Presentation

Asano: Hello, I'm Asano.

Thank you very much for attending today's R&D Meeting in spite of the snowy weather. We also have a large number of attendees online. Thank you very much.

Our R&D meeting began in 2004, which is 20 years ago. This year will mark the 21st anniversary of the event. During this period, based on our corporate philosophy, we have created innovations through various technological developments in the field of *In Vitro* Diagnositics (IVD) testing to achieve business growth and contribute to solving social issues.

And in April 2023, we will accelerate our efforts to achieve further growth and solve social issues under our new long-term vision, “Together for a better healthcare journey."

In our growth strategy, we are working on the three axes of emerging market strategies, reinforcement of existing businesses, and expansion of new businesses. We are promoting what we call ambidextrous management, which means deepening existing businesses and expanding new businesses. Innovation is necessary to achieve this, and of course, a major element of innovation is technology. Since last April, we have been working on this under the new CTO, Yoshida.

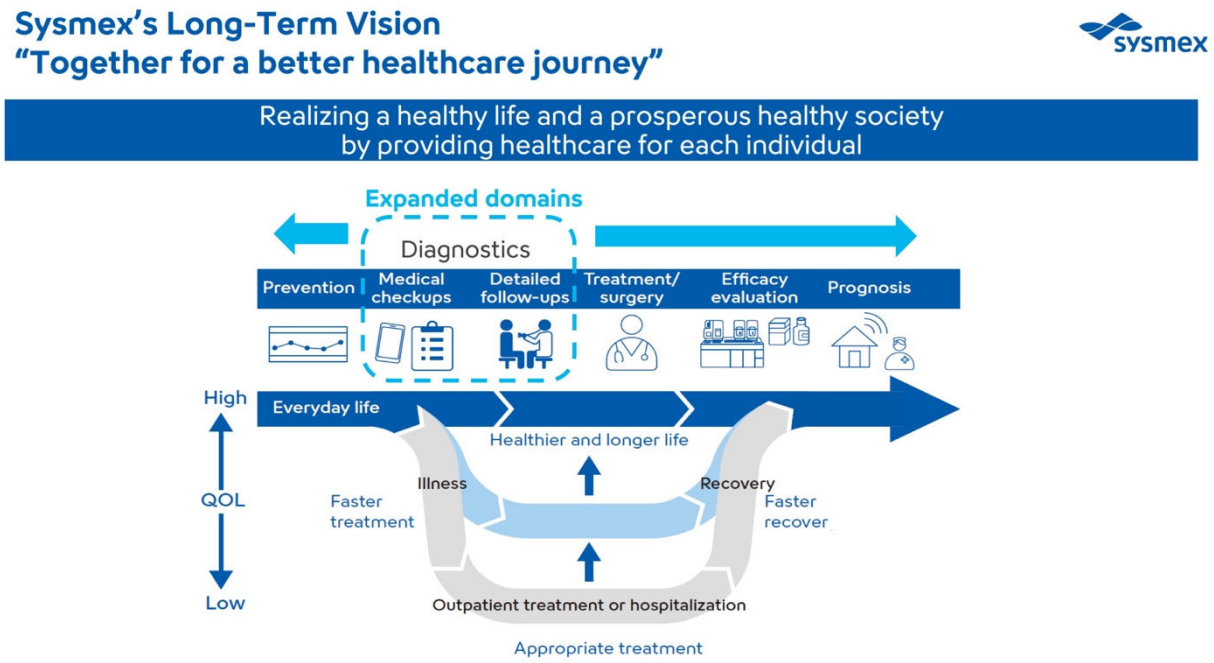
Today, Mr. Yoshida will explain the overall picture of those initiatives, and the details will be explained by those in charge of each initiative.

Thank you for your cooperation today.

Moderator: Okay. Next, Mr. Yoshida, Member of the Managing Board and Senior Executive Officer, Managing Director, please start.

Yoshida: Okay. My name is Yoshida. Thank you for your attendance today.

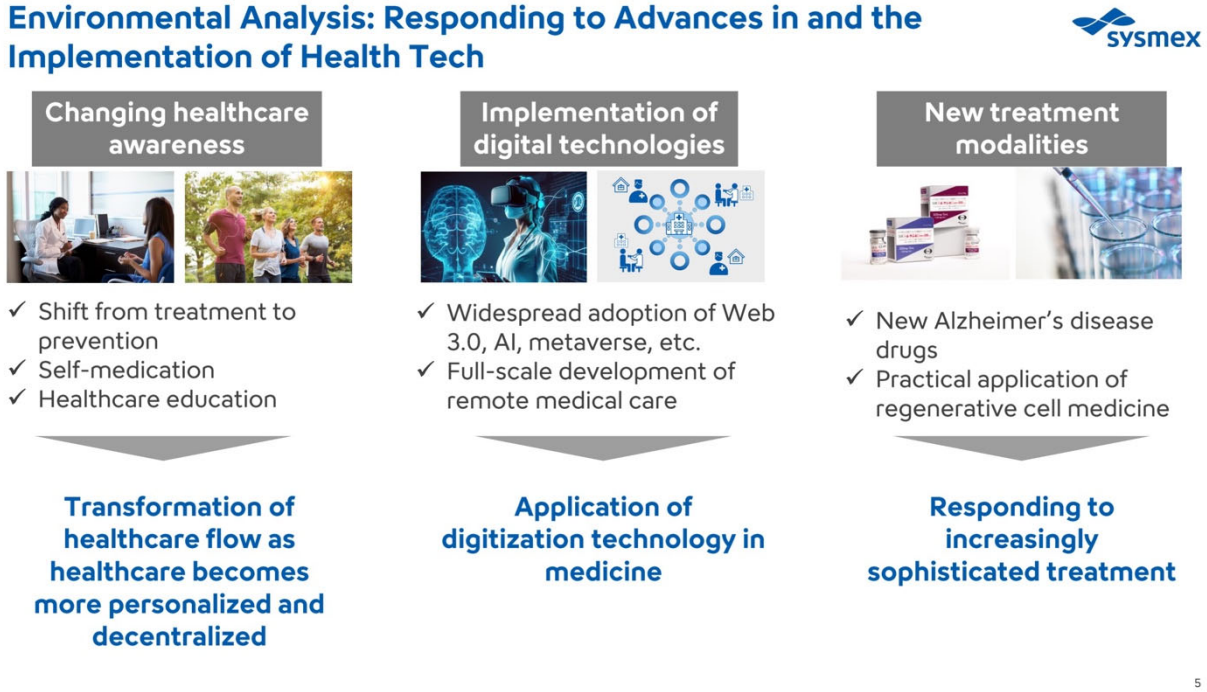
First and foremost, I would like to talk about our research and development efforts to realize the healthcare journey.



First of all, this is the vision that Sysmex has set forth as a major part of this new corporate strategy, which we hope you will understand: Together for a better healthcare journey

In the middle of this slide, it says expanded domains. In our existing technologies and businesses, we have delivered value to a wide range of stakeholders. In addition, as mentioned in the section on prevention of illnesses, before getting sick, people are naturally anxious about not getting sick. Furthermore, we will respond to your concerns for faster healing and better treatment when you become ill. Also, it indicates that after the treatment is over, we want to fulfill the desire for health, that is the desire not to be sick anymore.

This is one of our goals to make Sysmex's presence and testing presence more accessible to the public. In this way, SYSMEX will continue to provide services, products, and information in a variety of settings, including the home, school, company, society, and medical institutions, in order to realize a healthy life and a healthy society.



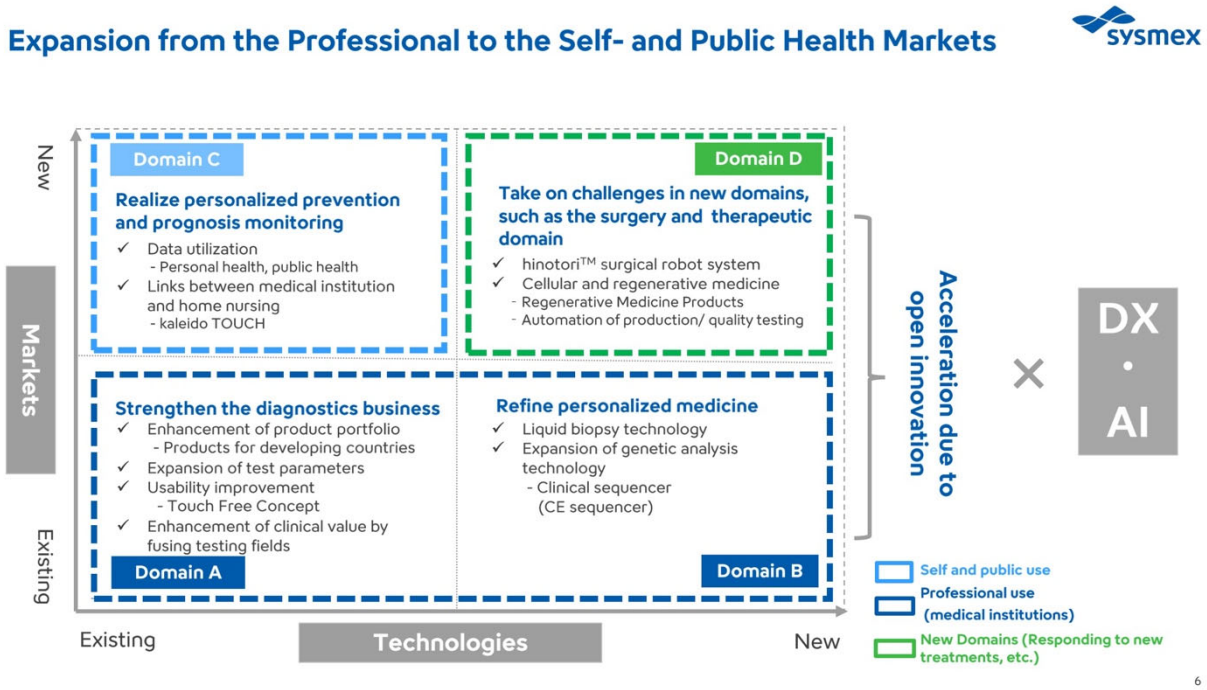
As you all know, there are many major changes in this kind of environment.

For one thing, the COVID-19 pandemic has brought about a major shift in health care awareness. You don't want to be ill rather than cured, and you want to take care of your own health. In terms of how to judge the flood of health information, medical care is becoming more personalized and decentralized. We believe that the flow of medical care will change largely.

As you all know, it is easy to imagine that digital technologies such as Web 3.0, generative AI, metaverse, and even telemedicine will be applied in the field of medicine and healthcare.

Furthermore, new and more advanced therapies are being implemented in the world, such as CAR-T, exosomes, nucleic acid vaccines, drugs for dementia, as well as regenerative and cellular medicine and gene therapy. In these areas, of course, a set of medical care that includes diagnosis and treatment is necessary.

We feel that it is necessary to respond to each of these issues, including these areas.



In order to maximize Sysmex's uniqueness in response to these changes in the environment, we will define each area as shown here, determine the technological points for each area, and strategically promote these areas. This is the innovation stream that we are introducing, and that is what we are working on.

In Domain A, we have been engaged in the diagnostics business as an existing domain.

We have also been working to strengthen our platform of proteins, genes, and cells, by doing so, we have made extensive use of liquid biopsy and refined personalized medicine. (Domain B)

In addition, we are providing the corporate strength and technological development capabilities obtained in these areas to the markets that will emerge in the future, which we have described as Domain C.

In addition, we have started to take on new challenges in the surgical field, starting with hinotori surgical robot system, and we would like to utilize our diagnostic technologies and business experience to expand into the therapeutic field, as I mentioned earlier.

In addition, we are also considering how to accelerate the pace of change through open innovation, which is a means to respond to the rapid pace of change in the world, as well as to combine DX and AI in all areas.

We are now moving from the professional health activities used by professionals to the self-care and public health markets, as well as to new areas, with a focus on technology and partnering. We are conscious of this.

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

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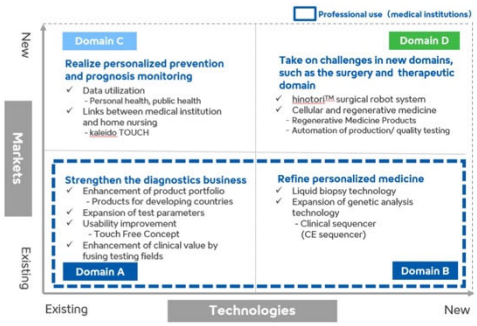
Achieving greater efficiency and precision in healthcare



- **Strengthen the diagnostics business**
  - ✓ Expansion of testing parameters
    - Utilization of alliance partners
  - ✓ Unparalleled differentiation through operational value
    - Integration of hematology and hemostasis
  - ✓ Integration of diagnostic results across testing fields utilizing AI
- **Refine personalized medicine**
  - ✓ Expansion of liquid biopsy
    - Realization of minimally invasive and personalized medicine
    - Hepatic fibrosis, dementia, cancer
  - ✓ Realization of clinical sequencing
    - Utilization of CES technology: cancer genomics, genetic diseases

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As for the deepening of the diagnostics business, we will naturally expand the number of test parameters, and as Mr. Nagai will explain later, we will also consider the technology we have cultivated as a leading hematology company as a differentiating factor in the form of operational value. In addition, we are also considering the use of AI to provide medical care by integrating more complex tests and cross-diagnosis results based on the data we have cultivated here.

As for the other point regarding the refinement of personalized medicine, the expansion of blood and liquid biopsy as I explained earlier, we would like to deliver more appropriate products with appropriate measurement targets in new areas, such as dementia and cancer. In addition, as clinical sequencers, we are also considering the possibility of utilizing the gene sequence information from the current next-generation sequencers in more places.

Transformation of Initiatives

Accelerating R&D through Open Innovation (1)

sysmex

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

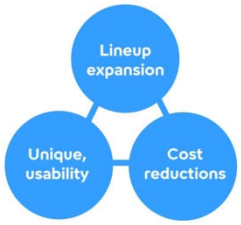
Strengthen competitiveness through collaboration and establish absolute superiority through proprietary technologies

sysmex × FUJIREBIO

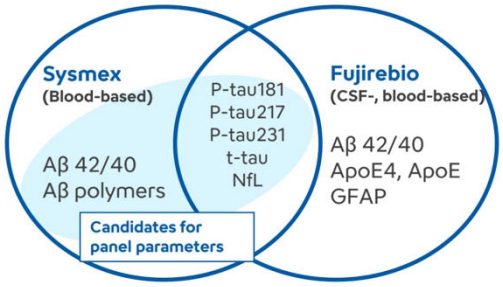
- High-quality equipment design technology
- Simultaneous development of reagents and instruments
- Global sales network

- Raw material lineup
- Immunochemistry reagent development (CDMO)

Automated Immunoassay System HISCL™-5000



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



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One of the measures we are taking is to accelerate R&D through open innovation in the A and B domains, as you all know, and we have begun collaboration with FUJIREBIO.

We believe that we can establish a competitive edge in this area by combining the technologies that Sysmex has cultivated in the immunology business of HISCL with FUJIREBIO's capabilities in the development of raw materials and immunological reagents.

This is just one example, but for neurodegenerative diseases, or Alzheimer's, disease test parameters, Sysmex and FUJIREBIO have been developing them, respectively. We believe that the combination of these will lead to a more precise diagnosis and treatment of dementia.

Transformation of Initiatives

Accelerating R&D through Open Innovation (2)

sysmex

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

Challenges for genomic medicine

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

sysmex × HITACHI Inspire the Next

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

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

Capillary electrophoresis sequencer

Promoting new product development through collaboration

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

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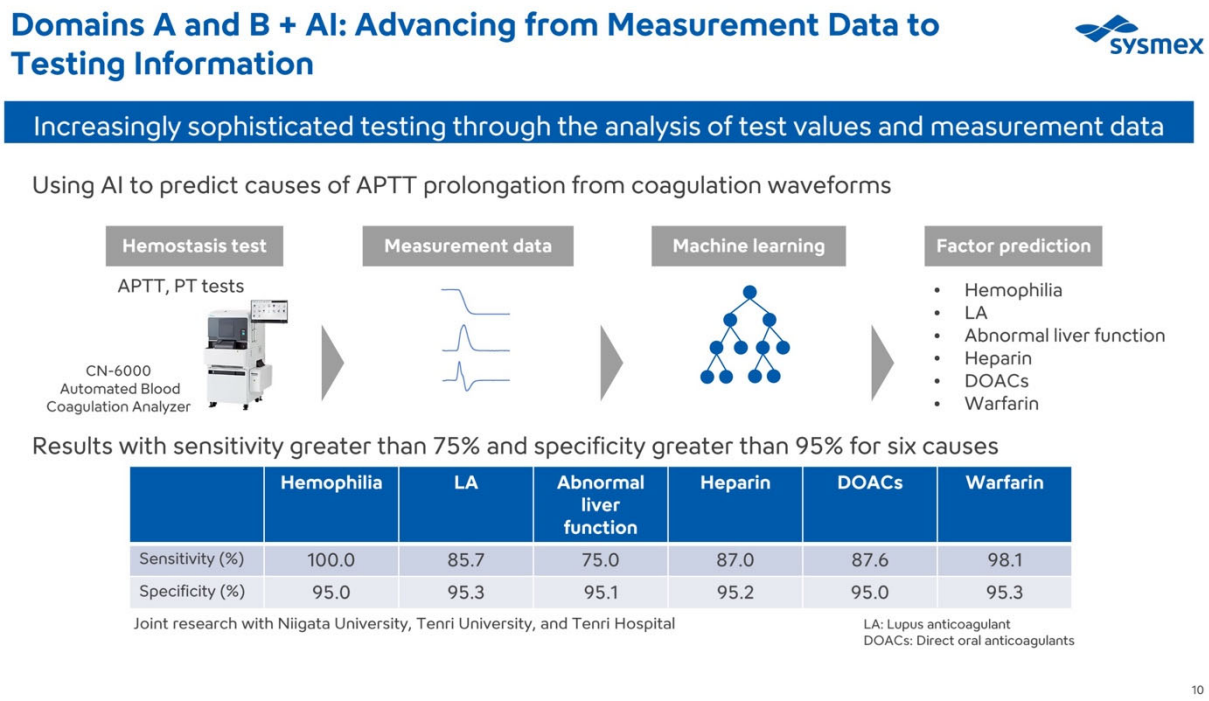
In terms of another open innovation measure, as you all know, genome medicine is becoming more active in Japan and is being used more and more, especially in the field of oncology. We believe that there are still many challenges in genomic medicine.

There is of course the question of whether the large amount of information coming out of the sequencers is really considered necessary for clinical applications, and then there is of course the high cost of testing. We believe that increasing the number of medical institutions that are able to implement such genomic medicine on their own will lead to the fulfillment and enhancement of this genomic medicine.

In this context, we would like to create a new, reasonably priced clinical sequencer that can be used at a wide range of medical institutions by combining Sysmex's instrument design technology, reagent development, and, of course, our global sales network with Hitachi's capillary electrophoresis sequencer.



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

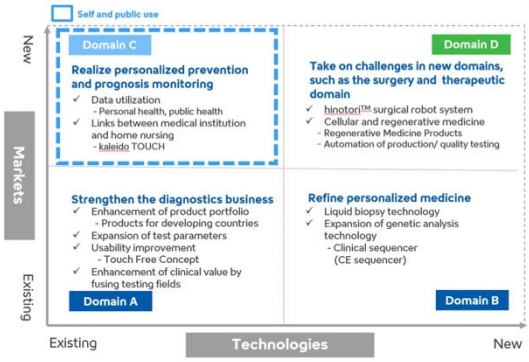
Furthermore, it says test values and measurement data, but in the hemostasis test, this kind of waveform data can be obtained. By learning these things, we have been conducting research and development to understand what is happening in this hemostasis test and where the problems and issues are.

The results are shown in the lower part of the slide as sensitivity and specificity, and the level has risen to the point where a single test can predict this many factors. We believe this indicates the potential for advanced analysis of measurement data as medical information.

Domain C: Rolling out Existing Technology into New Markets

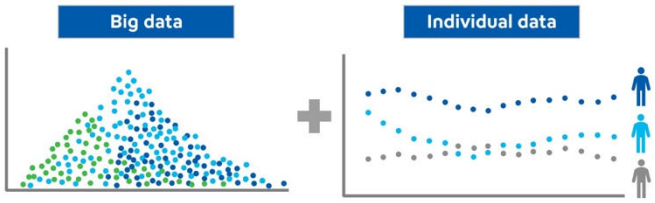
sysmex

Creating new markets by utilizing data and strengthening medical collaboration



● **Prevention and prognosis risk monitoring**

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



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The next section is called Domain C.

Here, we show that we are leveraging data. As public health, of course, analyzing big data is a way to understand where the patient, or the person being examined, is located and in what situation. By capturing such data individually and as a time series, we believe that it can be used for prevention and postoperative management and monitoring.

We believe that new markets have great potential and possibilities in these areas, and as a start, we have launched Kaleido TOUCH.

Domain C: Medical Collaboration Platform

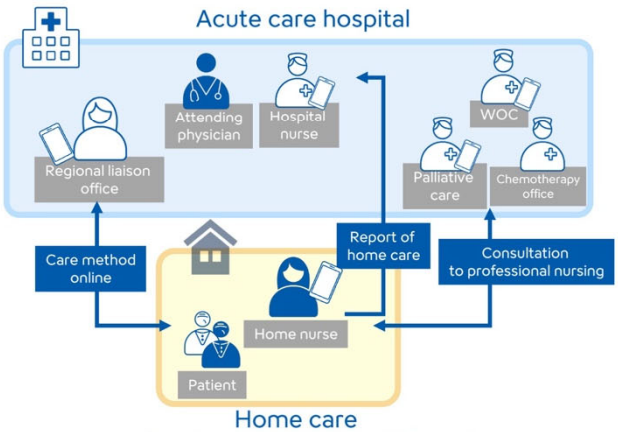
sysmex

Development of Medical collaboration system compatible with decentralization of medical functions using nurse-to nurse collaboration APP "Kaleido TOUCH™"

Nurse-to nurse collaboration APP connecting hospital care and home care "Kaleido TOUCH™"

kaleido TOUCH

Nurse-to nurse collaboration APP "Kaleido TOUCH™"



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

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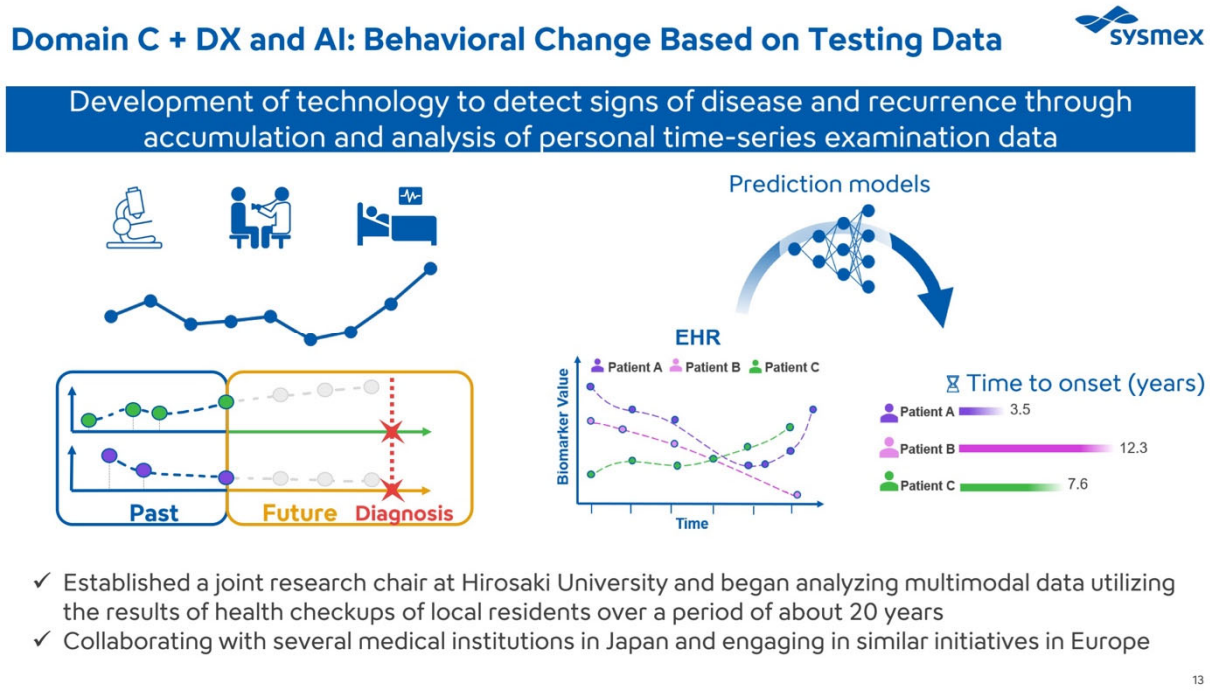
As shown here, this Kaleido TOUCH is, first of all, a form of collaboration and connects home nursing and professional nursing. Naturally, this will be based on information from nurses in home care, but it will be extended to patients as well. In addition, by having healthcare provider from other medical departments use this platform, medical information can be delivered to those who need it and when they need it. We believe that this type of real-time service will expand, and naturally, we believe that it can be used for telemedicine in rural areas.

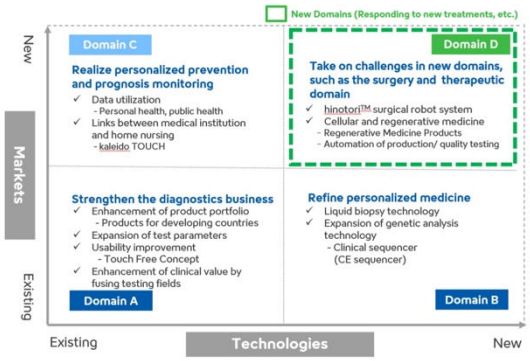
As you can see on the right side of the slide, we are currently examining the possibility of using the system for palliative care and for patients who are taking outpatient medication.



Furthermore, in Domain C, we believe that by accumulating time-series data, we can predict the onset and recurrence of diseases by understanding their fluctuations. We are now starting to analyze the data in a multimodal manner with the cooperation of many local residents.

In addition, we have also started global verification of these activities, taking advantage of the foundation of Sysmex's global activities, as a matter of course. However, this forecasting model, in these areas, still has a high level of technical challenges, and we believe that cooperation with many people is necessary.

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



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

AlliedCel JUNTENBIO Mega karyon

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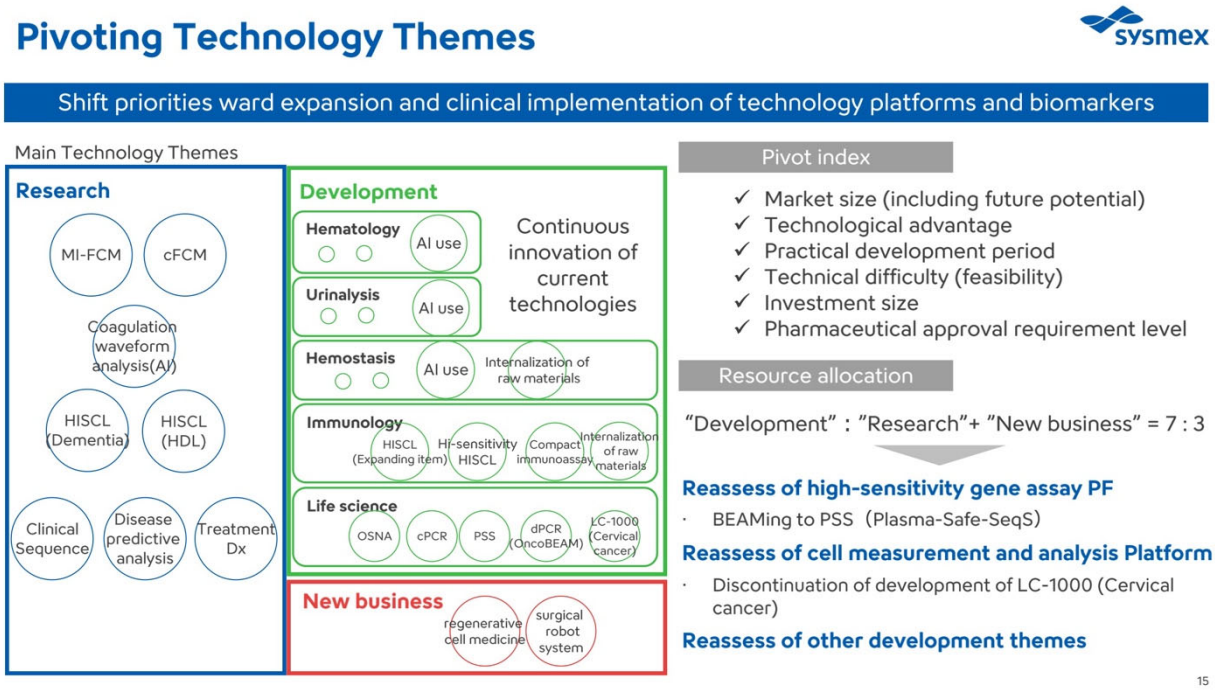
This is Domain D, a new challenge area, but this area is really about treatment and surgery. In the surgical field, we are making great progress as a new opportunity by integrating IoT with the surgical robot hinotori as a DX.

Furthermore, we believe that we can create new highly effective therapeutic drugs and diagnostic methods that can be paired with them by utilizing the advanced measurement technologies we have cultivated in our existing diagnostics business and personalized medicine, such as those applied to quality control. We believe that this is an area where we can take on challenges together with AlliedCel, JUNTEN BIO, and Megakaryon, and we would like to equip ourselves with the necessary technologies.



In the course of these activities, we have been strategically strengthening our technology platform and acquiring biomarkers to ride on top of that technology platform. In fact, we believe that we are now at the stage where this technology platform and its biomarkers are close to clinical implementation. In these areas, it is still important to change priorities.

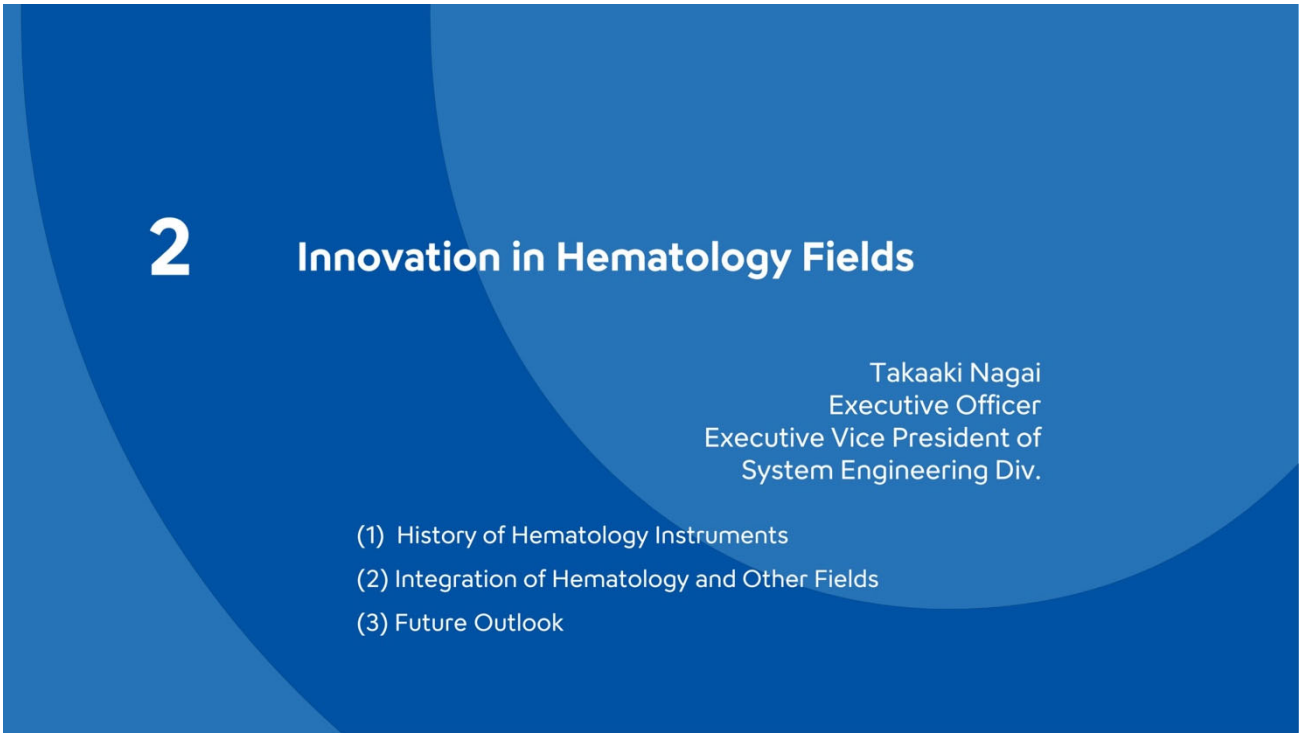
We will examine whether or not there is technological superiority in what we have been working on, including the size and potential of the market, and whether or not we can really develop practical applications in a timely manner. The scale of investment and the level of regulatory approval requirements have also changed. In light of those things, we are actually revamping our effectiveness measurement platform and changing from digital PCR to more sequencing-like information.

We have also narrowed our priorities in the area of cell measurement and analysis platforms. In particular, we have set a guideline for investment in product development in order to achieve the goals of the Medium-term Management Plan.

We will review each of these activities and systems, and in fact, we would like to realize the healthcare journey that I have just described, one step at a time and in a big way.

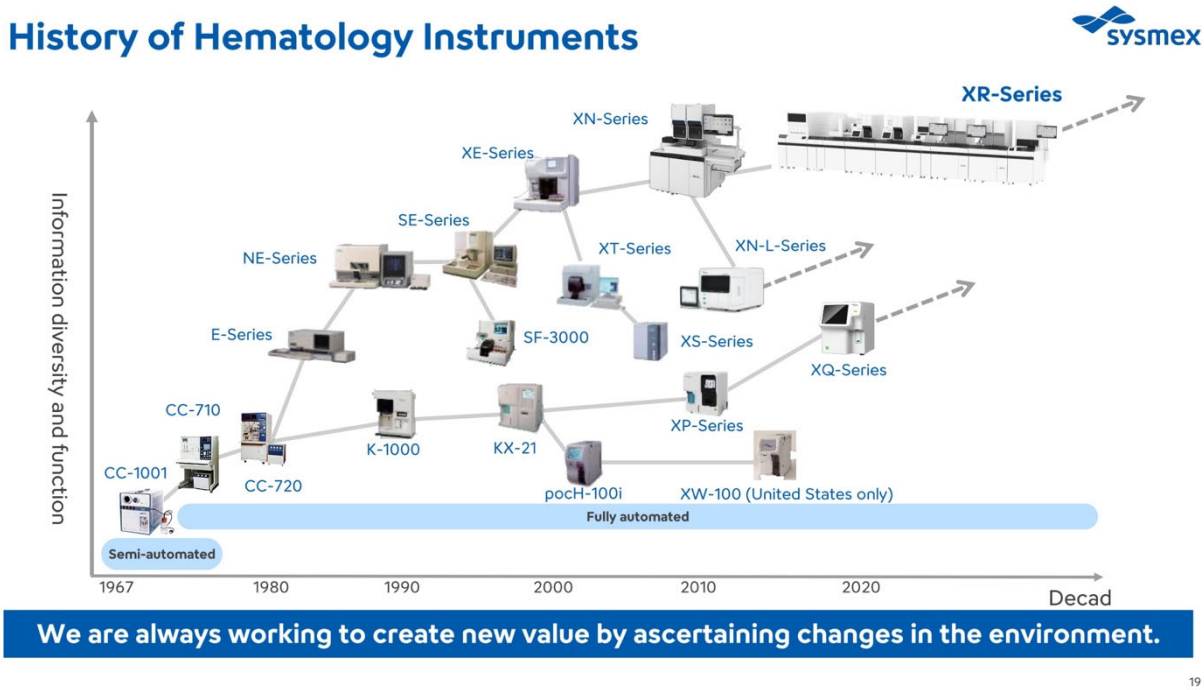
That is all. Thank you very much.

Moderator: Now, next, Mr. Nagai, Executive Officer, please start.



Nagai: Good morning again, everyone. My name is Takaaki Nagai, system engineering division.

Today, I would like to explain about innovations in hematology, starting with the evolution of hematology instruments and the future prospects for this area.



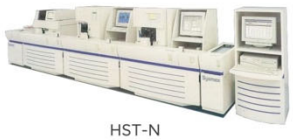
First, there is the transition of hematology instruments.

In 1963, we launched the CC-1001, and since then, we have greatly advanced the automation of hematology worldwide. We have been able to successfully capture changes in the environment and have always provided new value.

Rollout of Transport Systems in the Hematology Field

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

HS-Series



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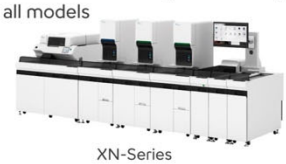

XN-Series

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In the field of hematology, since the 1980s, we have made a significant contribution to the automation of testing in the field of transport systems that automatically supply blood samples and test tubes to various analyzers.

Providing New Value through the XR-Series

Healthcare issues, needs

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

XR-Series

Operational value

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

Touch-free concept

Clinical value

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

Managerial value

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

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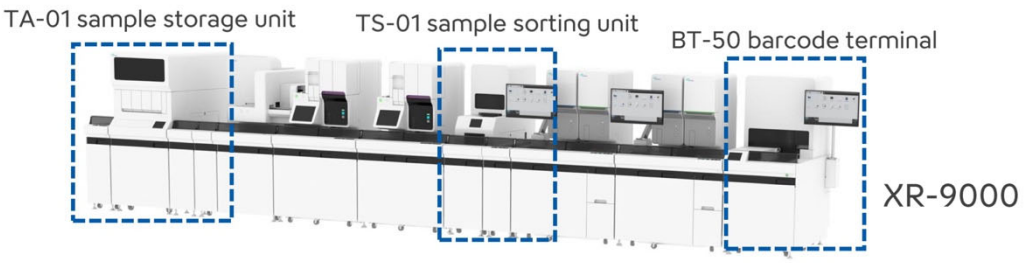
The XR-Series is currently being introduced to the global market.

This series of products includes operational value, clinical value, and managerial value. In particular, we have evolved this operational value as the touch-free concept, which offers great value to our customers, and continue to develop products based on this.

Touch-Free Concept, Phase 1

Note: Announced at the 19th R&D Meeting



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

Note: Patent pending

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

Eliminates manual pre- and post-testing operations

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The first version of the touch-free concept was presented at a briefing session held online the year before last. The market introduction of the touch-free concept is progressing very well on a global scale, and it has been very well received by our customers.

This technology eliminates the need for manual pre- and post-testing processing, quality control can be completed at home, and when you go to the laboratory, everything is already ready for testing. In China, this is even called at home QC. This is a cool catchphrase, but it has been very well received, and our sales staff in China has been able to sell the products with a high level of awareness.

Touch-Free Concept, Phase 2

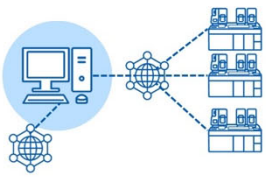
Expanding application of the touch-free concept from pre- and post-testing to the entire testing process

- ✓ No need to change reagents during testing

(1) RM-10 reagent supply unit

Note: Patent pending

- ✓ No need to perform checks in front of instruments



(2) Hematology dashboard

From “easy to operate” to “zero operation”

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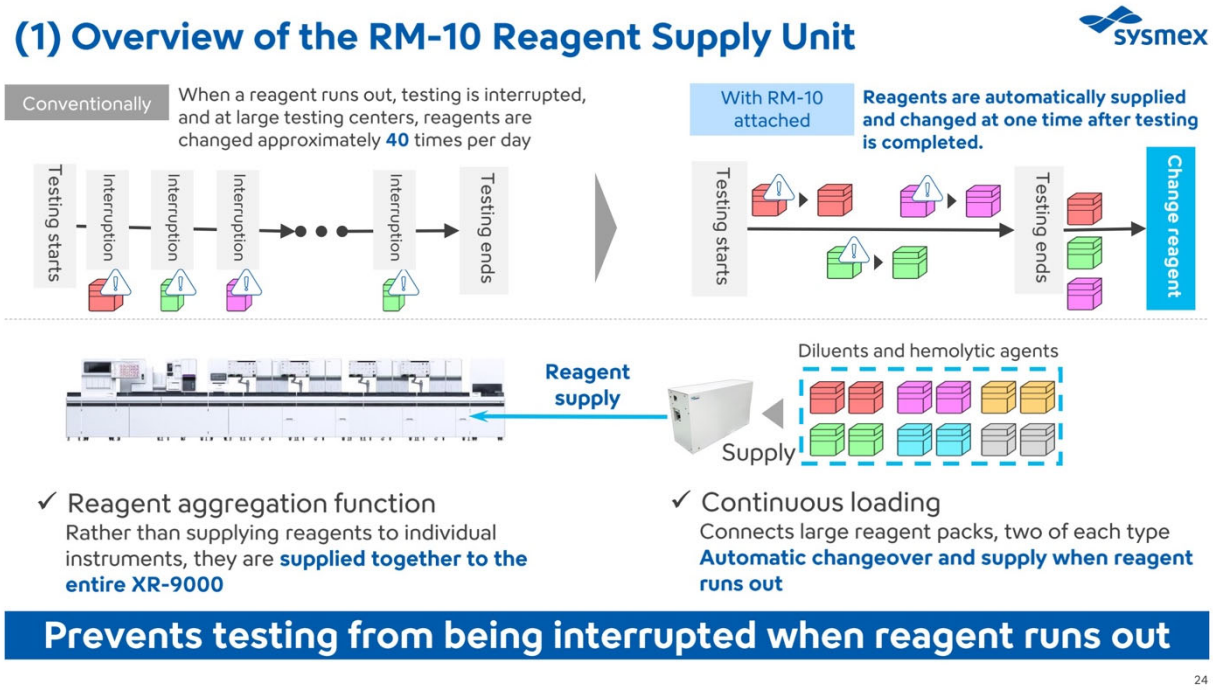
The main topic I will discuss today is the Phase II of the touch-free concept.

Over the years, we have constantly developed instrument that is easy to operate. However, we have made a major policy shift, moving from the concept of easy operation to the concept of non-operation, and our developers are working hard to achieve this policy. I believe that in the future, it will become more common in laboratories to not operate instrument, rather than to make it easy to use, which will contribute to productivity.

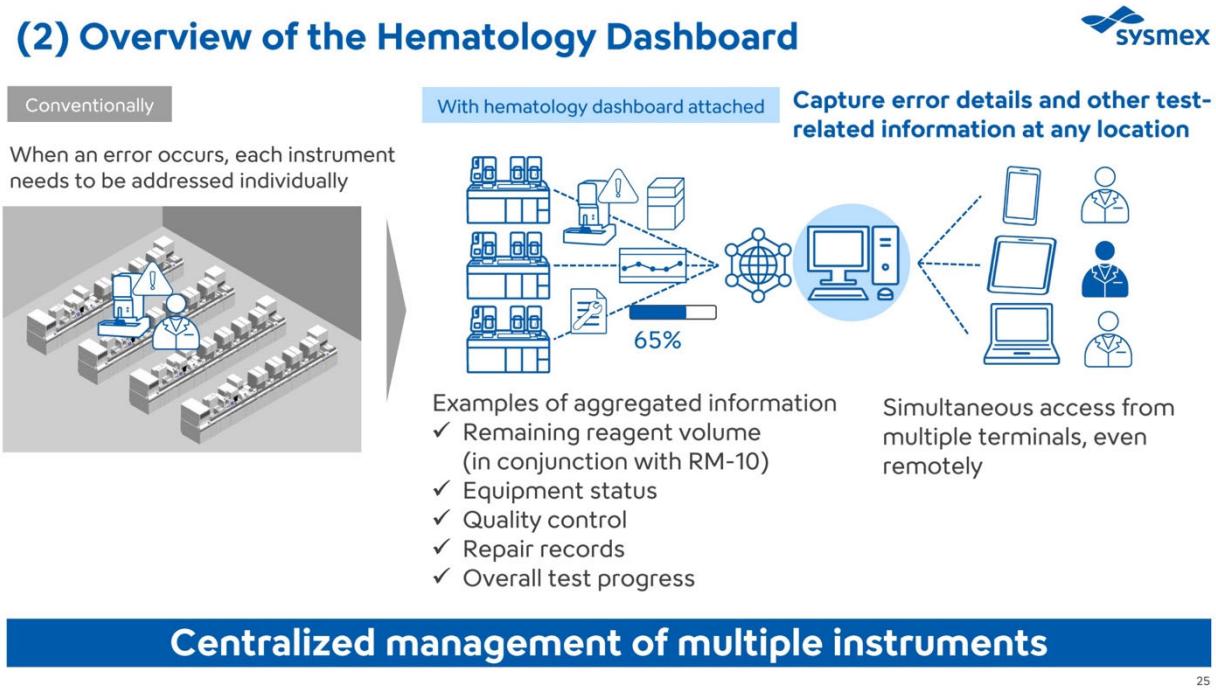
On the left is the RM-10 reagent supply unit, which eliminates the need to change reagents during testing. On the right is the hematology dashboard, a system that eliminates the need to go to the machine every time to check the status of the machine and reagents.



First, the RM-10 reagent supply system.

By connecting these units, which are not that large, but about this size, we were able to eliminate the possibility of running out of reagents during testing.

In the past, many large centers measured about 30,000 samples per day. About 30 analyzers are connected, and reagents had to be changed about 40 times during a day. However, with the newly developed RM-10, reagents can be changed in one batch after or before testing. This eliminates interruptions in testing due to running out of reagents and also drastically reduces the man-hours required for technologists to go to the machine to change reagents in the middle of tests.

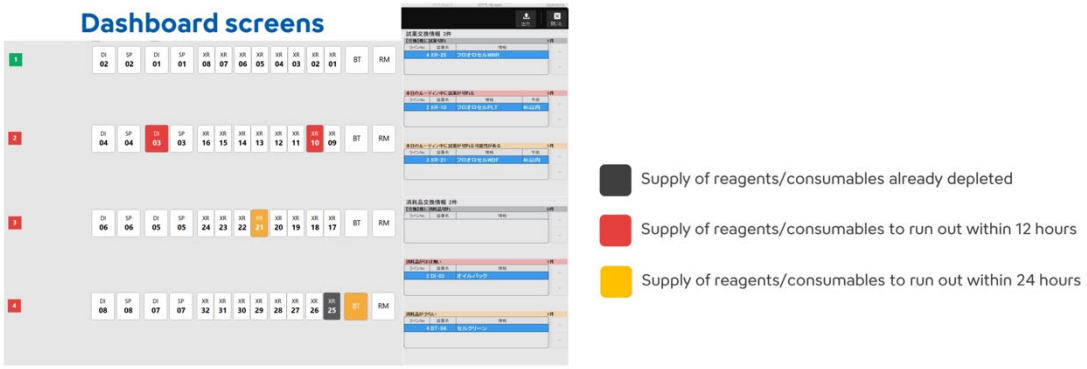


Next is the hematology dashboard.

This product enables batch centralized management of multiple instruments As shown in the figure on the left, in commercial laboratories that handle many machines, it is necessary to go to the front of each machine to check the status of the machine, for example, the amount of reagent remaining, the state of reagents, and the progress of the test. However, with the introduction of this system, information such as the contents of errors can be accessed from any location, even from remote locations if security is provided, so that people outside of offices and laboratories can also grasp the status of tests.

Details of the Hematology Dashboard

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



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

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A detailed description of the hematology dashboard.

The most unique aspect of this system is that the condition of the instruments can be checked before the testing. In other words, we have a forecasting function. This allows laboratory technicians to feel comfortable prior to testing.

Let me explain in detail. There are four rows of instruments in the horizontal direction. 40 squares represent instruments, and the black-colored instruments are those that have already run out of reagents. I think this is common, though.

The next interesting point is that the red area indicates that the reagent will run out within 12 hours. This is done using various AI and other technologies to predict when reagents will run out in this laboratory.

The yellow area indicates that the reagent is expected to run out within 24 hours, so the entire test and the entire instruments can be seen at a glance, allowing technologists to perform today's tests

Example of a Large Commercial Lab

Each day,

during 10 hours of operation,

an average of more than

tens of thousands

of tests are performed

Makes the most of touch-free operations

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This is a specific example of a large commercial laboratory.

Although there are only a few people who have visited a commercial lab, it is a very large facility, processing tens of thousands of samples per day. They operate about 10 hours a day under these conditions. As I explained earlier, the reduction in workflow for laboratory technicians through the reagent supply unit and hematology dashboard has been very effective.

Summary

Phase 1	Phase 2	
TA-01 sample storage unit TS-01 sample sorting unit BT-50 barcode terminal	RM-10 reagent supply unit	Hematology dashboard

Realizing the touch-free concept helps improve lab productivity

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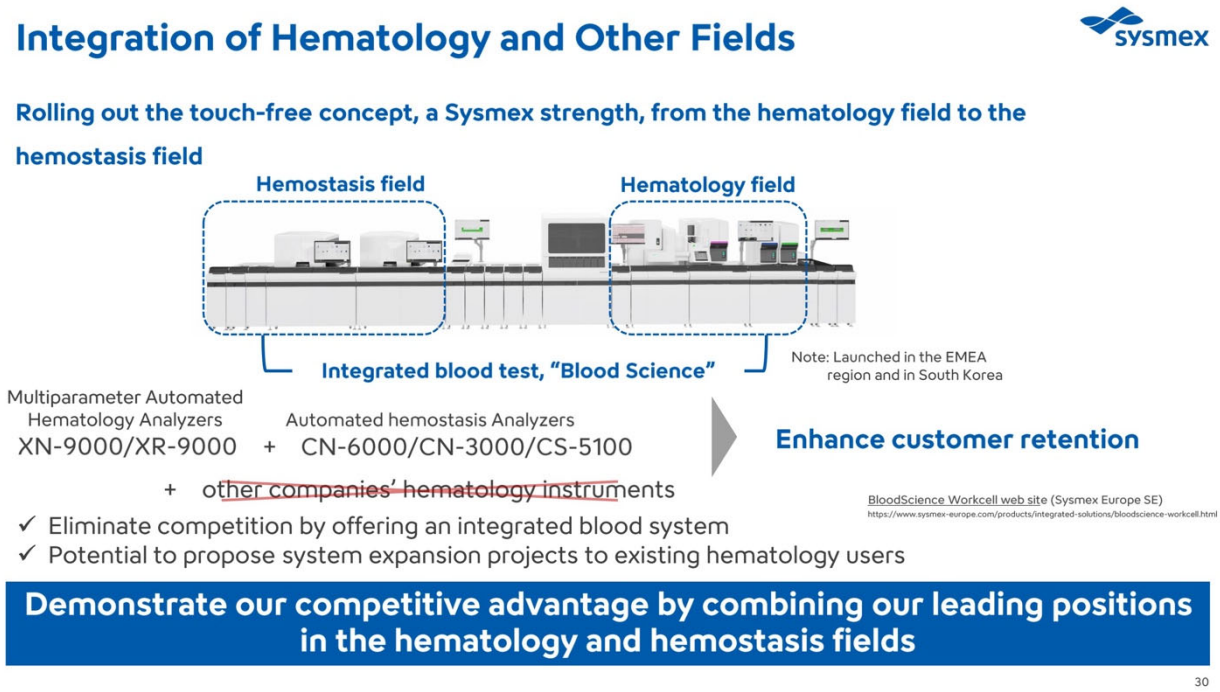
To summarize the Phase I and Phase II touch-free concepts, the first concept greatly reduces pre-testing work. Also, as I mentioned earlier as home QC, this technology allows laboratory technicians to prepare machines for testing from the comfort of their own home.

I explained in detail about the second phase, the RM-10 reagent supply unit and hematology dashboard. This is another example of technology that has been realized based on the concept of not having to touch the instrument during testing, which has contributed greatly to laboratory productivity.



Next, I would like to touch a little on how we can expand our hematology strengths to other fields, which I am sure you are interested in. We would like to expand the touch-free concept and unique technology we have developed in hematology to other testing fields, so I would like to explain it to you.

The first thing we are working on is the integration of hematology and hemostasis testing. As you can see at the bottom of the page, we are already number one in the world in the field of hematology. We are also number one in the world in testing in the field of hemostasis. We are aiming for 1 + 1 = absolute number one, not 1 + 1 = 2, and we are determined to demonstrate our competitive superiority.

First of all, we have unified the fields of hematology and hemostasis. As shown in the slide, one laboratory technician inserts a test tube from the black box in the middle, and a blood collection tube for hematology and a blood collection tube for hemostasis are automatically assigned to the hematology test and hemostasis test, respectively. This system allows a single person to perform all hematology and hemostasis tests, reducing the number of personnel in charge, and I think it has contributed greatly to the shortage of human resources.

Increasing Usability

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

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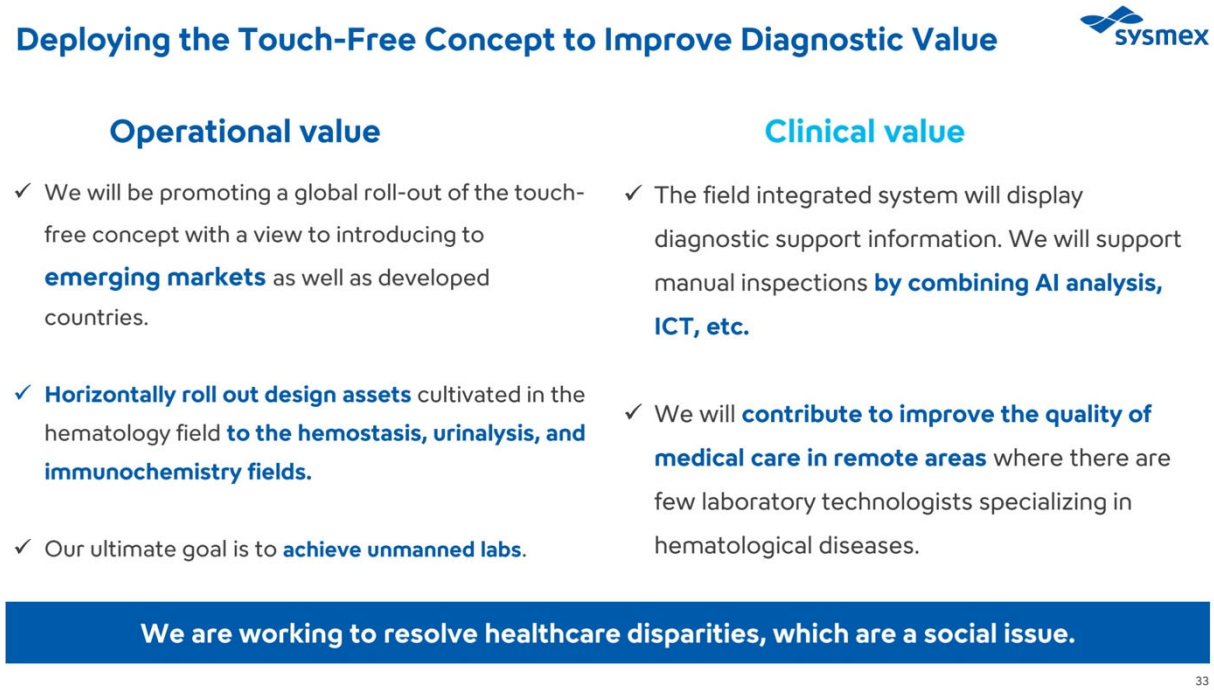
If I may elaborate a bit more, by improved usability, I mean, as I mentioned earlier, that multiple instruments can be easily operated by a single person.

Hematology and hemostasis tests are performed in similar laboratories around the world. The results of these tests themselves are also well integrated. Naturally, platelets are also measured in hematology, and platelets are very important information on hemostasis factors, so we plan to integrate this information to automatically extract the optimal test using AI and other methods, and automatically perform optimal operations. We believe that it is possible to achieve a touch-free experience.

In addition, we are very much a global company, with customers in over 190 countries and regions. Our strength lies in the field of hematology. We would like to apply this to the hemostasis field as well.

In the event of a breakdown, you used to have to call Sysmex for hematology and another company for hemostasis or send an e-mail. Since you do not have to do any of these things now, we believe that we can provide our customers with one-stop peace of mind by taking advantage of the services we offer at hematology.



This will be the last slide.

As I explained today, we are working on operational value, clinical value, and managerial value, and in operational value, we are developing a touch-free concept.

However, some people say that the examples I just described are only applicable to state-of-the-art hospitals or to large hospitals, but this is not the case. This touch-free concept is meant to compensate for things like manpower, personnel, and skill shortages. We believe that this is a technology that can be used in remote areas, underpopulated areas, and emerging countries, and we would like to expand our business not only to developed countries but also to remote areas and emerging markets. As I mentioned earlier, we would like to apply the strengths and technologies we have developed in hematology to other fields of testing instrument, such as hemostasis, urinalysis and immunochemistry..

Lastly, as for my dream, there are many unmanned factories and warehouses these days, and there are almost no people in them anymore. However, in the case of laboratories, I don't know if you are aware of this, but if you take a look at a hospital, you will see that there are many laboratory technicians running around in the laboratory. My dream is to somehow make this unmanned lab a reality.

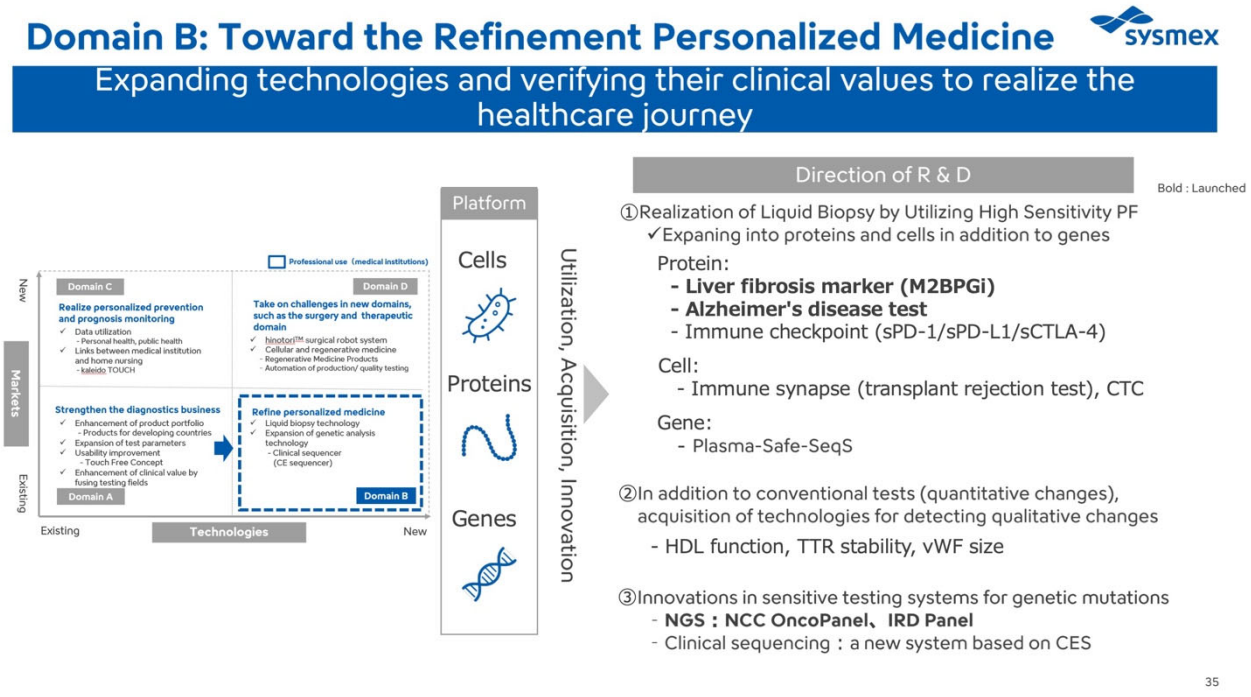
As written on the right, clinical value, of course, includes the operational part, but there are regions around the world where it is difficult to receive high-quality medical care through the use of AI and ICT, and of course, there are such areas in Japan. Here in Tokyo, there are many excellent hospitals, but of course, when you go to remote islands, it is difficult to receive such medical care. Of course, if we look at the world, we can see that this is even more pronounced, so we would like to contribute to society by addressing one of these social issues, the medical disparity, through our touch-free concept and by improving clinical value.

Thank you for your attention.

Moderator: Now, please step down from the stage, Mr. Nagai, Executive Officer.

Now then, Director Sato, please start.

Sato: My name is Sato from the Central Research Laboratories. I will focus on Alzheimer's, HDL function, and genetic testing in the context of the refinement of personalized medicine.



First of all, the overall picture, the direction of research and development is shown on the right.

First, we aim to realize liquid biopsy through the use of a highly sensitive platform.

The second point is to acquire detection of qualitative changes in addition to conventional testing. Traditionally, protein was evaluated by quantity, but we will evaluate quality.

The third point is to innovate a highly sensitive gene mutation measurement system. As Mr. Yoshida explained earlier, this involves capillary electrophoresis sequencers. Items in bold are those that are already on the market. Some of them will be released in the future. I will explain them to you.

Global Dementia Trends

sysmex

Contributing to the advancement of healthy lifespans and an aging society

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

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

- Countries with national dementia facilities
- Countries that are planning dementia measures
- Countries that have no dementia policies in place or that are not planning measures

Emergence of disease-modifying drugs

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

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

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

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

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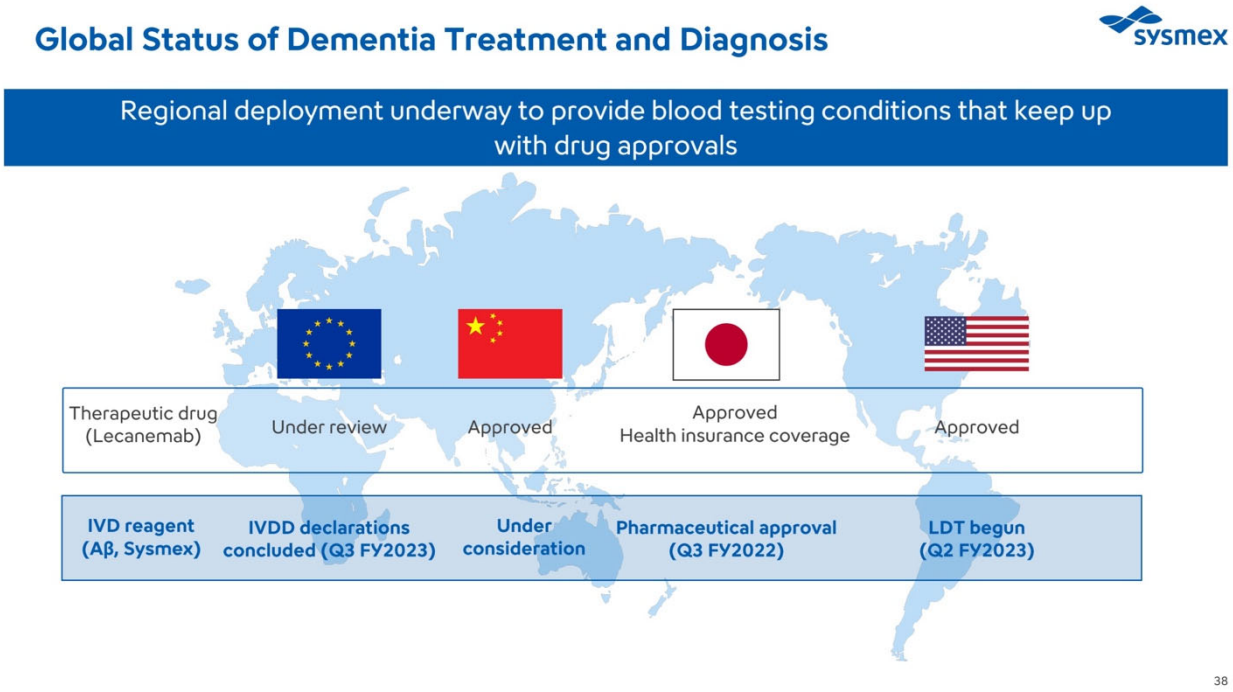
First, there is Alzheimer's disease.

As you all know, the number of dementia patients will increase all over the world. With that, development of drugs for Alzheimer's disease has been active, and I am sure you are aware that lecanemab was just recently approved. Several other therapeutic agents are also being developed.



We are conducting research and development to provide tests in conjunction with therapeutic drugs, and this figure shows the global situation.

In Japan, the therapeutic drug lecanemab, shown in the upper row, is covered by insurance, and our diagnostic agent has also been approved by the pharmaceutical affairs bodies.

Similarly in the US, lecanemab has been approved and we have started LDT for our diagnostic agent.

On the other hand, China has approved lecanemab, but our tests are still under review.

In Europe, the situation is a bit opposite. Lecanemab is still under review, and our tests have been declared IVDD.

We will continue to offer as many tests as possible in conjunction with the approval of therapeutic agents.

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

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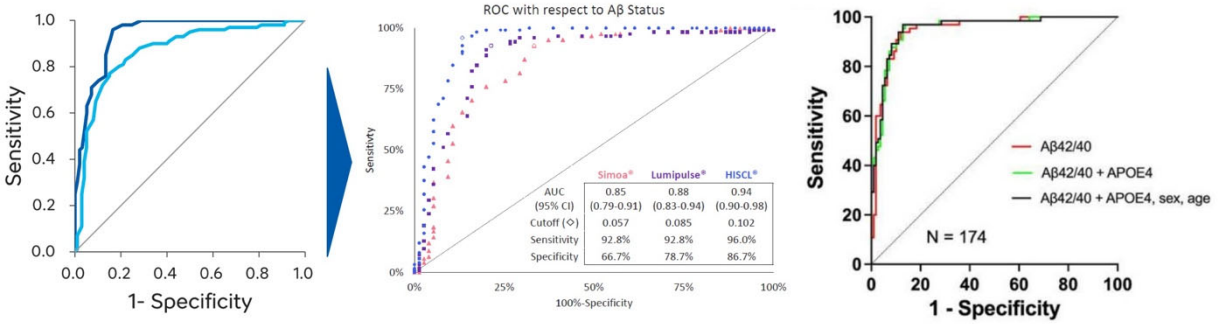
Excellent diagnostic performance for amyloid pathology confirmed at multiple facilities



In-house data (exploratory and validation studies)

AUC: 0.868～0.941

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

AIBL cohort (Australia)

AUC: 0.94

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

Keio University Memory Clinic and others

AUC: 0.949

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

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We are continuing to verify the actual performance of our first Alzheimer's test reagent, Amyloid beta (Aβ) 42/40.

The leftmost figure shows the data we used to apply for approval. The higher the AUC value, the better the performance, and we submitted an application for approval in the range of 0.87 to 0.94.

The figures in the middle and on the right show the results of performance evaluations conducted by other institutions without our involvement, and the AUC values of 0.94 and 0.95 are very high. We believe that this test reagent can be used in clinical settings with high performance.

The Growing Need for Dementia Biomarkers

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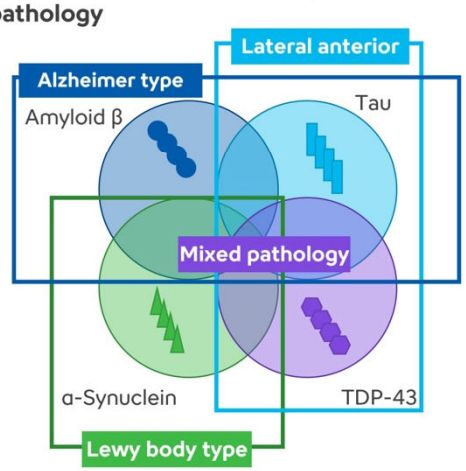
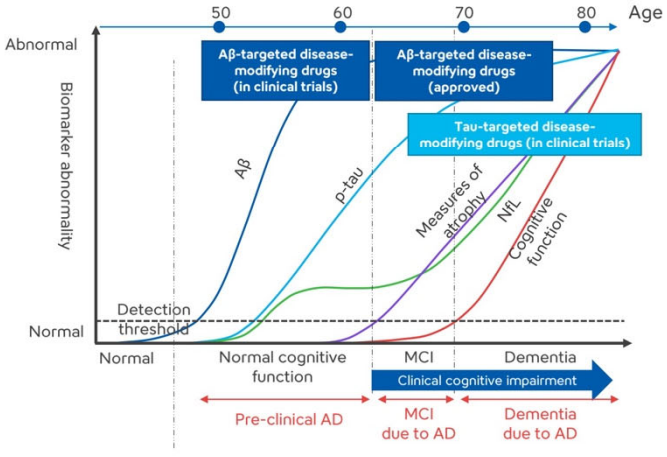
The development of biomarkers corresponding to the stratification of dementia patients and therapeutic agents for each disease stage is required.

Accelerating trend toward dementia stratification based on background pathology



Progress in the development of therapeutic agents according to disease stage



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

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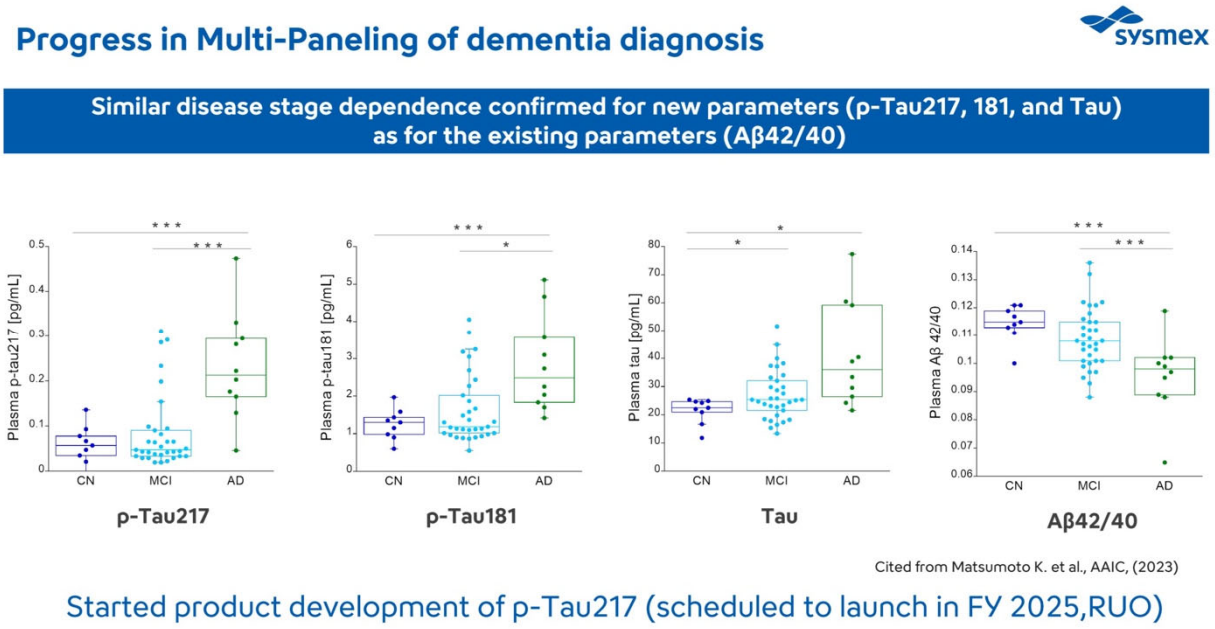
We have just discussed about Aβ42/40, but there are many other biomarkers of recognition disease that are in demand.

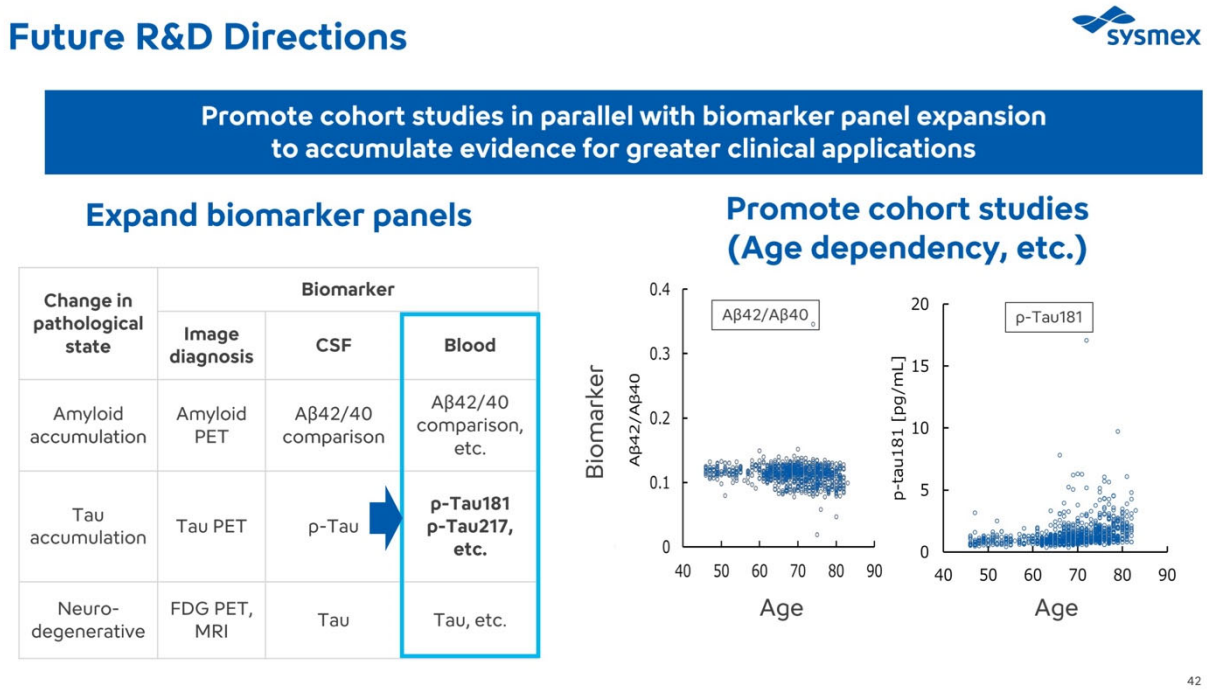
One is not only Alzheimer's disease, but also other dementias, for example, Lewy bodies, frontotemporal type, for example, in the figure on the left. The figure on the right shows how biomarkers can distinguish whether the disease is early or advanced, and how treatment will vary. Therefore, there is a need to develop various biomarkers to distinguish dementia other than Alzheimer's disease and to distinguish the stages of Alzheimer's disease. Many companies worldwide are conducting research and development for this purpose.



Sysmex, of course, has also conducted a multi-panel study after Aβ42/40, and this figure shows the results of the performance of various markers, such as p-Tau217, p-Tau181, and Tau.

I'm afraid the figure is a bit small and hard to see, but CN indicates healthy, MCI indicates mild or greater, and AD indicates Alzheimer's disease, and in all reagents, the values increase as the stage progresses.

Sysmex has been working on the development of a panel of multi-markers and has given priority to the commercialization of p-Tau217, which will be released for research use by the end of FY2025.

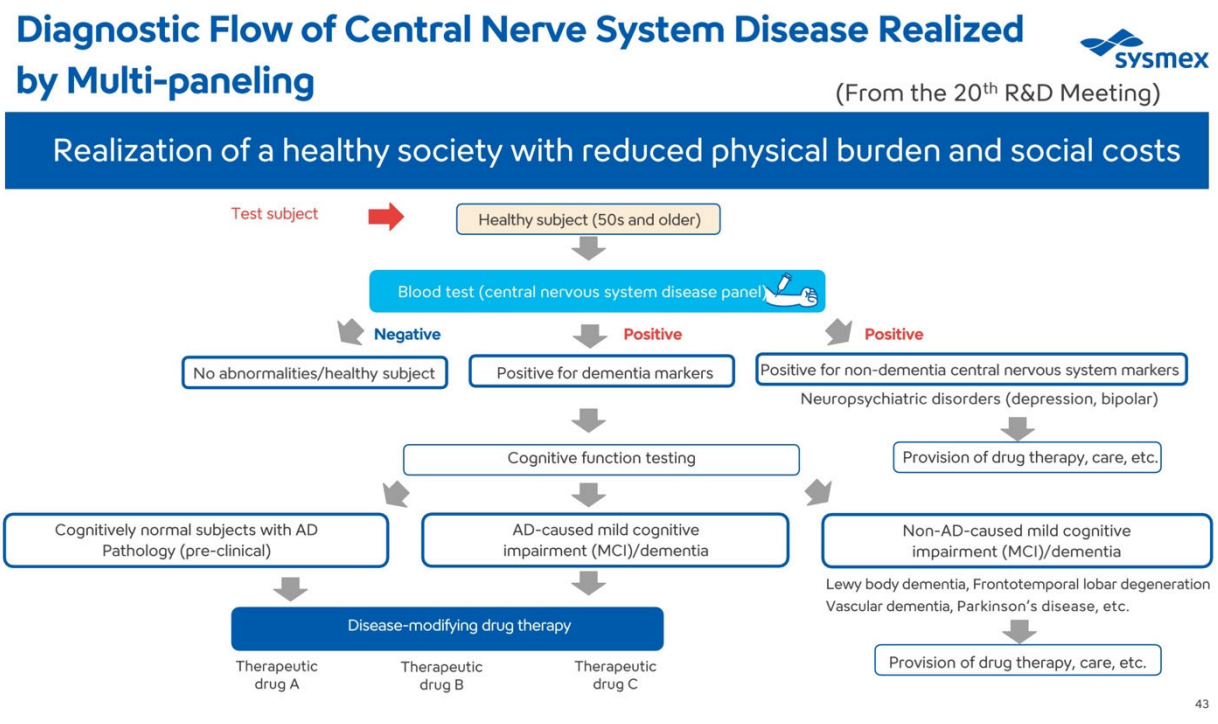


This is about future research and development policy.

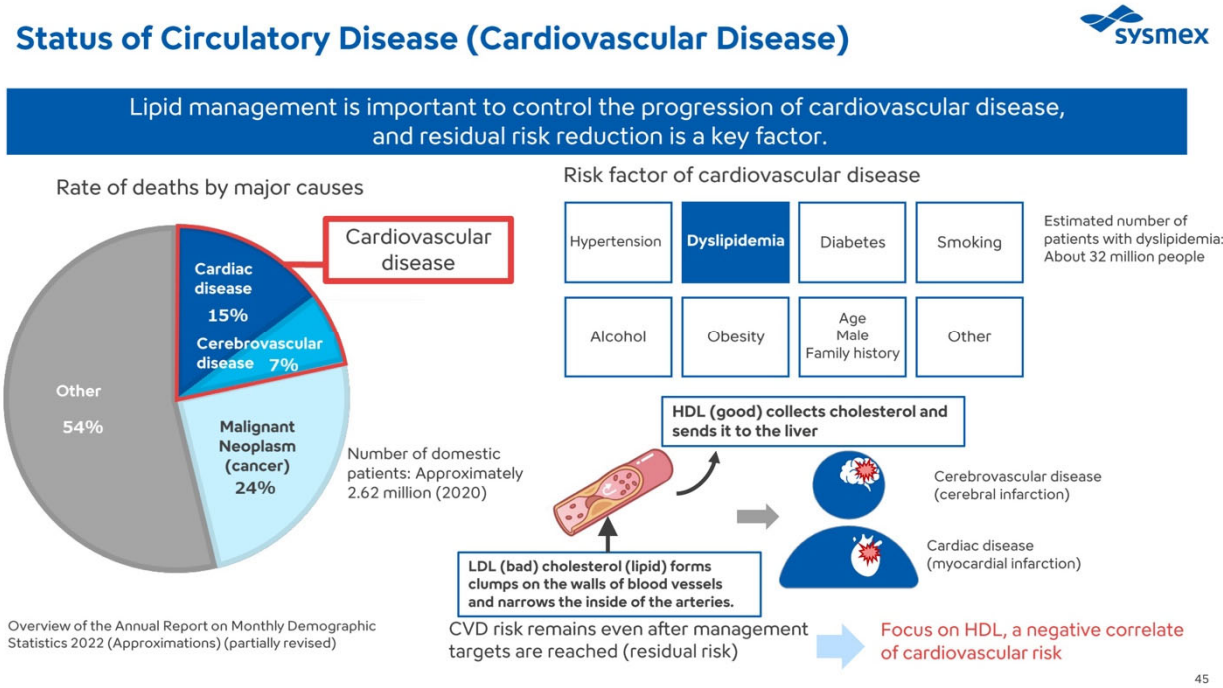
On the left side, as I mentioned earlier, we will be expanding the panel of biomarkers.

On the right side, you see that we are promoting cohort studies, but first we are studying whether Aβ42/40 and amyloid pathology is accumulating or not. We have been using the test for people with cognitive function or higher as a means to link this to medication, but we would like to expand the application of the test in the future. We are accumulating a variety of evidence for this purpose, and one example of accumulating evidence is this age-dependent result.

If you look at it, this is for cognitive function, for people who are all normal. However, Aβ42/40 values still change in an age-dependent manner, even when cognitive function is normal. So how do we diagnose the future based on this? We are proceeding with the verification of such things while creating solid evidence.



This document is a re-publication of the material from the previous R&D meeting, but we would like to apply our tests from the healthy level in the future. In short, we do not want to test people for dementia after they have it, but rather to test them thoroughly at an early stage and link them to treatment, so that in the future we can achieve a healthy society with limited physical burden and social costs.

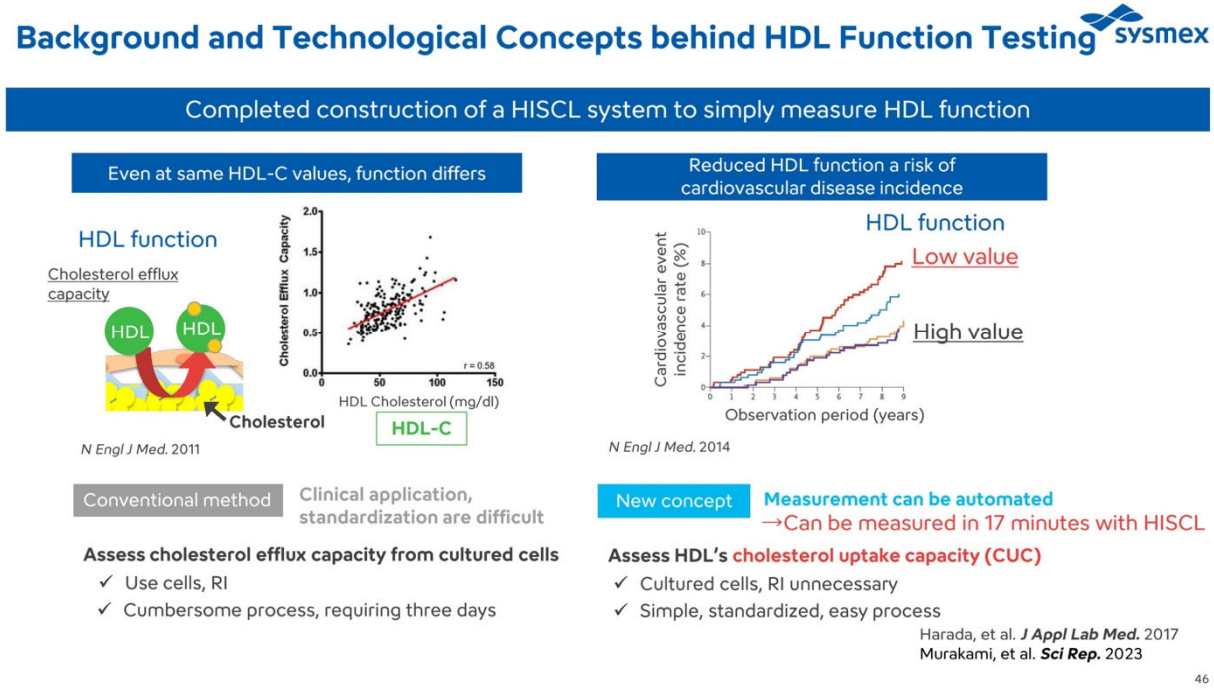


Next, we will discuss cardiovascular disease.

Although dementia is often the focus of attention, cardiovascular disease is also a very important disease, and as shown in the figure on the left, cardiovascular disease is currently responsible for almost as many deaths as cancer.

In cardiovascular disease, one of the major risks is lipid abnormalities, i.e., high cholesterol levels. The figure below explains LDL cholesterol and HDL cholesterol. As you are probably well aware, there are good cholesterol and bad cholesterol, and LDL is the bad cholesterol.

Until now, treatment has focused on how much the bad cholesterol can be lowered. However, the fact is that even if the bad cholesterol is lowered to the standard level, it is difficult to fully suppress cardiovascular events. As the comments in red are shown in the lower right corner, attention is being paid to the fact that other factors, not LDL but HDL, should also be well controlled for this purpose.

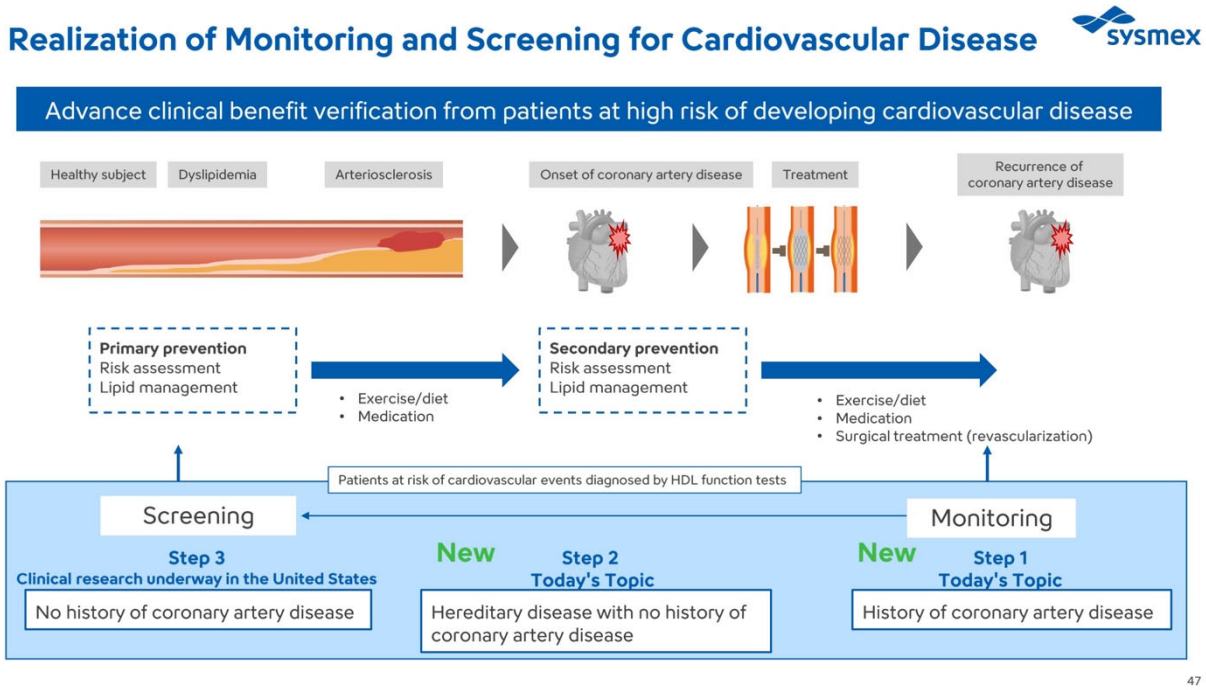


It is true that HDL cholesterol is normally measured during health checkups, but in fact, the amount of HDL cholesterol alone is not sufficient to suppress cardiovascular events, so we have focused on measuring its function and have been developing a measurement system.

Although the amount of HDL cholesterol is the same, if the function of HDL is different, HDL's essential function of returning cholesterol that has accumulated in the blood vessels to the liver does not work adequately. This figure on the right shows that low HDL function makes you more likely to develop cardiovascular events and high HDL function makes you less likely to develop cardiovascular events, which was published about 10 years ago in a very prestigious paper called the *New England Journal of Medicine*.

It says here that it can be done easily at HISCL, but in fact, the instruments for which evidence has been obtained so far are very difficult to perform using cells and radiolabeling and take about three days to perform. In fact, we have succeeded in achieving this in 17 minutes, instead of the three days it would have taken with cells and radiolabeling.

The cholesterol uptake function of HDL is called CUC. I will now explain the evidence for it.



We are now in the process of obtaining clinical evidences on how to use this developed test for cholesterol uptake capacity of HDL on HISCL in the world. There are two major phases.

One is a general measurement at what is called a health examination to determine the risk of cardiovascular disease in the future or not. In a sense, this will be aimed at a very large market.

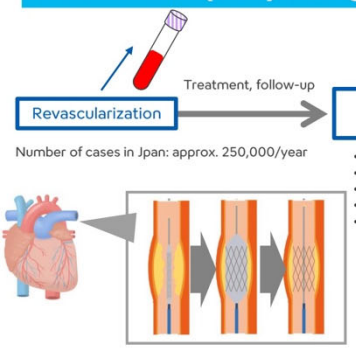
The other is monitoring. The second point is that patients who have had a myocardial infarction and have a stent placed, for example will look at this indicator to reduce the recurrence of the infarction.

We have been conducting clinical studies to verify the results of these studies, and I would like to explain two clinical studies.

Step 1: Verification toward Recurrence Risk Testing

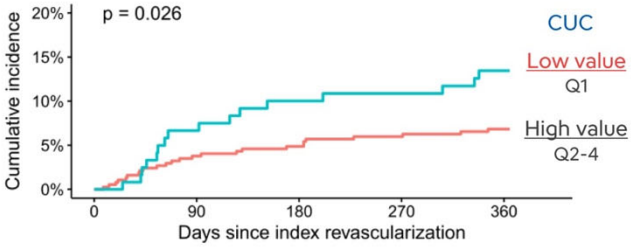
There was an association with postoperative serious cardiovascular events in patients undergoing revascularization, indicating the potential for appropriate intervention in high-risk patients

HDL function (CUC) testing



New

Evaluation in a case at the National Cerebral and Cardiovascular Center



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The first is validation for recurrence risk diagnosis.

The results of our measurements to stratify patients who actually underwent stenting, etc., are shown on the right. Those with low CUC had a higher risk of developing the disease, and those with high CUC had a lower risk, confirming that it is useful as an indicator. In fact, a small-scale study was conducted at Kobe University several years ago, and now the **National Cerebral and Cardiovascular Center**

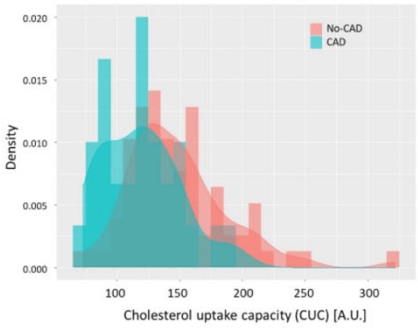
has produced results on a slightly larger scale.

Step 2: Verification toward CVD risk monitoring for hereditary disease patients

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

New

Evaluation of cases in Kanazawa University



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

Familial hypercholesterolemia

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

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

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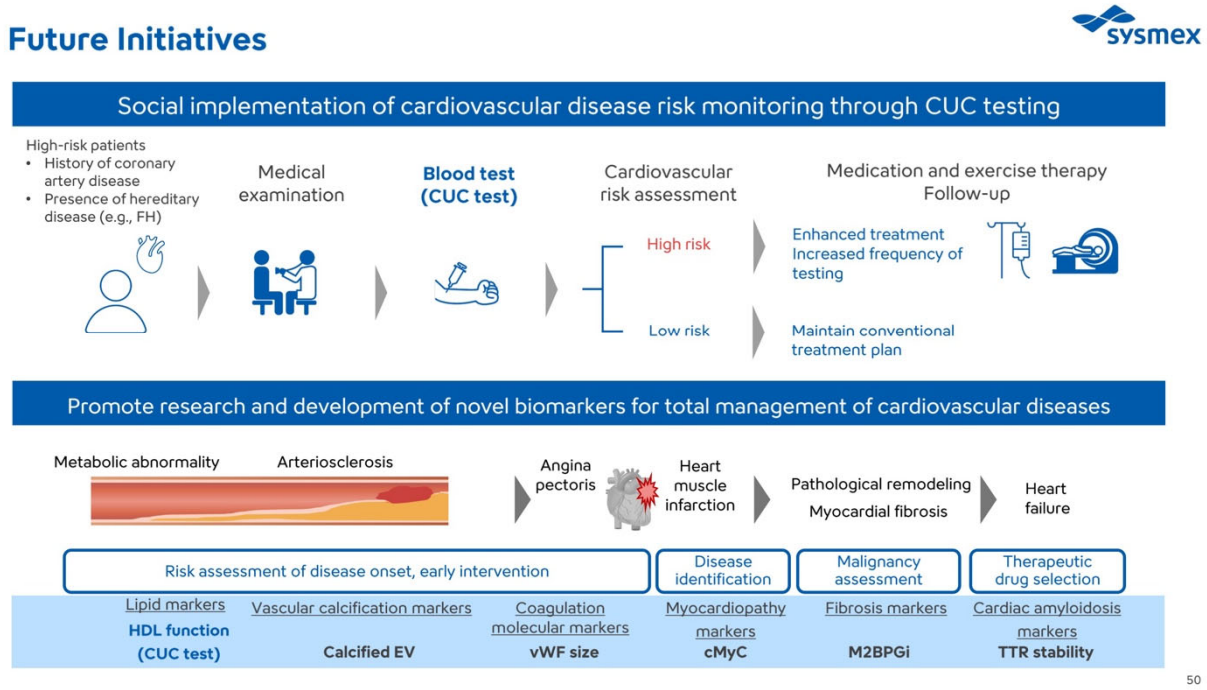
The other is risk monitoring.

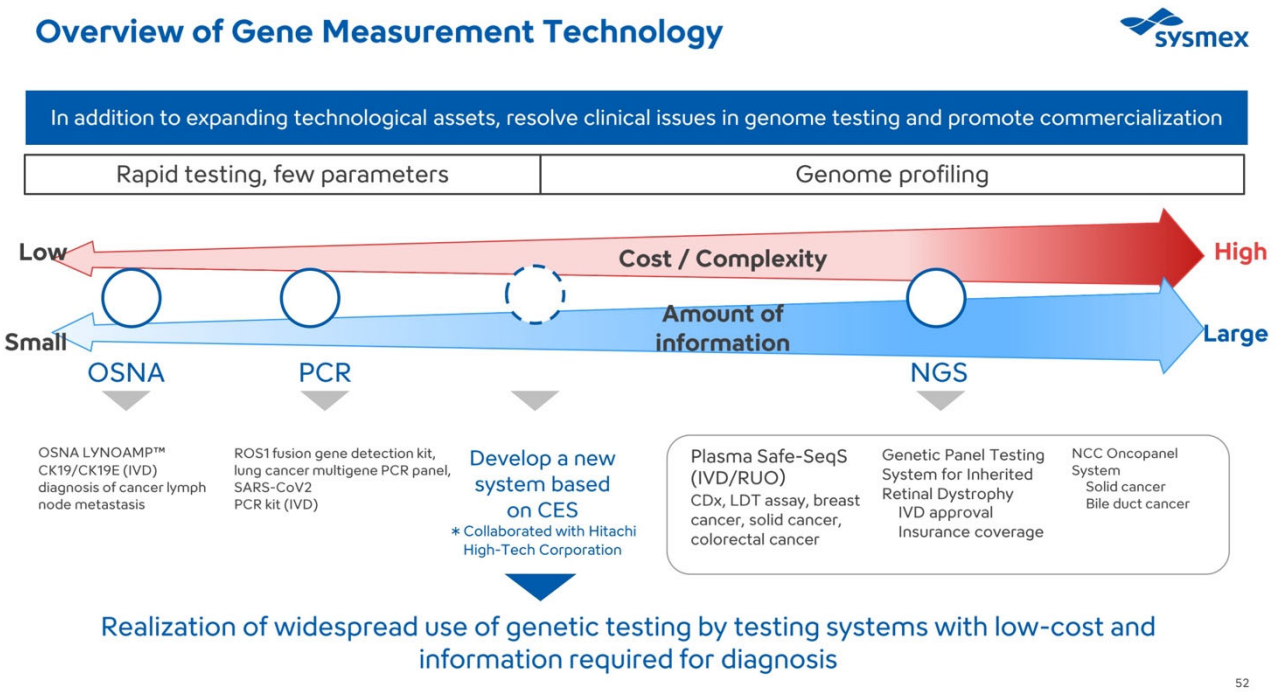
This is monitoring to see if it can be used in a health checkup. It is a little difficult to suddenly evaluate the results in a wide range of health examinations, so we are evaluating patients with a specific familial hypercholesterolemia, a genetic disease.

In the figure on the left, the red line indicates that the person did not develop an event and the green line indicates that the person did develop an event. Evidence was obtained that people with higher cholesterol uptake capacity on the horizontal axis were less likely to develop an event.

The figure on the right, although a bit difficult to understand, is actually an evaluation result that shows that what cannot be understood by the amount of HDL cholesterol or LDL was found by looking at the function of HDL this time.



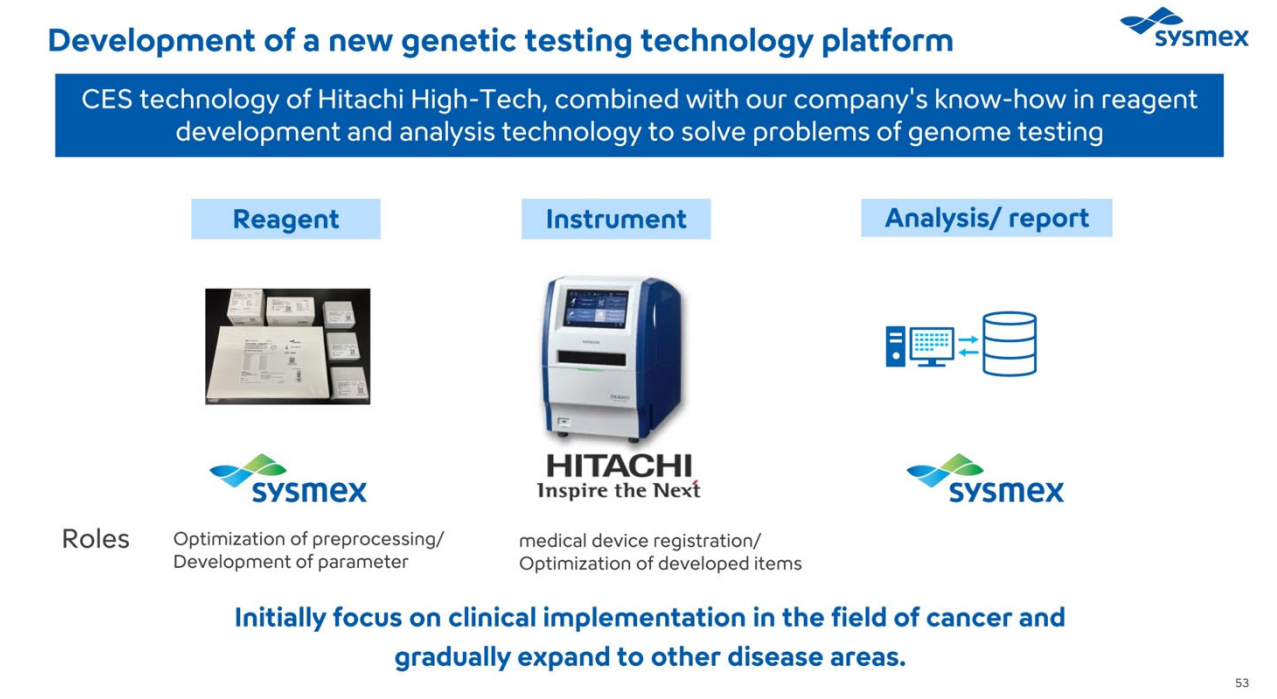
One of the major points for us in the future is to bring this into clinical implementation, and another is that cardiovascular diseases also have a fairly long stage. Development of markers applicable to each is under way in parallel.



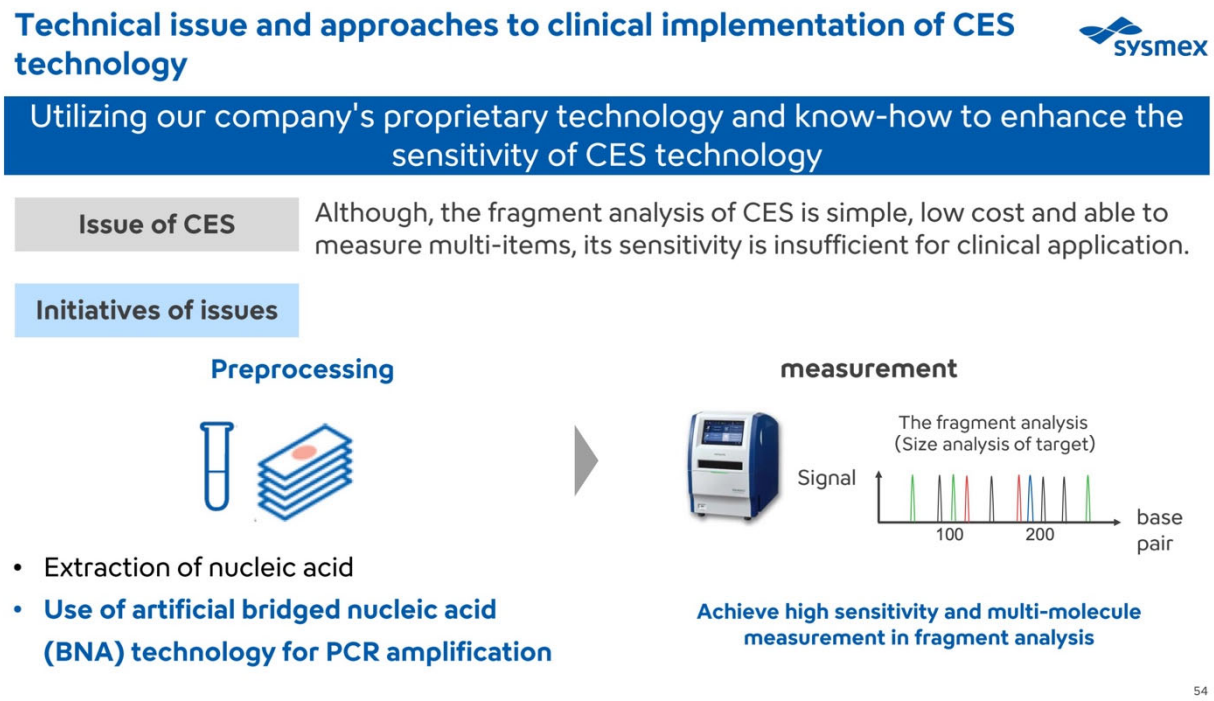
Finally, I will explain about genetic testing.

We already have various platforms for genetic testing, OSNA, PCR, NGS. NGS is not a platform but a panel, and each has its own characteristics.

With OSNA and PCR, the amount of information is small, but it can be measured very easily and at low cost. When we try to do NGS, we get a lot of information, but it is not easy. It also costs money. We are in between. By developing a low-cost method of obtaining only the truly necessary information, we are considering the clinical implementation of genetic testing, including domestic production, in partnership with Hitachi.

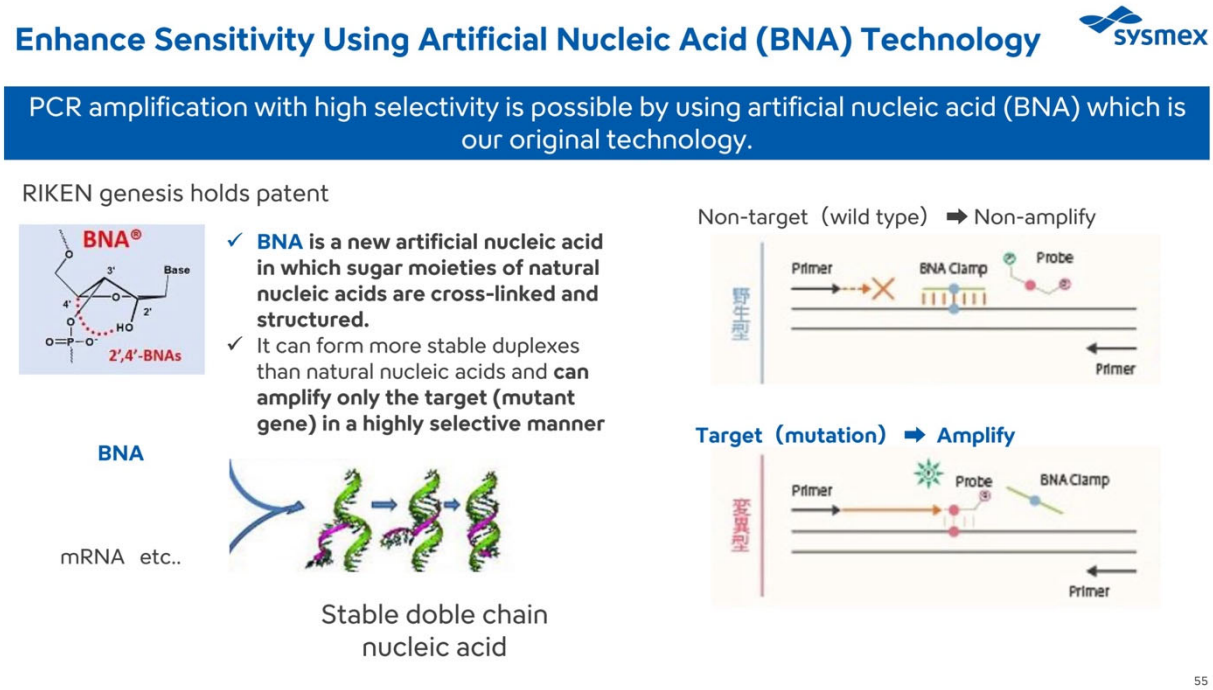


As Mr. Yoshida explained in his slide, using Hitachi High-Tech's cavitary electrophoresis sequencer technology, we will develop pretreatment reagents and Hitachi will register capillary electrophoresis medical devices to optimize each development item. At the end, we will analyze and report on the results, and we will work in collaboration. We are considering to target the area of oncology first and then gradually expand the disease area.



Here is a simple statement of what the challenges are in bringing this technology to the world.

In a nutshell, one mode of this technology is simple, low cost, and capable of measuring multiple parameters, but lacks sensitivity. Therefore, we have adopted a policy of using SYSMEX's technology to increase sensitivity before electrophoresis to achieve multi-parameter, simultaneous measurement, simplicity, and high sensitivity. The means to achieve this is to use Sysmex's artificial nucleic acid, BNA, technology.

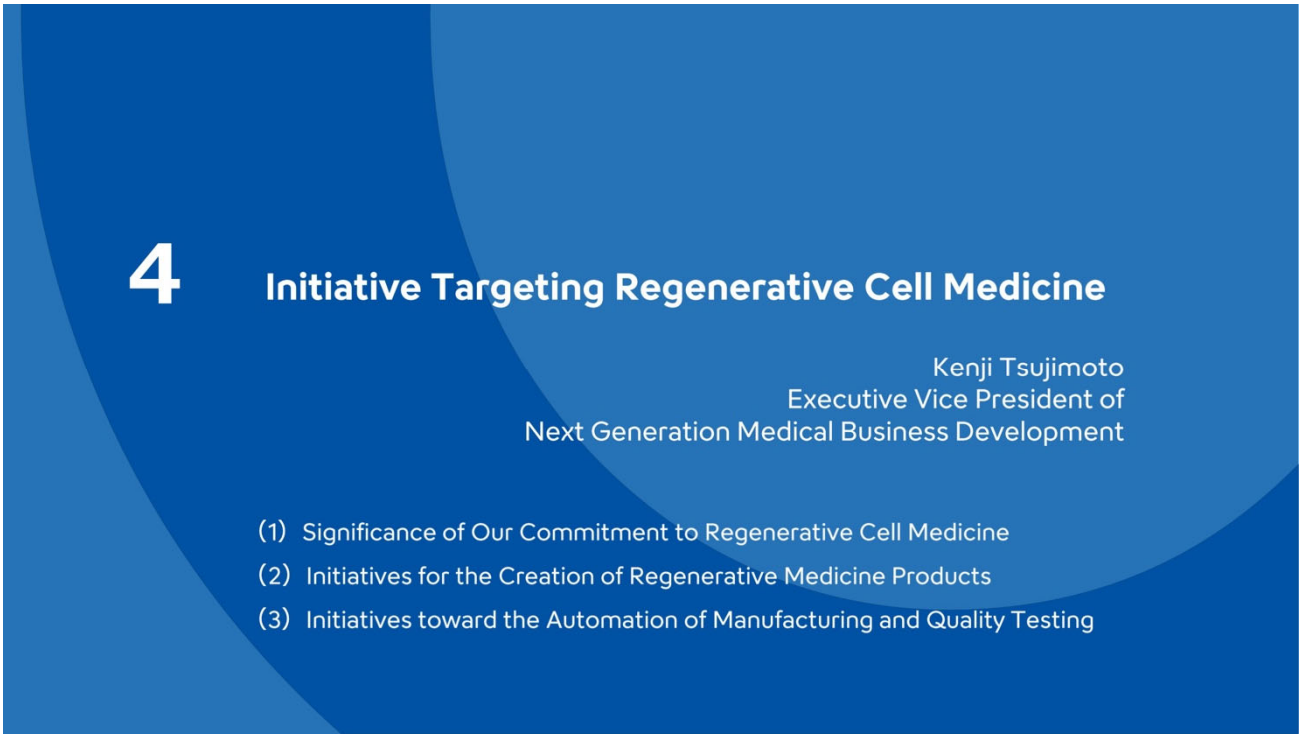


Using our BNA technology, PCR can be used to amplify with high sensitivity only those genes that have specific mutations, for example, those of cancer origin. Since this is a patented technology, our policy is to maximize the use of this technology to realize capillary sequencers and sequencing systems with higher sensitivity.

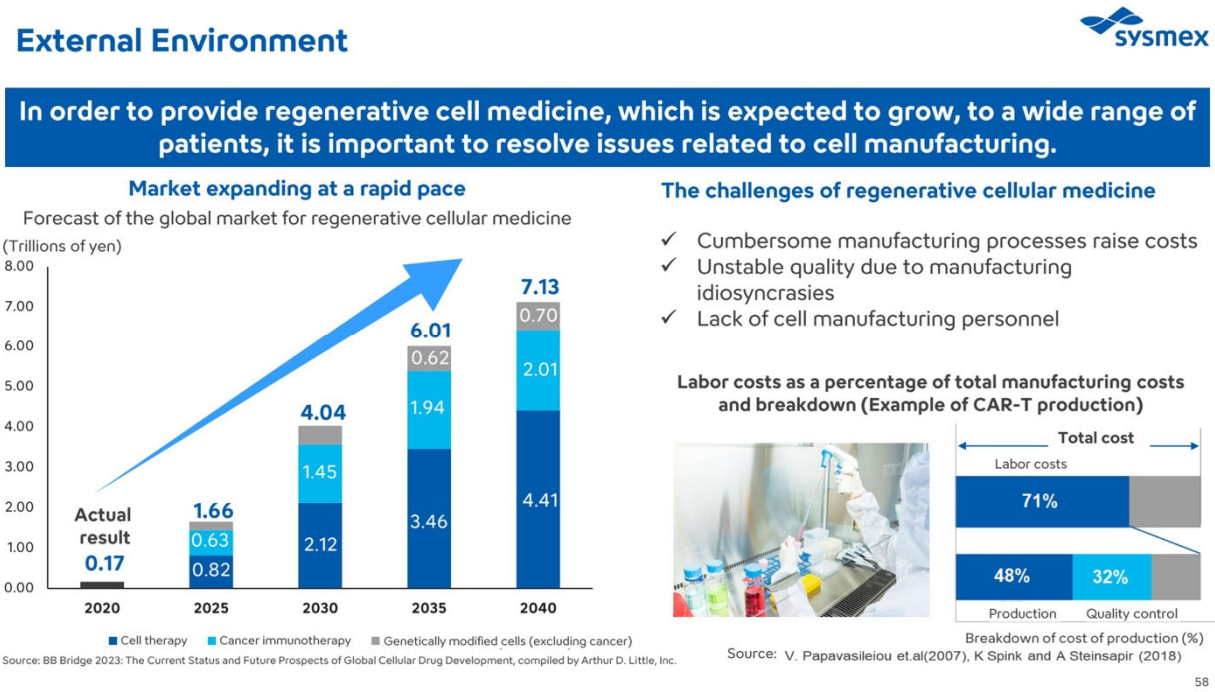
That is all.

Moderator: Mr. Sato, please step down.

Now then, Mr. Tsujimoto, please start.



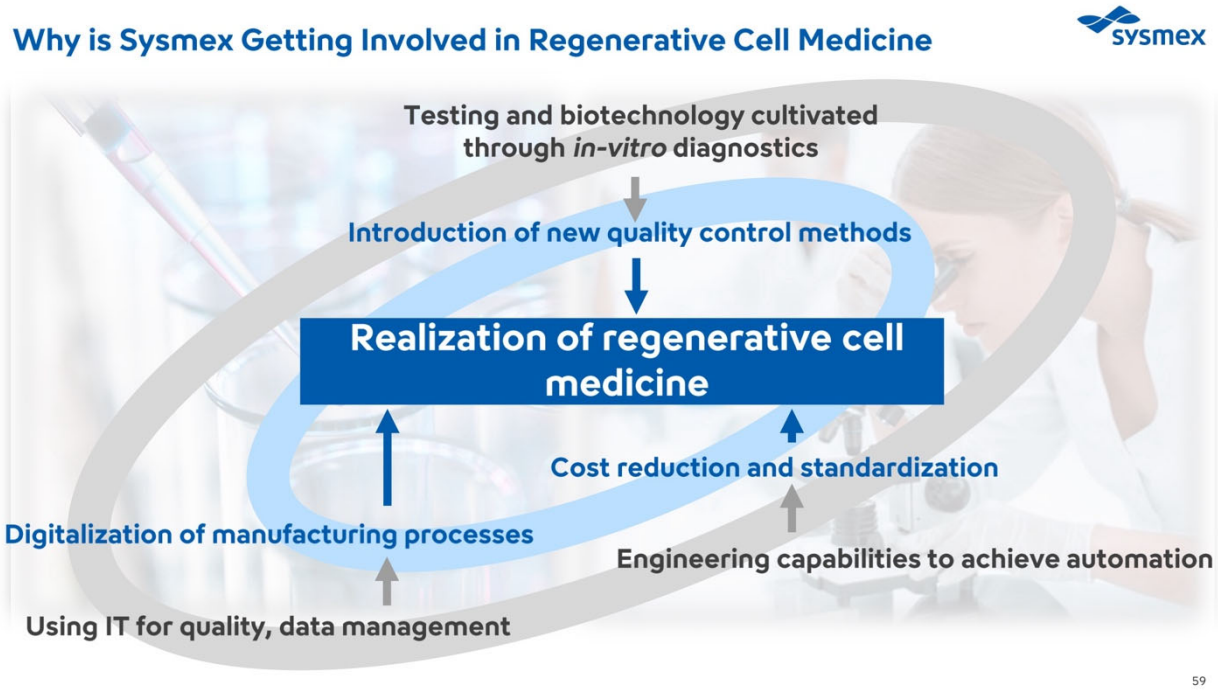
Tsujimoto: I would like to make a presentation on our approach to regenerative cellular medicine.



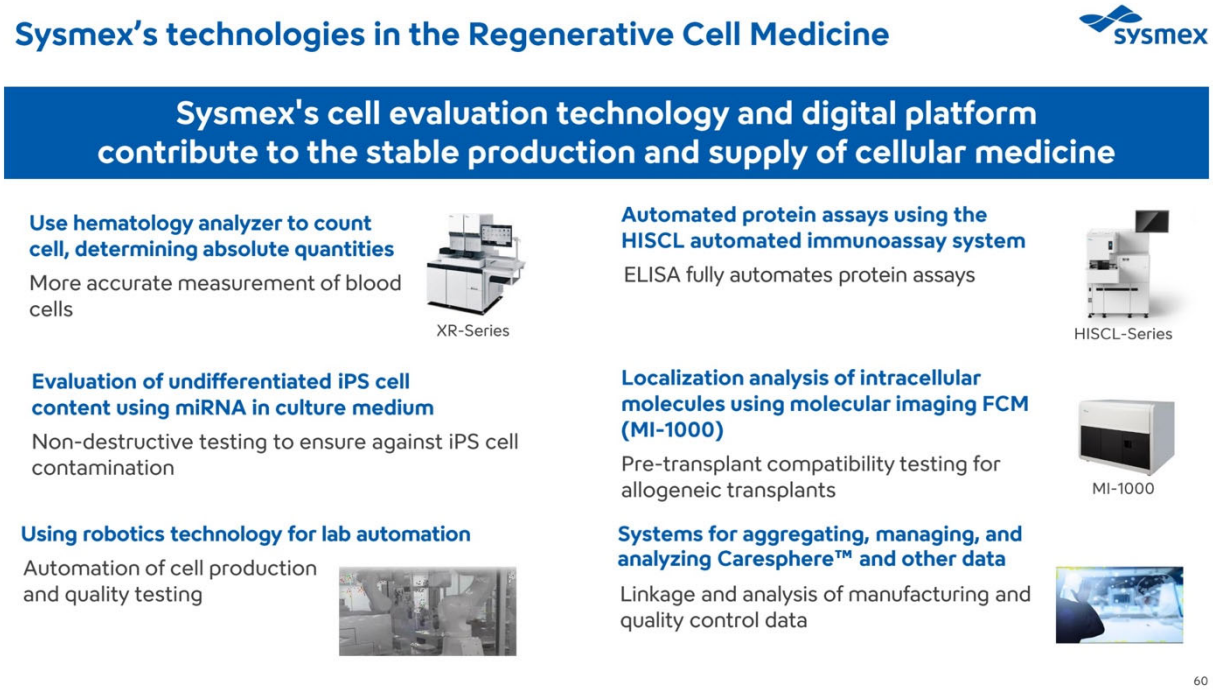
First, this slide summarizes the significance of our involvement in regenerative cellular medicine and the external environment for us at SYSMEX.

As you can see on the slide on the left, the growth of this market is projected to be JPY7 trillion by 2040. However, in order for this market to expand, there are several issues that need to be addressed, including the various issues related to the manufacturing process as shown on the right. This manufacturing process is still quite complicated and involves a large number of people, and the challenges of human resources being hard to find are becoming more apparent as the market continues to expand.

As a result, as you can see in the lower right, the labor cost as a percentage of the cost is not small, and we believe that this is a much higher than the average for normal industrial products.



This is the material that I explained at last year's R&D meeting. We believe that our technology and experience can address the manufacturing issues that I have just mentioned, and that we can contribute to the solution, even if only a little.



Some of the technologies and examples are shown here. The cell measurement, gene measurement, protein measurement, and Caresphere are shown in the lower right corner. Data management is also very important in the manufacturing process. We believe that the laboratory automation technology that Sysmex has delivered to laboratories can also be used in this area to promote the automation of manufacturing processes.

Our Overall Approach to Regenerative Cell Medicine

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

Creating regenerative medicine products

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

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

Automation and digitization of cell production/quality testing

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

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Based on this approach, during the past year, we have been working to strengthen our pipeline in terms of the creation of regenerative medicine products. We are currently promoting these three pipelines through open innovation with our subsidiaries and other companies.

In the creation of such regenerative medicine products, we would like to incorporate our technologies and capabilities in abundance and are considering the possibility of developing the quality control and automation solutions that would result from this process as a stand-alone business.

Regenerative Medicine Product Pipeline

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

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

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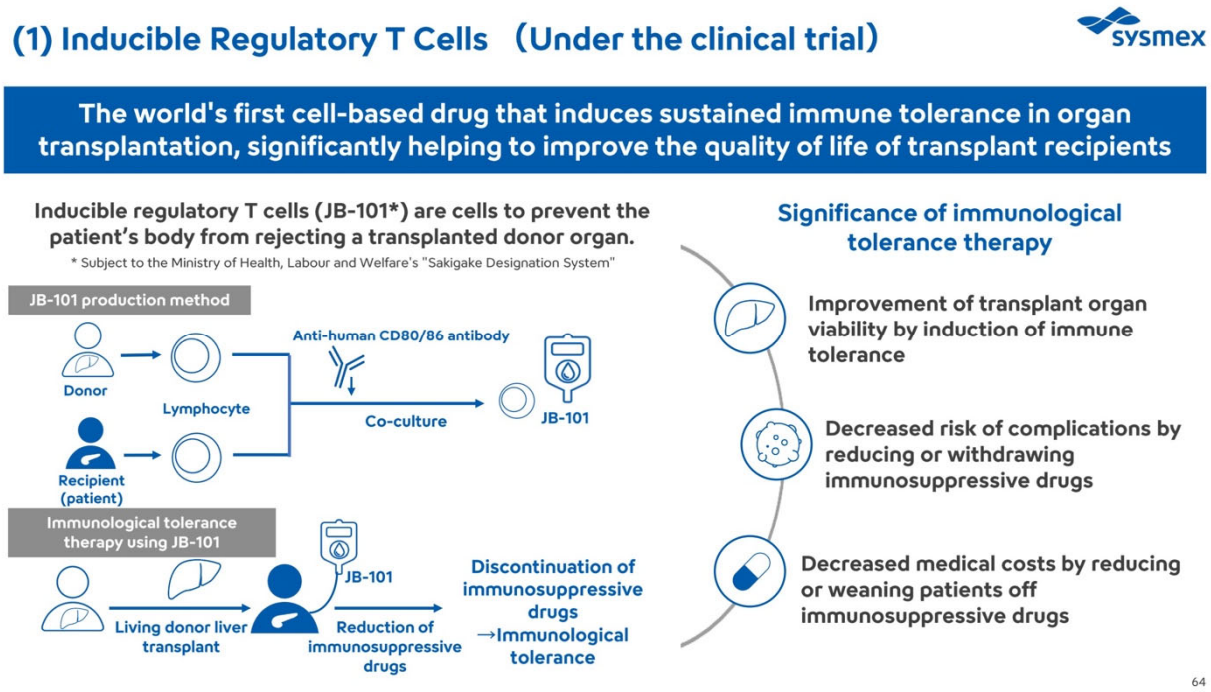
Now, from here, first of all, in the area of initiatives for the creation of regenerative medicine products, page 63 shows the main characteristics of these three pipelines.

Let me explain in turn.



The first is inducible regulatory T cells, which we licensed from JUNTEN BIO, which we released in a press release last November. Our subsidiary, AlliedCel, holds the rights to manufacture and sell the product.

The product is characterized by its ability to promote organ retention after transplantation in patients undergoing organ transplantation and to reduce the use of immunosuppressive drugs and to wean patients from them. This is currently undergoing a physician-led clinical trial. As you can see in the upper middle of the page, we are currently undergoing the Sakigake (pioneering review) designation system by the Ministry of Health, Labor and Welfare. We are working diligently to complete this trial so that we can apply for manufacturing approval.

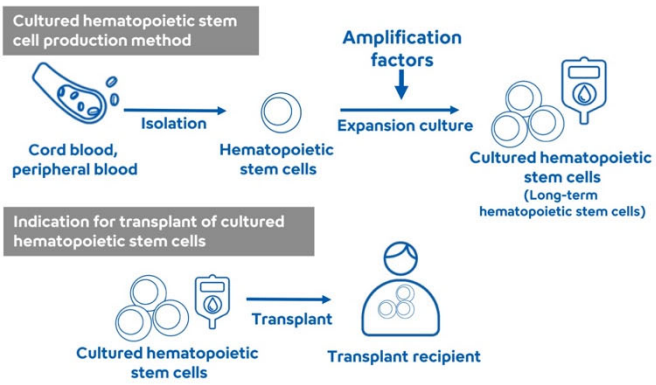
To be more specific, as the picture to the left of the center depicts, the blood of the donor and recipient are mixed, and an antibody cocktail is added to the mixture to produce a preparation called JB-101.

This can be directed not to attack organs that will later become the recipient's. It is full of such cells, and the effect will be to train the patient's other T cells not to attack this organ, thereby promoting the patient's organ retention and enabling withdrawal from immunosuppressive drugs.

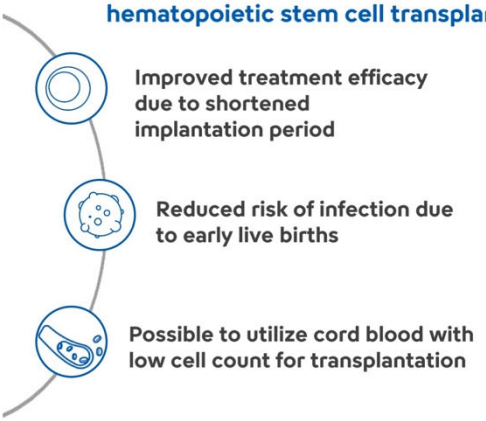
(2) Cultured Hematopoietic Stem Cells

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

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



Significance of cultured hematopoietic stem cell transplants



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From here, I would like to talk about our progress on cultured hematopoietic stem cells, which we reported on last year.

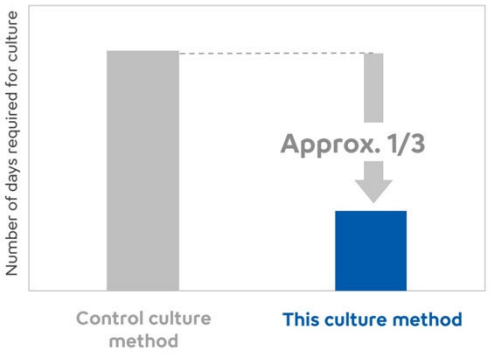
Again, there are approximately 6,000 HSCT transplants performed in Japan today. However, not all patients receive HSCs due to HLA mismatch, low cell counts, or various other reasons.

We believe that we can address these issues by using cord blood as the raw material, amplifying it in vitro, and preparing products that are sufficient in quantity and HLA-matched.

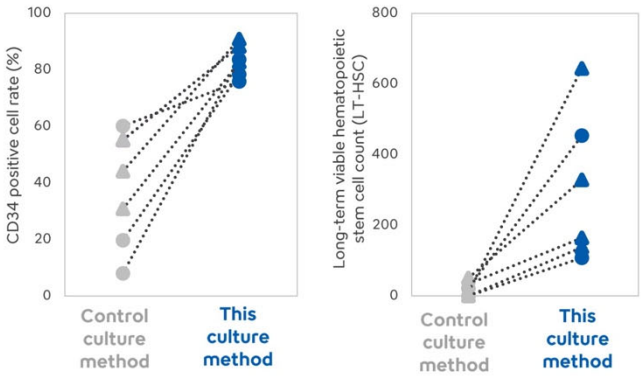
(2) In-vitro Performance of Amplified Culture Technology for Hematopoietic Stem Cells

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

Significantly shortens the time required for cell amplification



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



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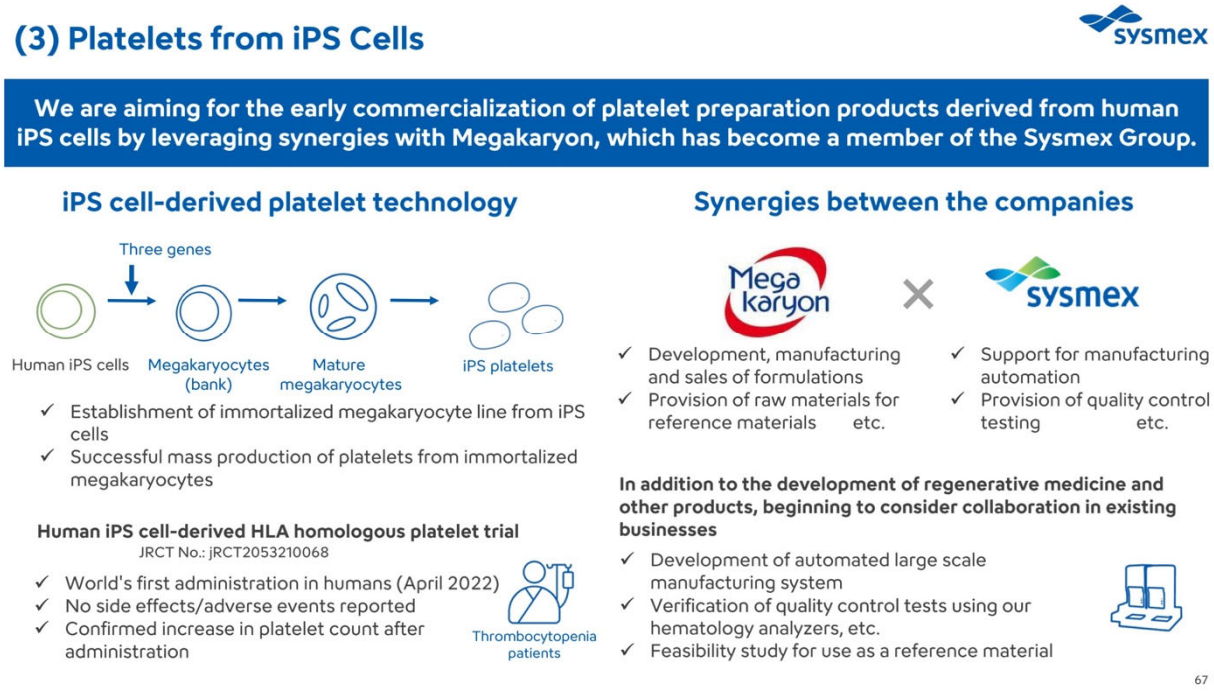
The following slides show some of the main in vitro performance data that have emerged over the past year.

First, this technology is characterized by a very short incubation period. Patients undergoing hematopoietic stem cell transplants are very often critically ill, so time is an extremely important factor.

When administered, both CD34-positive cells and long-term viable hematopoietic stem cells will eventually become legitimate as new hematopoietic stem cells in the patient. This is a very important population for differentiation of the blood cell lineage. The ability to amplify these cells and populations much more dramatically than the control culture method is also a feature of this method.

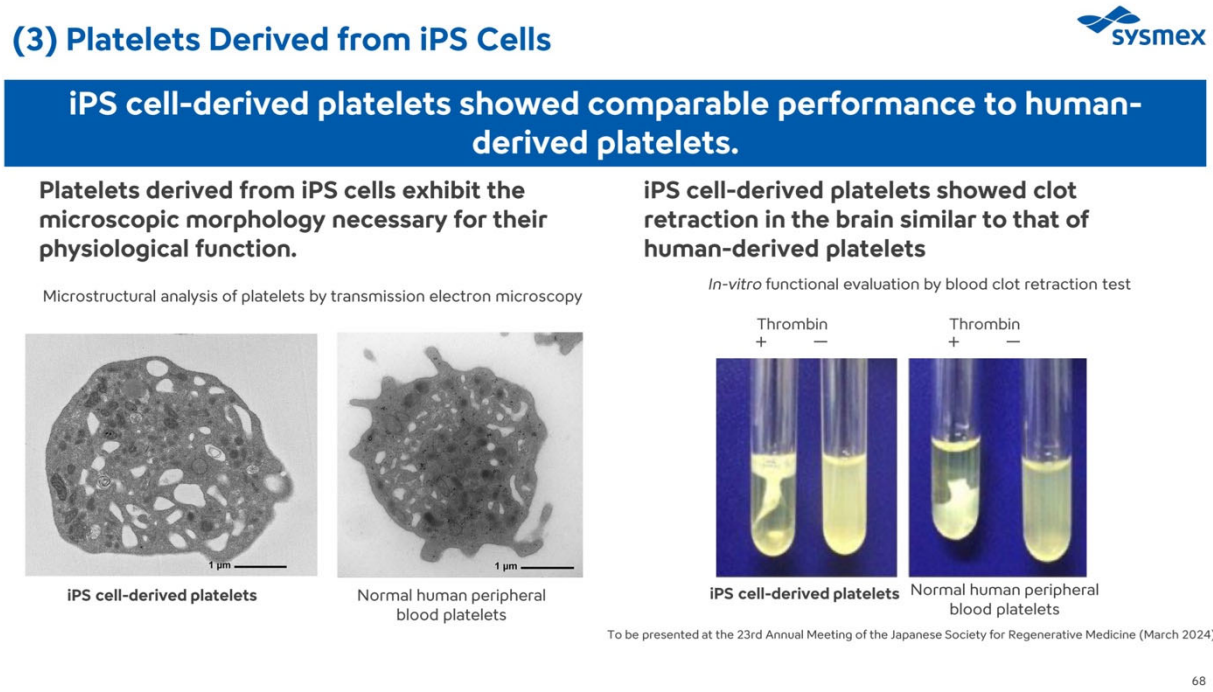
From the next fiscal year onward, we will begin in vivo animal studies and steadily move toward the start of clinical trials.



I will use a few pages from here to report on the technology and synergies of Megakaryon, which we acquired in December.

As some of you may already know, Megakaryon is a company that has a series of technologies to differentiate platelets from iPS. As shown below left., clinical trials have also been conducted once with homologous strains of HLA.

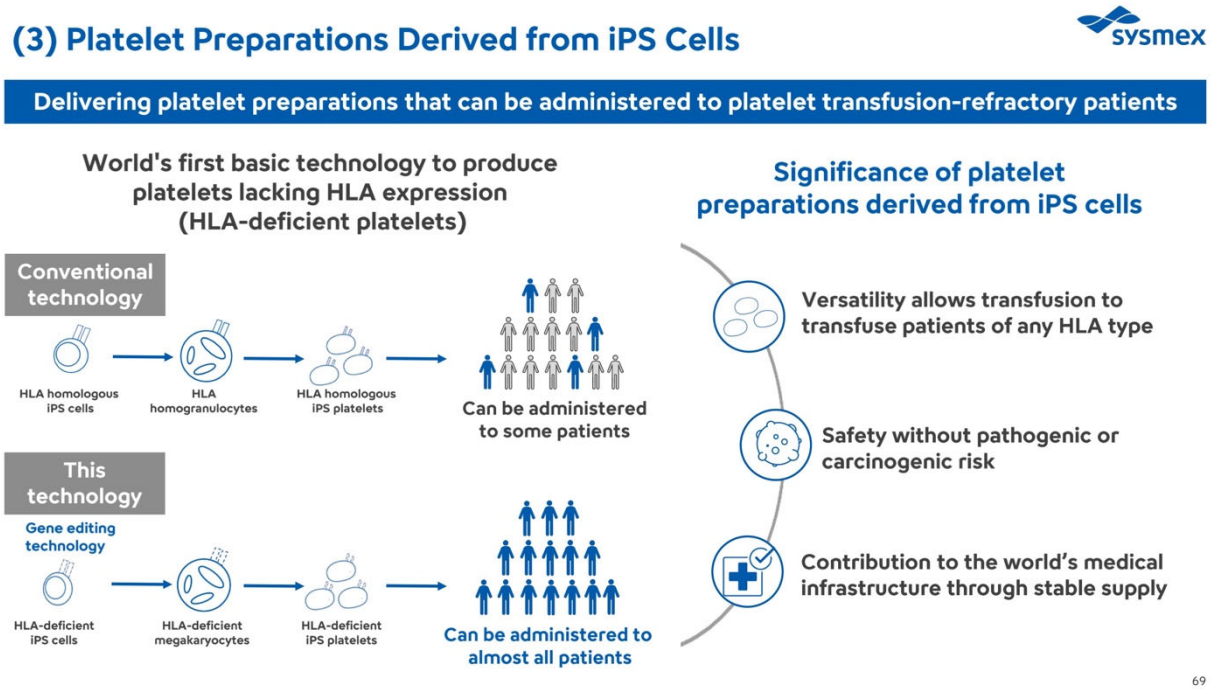
Our relationship with Megakaryon began with a partial shareholding, and over the past year or so, we have conducted what is called due diligence, and we believe that there are synergies as shown on the right side. We believe that there are synergies between the two companies. We will automate Megakaryon's manufacturing process and provide quality control technology, and Megakaryon may be able to provide us with reference material for hemostasis tests, for example.



This slide shows some of the characteristics of iPS platelets using some data.

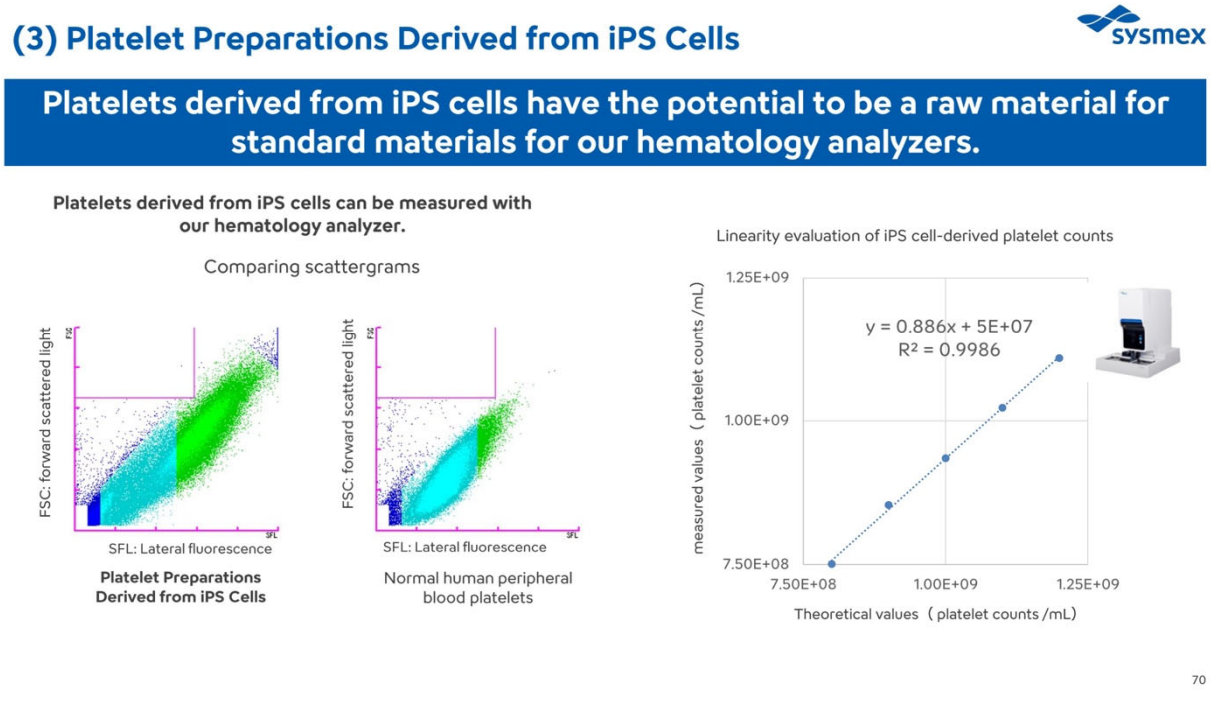
In terms of morphology, iPS platelets closely resemble normal platelets, and in terms of function, not only in terms of hemostasis ability in test tubes, but also in terms of performance in a hemostasis test using a rabbit model, although not shown here. Furthermore, as I have already mentioned, it has been confirmed that iPS-derived platelets exist in the circulatory system of the human body for a certain period of time.

As you can see in the lower right corner, the details of this data will be presented at the Annual Meeting of the Japanese Society for Regenerative and Cellular Medicine at the end of this month in Megakaryon, so if you have time, we would like you to come.



Regarding iPS platelets, we are currently trying to develop a null strain of HLA or a strain in which the HLA has been knocked out. We believe that this will allow us to administer medication to almost all patients with platelet refractoriness.

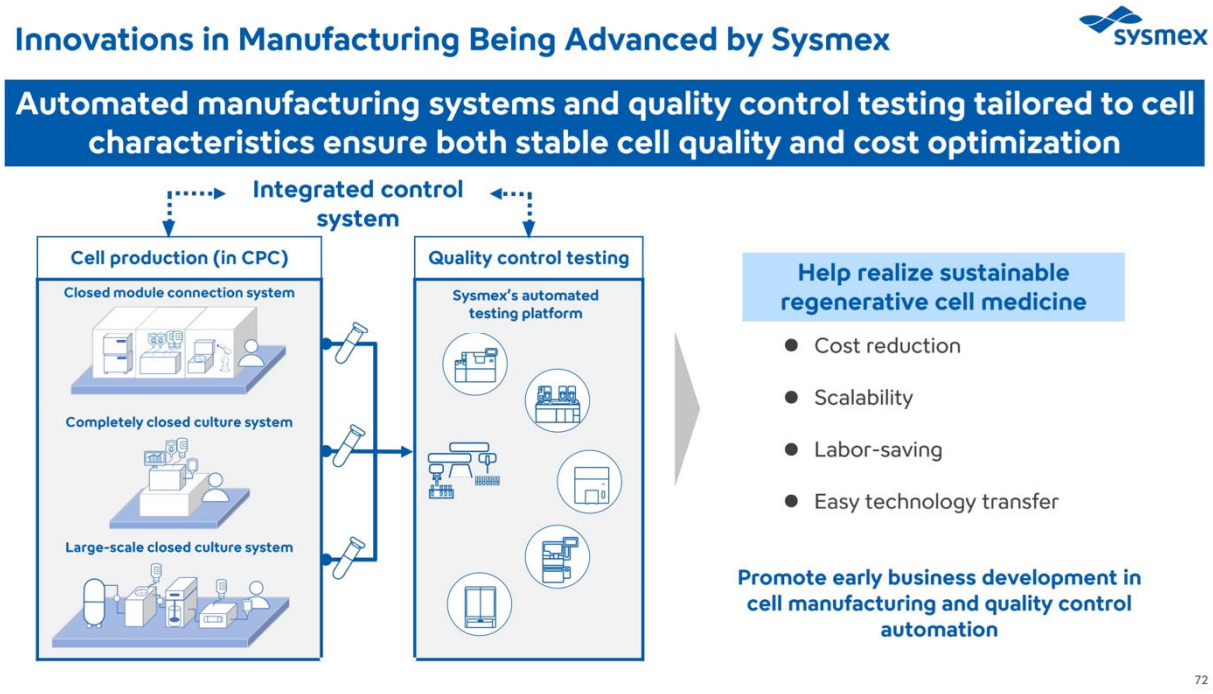
Not only in terms of therapeutic drugs, but also in terms of blood products, there may be a need for such blood products in case of emergencies that occur around the world. In some countries and regions, there is also the issue of infectious diseases caused by blood transfusions, so we believe that there is potential to address not only treatment but also global healthcare and social issues.



On the next slide, I discuss a few of the synergies with our company.

On the left is a scattergram, comparing normal human platelets to Megakaryon's iPS platelets. The platelets from Megakaryon are freshly prepared platelets, and in this sense, although many of the platelets are a little large in size, they can be firmly detected by the platelet channel of our hematology analyzers. As you can see on the right, the dilution linearity has been well obtained, and we believe that it can be used as a raw material for the reference material of our hematology analyzers.

Although not included on the slide today, the shelf life is also a very important factor, and in the past, Megakaryon has been engaged in R&D with some companies to extend the shelf life of human blood, which is very short, only four days. We would like to work on this as one of the synergies.



As we develop these regenerative medicine products, we are also working to automate manufacturing and quality testing.

This slide is just an overview, and I will provide specific examples later, but we would like to use our engineering and automation technologies to automate the manufacturing process, as shown on the left side, the manufacturing process in CPC.

Depending on the manufacturing process, there are several types, as shown here. Is it pretty much a matter of whether it uses a lot of culture medium or a fairly small amount, or whether it requires some steps or a special process? Also, if mass culture is necessary as well. The three types shown here are knowledge gained from our experience in the development of our pipelines. As I will explain later, Megakaryon has begun to create a very concrete image of the automation of the manufacturing process.

And by combining quality control testing, we hope to take on the challenges of regenerative and cellular medicine as shown on the right.

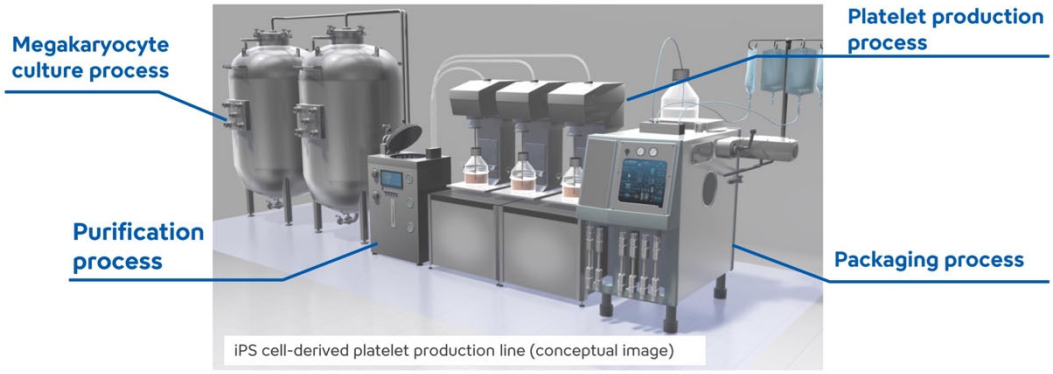
(Example) Initiative with Megakaryon

sysmex

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

Concept

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



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The next slide shows an image of Megakaryon's manufacturing automation process after completion. This is just an image. The actual process will be progressing from now on. In the large tank, megakaryocytes are cultured, then purified, and in the three flasks in the middle, megakaryocytes are matured and platelets are produced, which are then purified in the device on the right. We hope to work together in the future to produce a preparation like the bags depicted in the upper right-hand corner.

Quality Control Testing Automation Initiatives: Fully Automated Immunoassay System

sysmex

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

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

*Launched as research use

Characteristics

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

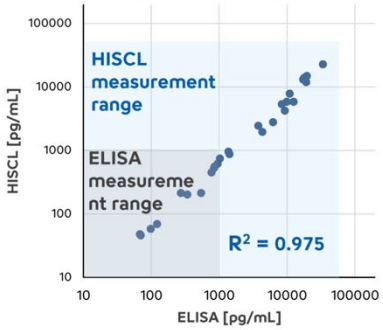
Vascular endothelial growth factor (VEGF)

Central molecule for angiogenesis, an indicator of organ bioproduction

Pigment epithelium-derived factor (PEDF)

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

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



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

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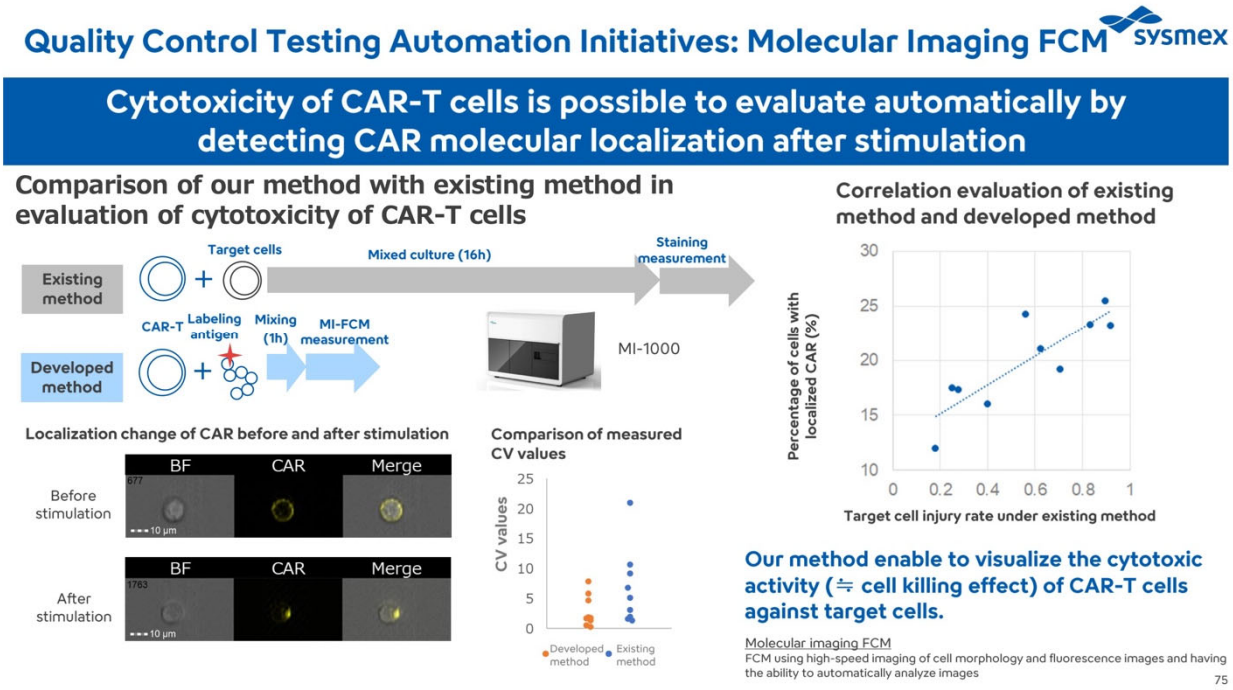
The next three slides from here show recent progress with respect to quality control tests.

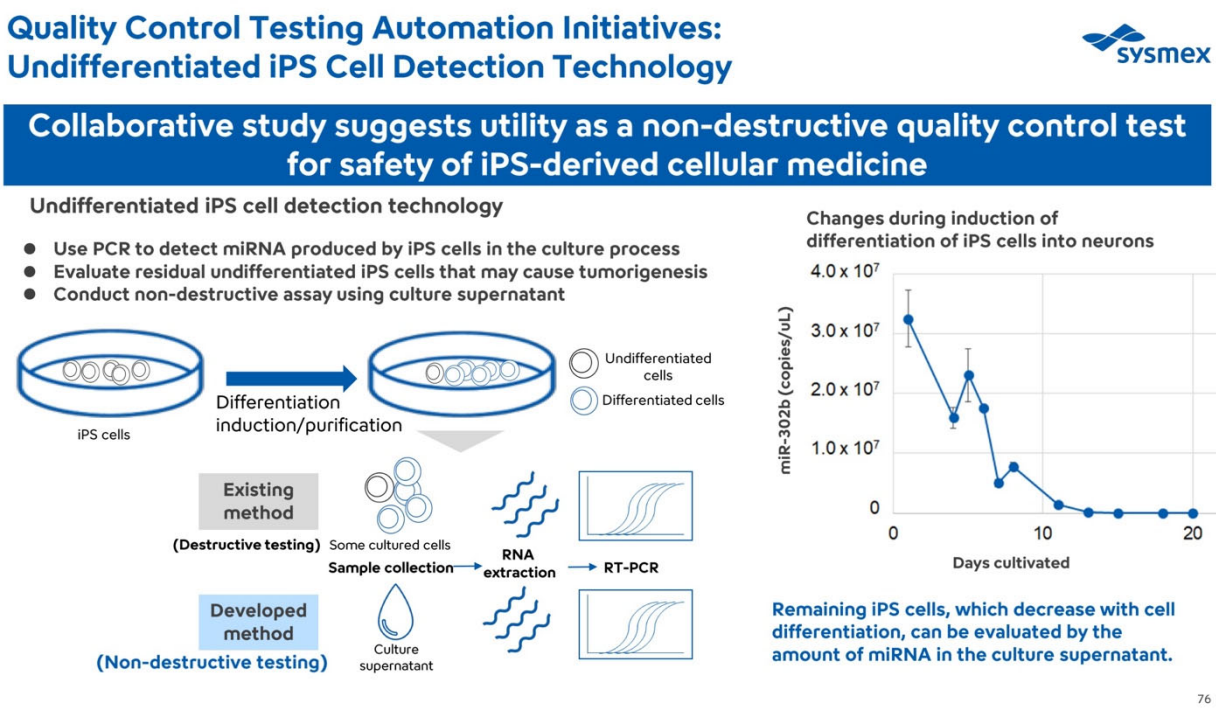
The first is our HISCL, protein test parameter. We expect to be able to introduce a reagent called VEGF/PEDF to the market in Q1 of the next fiscal year.

On the right is the measurement range of HISCL. Normally, this kind of test is done by ELISA, a manual method. The range is very wide, and although it is not very flashy, it has the advantage of simplifying quality control by eliminating the need for dilution for those who are actually performing quality control in the process.



This is about FCM, cellular testing.

As for CAR-T, it is not in our pipeline, but it is a very important test worldwide. The existing method to determine the function of CAR-T takes more than 16 hours, as you can see above. However, using our molecular imaging FCM, it is automated and can be performed in a much shorter period of time. In addition, as you can see from the CV values, there is little variation, and as you can see on the right side, the data shows that the match rate is very high compared to existing methods.



The final is genetic testing.

The purchase of iPS undifferentiated cells is a major issue for iPS preparations, but our technology has the potential to measure contamination or residuals of undifferentiated cells non-destructively in the culture supernatant.

Today, as you can see on the right side, new data has been obtained on the differentiation and residual state of iPS cells measured in this way using nerve cells, and some of the measured values are approaching zero as the number of days in culture increases. I believe it is very versatile.

While advancing our regenerative medicine products, we will continue to advance quality control and automation in step with the realization of our regenerative cellular medicine business.

That is all from me.

[END]