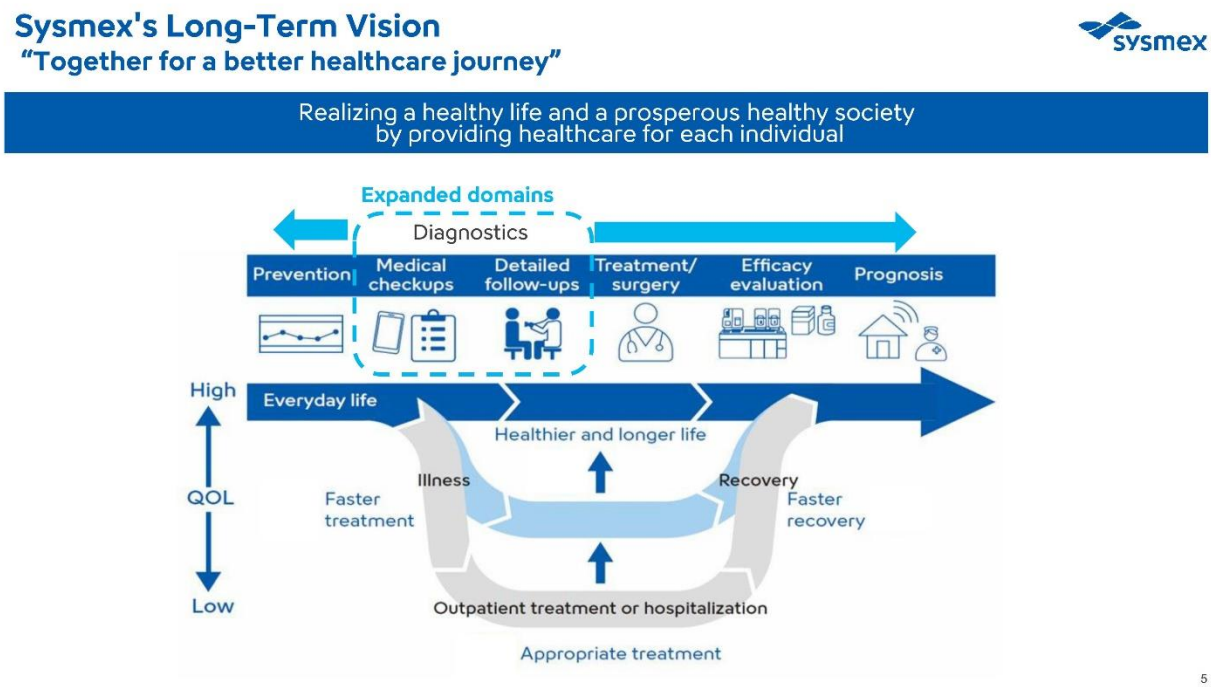
Presentation

Yoshida [M]: My name is Yoshida of Sysmex Corporation. Thank you.

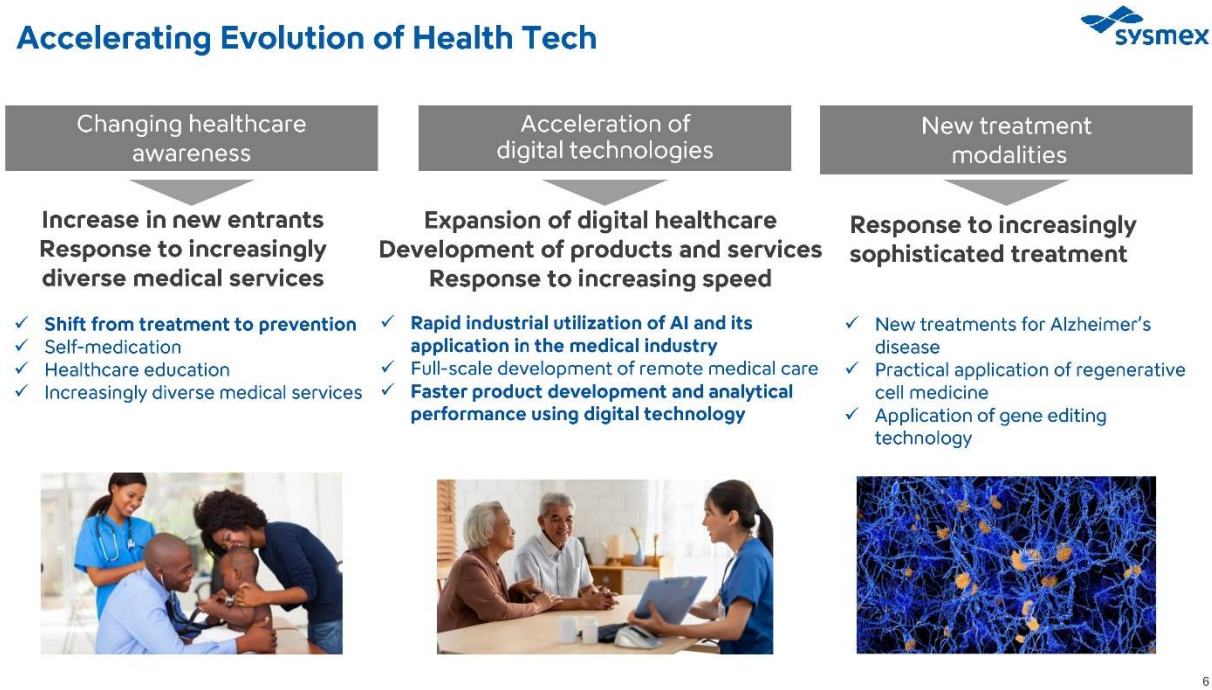
I will now explain our current R&D efforts and our future direction in the context of this technology briefing.

On to the next slide. Today's content consists of these four components.



I will now explain our efforts to realize the healthcare journey and the associated strengthening of R&D functions and systems.

First of all, shown on the slide is Sysmex's long-term vision, which you are all familiar with: “Together for a better healthcare journey.” With this in mind, we have been promoting each of our activities, focusing on how to expand our existing technologies, products, and business experience to prevention and prognosis management.

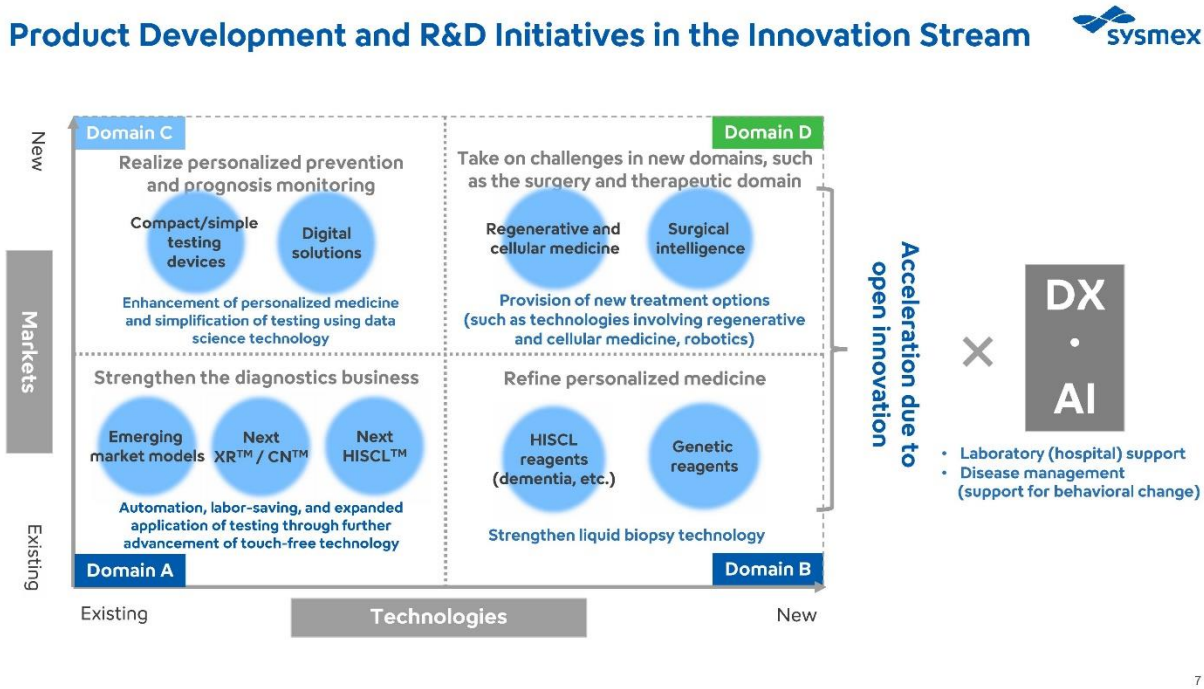


Next slide.

In fact, as you are already aware of the market environment related to healthcare journey, we are already seeing a lot of digital technology being used in our daily lives and in healthcare in particular.

In this context, the shift in awareness of healthcare is naturally a shift toward prevention after the COVID-19 pandemic, and even within this context, diversified medical services are expanding in the form of digital technology.

On the other hand, in the same way, in the world of medical treatment, the development of products and the use of such services are changing at a dizzying pace by combining the advances in knowledge and science with digital technology.



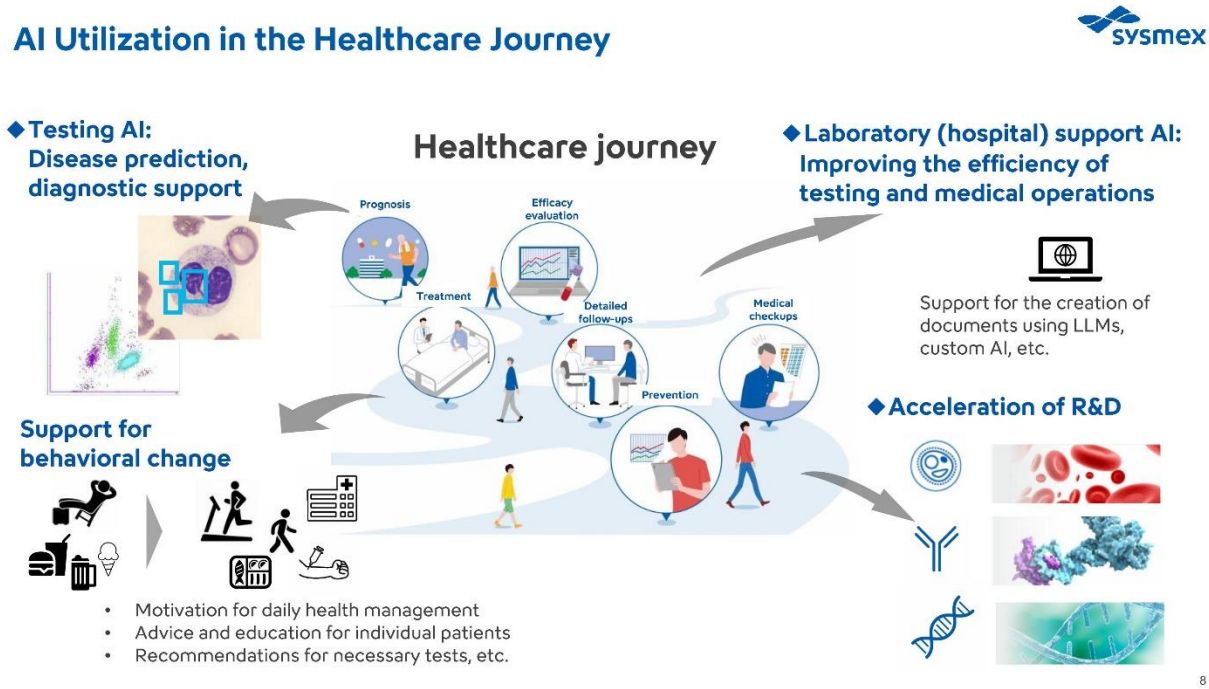
In the midst of these changes in the market and environment, we at Sysmex R&D, as shown here, have set up an innovation stream to expand our existing businesses, new markets, and technologies. The other is to create new medical care, and we are working on each of these four areas.

From the perspective of strengthening our diagnostics business, as stated here, we are building upon our existing technologies to develop attractive and valuable products. I will introduce this later, but we have already taken steps toward next-generation development, particularly in the area of touch-free technology, which enhances laboratory efficiency and improves the quality of testing.

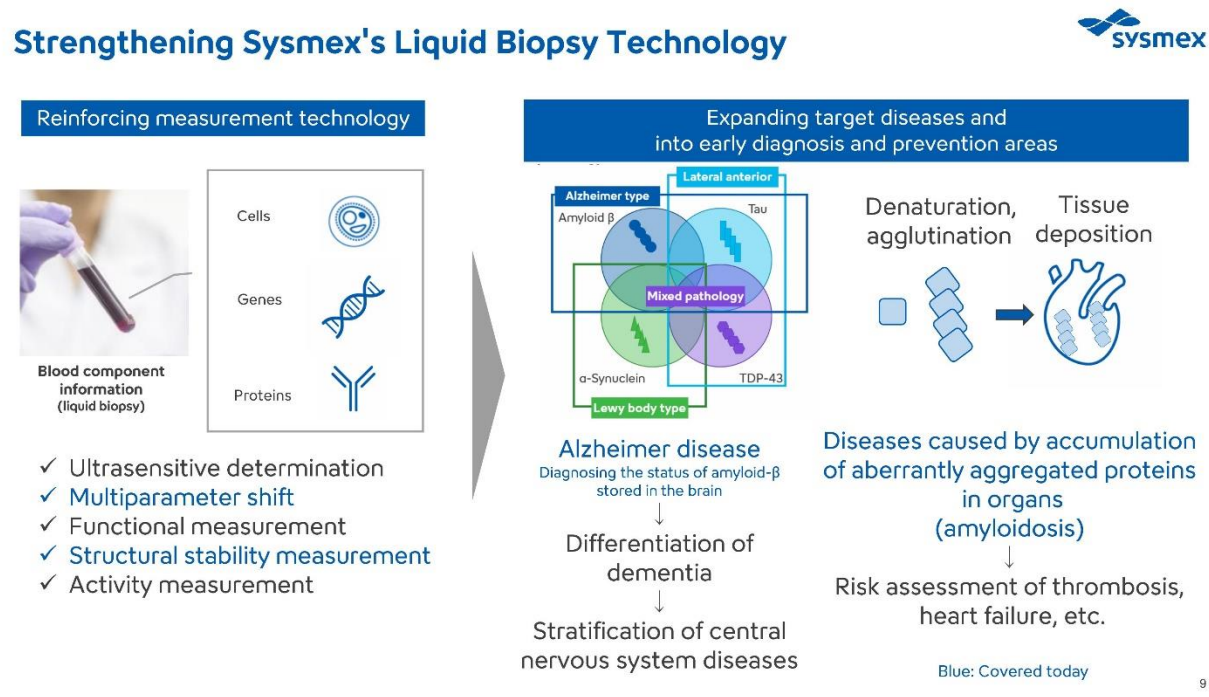
Another area is the use of such technology to further refine personalized medicine. As you are already aware, we are developing technologies to enhance and deepen liquid biopsy. Another area of R&D is personalized preventive and prognostic monitoring, which is being conducted using data science and various miniaturization technologies, with the aim of bringing such products to new markets.

In addition, as you already know, there is the area of surgical treatment, and there is also the area of regenerative and cellular medicine, which is now being promoted at a really accelerated pace. We are taking advantage of the fact that it started in Japan, and we are aiming to create a market that makes use of the technologies we have cultivated so far.

Furthermore, regarding our approach to DX and AI, we will provide a separate explanation later today. In this area as well, we aim to highlight Sysmex's strengths and what makes us unique in the industry. I hope to be able to tell you what is different from what is generally done now.



In fact, we believe that the use of AI will be handled in this way in each stage of the healthcare journey, and we are trying to find ways to incorporate what we have cultivated so far in our R&D activities. We believe that by putting all of these things together, we can create this healthcare journey. I will explain this in more detail later.



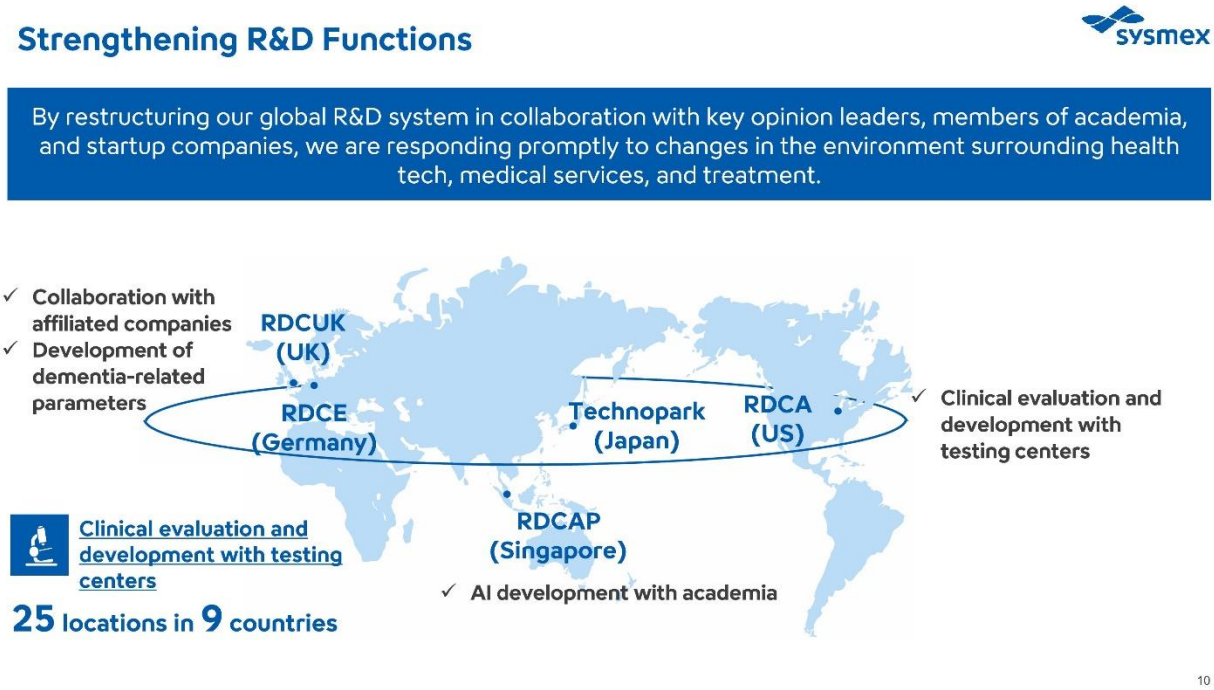
The most powerful technological asset we consider is liquid biopsy, a blood-based diagnostic approach as depicted in this slide. We believe this is one of our greatest strengths, built upon over 50 years of expertise in measurement technology.

Naturally, this includes advancements in high sensitivity, the ability to analyze multiple parameters, panelization, and the integration of new insights. By capturing these components within the blood, we see this as a key competitive advantage.

Looking at the example, this is the state of the brain. It is becoming more realistic to use blood to detect microscopic phenomena, and as you can see from the global situation, there are activities to increase the value of this biomarker in combination with these biomarkers.

One of the key points is to keep up with this trend, and we are also considering expanding this technology to other areas, such as cardiac and vascular diseases.

We believe that one of our major information and technological strengths lies in the combination of conventional tests with information that can have an impact on treatment, especially in the form of rationalized biomarkers.



In order to steadily and reliably implement these initiatives, we believe that one of the key points is to continue to strengthen our R&D functions.

We have been operating 25 R&D bases in nine countries so far, as shown in this slide. By strengthening our functions in a way that is appropriate for each region, we will enable better cooperation between the bases in England, Germany, Singapore, and the US and our core Techno Park in Japan.

In terms of RDCE and RDCA, we have already started evaluation of their instruments and biomarkers, and in Singapore, we are also working on AI development with academia.

By adding product development functions to R&D in Japan and other regions, we will accelerate global development, which we see as our next challenge.

Promoting the Evolution of Hematology Systems

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

Pre-testing management

TA-01 sample storage unit

TS-01 sample sorting unit

BT-50 barcode terminal

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

Reagent management during testing

RM-10 reagent supply unit

- ✓ No need to change reagents during testing

Instrument management

- ✓ Visualization of instrument status

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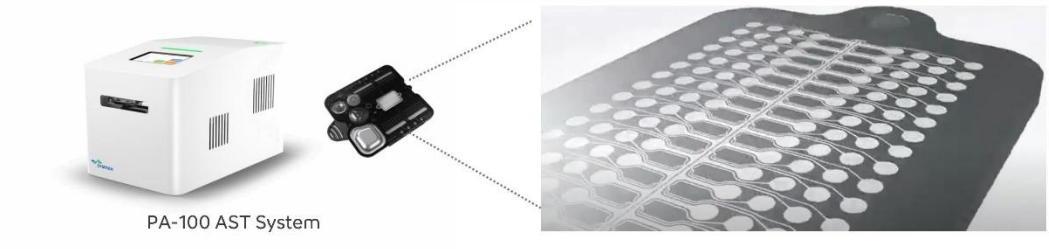
Today, one of the key developments we would like to highlight is our hematology system. We hope you will experience firsthand how we enhance every stage of the testing process, from pre-test management to in-test procedures, while ensuring greater reliability and confidence in diagnostics.

Topics

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

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



PA-100 AST System

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

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

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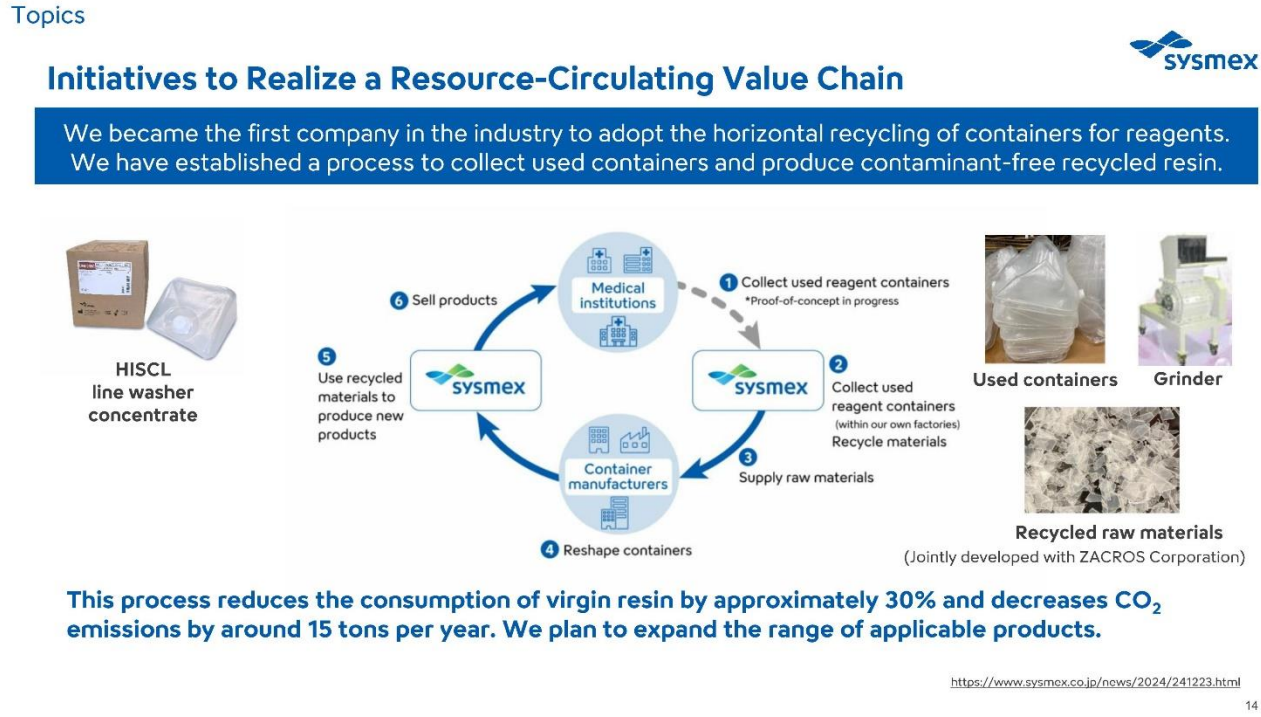
Continuing, a little regarding R&D. I would like to introduce some topics.

This instrument is not yet seen in Japan, but as noted here, it has been awarded the Longitude Prize, the largest scientific award in the UK.

In particular, this instrument provides a breakthrough solution for the currently significant issue of urinary tract infections by detecting the presence of bacteria and evaluating antibiotic effectiveness. This product stands out for its ability to deliver results in less than an hour.

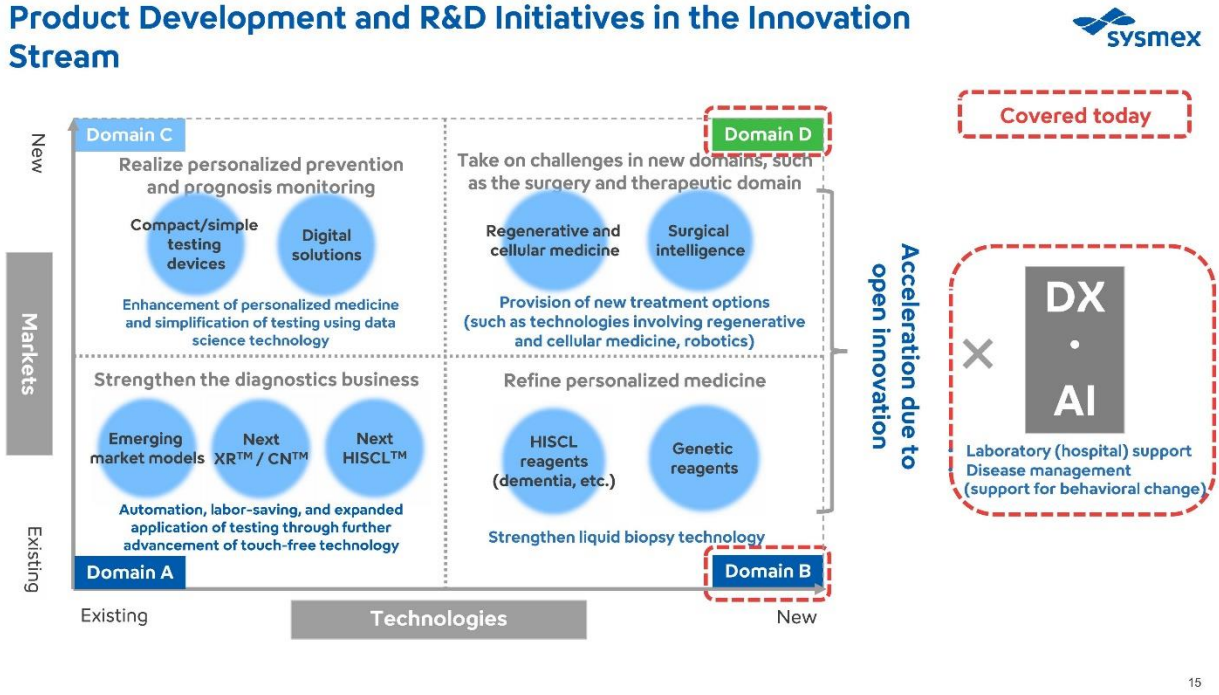
We believe further advancements in this technology will enable its application in more personalized and remote medical care.



I would also like to introduce one of our key initiatives addressing a major social challenge: our commitment to the SDGs.

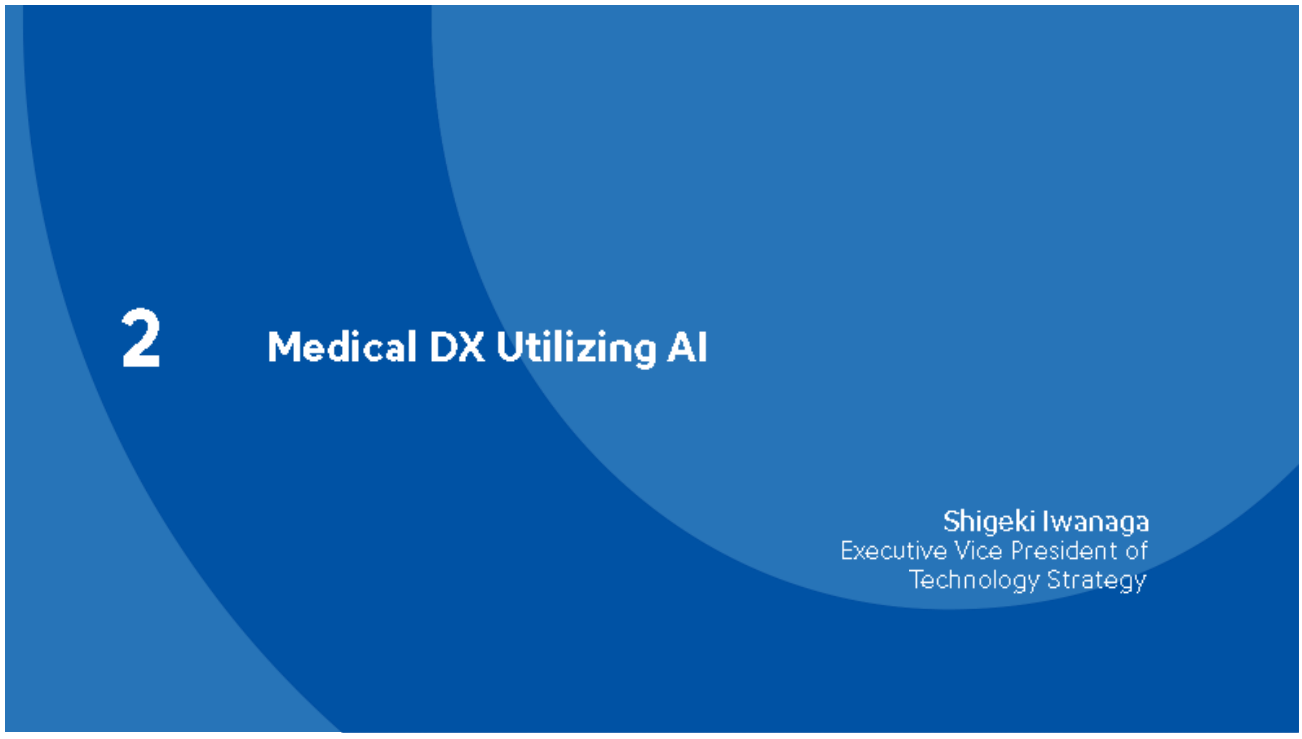
As shown here, and as many of you are aware, medical institutions generate a significant amount of waste daily as part of the testing process. In our efforts to reduce this waste, we believe there is much we can contribute through technology and product development. With the cooperation of manufacturers, we are actively promoting the adoption of closed-loop recycled containers as part of our sustainability initiatives.

As noted here, this initiative has impact of reducing 15 tons of CO_2 annually. We are continuing our efforts to expand the application of this technology to a wider range of products under development.

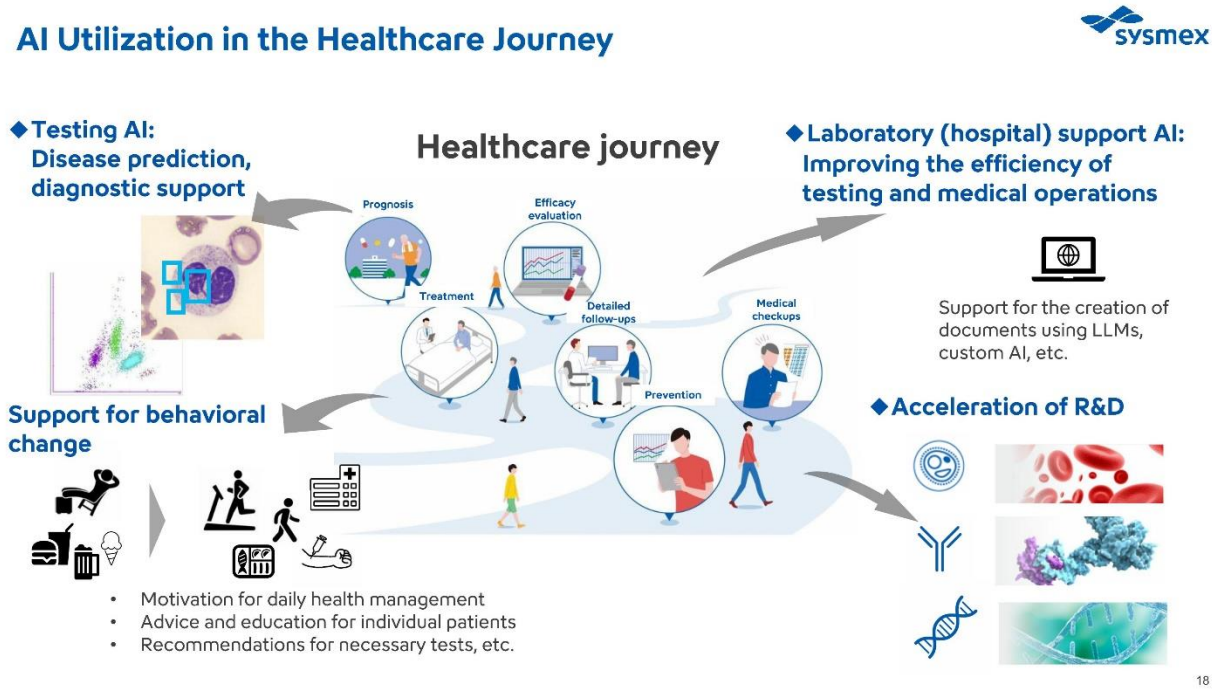


Last but not least, we will continue to aggressively promote R&D in order to expand the existing market to new markets and new applications. In this way, we will continue to realize a new form of medicine, the healthcare journey, by making full use of advanced science and information science. We look forward to your support. Thank you.

That's all from me. Thank you very much.



Iwanaga: My name is Iwanaga. Thank you. I would like to explain about AI-based medical DX.



As Yoshida mentioned, this section illustrates the use of AI in the healthcare journey. Here, we have outlined three key AI-driven approaches.

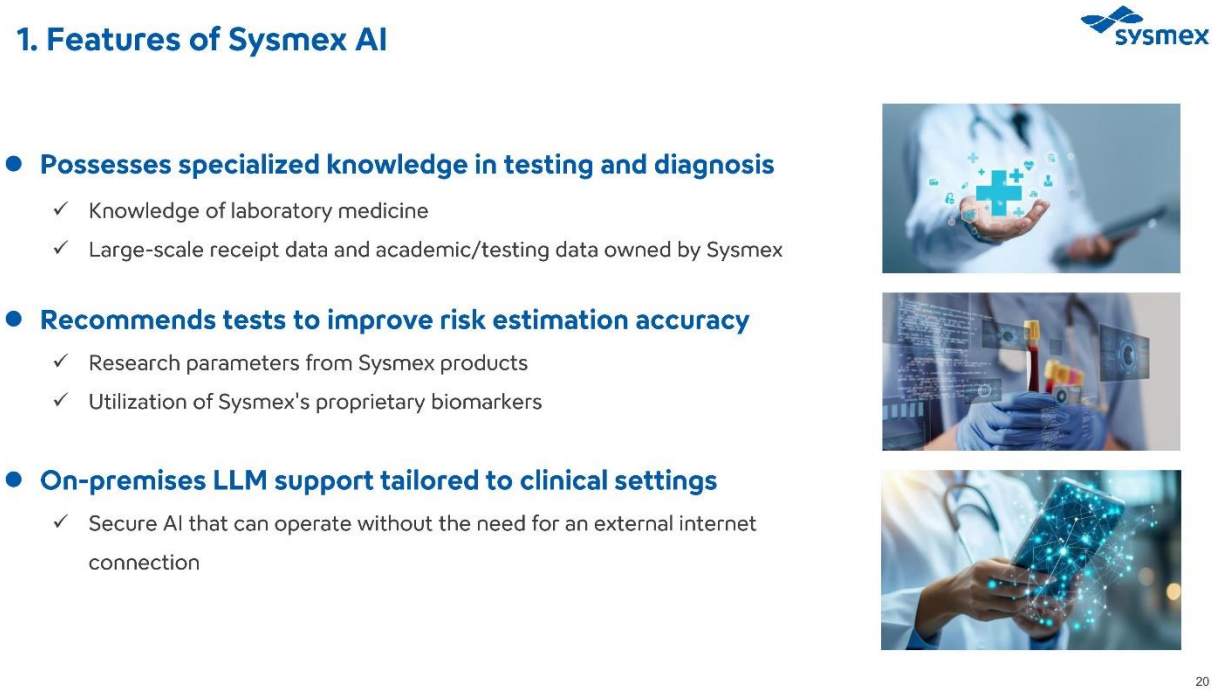
We believe that AI in disease management can provide disease prediction, diagnostic support, and behavioral transformation support. In addition to this, we believe that AI can be used to improve the efficiency of laboratories and hospital operations. Third, as an internal activity, we believe that this type of AI can be used to accelerate R&D.

Development of Sysmex AI

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

In this context, we are developing our own AI, Sysmex AI.

Due to time constraints today, we will focus on explaining two AI applications listed here: laboratory (hospital) support AI and disease management AI.

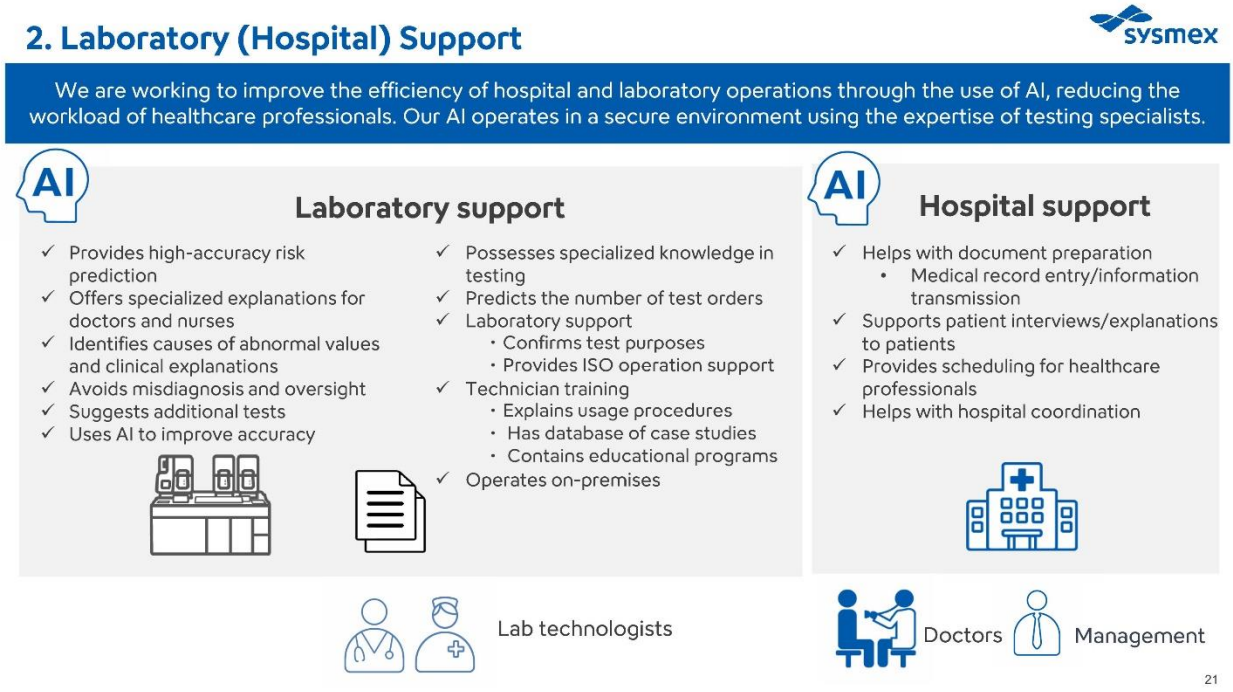


First of all, let me explain the characteristics of Sysmex AI.

As you can see here, Sysmex AI has three key features. The first is to have expertise in testing and diagnosis, such as laboratory medicine knowledge, large-scale receipt data, and our own academic and laboratory data, which we will use to train AI.

The second is test recommendations to improve the accuracy of risk estimation. The AI is designed to improve the accuracy of risk estimation by utilizing the research items of our products and our own biomarkers.

Third, we are developing an on-premise LLM for clinical sites, a secure AI that can operate without requiring an external Internet connection.



The first AI we intend to develop using this type of AI will be AI for laboratory (hospital) support.

Through the use of this AI, we hope to improve the workload of healthcare professionals by streamlining operations within hospitals and laboratories. The AI we are developing will be an AI that will be used where we possess the knowledge of testing specialists and can operate in a secure environment.

On the left side, in the section on laboratory support AI, we have listed the characteristics of each of these products in text form. We would like to realize highly accurate risk forecasting, which cannot be achieved with ordinary AI, by utilizing and learning characteristic data from our products.

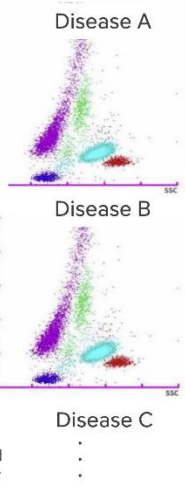
The laboratory support AI is currently under development with a plan to launch it in the fiscal year ending March 31, 2026, and we are working to expand the scope of its application in the area of hospital support AI.

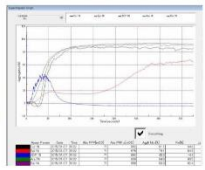
2. Laboratory (Hospital) Support: Examples of Research Parameters Utilized

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

XR-1000 multiparameter automated hematology analyzer

CN-3500/6500 automated blood coagulation analyzer



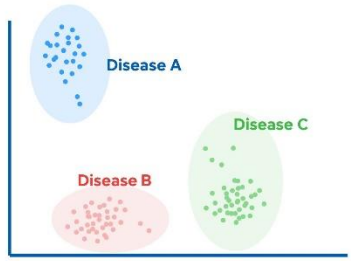


AI Algorithm

Features (parameters)

RBC/PLT Reportable	WBC Reportable	WBC Research	WBC Sensitivity
RBC	WBC	TNC	NE-SSC
HGB	NEUT#	(WBC-N)	NE-SFL
HCT	LYMPH#	(TNC-N)	LY-X
MCV	MONO#	(BA-N#)	LY-Y
MCH	EO#	(BA-N%)	MO-X
MCHC	BASO#	(WBC-D)	MO-Y
PLT	NEUT%	(TNC-D)	NE-WX
RDW-SD	LYMPH%	NEUT#&	NE-WY
RDW-CV	MONO%	NEUT%&	LY-WX
NRBC#	EO%	LYMP#&	LY-WY
NRBC%	BASO%	LYMP%&	MO-WX
(PLT-I)	IG#	HFLC#	MO-WY
MicroR	IG%	HFLC%	NEUT-RI
MacroR	Q-Flag[LS]	(BA-D#)	NEUT-GI
R-MFV	Q-Flag[At-Ly]	(BA-D%)	
P-MFV			

Classification of diseases through reanalysis of measurement data



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Next, this is our laboratory support AI that leverages research parameters. By integrating testing data from our instruments with multivariate analysis of blood cell counts, we aim to stratify diseases that were previously difficult to distinguish.

Here, we have presented a conceptual diagram illustrating how we utilize data from our hematology and hemostasis instruments to enhance disease classification. Although we have not been able to provide detailed information to date, we have been able to demonstrate this in several areas of research.

3. Support for Behavioral Change

We are utilizing digital data and proprietary AI to promote medical schemes and individual behavior change.

Predictive, **P**reventive, **P**ersonalized, **P**articipatory

Detection of onset	→	**Prediction** of onset
Treatment of disease	→	**Pre-disease** care and **prevention**
Standardized treatment	→	**Personalized** medicine
Healthcare professional-centered	→	**Active** individual **involvement**
Medical checkups, detailed follow-ups	+	Value provision through digital and AI

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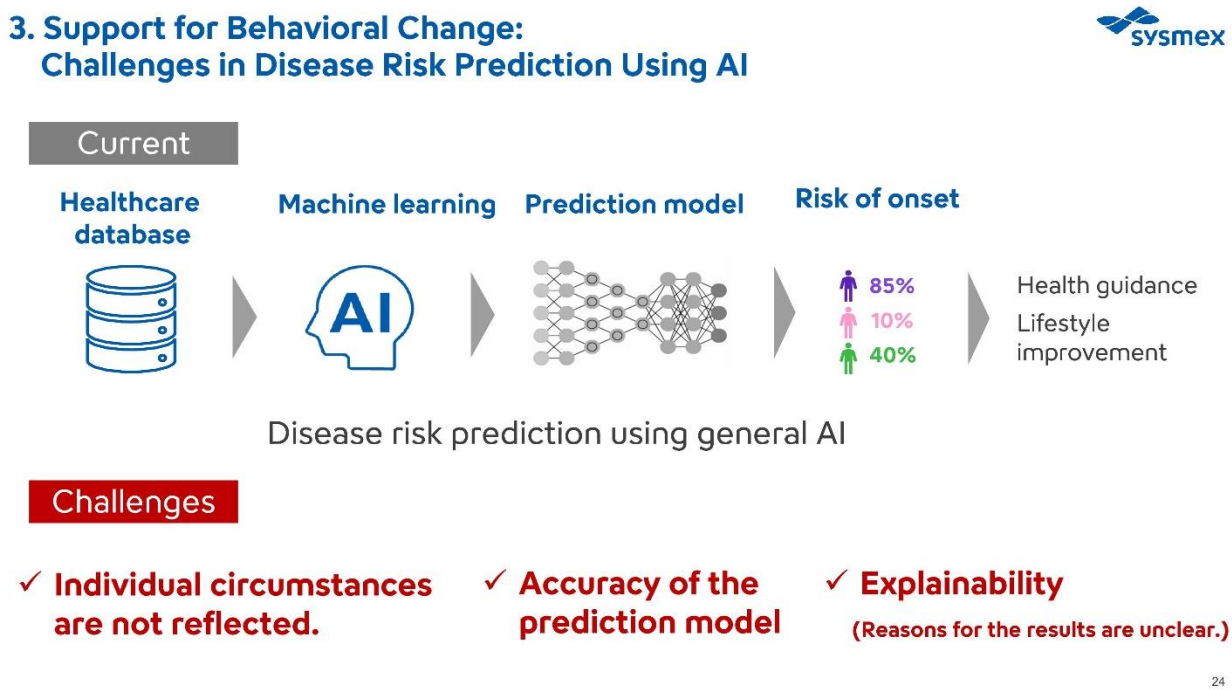
Another AI we are working on is a behavioral transformation support AI.

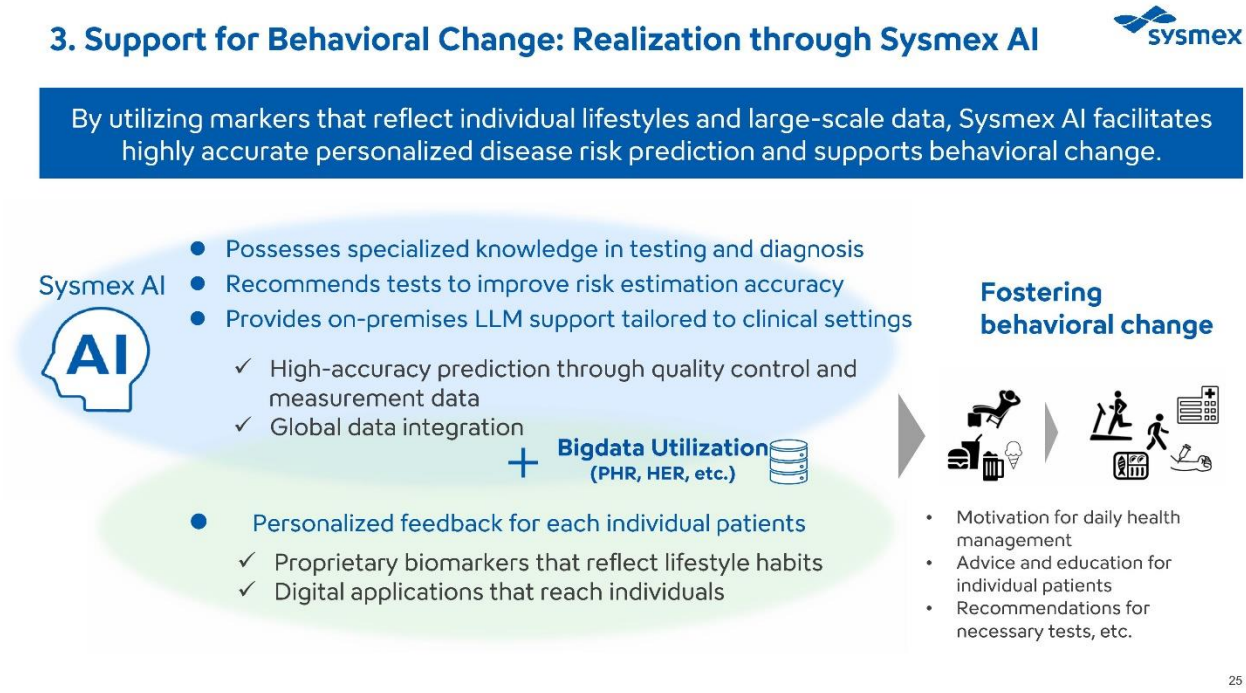
In 2011, an American researcher proposed P4 medicine. It will be a new medical concept expressed by the English words beginning with the four P's written here. In the context of prediction, prevention, personalized medicine, and patient engagement, active participation by individuals in their own treatment process is crucial.

We hope to make good use of AI in these areas to realize new medical processes. Through these AI initiatives, we hope to move from the existing medical process to a new medical process that utilizes digital and AI.



In terms of the challenges of disease risk prediction using AI that have been addressed so far, we have used machine learning to learn big data from population-related medical data to create predictive models.

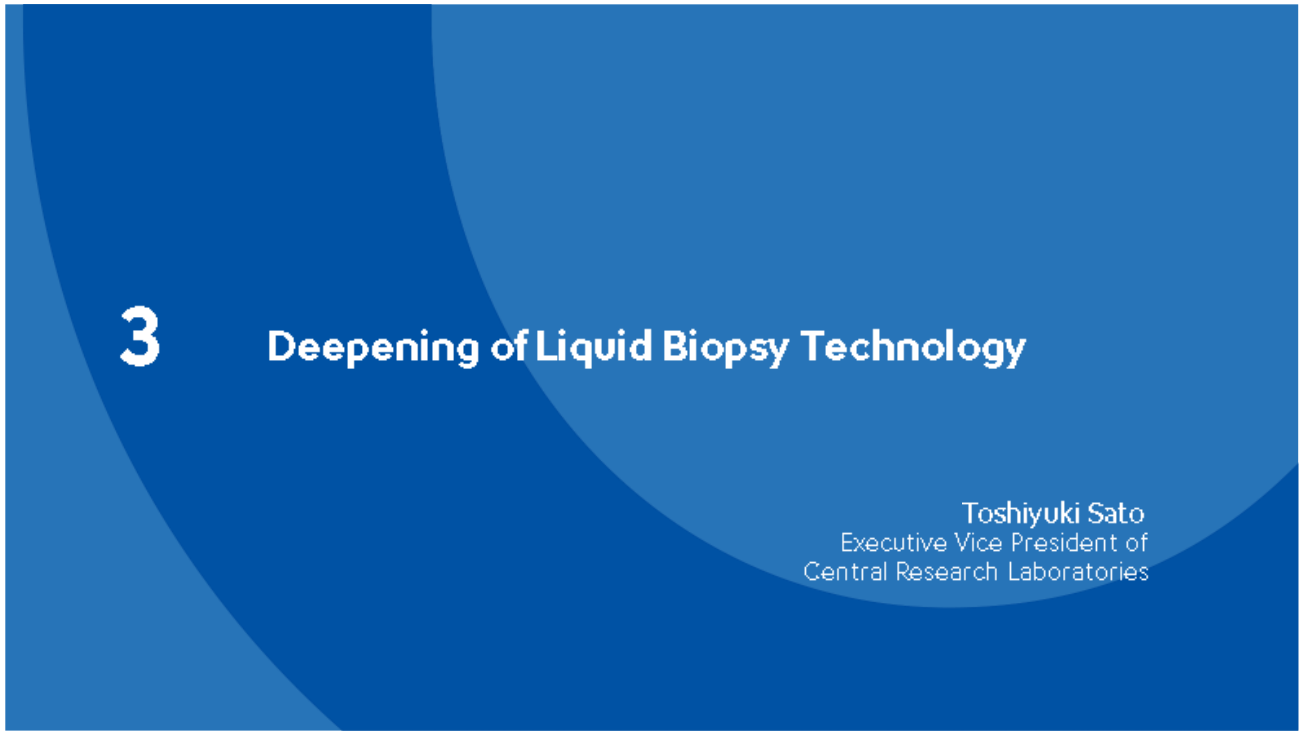
Traditionally, health guidance and lifestyle improvements have been based on population-level stratification, using predictive models for groups rather than individuals. However, this approach presents several challenges: individual data is not fully reflected, the accuracy of predictive models for individuals remains limited, and the interpretability of prediction results is often insufficient.



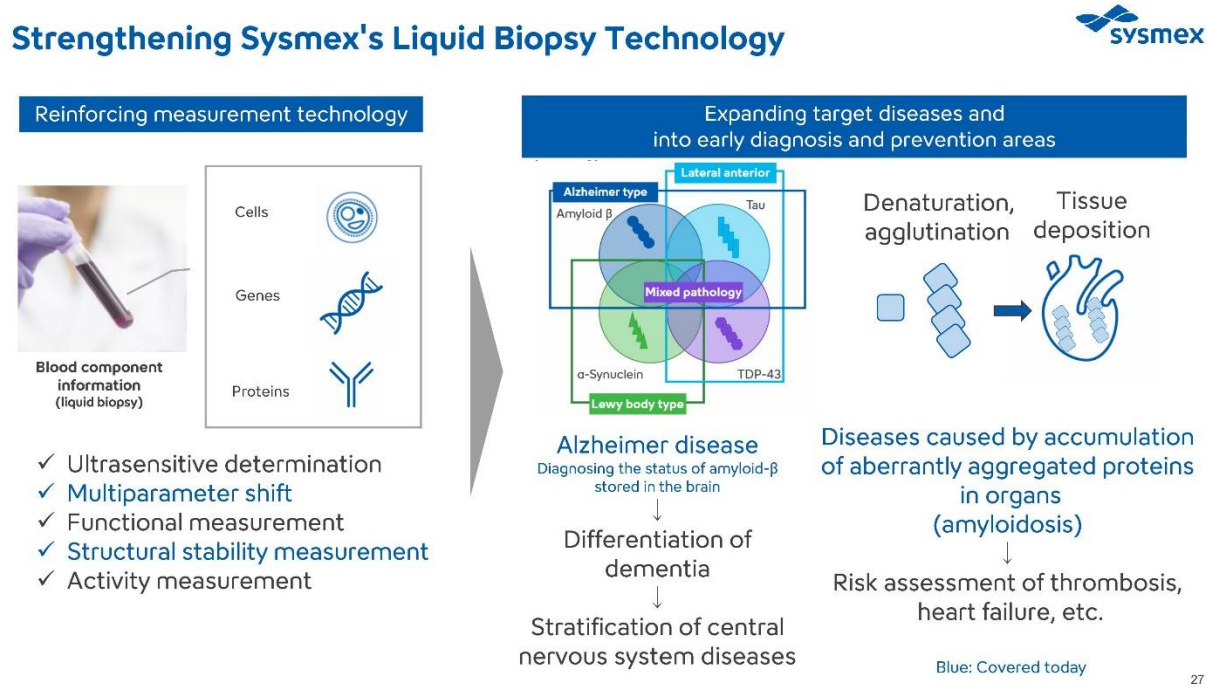
To overcome the abovementioned challenges, we leverage Sysmex AI, which builds on the unique capabilities of our products to deliver higher-precision predictions. By utilizing our global data collection network, along with large-scale datasets from PHR and EHR, we are combining those data with that of new biomarkers and digital applications which can obtain personalized patient data. Through these advancements, we strive to realize new AI-driven solutions that contribute to behavioral transformation in healthcare.

We would like to further promote these activities and provide products that can contribute to the field of prevention and be more useful to patients.

That's all from me.



Sato: This is Sato and I will explain about liquid biopsy.



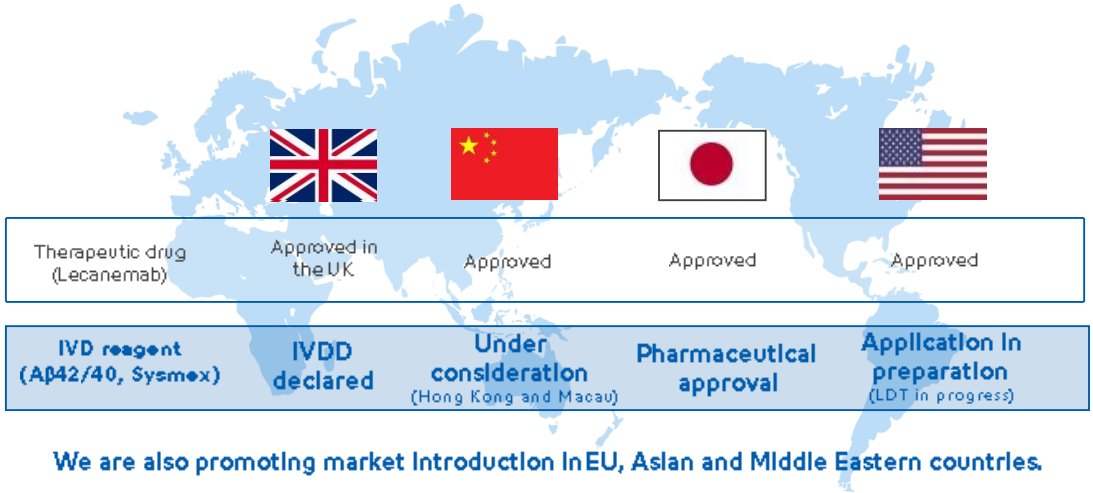
As Yoshida explained, we are working to deepen our liquid biopsy technology to increase the number of diseases that can be measured by it, and to diagnose diseases at an even earlier stage.

Today, I will explain our efforts in Alzheimer's disease and its expansion, and also in the new field of amyloidosis, which is shown here.

Developing Amyloid-β Testing Reagents

sysmex

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



We are also promoting market introduction in EU, Asian and Middle Eastern countries.

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First, I will present a slide that we shared last year, which provides an update on the Amyloid beta testing reagents and their current status. Although some countries are still considering or have applications pending, we are steadily introducing the product to the market in Europe, the Middle East, and Asian countries.

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

sysmex

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

APOE genotype: association with the incidence of side effects from Lecanemab

ε2/2, 2/3, 3/3, 2/4, 3/4, 4/4 types exist

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

Confirmed 100% accuracy rate of the diagnostic reagent

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

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

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

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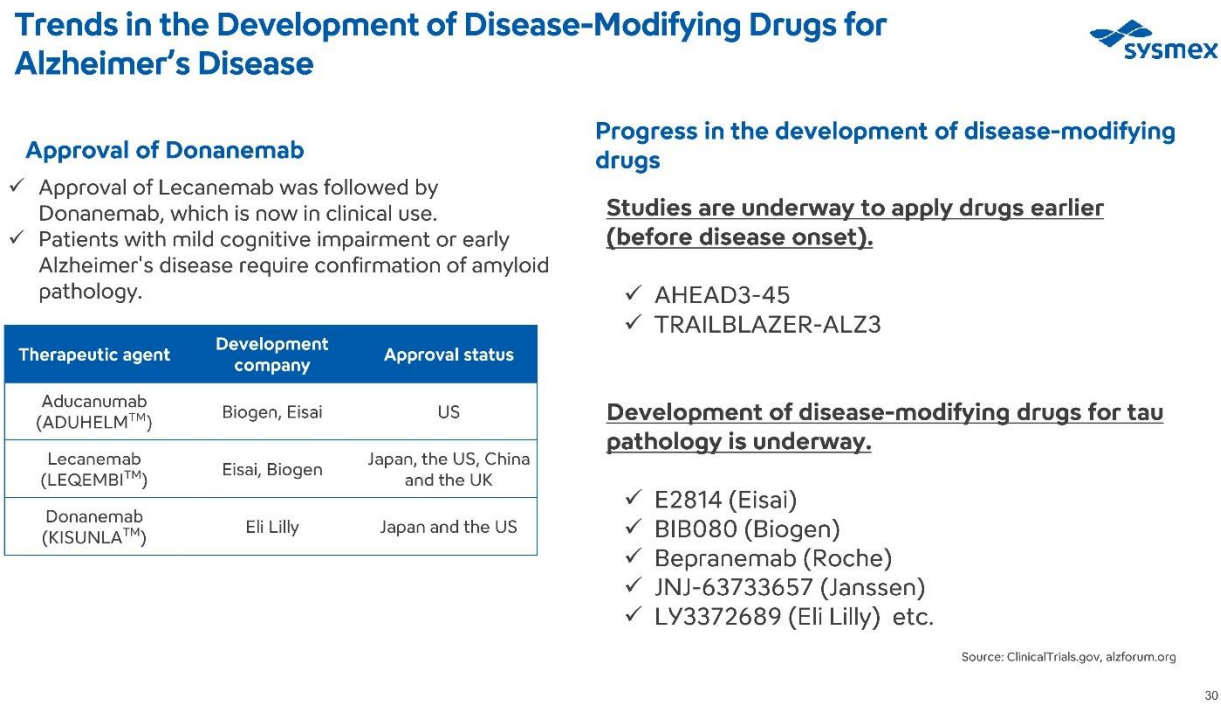
The other is that we have completed the application for manufacturing and marketing of a test reagent to determine the risk of side effects of therapeutic drugs.

This reagent is designed to measure the APOE gene, which has three variants: APOE2, APOE3, and APOE4. Each individual inherits a combination of these from their parents. Research has shown that individuals who

inherit two copies of the APOE4 variant face a significantly higher risk of side effects when treated with lecanemab.

The guidelines also call for measuring the APOE genotype when administering medication, if possible, but there is no insurance-covered test in Japan yet, so we have developed a test method. The right-hand side shows the performance of the test. We have created a highly accurate test that is 100% consistent with the reference method, applied for manufacturing and marketing approval, and are now in the process of applying for insurance coverage.

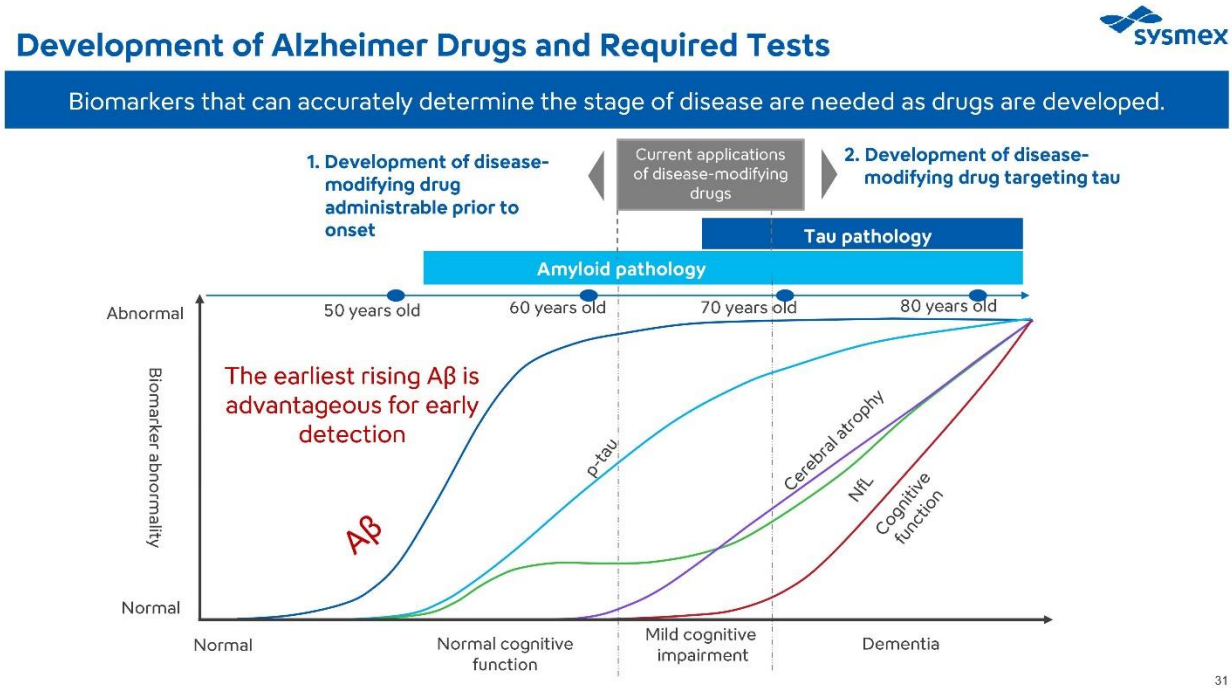


So far, we have covered key topics, but now I will discuss our future direction, considering environmental analysis and drug development trends.

First of all, on the left side. As many of you may already know, following lecanemab, a new drug, donanemab, has also received approval.

The key point related to our discussion today is shown on the right side. One is that studies are underway to administer medication at an earlier stage, before cognitive abnormalities appear. Another key aspect is the later-stage developments in this field. Beyond amyloid pathology, there is ongoing drug development targeting tau pathology.

While only five treatments are listed here, many more are currently in development. In response to this, the question becomes, what are we going to do about it?



This diagram, which we have presented several times in past briefings, horizontal axis represents age or how some individuals progress toward dementia over time.

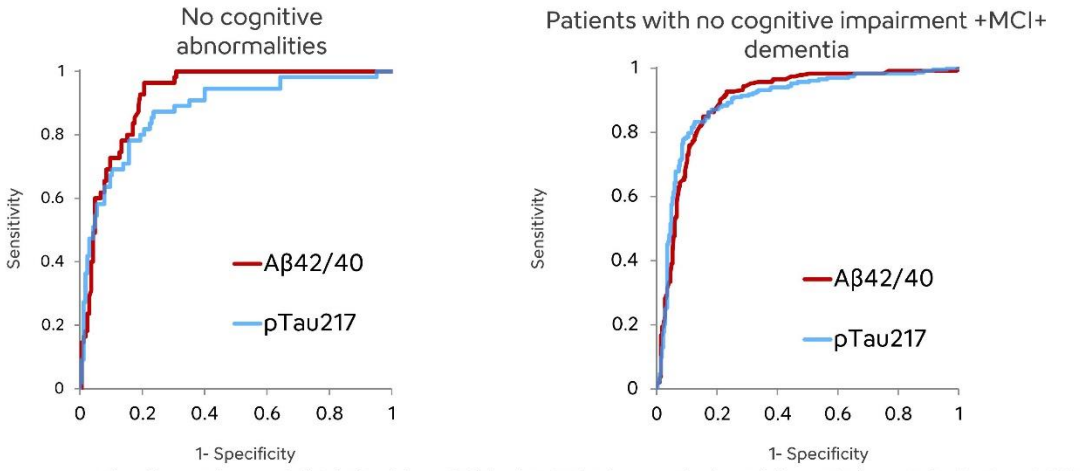
In this model, cognitive impairment increases as you move upward. It suggests that around 20 years before symptoms appear, Amyloid beta begins accumulating in the brain. This is followed by the emergence of tau pathology, which leads to neuronal cell death, ultimately resulting in cognitive decline. Currently, lecanemab and donanemab are only approved for mild cognitive impairment or early-stage dementia, making their applicable patient population very limited.

Earlier, two key aspects were highlighted in the environmental analysis: one of them is the study exploring whether these treatments could be administered at an even earlier stage, before cognitive impairment appears, during the normal phase. Additionally, tau-targeting drugs are being developed as a potential treatment for patients who are considered too late for amyloid-targeting therapies. The question is how we will respond to this.

Point number one. When it comes to early-stage detection, we believe our Aβ biomarker plays a key role and offers a significant advantage. In principle, Aβ is the earliest biomarker to appear, making it the first indicator of disease progression. Therefore, by accurately measuring Aβ, we aim to contribute to earlier intervention at point one of the disease progression.

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

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



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

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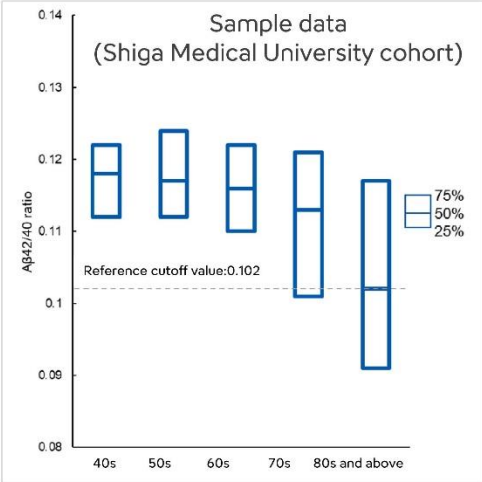
In fact, evidence is emerging. The ROC curve may be a bit complex to interpret, but essentially, the higher it is, the better the diagnostic performance of the test.

In the context of amyloid detection, our test has shown better results when compared to phosphorylated Tau217, especially in the early stages where there are no noticeable cognitive impairments. However, when considering the entire number, including individuals who already exhibit cognitive impairment, the differences become less pronounced.

This result suggests that our Aβ42/40 reagent is particularly valuable for determining treatment decisions at the pre-symptomatic stage, before cognitive abnormalities appear.

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

The performance verification of Aβ42/40 is being promoted in the real world at multiple cohorts and facilities.



<Evaluation in cohorts>

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

others

< Prospective real-world studies>

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

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

33

The Aβ42/40 assay has faced concerns regarding robustness and other factors. In response, we are actively working to accumulate real-world data to strengthen its reliability. We have several facilities listed here, but we also do this at many others.

On the left. Here is one example, which provides an interesting insight into the Aβ positivity rate across different age groups. In their 40s, 50s, and 60s, the number of individuals testing positive for Aβ remains relatively low, with most cases staying above the threshold line. However, by the 70s, the data shows that 25% of individuals fall below the threshold, meaning one in four tests positive for Aβ. Half of those in their 80s are positive, which means that cognitive function is actually normal for all of them.

This indicates that such changes are already occurring in the brain, even though this trend is currently observed as age dependent. The next step is to examine how these patterns evolve when other disorders are present. We would like to accumulate evidence, including various types of stability, and link this to insurance treatment.

Initiatives to Develop p-Tau Markers

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

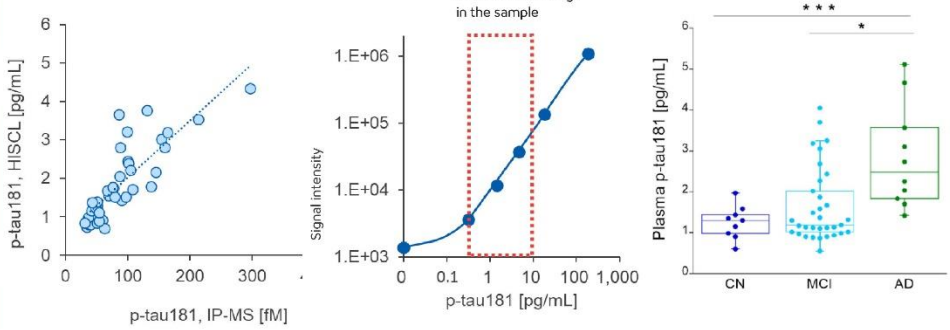
< Development Strategy >

Phosphorylated tau has many analogues, as in the case of Aβ.

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

Performance verification in clinical samples

Example of p-tau181



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

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Meanwhile, the development of a phosphorylated tau marker to detect amyloid is also underway in parallel.

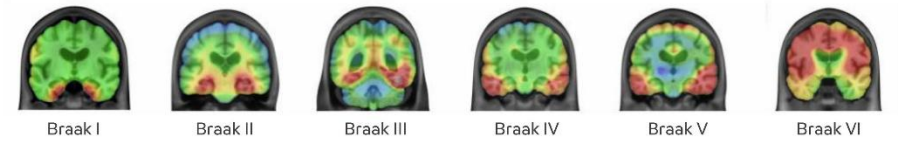
Sysmex's strength lies in the fact that we have built instruments that correlate with mass spectrometry, which is why we have achieved high performance in Aβ. We have several tau markers, and our strategy is to select antibody sets and reagent compositions that correlate well with mass spectrometry and measure patient samples for these markers.

The example shown here is for phosphorylated Tau181, but we have already obtained similar results for Tau217 as well.

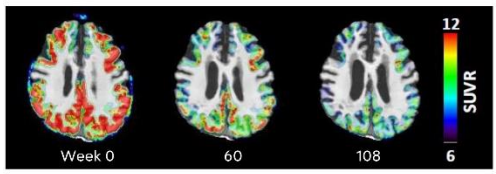
Need for Diagnostics/Liquid Biopsy for New Therapeutics

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

TauPET is needed to determine the status of Tau accumulation



The latest clinical trial data on tau-targeted disease modification (E2814) (time course of PET images)



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

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Next, we will move on to the discussion on tau. The discussion now shifts to the right side of the time-series diagram, focusing on the development of new treatments for patients with advanced disease stages, who are currently ineligible for lecanemab therapy.

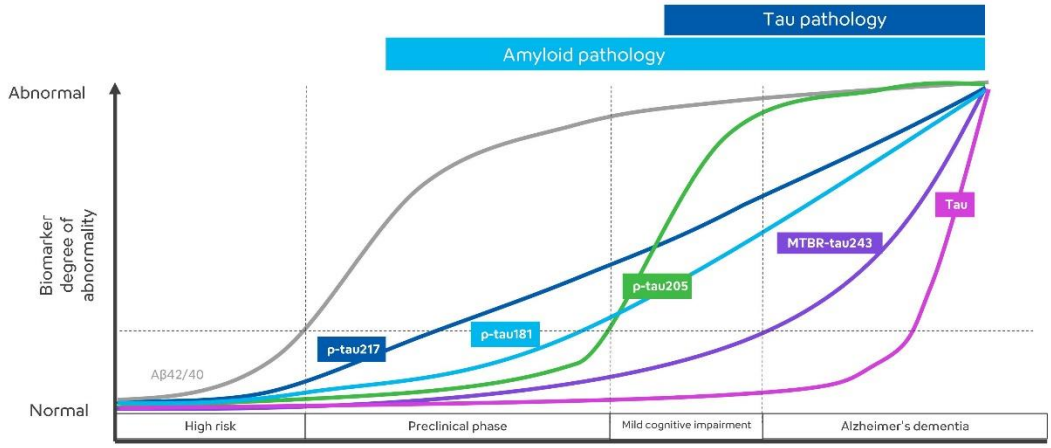
Currently, to examine how tau accumulates in the brain, the standard method used is TauPET, which corresponds to amyloid PET. As you can see very clearly in this, as the stage progresses, the red area increases and the location shifts. This is how we determine tau accumulation in these conditions.

One example from the earlier study involved E2814, a tau-targeting drug developed by Eisai. TauPET imaging shows that tau levels decrease drastically over one to two years after treatment initiation.

Currently, TauPET is required to evaluate tau PET. This is actually the same image as Aβ's roughly 5 to 10 years ago. One of the pillars of our R&D is to replace what is currently only available with PET with blood.

Biomarkers for Understanding Tau Pathology

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



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

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Several biomarkers have already been identified for assessing tau pathology. Since p-Tau217 levels start increasing at a very early stage, it reflects amyloid pathology rather than tau pathology.

In contrast, later-rising markers such as p-Tau205 and MTBR-tau are believed to better represent tau pathology. Our goal is to utilize HISCL technology to develop assays for these multiple biomarkers, enabling precise tau staging through comprehensive measurement.

Development of Biomarkers for Patient Stratification to Aid Treatment

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

AA 2024 diagnosis and staging criteria

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

* Seed Amplification Assay Blue: Under development

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

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

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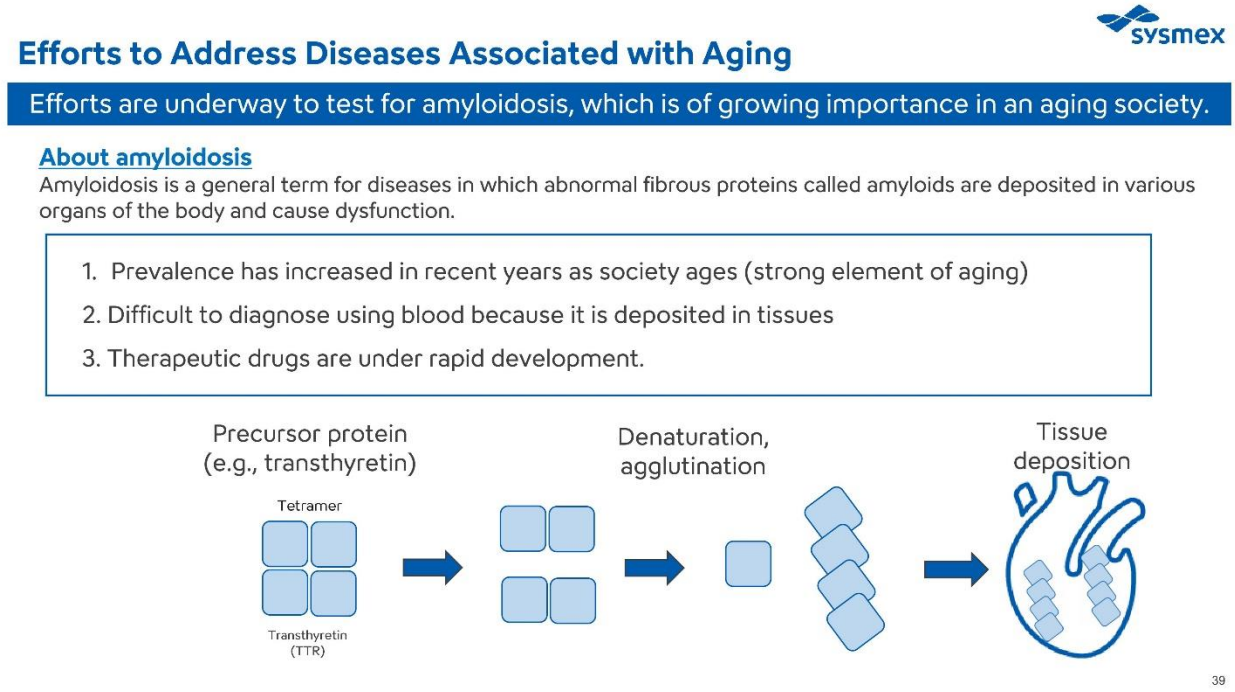
In fact, the 2024 guidelines have already proposed staging criteria, which were presented at academic conferences. These guidelines suggest that it would be beneficial to measure multiple biomarkers, including the ones mentioned earlier, using blood or cerebrospinal fluid.

Sysmex is actively developing almost all of the blue-marked biomarkers shown here in parallel. As each is completed, we plan to gradually introduce them to the market.



From this point forward, we will shift to a completely new topic, our latest initiatives. The effort is called amyloidosis.

This section, titled “Addressing Aging-Related Diseases,” highlights the need for diagnostic tests that align with an aging society. In this context, we are focusing on amyloidosis. Amyloidosis is a condition in which amyloid, a fibrous substance, accumulates in organs, leading to organ dysfunction. When amyloid builds up in the brain, it results in Alzheimer’s disease. However, amyloid can also accumulate in various other organs, affecting their function.

One key characteristic of these new initiatives is that they address conditions that are increasing with the progression of an aging society, many of which are closely linked to aging-related factors.

The second point is that these conditions involve tissue deposition, making blood-based diagnostics challenging. This challenge serves as a key motivation for exploring liquid biopsy as a potential solution.

The third point is that these initiatives are not just about diagnostics—they are closely linked to treatment options, ensuring a direct connection between testing and therapy.

Approach to Cardiac Amyloidosis

sysmex

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

About transthyretin cardiac amyloidosis

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

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

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

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

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

* heart failure with preserved systolic function

As our first effort in this disease, we are targeting the heart and working on cardiac amyloidosis. Among these, we have begun to focus on transthyretin cardiac amyloidosis, in which a protein called transthyretin accumulates.

These are exactly the three I mentioned earlier. With the progression of an aging society, one key focus is HFpEF, a form of heart failure. It is estimated that 30 million patients worldwide could be affected by this condition.

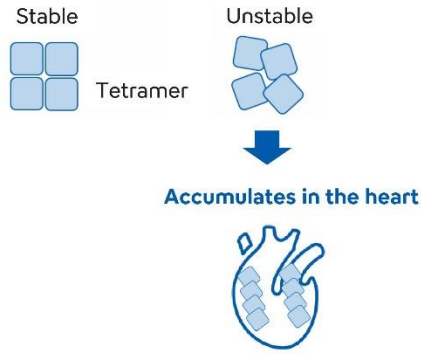
Another challenge is tissue deposition, which currently requires cardiac tissue biopsies or nuclear medicine imaging for diagnosis. These methods are invasive and complex, highlighting the need for alternative approaches.

In recent years, treatment options for amyloidosis have emerged, though they remain quite expensive. Notably, in the case of cardiac amyloidosis, it is estimated that 99% of patients remain undiagnosed. We aim to develop robust diagnostic solutions for these highly unmet medical needs.

Development of New Test Method for Transthyretin-Type Cardiac Amyloidosis

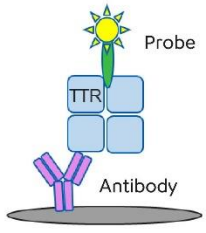
The development of an amyloidosis test using HISCL is underway.
We have applied for a basic patent through joint research with Kobe University.

Transthyretin (TTR) and its properties

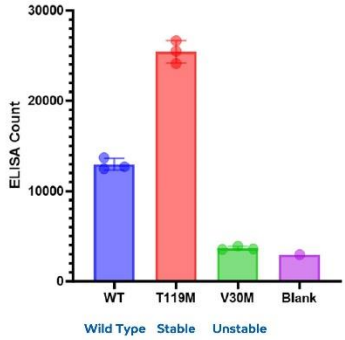


Construction of measurement system using immune reaction

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



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



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In fact, we are already conducting R&D and are collaborating with Kobe University. The basic principle has already been developed, and a basic patent has been applied for. This is where new liquid biopsy technology comes into play. Traditionally, we have focused on various measurement approaches, such as high-sensitivity detection and functional analysis. However, in this case, the focus is on measuring stability. When this protein becomes unstable, it begins to accumulate in tissues, so we created a meter to measure this stability and applied for a patent.

Expanding Efforts to Address Amyloidosis-Related Diseases

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

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

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

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

+

Enhacement of liquid biopsy technologies

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

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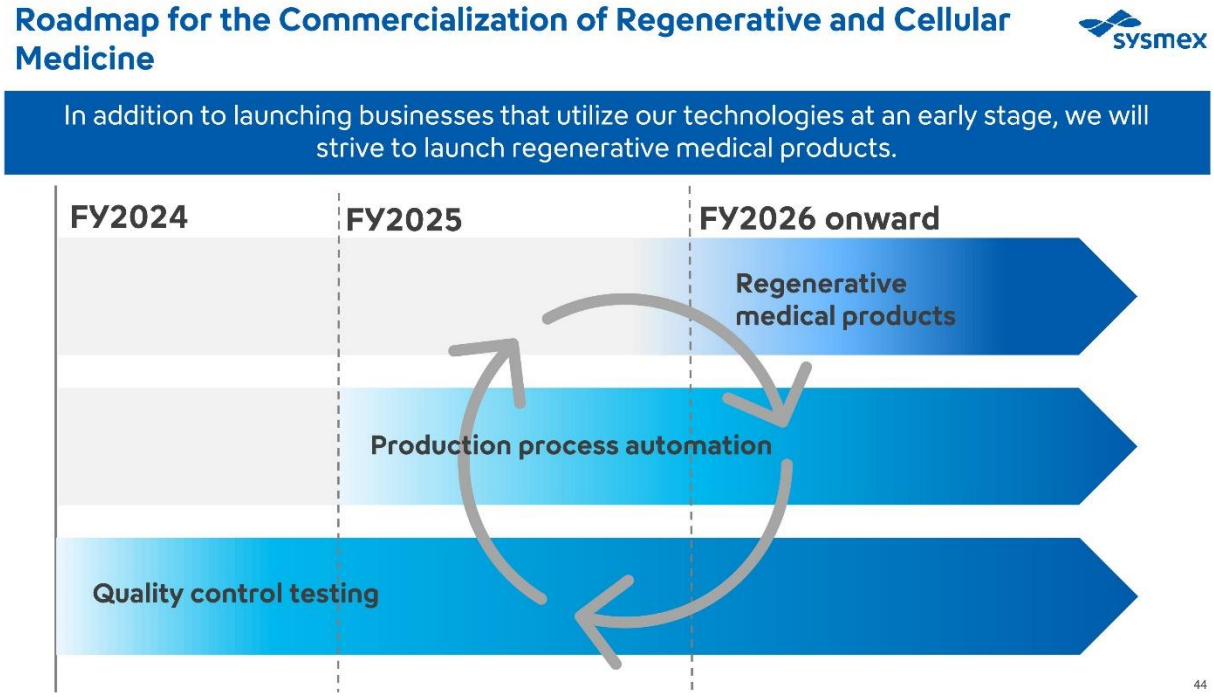
This is the last slide. While we previously discussed cardiac amyloidosis, there are various other forms of amyloidosis as well.

We have started a joint research project with Kumamoto University's Amyloidosis Center, which is one of the most advanced centers in this field in Japan.

Sysmex will continue to deepen its liquid biopsy technology and introduce new tests to the world for this area of high unmet needs.

That is all from me.

Tsujimoto: I will now provide an update on the progress made over the past year in regenerative and cellular medicine, as part of our efforts in Innovation Scheme Area D treatment initiatives.



This slide shows a roadmap of our efforts, with three themes.

The bottom section on quality control represents our initiative to apply the technologies developed for in vitro diagnostics to the cell manufacturing process. In the area of automation, our engineering technology can really be used in abundance to automate the cell manufacturing process. And finally, at the top right is the development of regenerative medical products.

In the center, you may notice a circular rotating arrow, symbolizing that these three elements are not progressing independently but rather influencing and enhancing each other in a synergistic manner. By working on regenerative medicine products, we can understand the essentials of quality control in great detail, and by working with other companies on quality control, the knowledge we gain can be applied to our own pipeline development.

Today, I would like to focus on quality control, which is starting to show some signs of commercialization, and automation, which is becoming more visible. However, simply mentioning these three elements without further explanation would leave the picture incomplete. Therefore, in the next slide, I will provide a brief update on regenerative medicine-related products.

Regenerative Medicine Product Pipeline and State of Progress

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

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

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

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These three pipelines are the same ones you have already seen at last year's R&D meeting. There will be no change in the timing of the regulatory filing.

The update pertains to the second column from the right, specifically the progress section. At the top, AlliedCel is advancing its inducible inhibitory immunoregulatory therapy. As for this area, the investigator-initiated study is progressing smoothly.

These three pipelines are the same ones you have already seen at last year's R&D meeting. There will be no change in the timing of the regulatory filing.

The update pertains to the second column from the right, specifically the progress section. At the top, AlliedCel is advancing its inducible inhibitory immunoregulatory therapy. As for this area, the investigator-initiated study is progressing smoothly.

The cultured hematopoietic stem cells in the middle are still in the early stages of development, but we will soon have key data.

Finally, Megakaryon is advancing its iPS-derived platelet formulations by focusing on establishing higher-yield cell lines, automating the manufacturing process, and exploring potential indications for clinical applications. The work has been done in a very multilayered manner.

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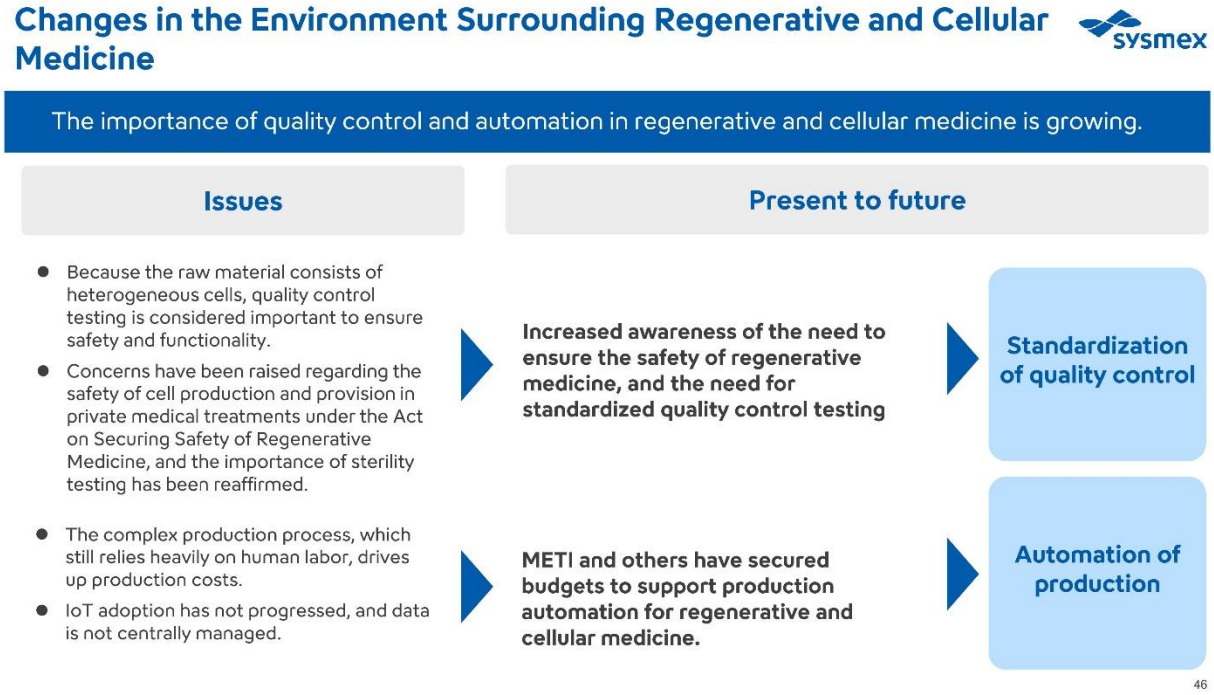
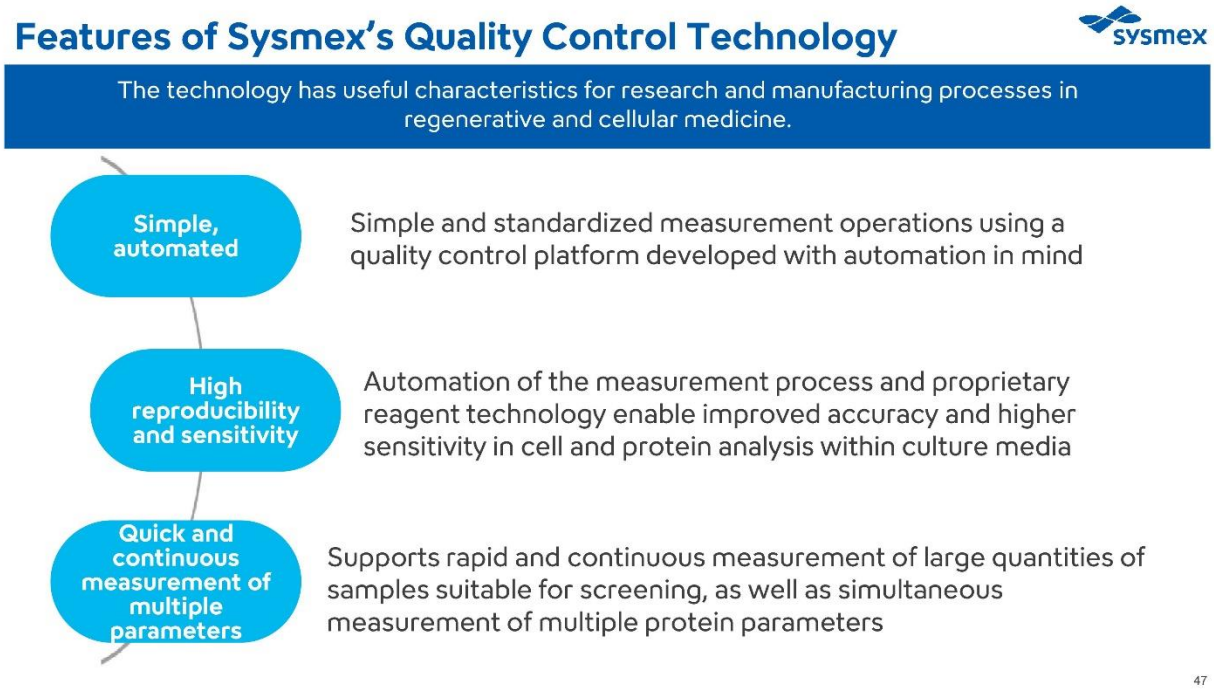


I will now report on today's focus on quality control and then on automation.

First, looking at the external environment surrounding these two areas, quality control plays a crucial role. As highlighted in the top two points on the left, cell-based therapies are inherently complex and challenging modalities. Ensuring rigorous quality control has long been recognized as essential in this field. Moreover, recent incidents, including cases where patients developed sepsis, have drawn significant attention. As a result, there is an increasing emphasis on strict sterility testing, reinforcing the importance of quality control in cell-based therapies.

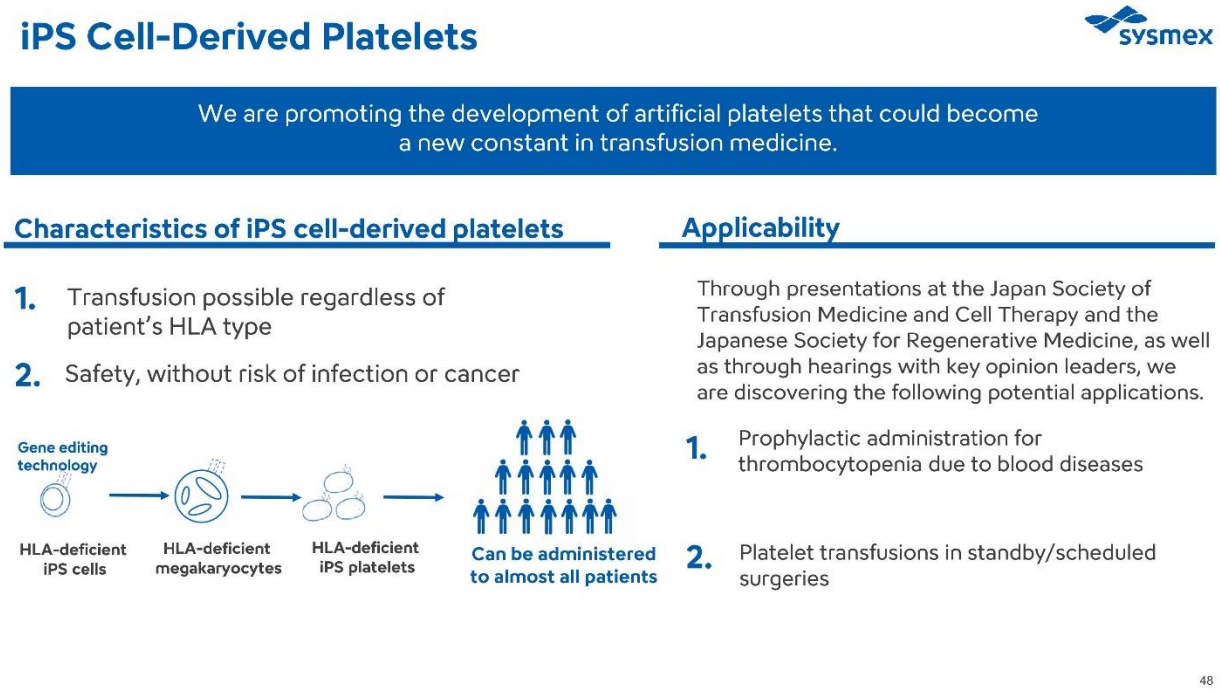
Additionally, the bottom two points highlight the complexity of cell manufacturing processes, which still involve many manual steps. This underscores the growing importance of automating production. The Ministry of Economy, Trade and Industry has announced plans to significantly invest in this sector in the current fiscal year. As key players in this field, we, along with others, aim to actively participate in these initiatives to accelerate automation.



Let me begin by reporting on our progress in quality control.

I don't think it is necessary to reiterate here the strength of our quality control technology, but I believe that what we are delivering as value in in vitro diagnostics can be used almost exactly as it is in the cell manufacturing process.

From the next slide, I would like to report on the actual situation in which we are demonstrating our value.

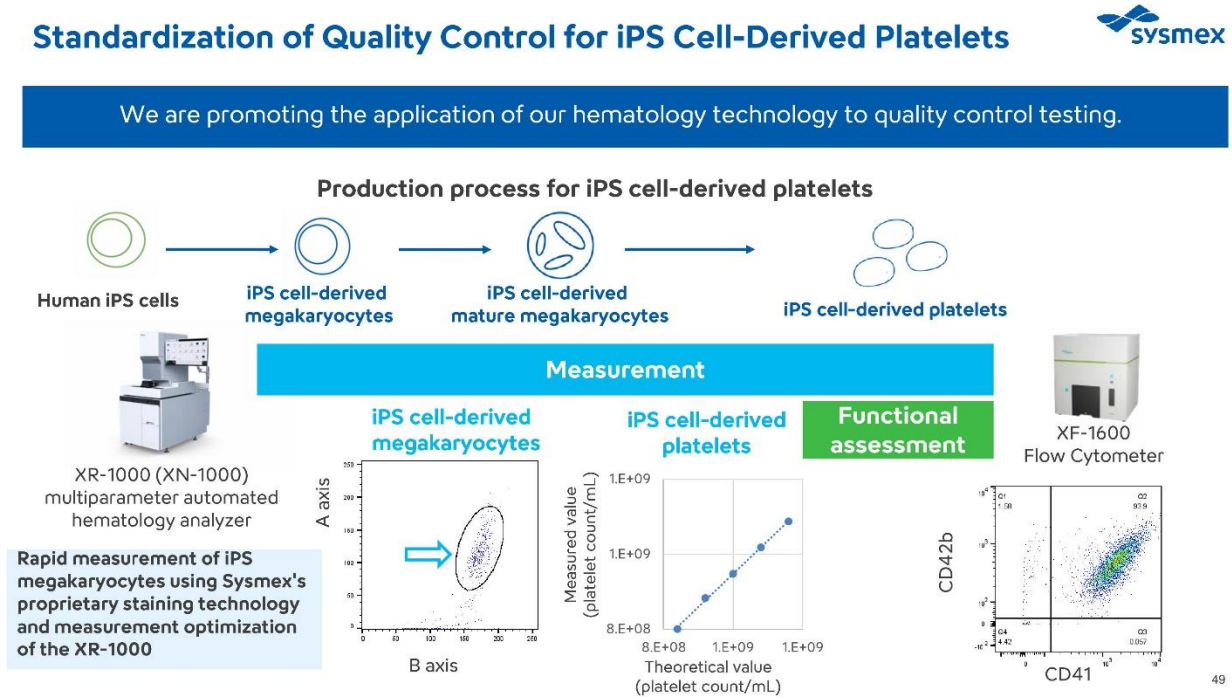


First, I would like to report on our efforts at Megakaryon from an internal perspective.

I would like to do a little recap regarding Megakaryon. On the left is an overview of the iPS cell-derived platelets Megakaryon is developing. Platelets also express a certain protein called HLA, which identifies a person's individuality, but by eliminating the HLA, we are creating platelets from iPS that can be transfused to any patient.

On the right are applicability. This also serves as a progress update. With Megakaryon joining our group, we are conducting various interviews together with hematology specialists, Japanese Red Cross representatives, and other key stakeholders we have established relationship with. While the findings may seem high-level and complex, we have recently gained a much clearer understanding of the unmet needs in this field.

We made some presentations at conferences in this fiscal year. Also, we would like to report on our progress at various conferences and other events next year to keep you up to date on our activities.



This slide presents case studies on the application of quality control in Megakaryon's manufacturing process.

In the iPS cell-derived platelet production process, iPS cells are differentiated into megakaryocytes, which then mature and produce platelets. This slide highlights how our XR-Series and XF-1600 technologies are being effectively utilized for megakaryocyte counting, platelet production assessment, and platelet functionality testing, all key hematology assays.

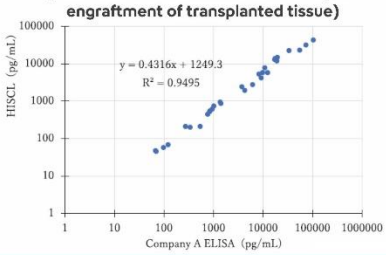
External Deployment of Our Quality Control Technology (HISCL)
First Launch of a Product for Research Use

We are starting to launch HISCL™ VEGF reagents (for research) and HISCL™ PEDF reagents (for research).

Correlation with existing ELISA kits

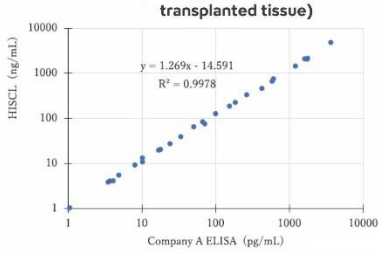
VEGF

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



PEDF

Pigmented epithelium-derived factor
(Neuroprotection around transplanted tissue)



Features

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

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

Reference: The market for immunochemistry testing for us in manufacturing quality control for cell and gene therapies is reportedly likely to reach approximately $1.1 billion by 2033.
Source: BIS Research, "2023–2033 Cell and gene therapy manufacturing QC market - A global and regional analysis"

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From here, I would like to report on how HISCL has been particularly useful in our efforts with the outside world.

This fiscal year, we have successfully launched two research-use-only reagents: VEGF on the left and PEDF in the center, as research-use-only tests.

Additionally, as indicated in the blue-bordered section below the center, we have found that many of our existing in-vitro diagnostic immunochemistry are highly useful for quality control in the cell manufacturing process. Leveraging our extensive assay portfolio, we have already begun providing HISCL as a quality control solution for several clients in cell production workflows.

Additionally, although it is written in small text at the bottom, there are projections that this market could exceed USD1 billion by 2033, according to some reports. I wanted to share this as part of our update.

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

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

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

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This section contains the voices of HISCL users and customers.

We consistently receive feedback from these three experts, as well as from corporate and facility representatives, that HISCL has significantly simplified the previously cumbersome and labor-intensive immunochemistry process. Additionally, due to HISCL's exceptionally fast measurement speed, what once required a full day of sequential experimentation—such as conducting tests, reviewing results, and then establishing a new protocol—can now be streamlined. Researchers can analyze morning results, adjust their approach, and conduct further tests in the afternoon, ultimately accelerating the overall R&D process.

Although these applications are still in their early stages, introducing HISCL at this point increases the likelihood that it will continue to be used in clinical trial drug manufacturing and commercial production in the future. This suggests that our HISCL assays will not only remain valuable for research but also play a sustained role in business applications, marking a significant step toward commercialization.

External Deployment of Our Quality Control Technology (FCM)
-New Possibilities in Sterility Testing-

sysmex

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

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

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

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

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

FR-500 flow cyclometer for research

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

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Another key point is the sterility testing mentioned earlier. We have collaborated with researchers from Juntendo University to present data suggesting that our RF-500 technology could serve as a new and effective sterility testing method.

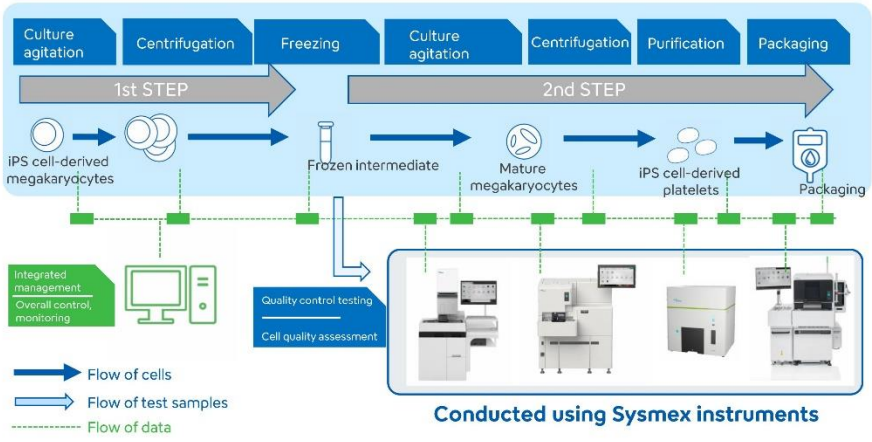
Beyond its performance, our RF technology has also shown advantages in terms of turnaround time and cost efficiency compared to existing methods. While we cannot discuss all details today, we believe that the practical adoption of RF-500 for sterility testing is not far off.

Automating the Production Process for iPS Cell-Derived Platelets

sysmex

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

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



Conducted using Sysmex instruments

Features

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

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

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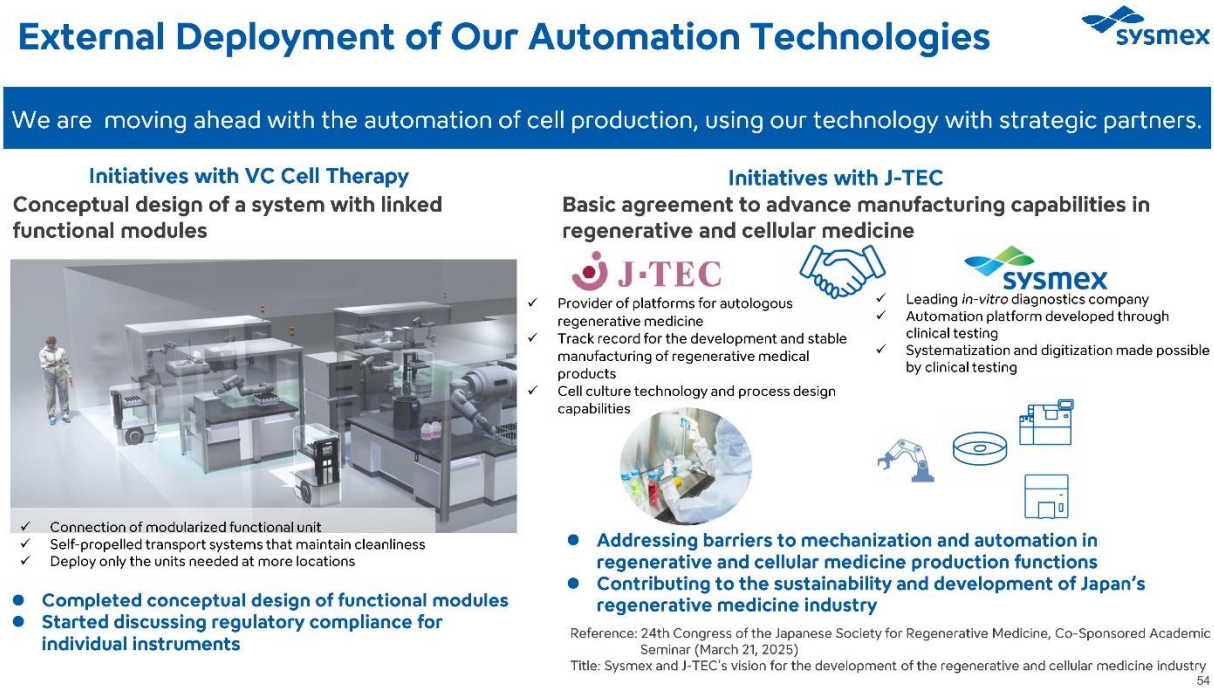
I will now continue with a report on our efforts regarding automation.

This is likewise composed of inside and outside initiatives. The efforts inside have once again featured Megakaryon. While we are not yet able to share photos or videos, over the past year and a half, we have closely analyzed Megakaryon's iPS-derived platelet manufacturing process in collaboration with them. Through this process, we have carefully examined where our technologies can add the most value.

We have identified three major areas where we can add value. The first is automating the transfer of culture media between process stages. Instead of manually transporting and transferring culture media, the goal is to enable automated flow of the culture media throughout the process.

Additionally, quality control plays a key role, as shown in the bottom center.

Furthermore, as indicated in green, we aim to digitize each process using IoT, enabling paperless operations and integrated data management. This data can then be used to optimize workflows, improving yield rates by identifying process adjustments that enhance efficiency. That is how the concept is established.



As you can see on the last slide, there are two initiatives for external automation.

On the left side, our collaboration with VC Cell Therapy, supported by a subsidy from the Ministry of Economy, Trade and Industry, focuses on iPS-derived RPE. This includes the implementation of automated transport robots, ensuring greater efficiency and scalability beyond just a single step of the process.

We plan to further materialize this initiative moving forward. Additionally, in December of this fiscal year, we issued a press release regarding our collaboration with J-TEC. By leveraging the strengths of both companies, we aim to integrate our automation and quality control technologies into J-TEC's current autologous regenerative medicine product manufacturing process, enhancing its efficiency and reliability.

As you can see at the bottom of the page, there will be a conference on regenerative medicine in Yokohama at the end of March. We are planning to hold a joint luncheon seminar on the 21st, so if you are interested in what our two companies want to do, please join us.

Thus, in the regenerative cellular medicine effort, there are three things, as indicated on page 45. Each of these three is promoting its business by delivering synergies to each other.

This year, in quality control and automation, we will further ensure commercialization and scale. We believe that we have obtained such a cornerstone.

That’s all for me. Thank you very much.

[END]

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