diseases of the brain and spinal cord
ctDNA	Cancer derived DNA circulating in the blood. A focus of growing attention as a non invasive cancer biomarker for testing using liquid biopsy.
Disease-modifying drug	A drug that suppresses the onset and progression of a disease by targeting the substance that causes the disease
Exon test	A test that analyzes regions called exons in the entire whole genome region. Although exonic regions make up approximately 1% to 1.5% of the whole genomic region, they are functionally important because they are regions that are translated into proteins, and many diseases are presumed to be caused by mutations in exonic regions.

Glossary

Fab’	A fragment that can be produced by enzymatic digestion and reduction treatment of an antibody and has the function of binding to an antigen
Immunological synapse	Molecular complexes formed at the interface between lymphocytes, which are important for immune response, and antigen-presenting cells or target cells
interference reactions	A reaction that affects the antigen-antibody reaction and causes false positives and false negatives.
IP-MS	A method that uses the affinity between antigens and antibodies to specifically separate the measurement target, then identify and quantify the separated product.
IRD	Inherited Retinal Disease. Hereditary diseases characterized by abnormalities in the photoreceptor cells or epithelial cells that adhere to the retina
IVDD	The European In Vitro Diagnostic Medical Device Directive (IVDD).
IVDR	The European In Vitro Diagnostic Medical Device Regulation (IVDR).
LDT	Acronym for “laboratory developed test.” LDTs, often testing methods that have not received regulatory approval, include highly sophisticated and complex IVD-testing that can only be performed in specific clinical testing labs.
Library preparation	The provision of a primer binding region necessary for reading the base sequence, an index sequence to distinguish which sample the sequence came from, or a UID to distinguish each DNA molecule in the sample to the target sequence for the sake of NGS analysis. The operation of assigning a UID sequence by PCR is called UID PCR, and the operation of assigning an index sequence is called Index PCR.
miRNA	MicroRNA (miRNA) is a single-stranded RNA molecule of around 20 nucleotides in length involved in controlling the expression of numerous genes and proteins, thereby making fine adjustments in vital phenomena. In recent years, attention has focused on the miRNA present in exosomes for diagnosing disease, as they are stable, preventing them from being broken down by enzymes in the blood, and their quantities and types vary substantially depending on various disease pathologies and degree of progression.

Glossary

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.
Mutation Allele Frequency	Proportion of alleles on the same chromosome that have genetic mutations but exist within a single population
NGS	Acronym for “next-generation sequencer.” May also refer to a next-generation sequencer, an instrument for reading gene base sequences at high speed.
NIA/AA diagnostic criteria	One of the clinical criteria for mild cognitive impairment or Alzheimer's disease according to the National Institute on Aging (NIA) and the Alzheimer's Association (AA).
Optical Isomer	Substances whose three-dimensional structures are in a mirror relationship and do not overlap even when rotated.
PET	Abbreviation for Positron Emission Tomography. One of the diagnostic imaging methods for cancerous and other pathologies or blood flow.
Plasmid DNA	A small DNA molecule that exists separately from a chromosome and replicates independently. It is considered non-essential for survival and is used in many research and industries as a vector for genetic engineering.
Plasma-Safe-SeqS	Acronym for “Plasma Safe Sequencing.” This pretreatment technology is used to discern between gene mutations and read errors by attaching tags to genes to be amplified.
RAS	One of the gene that is known to cause cancer when it mutates.
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.
Therapy Selection (CDx)	Predicting the effects and side effects of pharmaceuticals prior to administration and making appropriate treatment selections (Companion Diagnostics; CDx)

Lighting the way with diagnostics