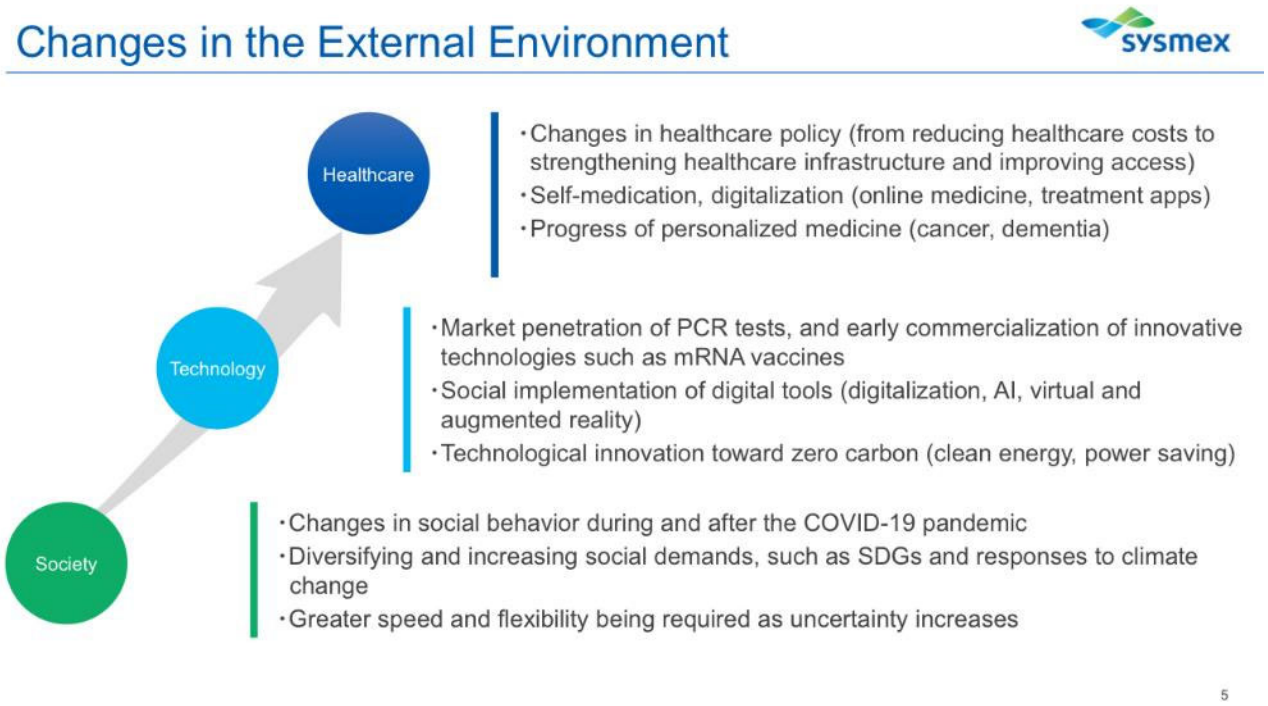
Presentation

Ietsugu: Good morning. This is Ietsugu. First, I would like to offer a few words on the occasion of this R&D Meeting. This is our 19th R&D Meeting.

We created the long-term management goals of SYSMEX in 2017 and announced them in 2018.

We have only three more years to go before we reach the goal in 2025. Based on the Sysmex Way, which is our corporate philosophy, we have set a long-term vision of becoming a unique and advanced healthcare testing company.

We have established these five positioning points for our further progress. On the other hand, however, since we set these goals in 2017, the situation is now changing considerably. In any case, it is very important that we continue to grow with the technology at the core.



Next, please. I would like to talk about changes in the external environment.

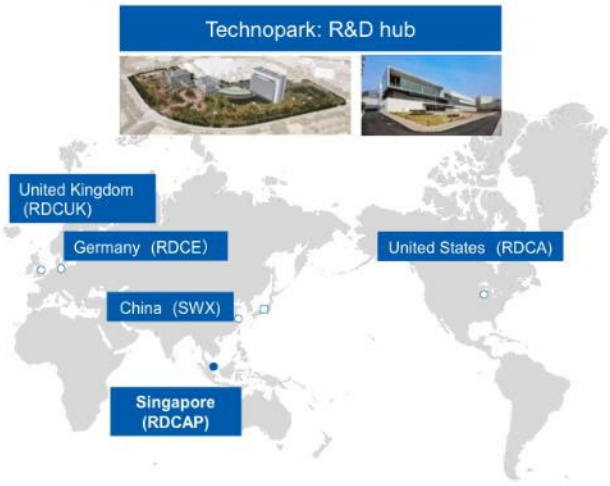
As you know, Covid-19 has had an impact on us for the past two years, and one of the major changes is that our lifestyles have changed dramatically, as we say, with coronavirus and after coronavirus.

On the other hand, sustainable management, including the SDGs, will become very important in the future. We are taking on this challenge, but the external environment has changed slightly since the time we set our long-term management plan, as I mentioned earlier.

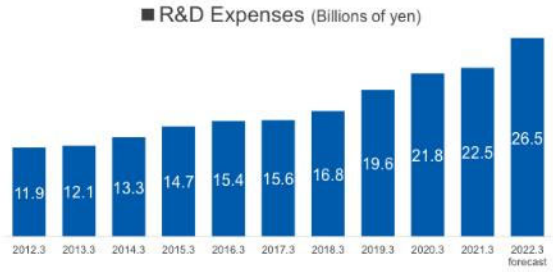
On the Technical side, PCR has become a common noun, and DX, digitalization, has become a very important factor, and we are working toward that. On the other hand, we are moving toward the goal of becoming carbon neutral.

The healthcare market and the market are changing dramatically due to COVID-19. Traditionally, developed countries have focused on how to curtail medical costs. However, this is no longer the case. Instead, we are looking to the strengthening of healthcare infrastructure, self-medication, digitalization, and, especially in Japan, the start of online medical care, which has been lagging behind, and, of course, personalized medicine is progressing.

Establishing a Global R&D System



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



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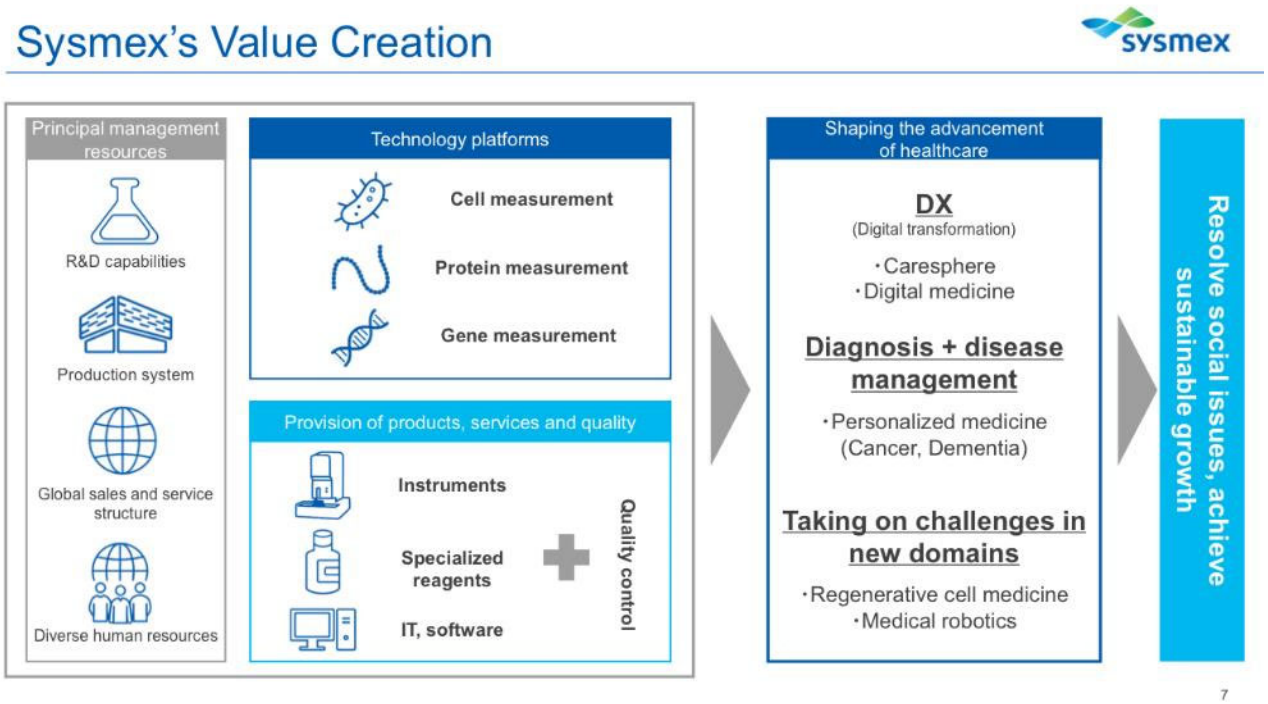
SYSMEX has established a global R&D structure, starting with the establishment of an R&D baser in 1993 at the Techno Center (presently Technopark), which has been in operation for about 30 years, and is now expanding overseas.

In particular, we will establish RDCAP in Singapore recently, meaning our global network will just been established. R&D expenses are now basically 7% of sales, and since SYSMEX has always been a technology-oriented company, we are certainly focusing on this area.



Next, it is the creation of value for SYSMEX.

As you can see on the left, our main resources are R&D, manufacturing, production, and our global sales and service network. In this context, we have a diverse human resources.

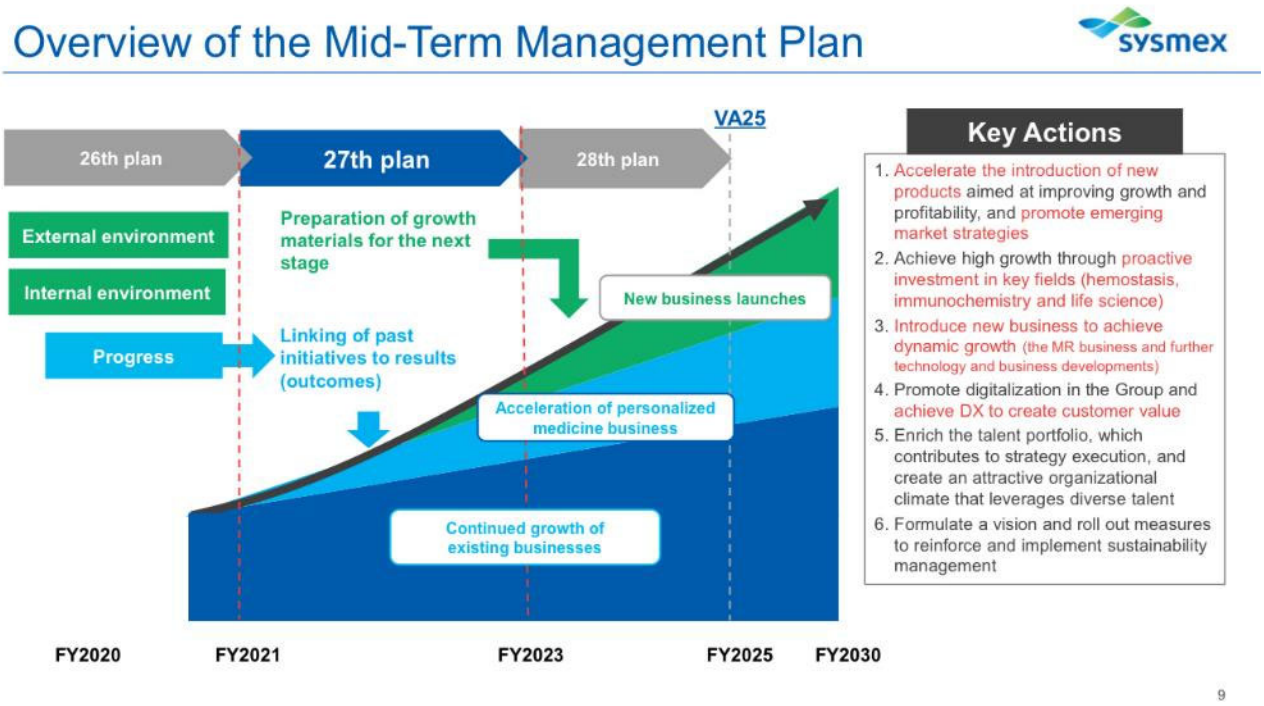
In particular, as I have said before, one of our goals is to make our three technology platforms more sensitive, cell measurement, protein measurement, and gene measurement. On the other hand, as stated in our provision of products, services, and quality, we are able to provide our customers with our own instruments, specialized reagents, and software. We are also able to control the quality of them.

And we are now taking on the challenges of DX, digital transformation, and at the same time, we believe that diagnosis, disease management, and personalized medicine are very important. We are developing these areas, including liquid biopsy. On the other hand, as you can see, we are also taking on the challenge of medical robotics and regenerative cell medicine as new domains.

In any case, SYSMEX is now focusing on solving social issues and achieving sustainable growth. That is all.

Moderator: Now, Mr. Asano, Senior Executive Officer, please start.

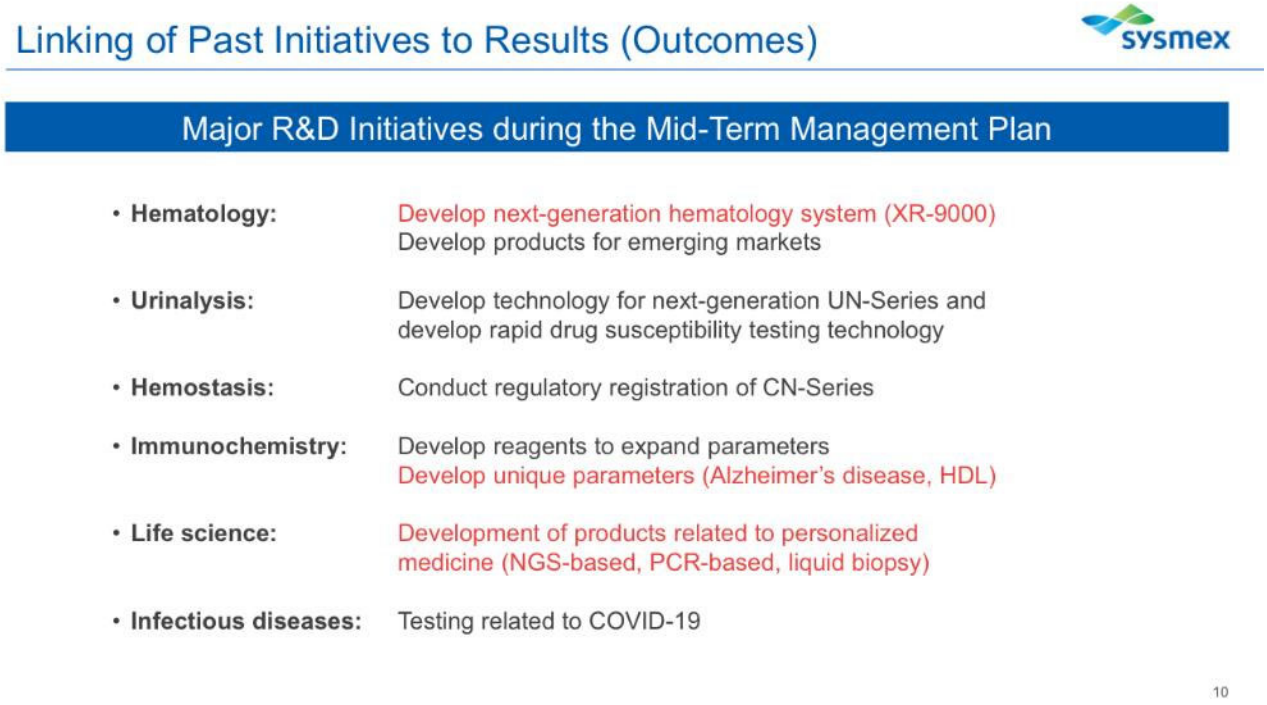
Asano: My name is Asano. Thank you very much for attending our R&D Meeting today.



This fiscal year, we have started a new medium-term management plan, and I would like to explain the R&D activities that we have undertaken during the period of this medium-term management plan.

The figure on the left of this slide shows our basic strategy. In the existing inspection field, we will strive for continuous growth by introducing new products. At the same time, in the area of personalized medicine, which we have been engaged in research and development since the past, as explained at the R&D meetings, we have entered the stage of full-fledged commercialization and will continue to promote it. Our basic strategy is to utilize our technological assets to cultivate new businesses in search of further growth opportunities.

In order to achieve these goals, this medium-term management plan sets and implements the priority actions shown on the right side of this slide. The red parts indicate areas related to research and development in particular.



More specifically, in the hematology field, we will develop the next-generation hematology system and products for emerging countries. In the urinalysis field, we will develop the next-generation UN-series technology and rapid drug susceptibility testing technology. In the field of hemostasis, we will work on the global registration of the CN-series.

In the immunochemistry field, we will expand parameters and develop unique parameters for Alzheimer's disease and other diseases. In the life science field, we will develop products related to personalized medicine. We will also continue to work on the development of COVID-19-related tests. The areas in red shown here will be explained in more detail later.

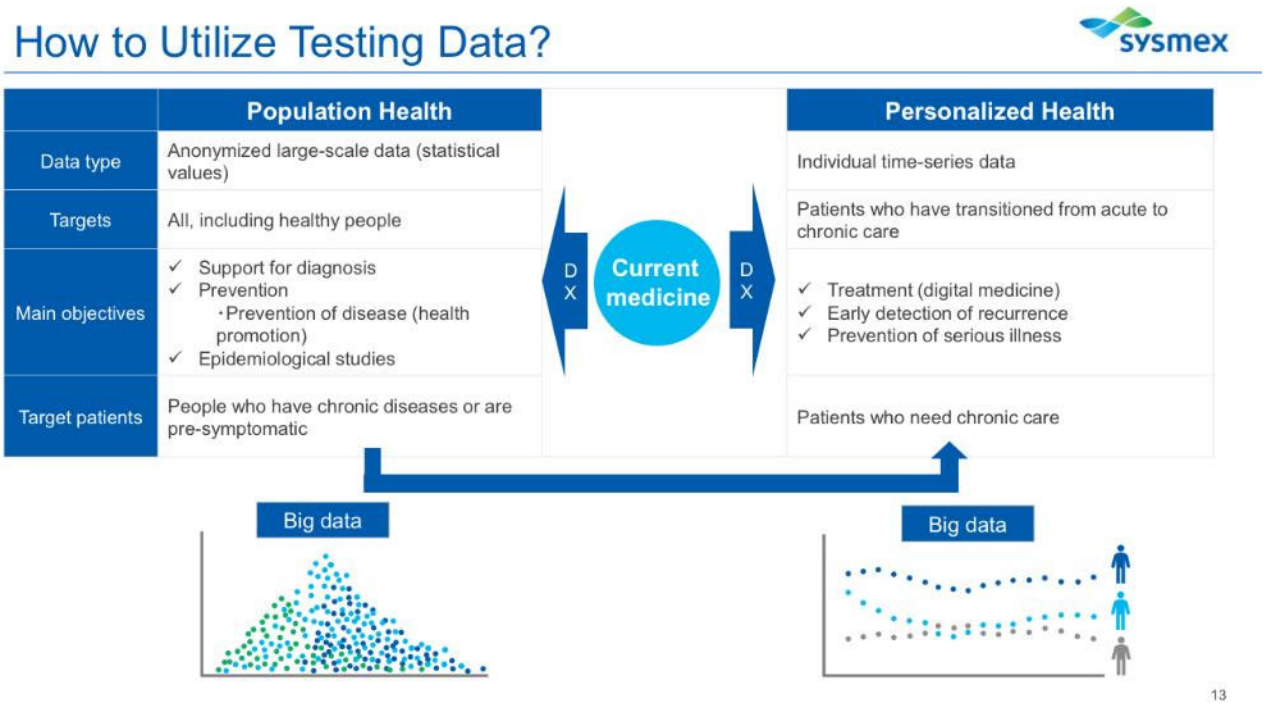
Next, as new business, we would like to work on the business shown on this slide.

The first is Medicaroid, “hinotori”. We would like to provide solutions centered on “hinotori” to the hospitals, rather than simply taking on a sales role as an exclusive distributor.

Specifically, we have developed a pretty good IoT system for “hinotori” called “MINS”. We would like to offer comprehensive solutions for the entire operating room using MINS, as well as a combination of robotic surgery and testing, especially in the life science field.

The second is regenerative and cellular medicine. We believe that our inspection technology can be directly utilized for quality inspection in the manufacturing process of regenerative and cellular medicine. In addition, the robot system that we launched as a result of the COVID-19 disaster can also be applied to the automation of manufacturing processes.

The third, as Mr. Ietsugu mentioned at the beginning of this presentation, digital medicine and digital transformation.



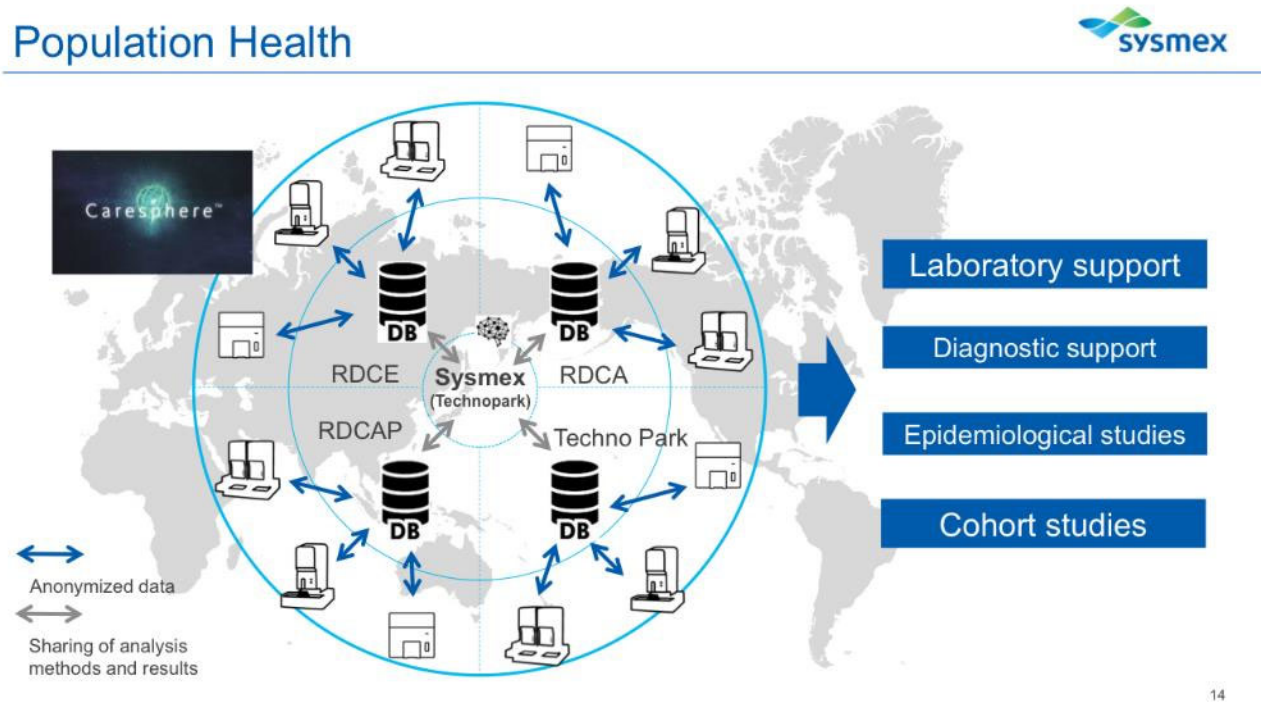
Since time is limited today, I would like to talk about the basic concept and direction of our company's digital medicine.

Before I proceed, let me tell you we are often asked how we use the testing data. We believe that there are two main types of utilization of testing data. One is the collection of unspecified data, or so-called big data, as described on the left side of this slide. This is where statistical values play a particularly important and meaningful role. The other is individual time series data. In this case, time-series patterns have meaning.

The former uses its statistical analysis values as prevention and diagnostic support information. For example, if a certain test value has this kind of value, the risk of disease in a group will be like this, and this is the so-called public health or population health use.

The latter estimate changes in an individual patient's condition based on time-series changes in the individual's examination. For example, a subtle increase or decrease in a test value can be used to detect signs of recurrence, which is an operation toward personalized medicine or personalized health care.

Of course, both are not independents, and clinical trials from the former's large data set will be utilized in the latter. I will explain our approach to digital healthcare from the two perspectives of these two directions, population health care and personalized health care.

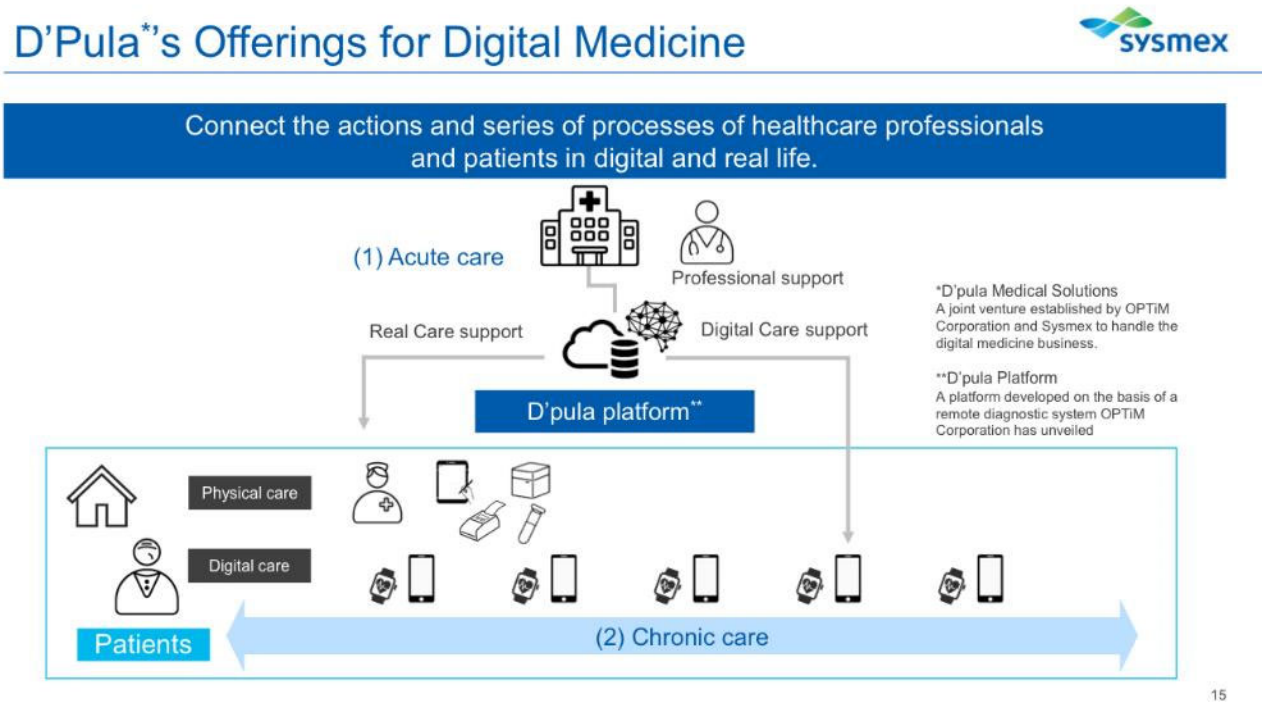


First, let me talk about population health care.

First of all, it is important to accumulate data. We will utilize the footprints of our hematology products and the Caresphere system to build a database or data lake of test values, of course with the consent of each facility.

In this case, due to regulatory and other factors, it would be difficult to integrate the database globally, so we would like to build a database at each regional R&D point according to the actual situation in each region.

Next, using the constructed data, we will develop applications ranging from laboratory support to diagnostic support, et cetera, as shown on the right side of the slide, and in doing so, we will share the analysis methods and results globally, centering on Technopark. We believe that this will enable us to deliver globally deployable applications to the entire world.



Next is the other one, personalized health care.

When a person is diagnosed with a certain disease, he or she will receive acute care in the hospital, for example, surgery in the case of cancer, and then move to chronic care at home.

A telemedicine system is needed to support this chronic patient population, but this is still limited, even though deregulation has taken place due to the coronavirus disaster. However, with an aging population and limited resources in hospitals, chronic care at home will undoubtedly become more important.

We have therefore launched D'pula Medical Solutions, a joint venture with OPTiM Corporation, an AI and IoT company, to address this issue.

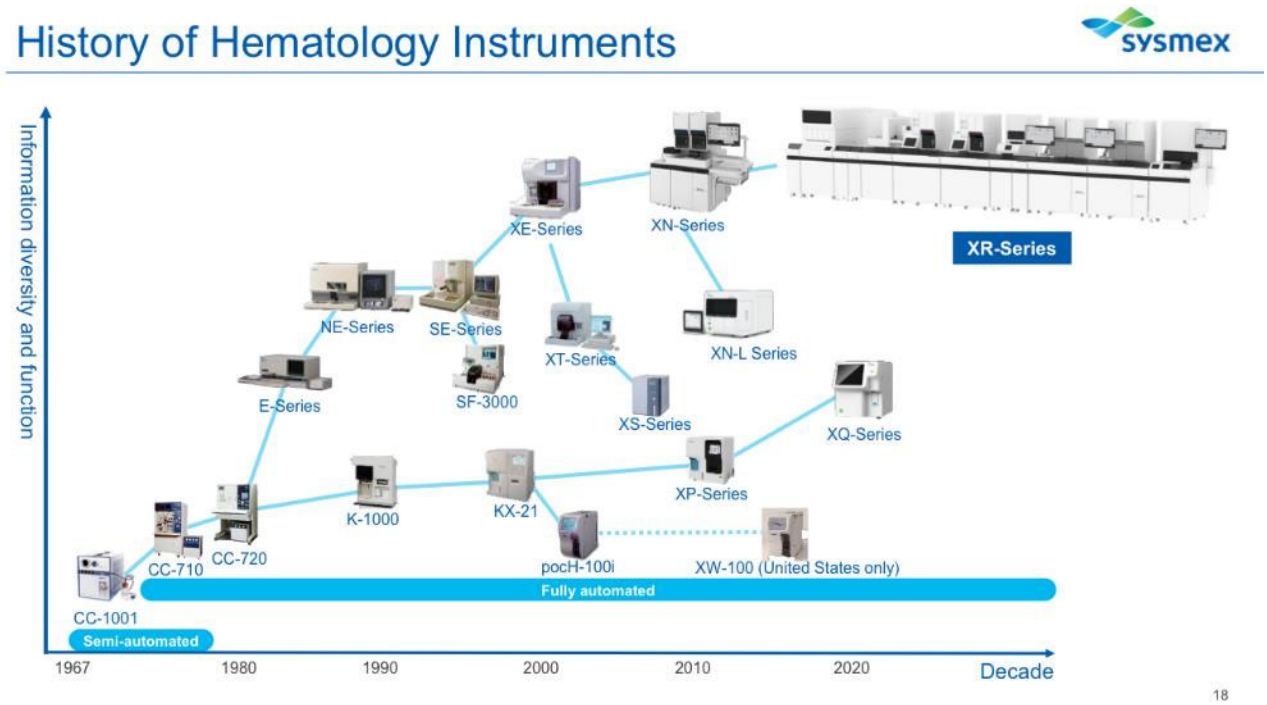
In other words, based on OPTiM's online telemedicine system, Pocket Doctor, we have built a platform with three functions: professional support function to support online remote guidance by specialist physicians and nurses; digital care function to support patients in providing their own care on their smartphones and healthcare devices; and real care function to support care of home patients by visiting nurses, et cetera.

This platform also features a more complete perspective of inspection at home. We plan to conduct various demonstration experiments using this platform in the future. These are the two directions of our digital medicine efforts.

We hope to be able to introduce specific initiatives in a timely manner. That's all from me. Thank you very much for your attention.

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

Nagai: Good morning. My name is Nagai of the System Engineering Division. This is my first time to be in charge of explaining our R&D Meeting, and I would like to thank you in advance for your participation. I will explain new value-enhancing technologies for hematology instruments.



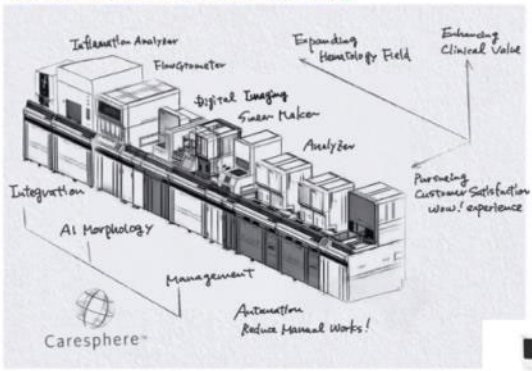
First, I would like to introduce the history of SYSMEX's hematology instruments.

At the top of this chart, you can see the top model of each decade. The top right of the figure shows the latest top-of-the-line XR-series, which was released last year and this fiscal year.

The XR-series is the successor to the XN-series, which is currently used in large- and medium-sized hospitals around the world.

Next-Generation Hematology Product Concepts

Shown at the 18th R&D Meeting



The first phase is to systematize the XR Series.

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The sketch image on the left was presented at last year's R&D Meeting.

We were able to develop the XR-series as a concrete product as the first product realization of the sketch.

The XR-Series Value Proposition

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

OPERATIONAL VALUE

Bringing surprise and pleasure to customer by reducing workloads (a "Wow!" experience)

Reduce manual operations thoroughly by shifting to automation, reduction and integration, and realize an environment where customers can focus on specialized work.

CLINICAL VALUE

Lighting the shortest route to diagnosis by utilizing test results

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

MANAGERIAL VALUE

Delivering best quality assurance to improve role and reliability of laboratory

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

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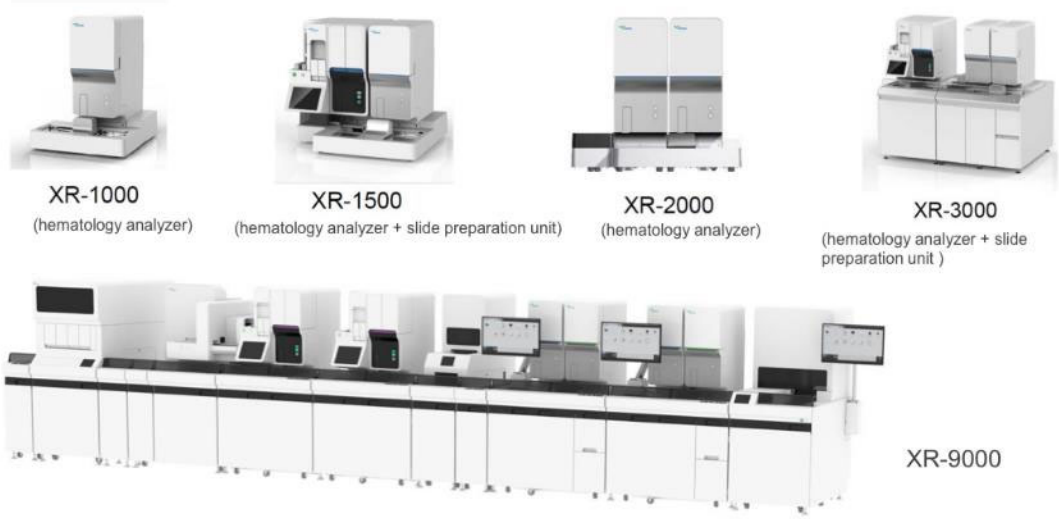
Next, I will explain the new value and detailed technology included in this XR-series.

The XR-series has been developed from the three perspectives of operation value, clinical value, and managerial value, with the aim of creating new value that solves market and customer issues.

XR-Series Product Lineup

Taking forward the modular concept from the XN-Series



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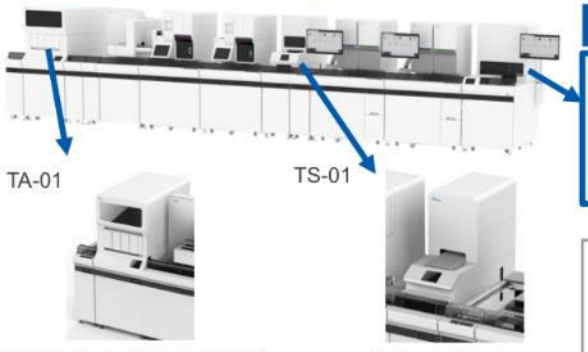
Let me explain the XR series in a little more detail.

The XN-series currently on the market employs the modular concept, which has been very well received by customers around the world, and the XR-series also inherits the modular concept.

Various instrument configurations can be realized by freely combining modules to fit various laboratories and workflows around the world. In addition, the XR-series offers 10% faster testing speed than the XN-series.

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

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



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

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

Plan to launch in Q2 FY2022

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

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

Reduced footprint and environmental impact
Size: Width reduced by 15%
Power consumption: down by 40%
(Compared with current XN Series)

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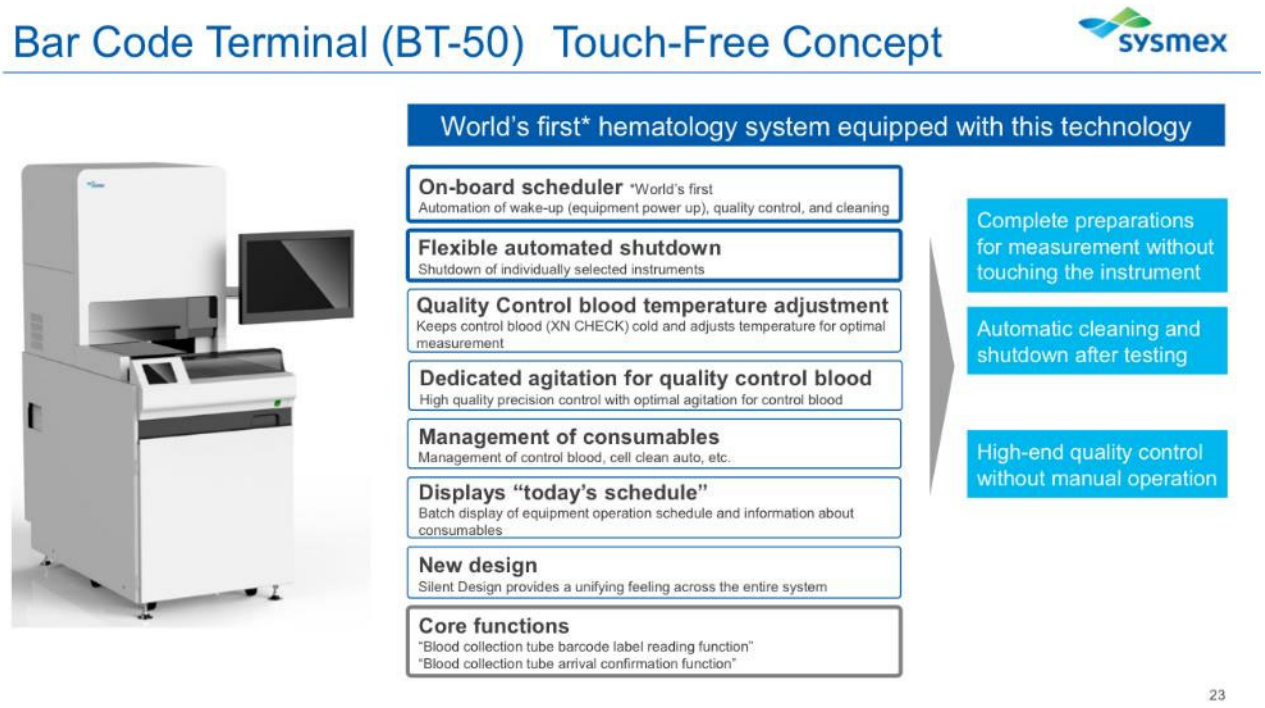
Next, I will go further and introduce the most distinctive modules of the XR-series: TA-01, TS-01, and BT-50.

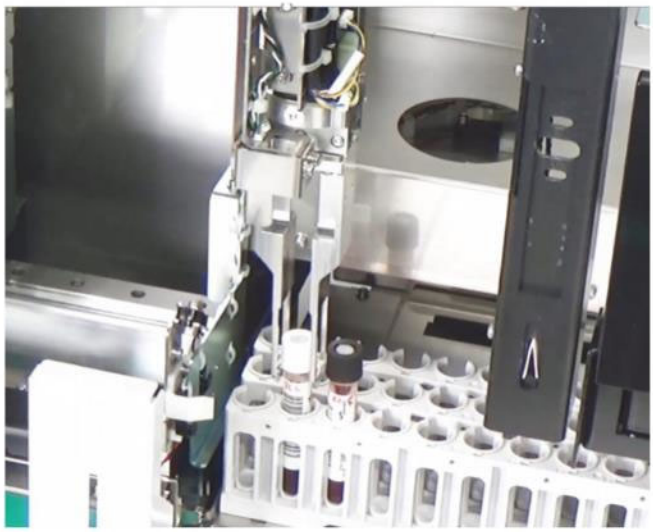
In the early stages of the development of the XR-series, our European distributors and other customers pointed out the time and effort required for quality control, or QC, work, as well as the variability in the quality control process.

In development, therefore, with the touch-free concept to minimize test operations, we developed the TA-01, a sample storage unit, the TS-01, a sample sorting unit, and the BT-50, the world's first hematology system with a scheduling function and automatic quality control function. The world's first BT-50 technology is described in detail in the pages that follow.

In addition, as an environmental response, the XR-series reduces power consumption by 40% and size by 15% when compared to similar modules in the existing XN-series, thereby reducing environmental impact.



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



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Today, I will discuss the most distinctive BT-50 in detail. This is BT-50.

I will explain the hematology system in the BT-50 and the world's first technology. As mentioned earlier, the BT-50 has been developed with the aim of achieving a touch-free concept.

In addition to the function of test tube barcode reading inherent in barcode terminal, many new technologies have been developed and implemented, including a scheduler that automatically performs test preparation and cleaning shutdown at times registered by the customer, flexible shutdown, and automated quality control that eliminates manual procedures and variations.

Scheduler Function

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

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

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

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

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

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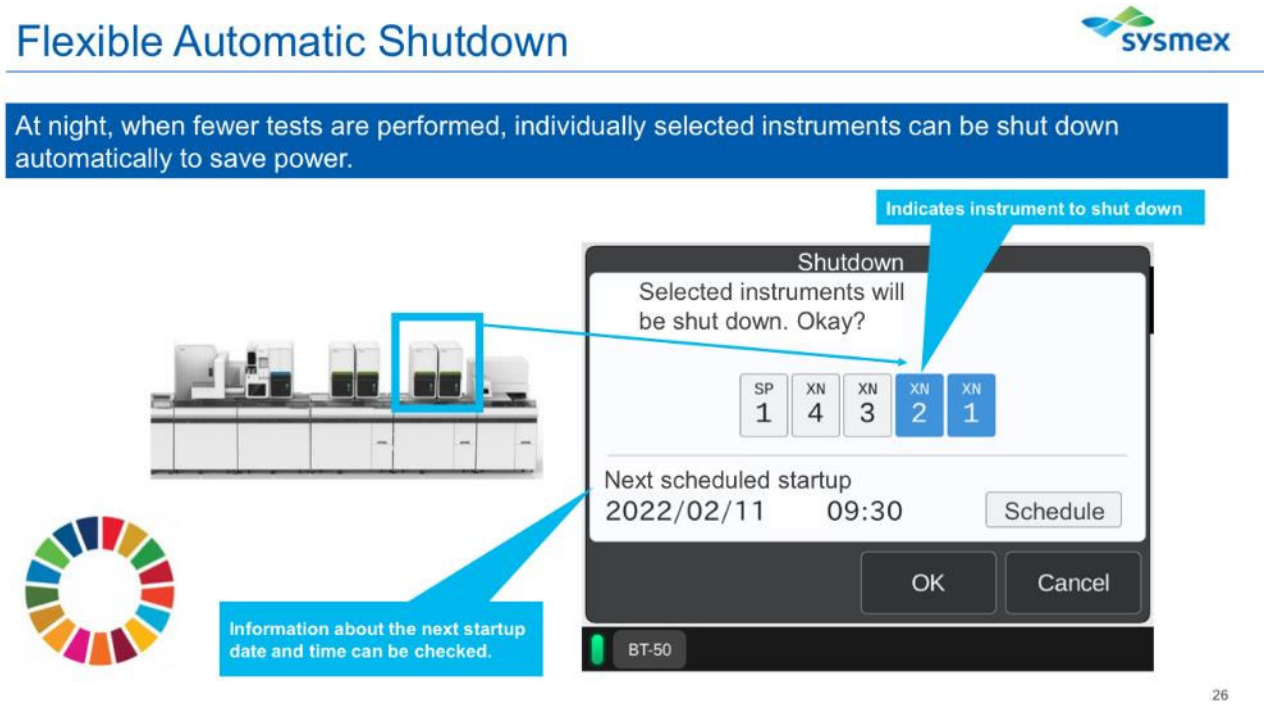
Next, I will introduce the scheduler function of the system in detail.

This is a useful function that uses ICT to automate wake-up, quality control, and cleaning, which are currently performed manually by technologists in laboratories prior to testing.

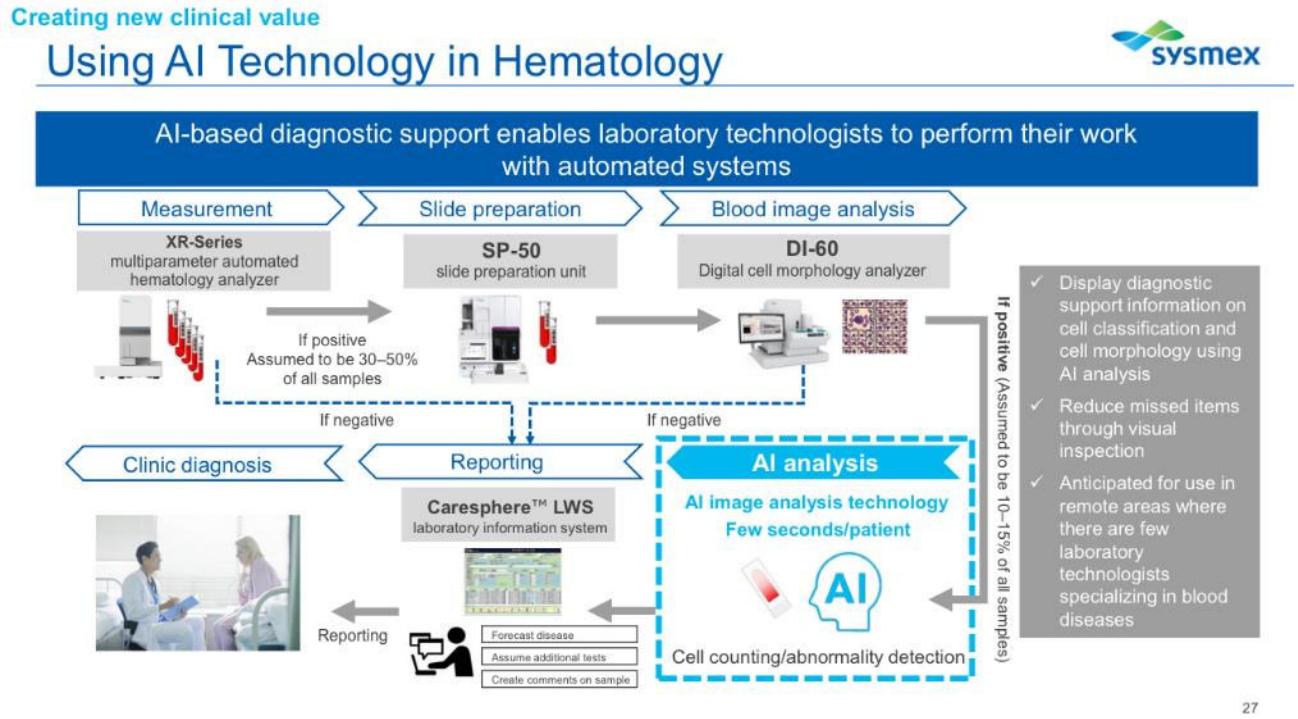
The scheduler allows you to register a schedule by inputting information on a simple, smartphone-like screen. On the other hand, inside the system, ICT can be used to recognize and control the module configuration and module air status of the entire system, allowing for detailed registration according to the laboratory`s operation rules and workflow of various hospitals around the world.



Next is the details of the flexible automated shutdown function.

This is a more detailed and convenient function that solves the problems customers face in nighttime testing in a typical hospital. Since the number of test is low at night, the number of hematology instrument on standby can be easily reduced without any hassle. At present, customers are turning off each instrument manually.

The system will be able to respond to various hospital workflows and automatically clean and turn off selected instruments, allowing for a more detailed response to each hospital. This reduces reagent and power consumption of the instruments, as well as the operating power of the laboratory's air conditioner. Although this is a small feature, we are strongly conscious of the environment and aim to develop inspection systems with a high level of maturity in the future.



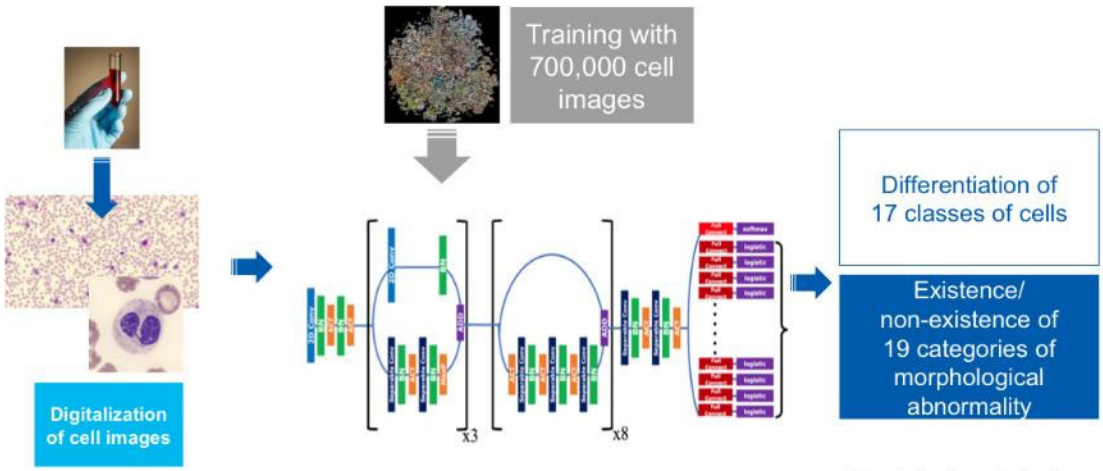
From here, the session will change from operational value to clinical value.

This is an explanation of the status of development using AI technology to improve clinical value. As explained in the previous R&D Meeting, we are developing a technology to take blood images, digitize them, and analyze them using AI.

We are working on the classification of blood cells and the development of diagnostic support functions. We are very much looking forward to the use of this technology in preventing the overlooking of abnormalities by microscopy and in regions where there is not an adequate testing system for blood diseases.

Using AI Technology in Hematology

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



*Convolutional neural networks

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When it comes to AI analysis of specific blood cells, specifically, 700,000 blood cells are imaged and digitized, and teacher data is created by laboratory technicians and other experts. We are developing analysis software that learns with this teacher data and finds cell type classification and presence of morphological abnormality.

However, there are challenges in applying AI technology to blood cell analysis that cannot be solved by data science alone. It also requires know-how. For this reason, we are collaborating with Juntendo University in the development of this software.

Using AI Technology in Hematology

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

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

CNN, convolutional neural networks

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

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

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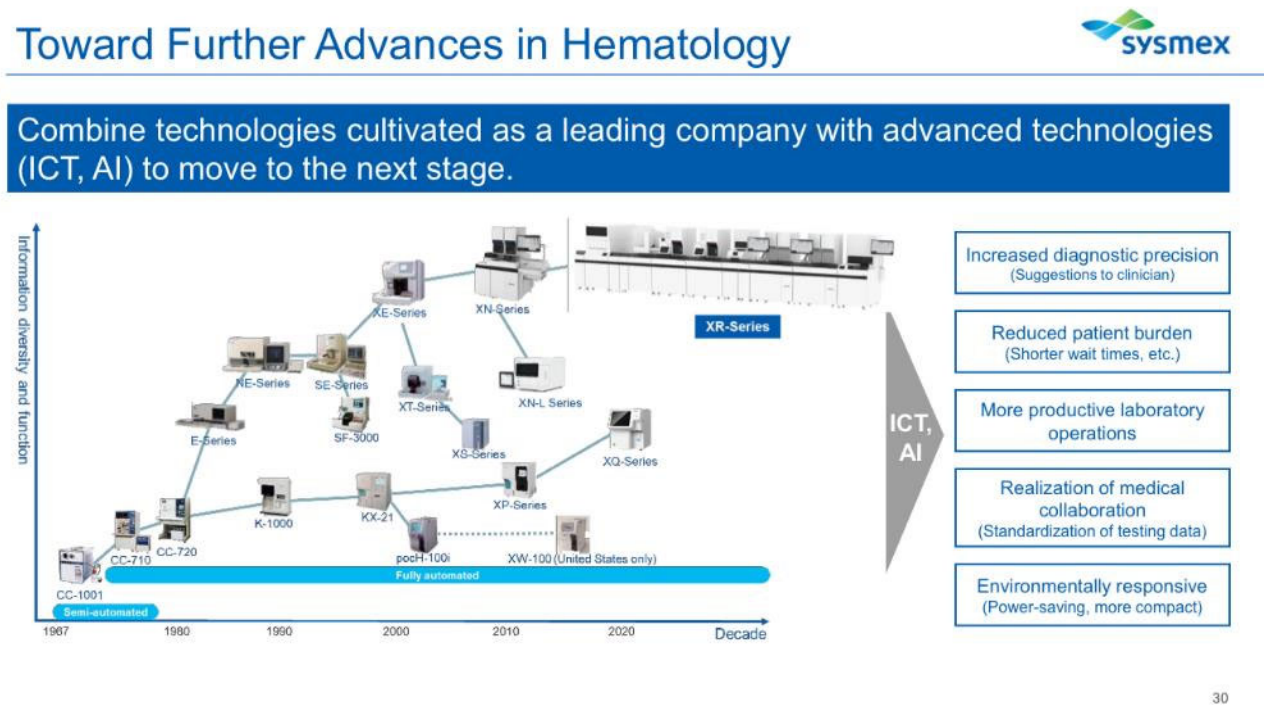
As for progress, we have achieved performance that far surpasses that of existing systems in differentiating cell types when AI is utilized. We aim to put this system to practical use through repeated evaluations and improvements at many facilities in the future.



The last slide explains the further evolution of hematology.

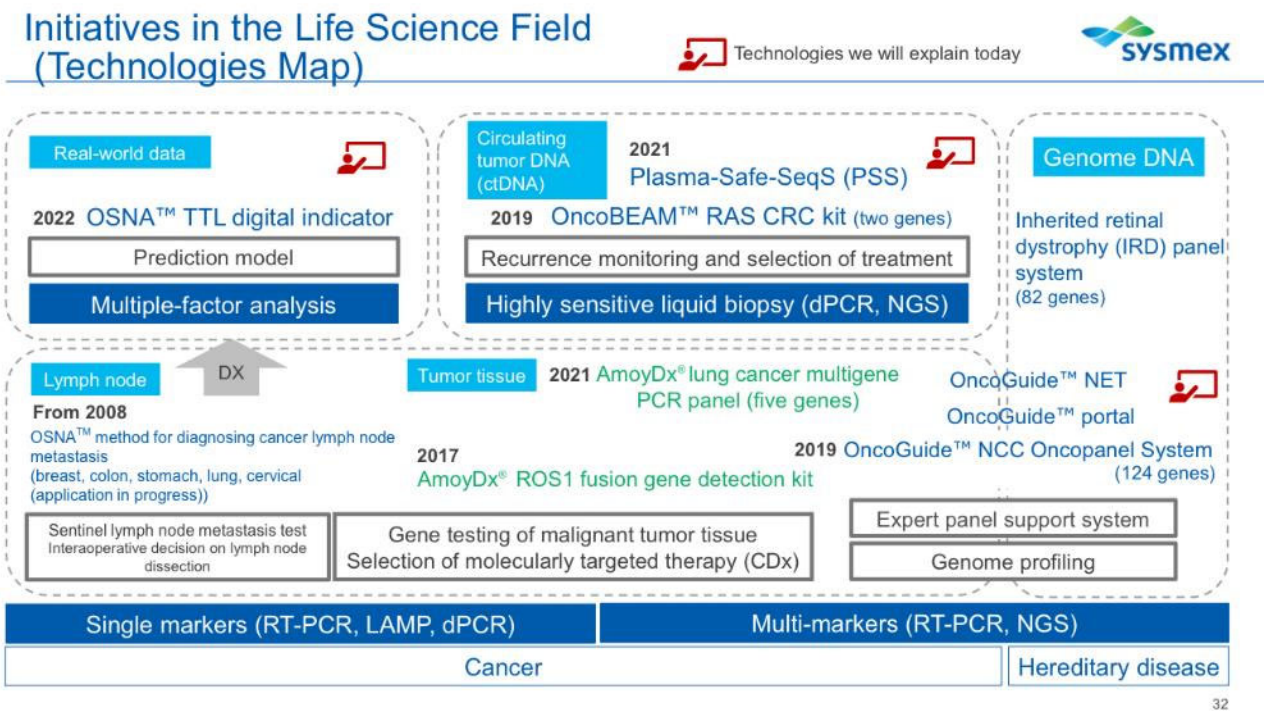
As a leading company in hematology, we at SYSMEX will combineIVD-testing instrument and ICT to realize a touch-free concept, and promote development that not only thoroughly improves testing productivity, but also aims to be environmentally friendly.

Furthermore, by utilizing AI technology, et cetera, we will contribute to medical care by eliminating variations in manual test and promoting automation and standardization of test, aiming to improve the accuracy of test results and, ultimately, diagnosis.

In addition, we will apply the ICT, AI, and other technological know-how we have cultivated in the hematology field, which I explained today, to other testing systems, such as hemostasis, urinalysis, immunochemistry, and genetic testing systems.

Thank you very much for your kind attention.

Moderator: Now, Ms. Watanabe, Executive Officer, please begin.



Watanabe: My name is Watanabe of Medical Affairs Division. I will explain about the creation of clinical value using cancer genetic testing technology.

First, among the life science field initiatives, the overall picture of the hereditary disease areas is represented in the technology map.

In 2008, the OSNA method for diagnosing cancer lymph node metastasis was clinically implemented for the first time as a lymph node metastasis test by detecting CK19 mRNA in breast cancer and lymph nodes.

This year, 15 years after its introduction, we have built a prediction model using the copy number of CK19mRNA obtained under the insurance treatment as a digital indicator combined with clinical information.

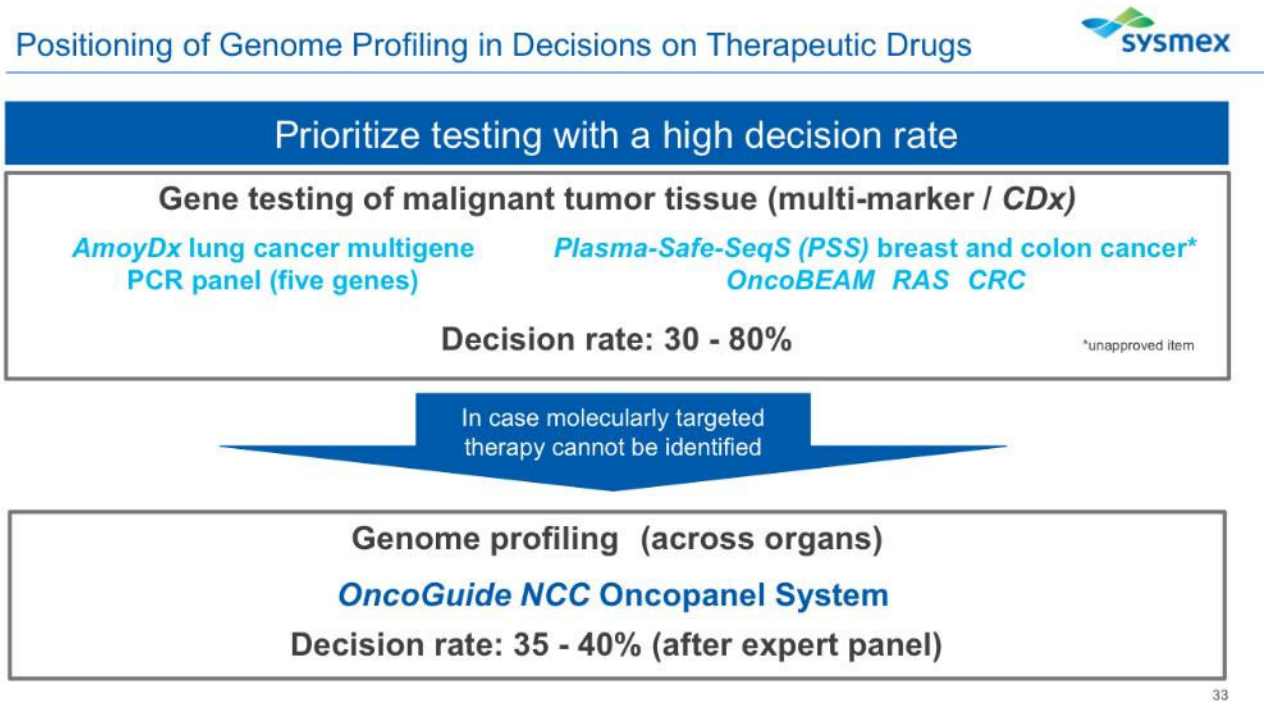
In the area of gene testing of malignant tumor tissue using tumor tissue, or companion diagnostics, our subsidiary RIKEN GENESIS CO., LTD. launched a multi-gene PCR panel that simultaneously tests five genes in non-small cell lung cancer this year.

In genome profiling test, we obtained partial change approval last fiscal year, and in parallel, we enhanced the expert panel support system “OncoGuide NET”. In this way, we have aimed to reduce the burden on physicians in the operation of expert panels, which are held to interpret profiling test results and make decisions.

The OncoGuide portal and OncoGuide NET will also support genomic profiling test for hereditary diseases such as hereditary retinal dystrophy in the future.

Meanwhile, we are also developing a highly sensitive liquid biopsy for cancer genes using NGS, which can detect minute amounts of circulating tumor DNA mutations in plasma.

Today, I would like to discuss our latest topics, including our proposal for efficient testing that leads to molecularly targeted therapy for patients, our efforts to reduce the burden on facilities implementing genomic medicine, the new clinical value of highly sensitive liquid biopsy, and finally, OSNA for breast cancer, which we introduced in 2008.

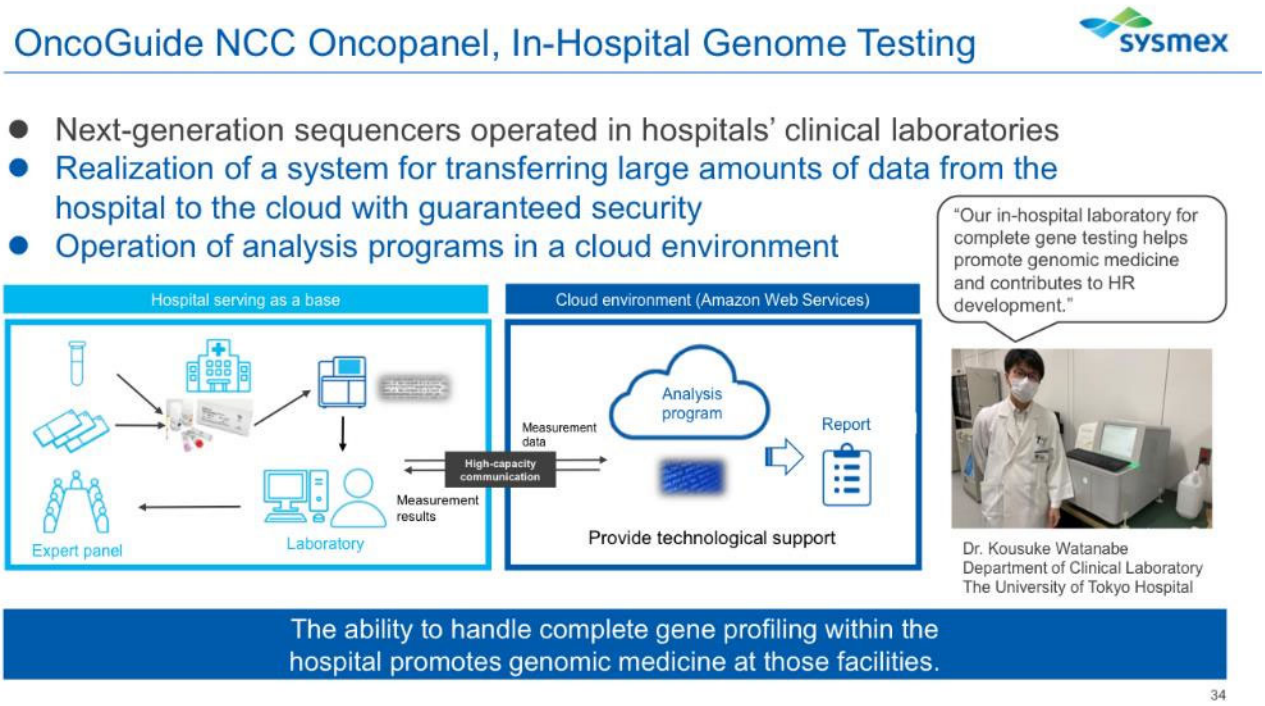


First, I will explain our view on the position of organ-specific companion diagnostics and cross-organ genomic profiling tests in the determination of therapeutic agents.

In advanced recurrent non-small cell lung cancer, colorectal cancer, and breast cancer, multiple molecularly targeted therapeutic drugs are being developed and implemented, and companion diagnostics that simultaneously test for these genes are expected to determine molecularly targeted therapies in 30% to 80% of patients.

Patients who do not find molecularly-targeted therapeutic drugs in this test are expected to undergo genome profiling test for potential cross-organ molecularly-targeted therapeutic drugs. To date, it has been reported that genome profiling has a 35% to 40% chance of finding a recommended treatment based on the expert panel's judgment.

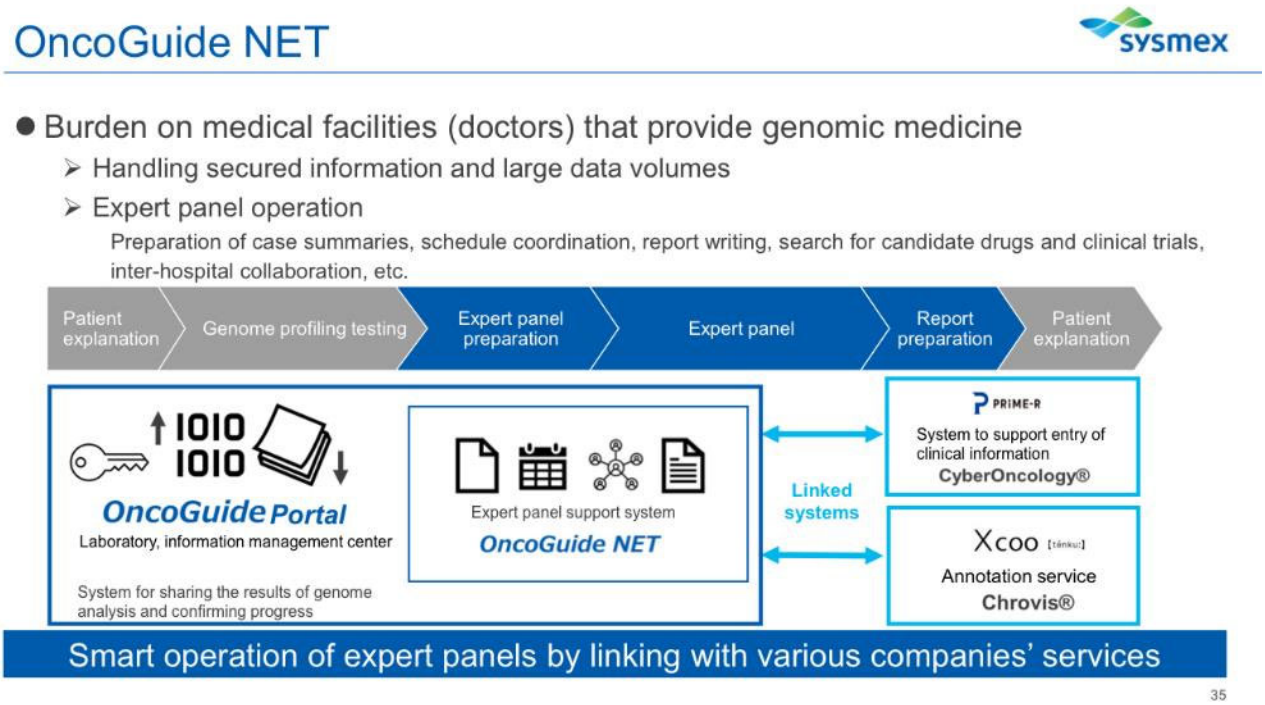
The treatment fee for genome testing of malignant tumor tissue for companion diagnosis, which can determine guidance for around 50% of patients, is around JPY100,000. On the other hand, considering the treatment fee for genome profiling and the time required to obtain the expert panel's decision, we believe that it is more efficient to conduct companion diagnostic tests first for possible cancer types.



Next, I would like to explain our in-hospital genome testing initiative.

Until now, genome testing has been outsourced to outside commercial laboratories because it requires complex analysis of large volumes of data obtained from next-generation sequencers.

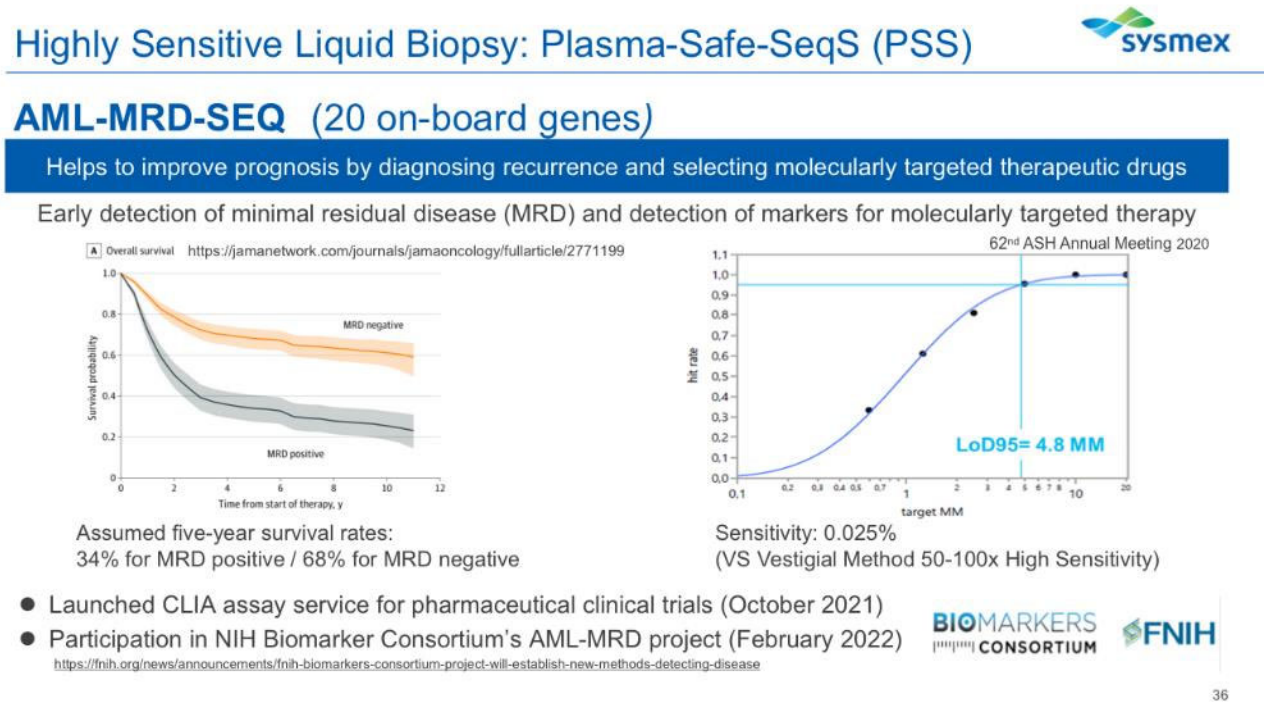
SYSMEX, SYSMEX CNA, and RIKEN GENESIS have developed a cloud-based NCC Oncopanel, which runs analysis programs in a cloud environment, with the aim of realizing next-generation laboratories that support genome medicine. From January 2022, the Department of Clinical Laboratory of The University of Tokyo Hospital has realized a medical institution-completed genome test. This initiative will support the promotion of genomic medicine, which has not progressed in Japan, and human resource development at medical facilities, and will also contribute to more efficient testing.



In order to smoothly promote genomic medicine, doctors at genomic medicine core base hospitals are burdened by the various tasks involved in handling patient information and large volumes of genomic test analysis data and in the operation of expert panels in an environment that can ensure security.

Aiming to reduce these burdens, we have provided the OncoGuide Portal, which supports the transfer of patient information and large volumes of data, and OncoGuide NET, which supports various operations of expert panels. The OncoGuide Portal has been adopted by 206 facilities, including cancer genomic medicine core base hospitals, and collaborating hospitals.

OncoGuide NET has now started system integration with "CyberOncology" of the PRiME-R, which automatically generates case summaries and supports the input of necessary clinical information from electronic medical records andan automatic transmission system to C-CAT. And OncoGuide NET has also linked "Chrovis" of Xcoo's annotation service with the latest information on clinical trials in Japan. This will support smart expert panel management. The OncoGuide portal and OncoGuide NET will be further expanded in the area of hereditary diseases.



So far, I have explained our efforts related to improving the efficiency of testing and reducing the burden on physicians. From here, I would like to introduce our new clinical value offerings.

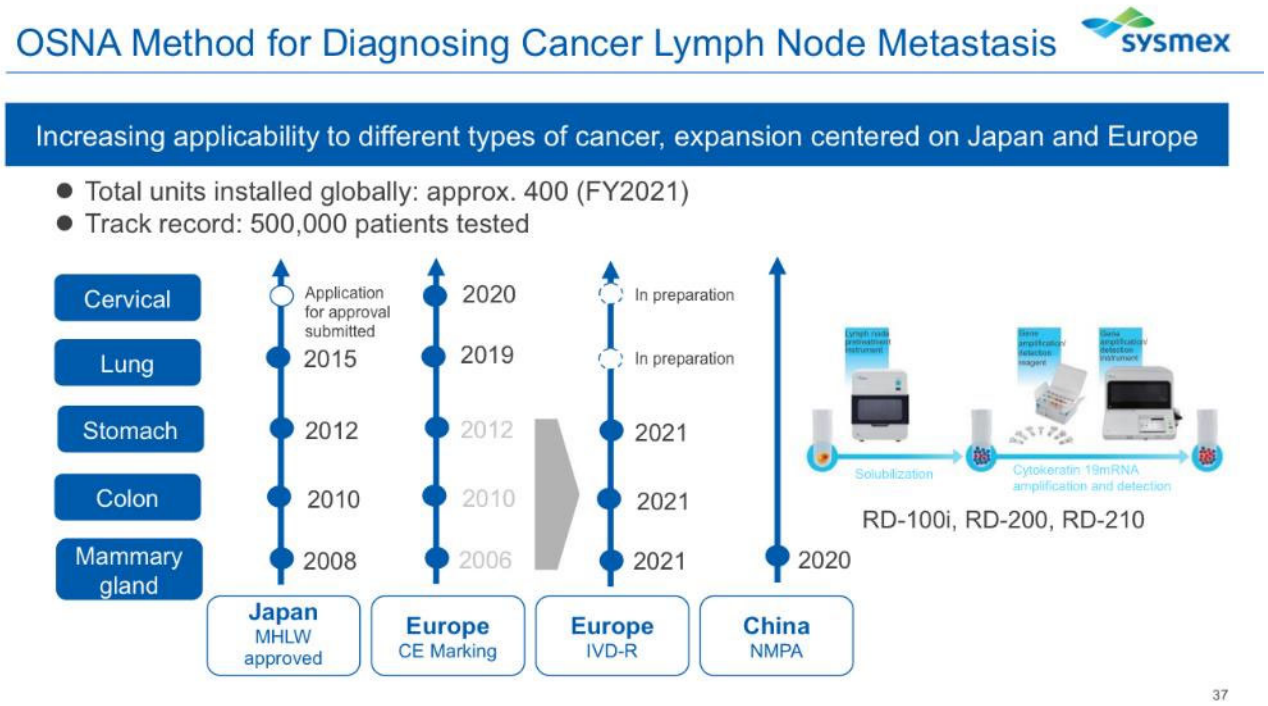
First, I will discuss the highly sensitive liquid biopsy using Sysmex Inostics' Plasma-Safe-SeqS. We are currently developing a multi-gene panel for colorectal cancer, head and neck cancer, breast cancer, and acute leukemia.

Today, I will explain our efforts in acute myeloid leukemia with 20 genes and AML-MRD-SEQ. This panel achieves a sensitivity of 0.025%, 50 to 100 times higher than the usual NGS test for hematopoietic tumors.

In acute myelogenous leukemia, an assumed survival rate of 34% was reported for patients with minimal residual disease detected after treatment, compared to an estimated 68% for patients with no detectable disease. The SYSMEX Group aims to achieve detection of target gene mutations for MRD and molecular-targeted drugs, and contribute to early diagnosis of recurrence and improvement of prognosis through selection of molecular-targeted therapy.

MRD is recommended by US guidelines for prognosis prediction because it detects earlier than current cytology, but it has not yet been implemented clinically. For this reason, consortium activities have begun at the NIH in the US to promote the use of minimal residual disease positivity as a treatment efficacy test, and the development of new molecular-targeted therapeutic drugs by various pharmaceutical companies is gaining momentum.

Sysmex Inostics has joined this consortium and started services for pharmaceutical companies in October 2021.

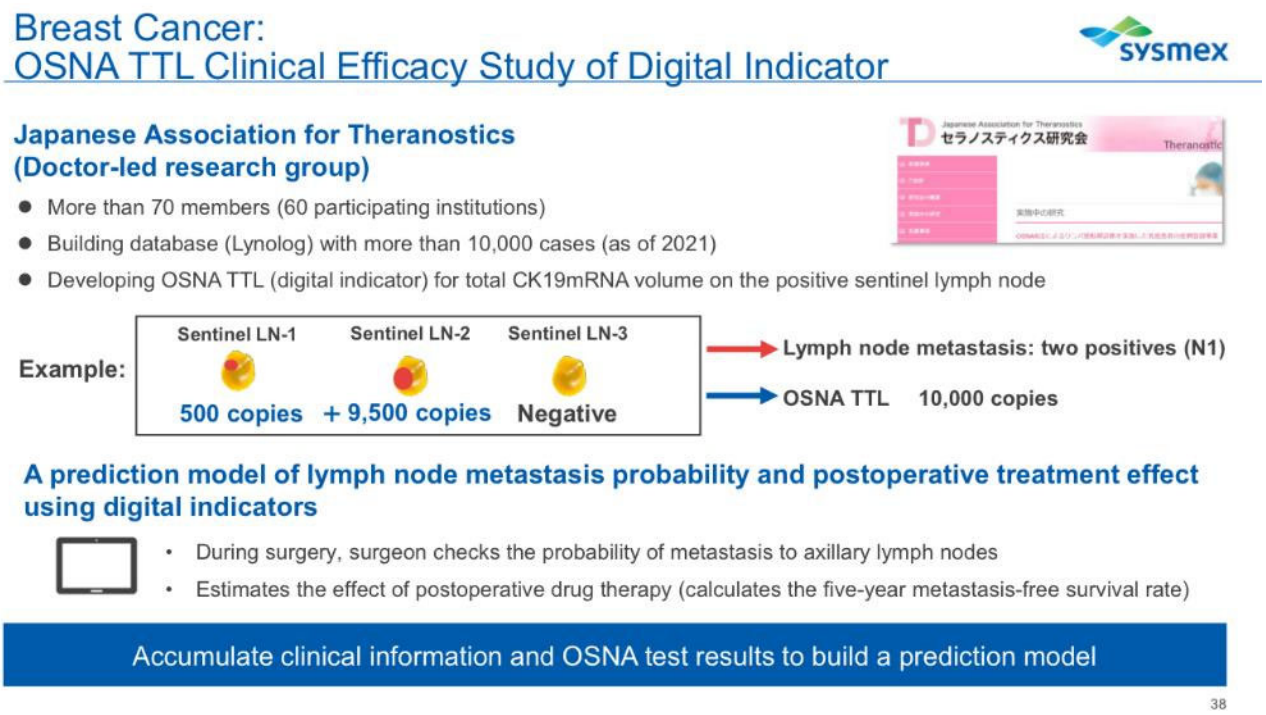


Finally, I would like to explain the OSNA method for diagnosing cancer lymph node metastasis, which utilizes data collected by insurance companies. Before that, I will briefly explain the current status of the OSNA method for diagnosing cancer lymph node metastasis.

Currently, approximately 400 units are in operation globally, and we have tested 500,000 patients. As I mentioned at the beginning of this presentation, in Japan, we have expanded the range of indications to include breast, colon, stomach, and lung cancer, and are currently under review by the PMDA for application to cervical and body cancer.

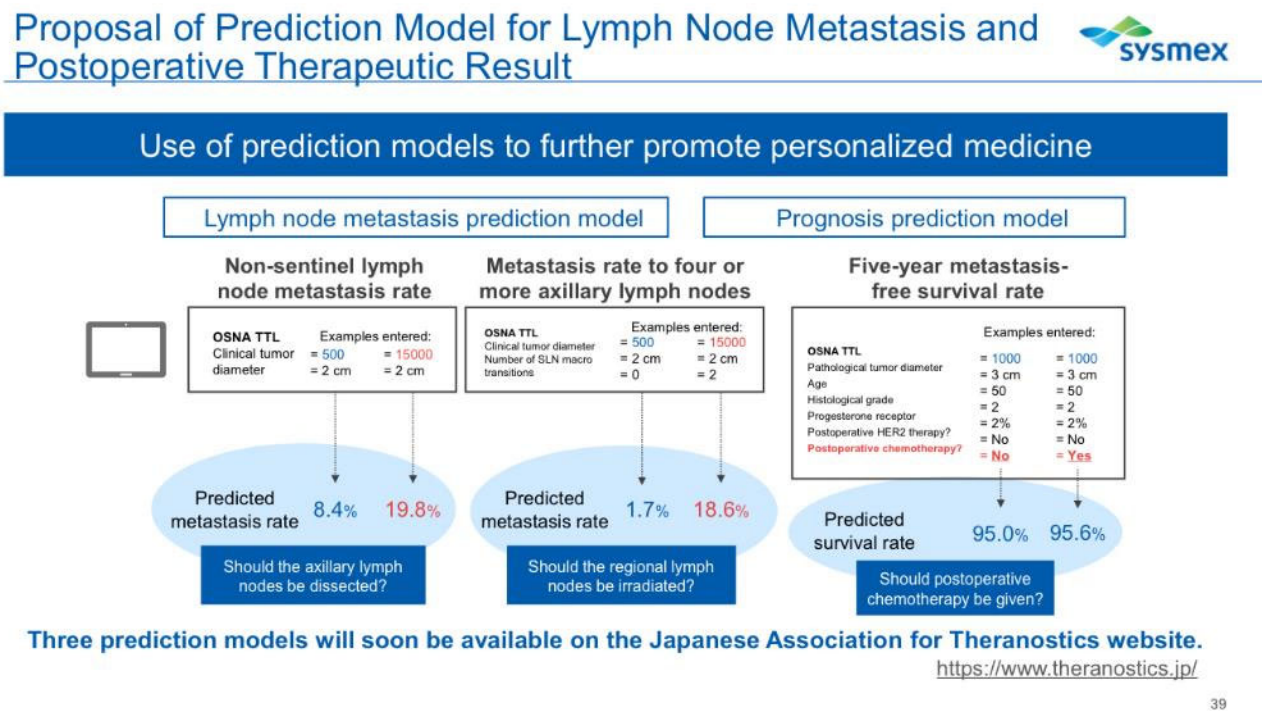
In Europe, we are similarly expanding the range of cancer types, and in 2021, we obtained IVD-R certification as a Class C product for breast, colorectal, and gastric cancer by the European certification body.

In China, we obtained NMPA regulatory approval in 2020. During this period, we have upgraded the gene amplification system from the original RD-100 to the RD-200 and RD-210, which ensure quantitative performance.



In 2008, when insurance started to cover breast cancer, Japanese Association for Theranostics, doctor-led research group, was launched by Sysmex. OSNA test results and clinical pathology information on more than 10,000 cases has been accumulated from 60 facilities in the database, “Lynolog”.

This Association has examined the molecular lymph node metastasis criteria of OSNA TTL, a digital indicator that replaces the number of positive lymph nodes by histopathology with the sum of the number of positive CK19 mRNA nodes, as well as the probability of lymph node metastasis using this indicator and the model to predict postoperative treatment efficacy.



Last, but not least, here is the predictive model that is the result of the Japanese Association for Theranostics.

The lymph node metastasis prediction model on the left side can calculate the probability of metastasis to non-sentinel lymph nodes and the probability of lymph node spread by inputting the sum TTL of CK19 mRNA in lymph nodes of two to three sentinel lymph nodes obtained during surgery, and the tumor size information obtained from the preoperative imaging test to a tablet.

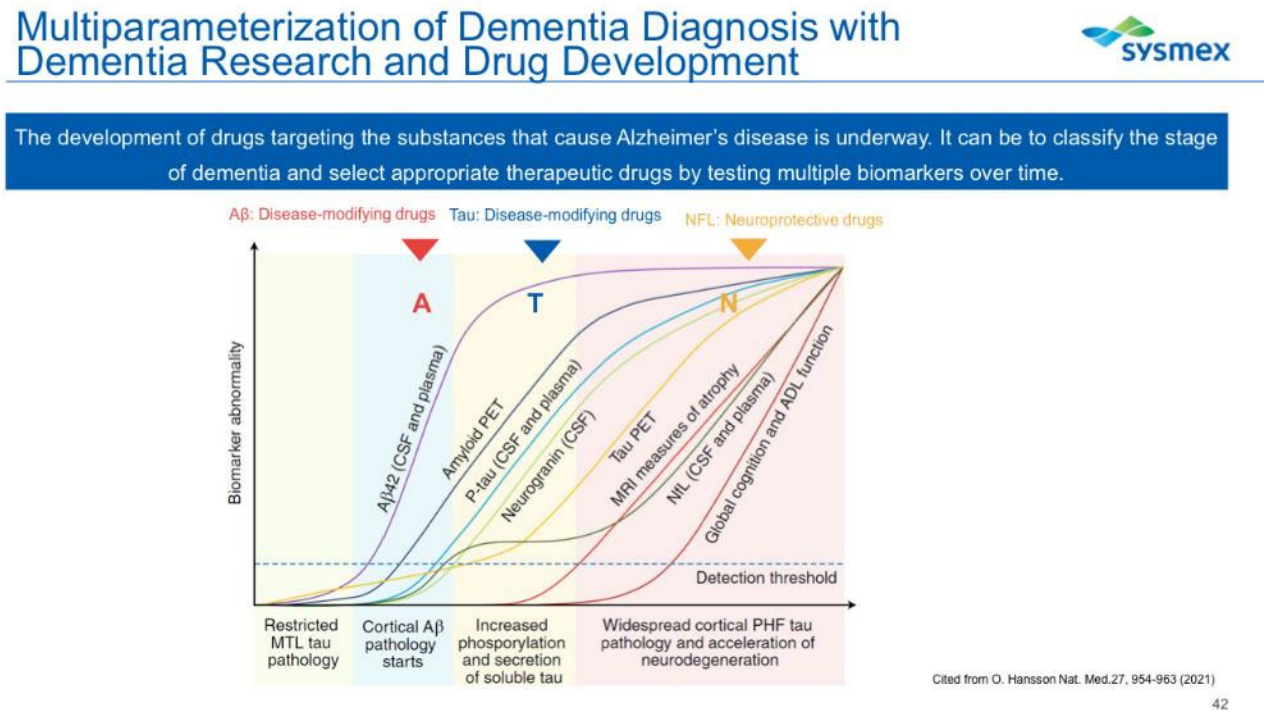
This information can be obtained while in the operating room, and is expected to help surgeons determine the extent of lymph node dissection, as well as the extent of postoperative radiation. The prediction model on the right uses OSNA TTL and postoperative pathology information to predict postoperative recurrence.

The model can easily be calculated using the results of existing pathological tests, and is considered to be important for the decision to perform single-gene testing to determine whether postoperative chemotherapy should be administered.

As described above, in the life science business, we will continue to expand the range of disease indications while incorporating new testing technologies to improve the efficiency of medical care from the patient's perspective, reduce the burden on medical facilities, and create new clinical usefulness.

That is all. Thank you very much for your attention.

Moderator: Now, Mr. Yoshida, Senior Executive Officer, please start.



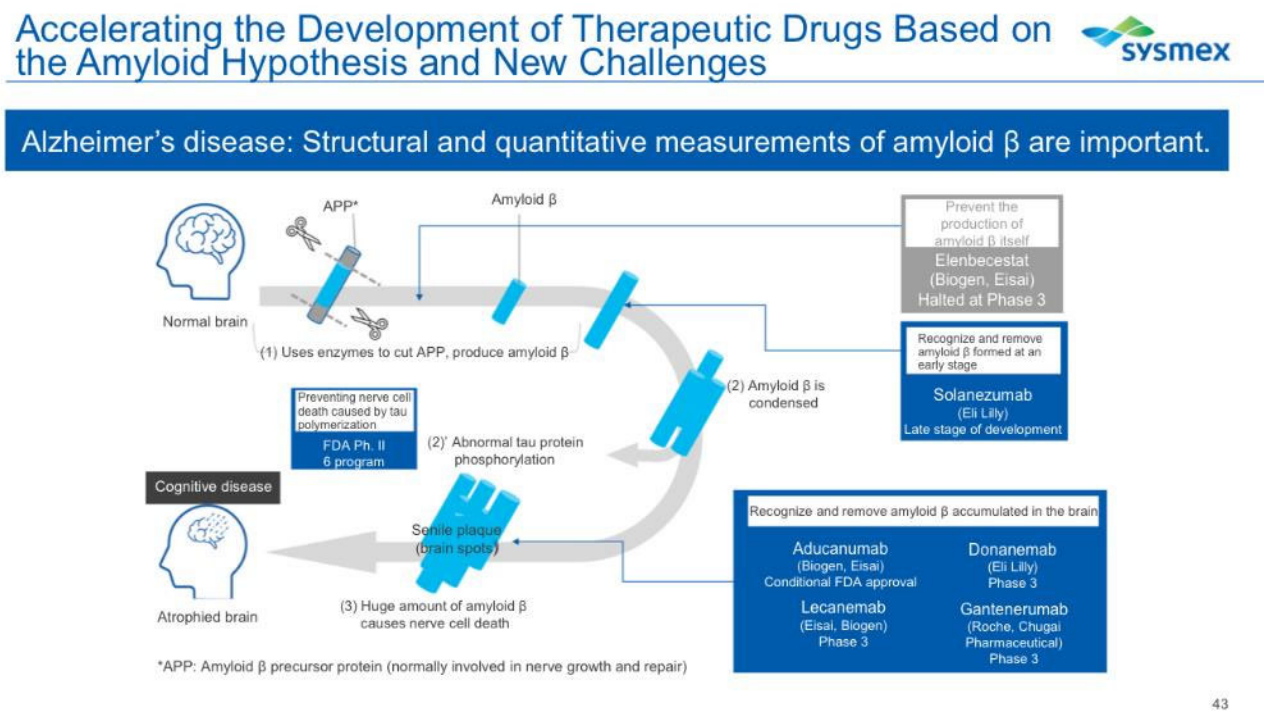
Yoshida: Good morning, everyone. Lastly, as the fifth theme, I, Yoshida, will explain our efforts toward the realization of personalized medicine.

The first is our Alzheimer's disease initiative. As you can see on this slide, various medical institutions and academia have conducted research on dementia, and through the development of therapeutic drugs, a variety of knowledge on dementia have been gathered.

In fact, as this article from *Nature Medicine* shows, during the early, middle, and late stages of dementia, various molecules fluctuate over time, and many therapeutic drugs are being developed at the clinical trial level to respond to these fluctuations.

For example, in the case of amyloid-β, as I will introduce later, by monitoring CSF and plasma levels, amyloid-β is administered at an earlier stage as a prophylactic drug against malignant transformation, called disease-modifying drugs.

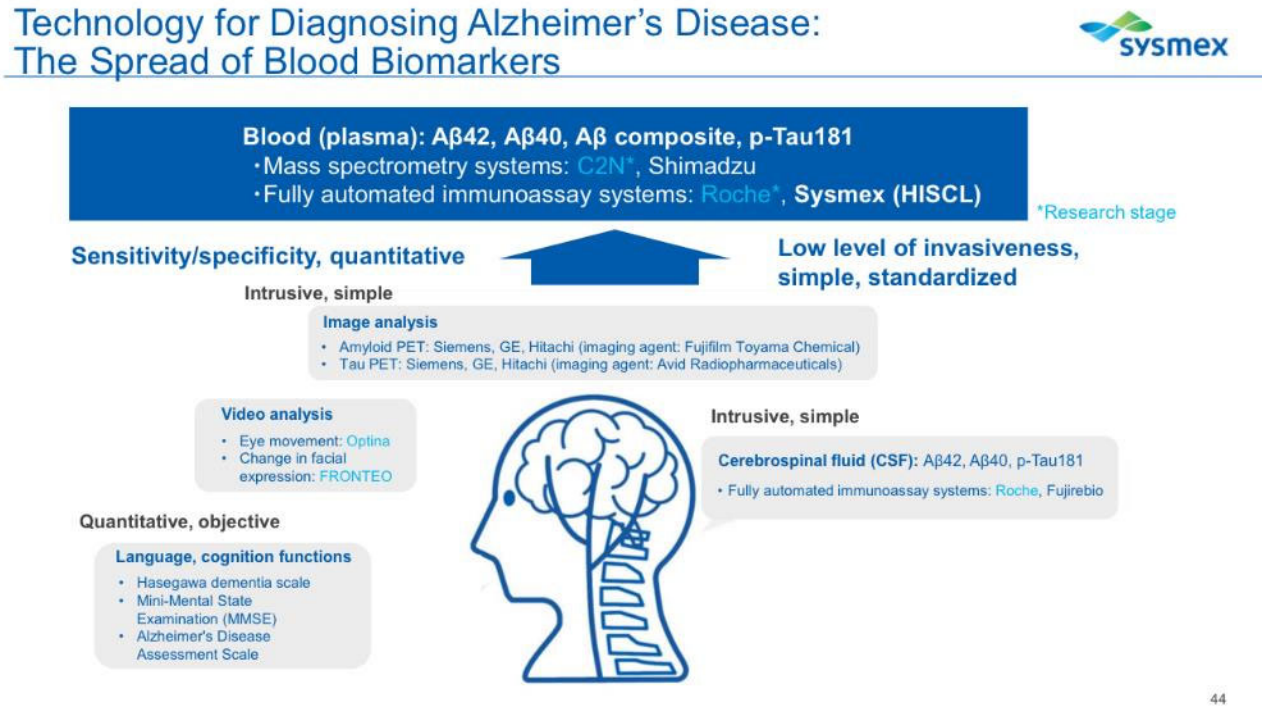
After that, it is recommended to treat dementia with a combination of drugs called neuroprotective drugs and tau. Therefore, as explained by Mr. Asano, it is necessary to classify the stage of the disease and select the appropriate treatment according to the progression of the disease by examining the individual patient over time.



This slide shows a model of amyloid-β in the form of a therapeutic agent according to the progression of the disease, as I explained earlier. As you all know, amyloid-β is produced, aggregated, and then phosphorylated by tau in cells, leading to abnormal cell tumors, which are regulated in such a way.

For such things, antibody drugs that recognize and remove amyloid-β, as shown here. In addition, there are drugs that have changed in form, for example, drugs that remove amyloid-β accumulated in the brain, as described as senile plaque. As you are all aware, aducanumab and other such drugs are currently in clinical trials or have been approved.

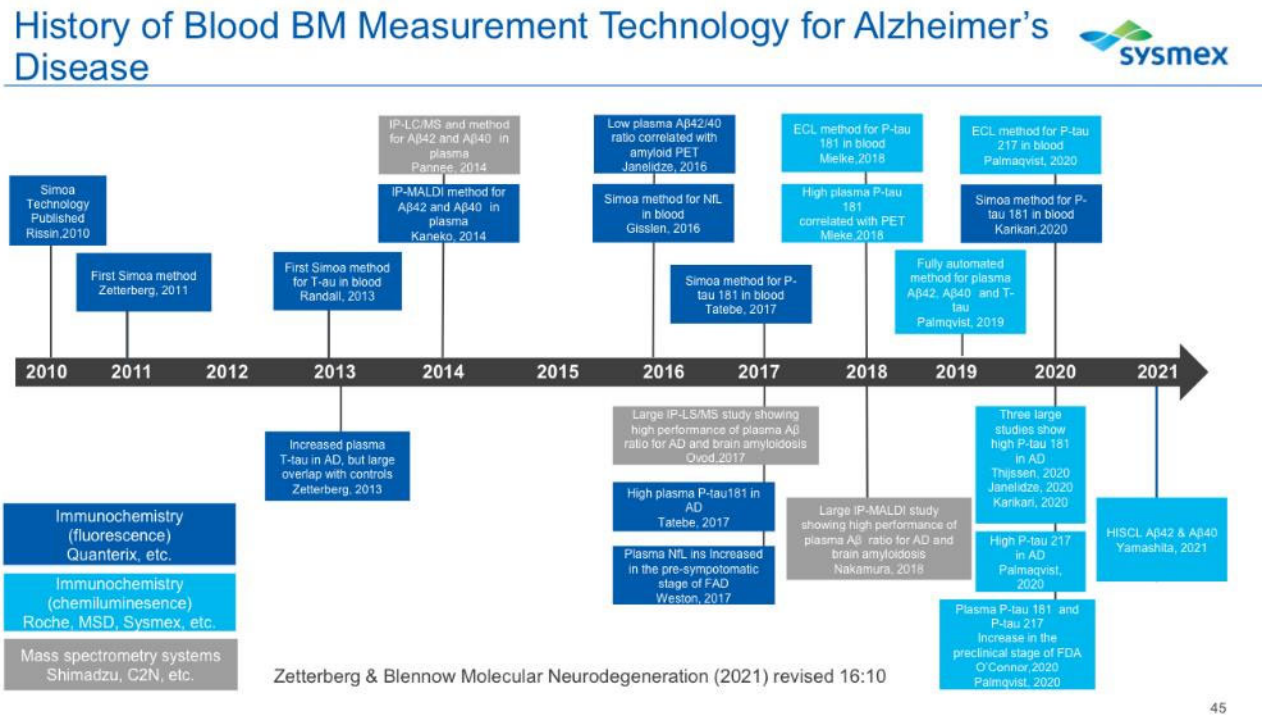
In these fields, it is important to understand the structure of amyloid-β and other quantitative changes.



On the other hand, such diagnostic technologies have naturally led to the expansion of blood biomarkers. Here is an image of the diagnosis that has been used so far.

First of all, the bottom row shows tests of language and cognitive function. More recently, we have been using video analysis to capture eye movements and changes in facial expressions. Also, measurement and analysis technologies have been developed for cerebrospinal fluid, describe as CFS, which is widely used in the medical field.

As one of the progresses, the image analysis, which is written in large letters, is now considered to indicate the state of the brain, but each of them is facing its own challenges. In order to solve such problems, we are now working on a method to look at the composition of amyloid in blood plasma using mass spectrometry, and also, as is becoming popular in science these days, a method to look at phosphorylated tau is expanding.



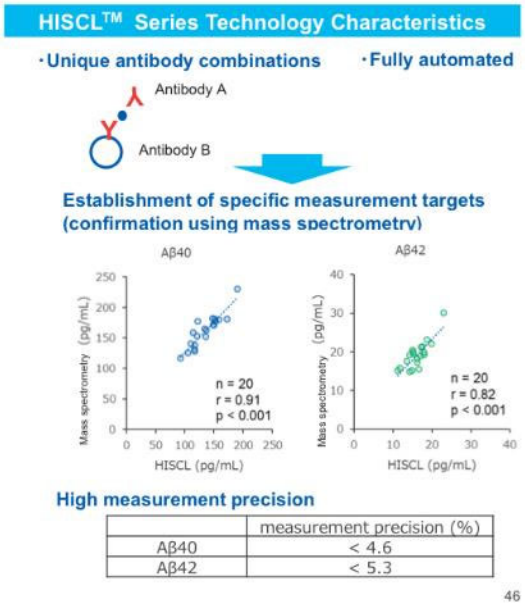
The trend in the measurement of blood biomarkers which detect Alzheimer has been active since 2010.

For example, the use of fluorescence, chemiluminescence, and mass spectrometry systems to quantitatively and easily measure amyloid-β, tau, and other molecules related to various dementia-related diseases has been increasing in the past 10 years.

Functions and HISCL™ Series Technology Characteristics

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

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



Against this background, we have been trying to utilize HISCL, which we have developed as an existing technology.

On the left side of the slide is a summary of the measurement principles and their performance that have been reported in articles and other publications. As you can see here, the HISCL we are developing is an immunoassay method using the Aβ42/40 comparison, but it is not inferior to any other method.

As shown on page 46, HISCL is characterized by its ability to combine various antibodies. HISCL's major strengths are its abilities to capture the structure, as I explained earlier, and eliminate wobbles and other problems by using methodologies such as mass spectrometry, which can support the scientific method, and full automation.

Apply to HISCL Series : Blood-Based Liquid Biopsy

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

Image-based screening

MRI, PET, CT

Spinal fluid test

Blood testing

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

Measurement parameters

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

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This is HISCL.

As shown on page 47, HISCL can be easily standardized for use in such inspections on a global scale. In addition, the advantage of our HISCL is its quantitativeness, the ability to use existing markers as described in the measurement parameters column, and the ability to easily add markers specific to the central nervous system.

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

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

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

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

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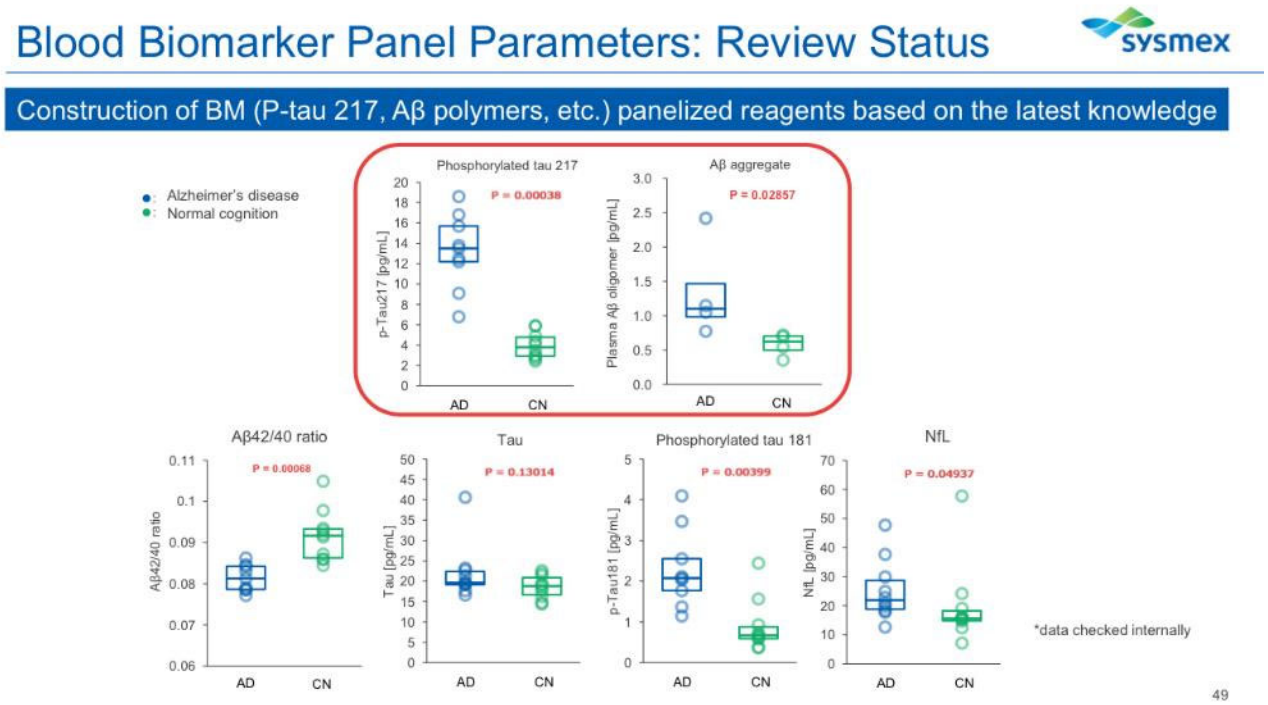
Page 48 shows the characteristic changes in biomarkers in cerebrospinal fluid that are currently being studied.

As you can see, even in symptoms similar to Alzheimer's disease, we can naturally see that these three markers alone change the way they move and fluctuate in the blood. We also believe that the movement in CSF also reflects the movement in the blood, and we would like to add these markers.

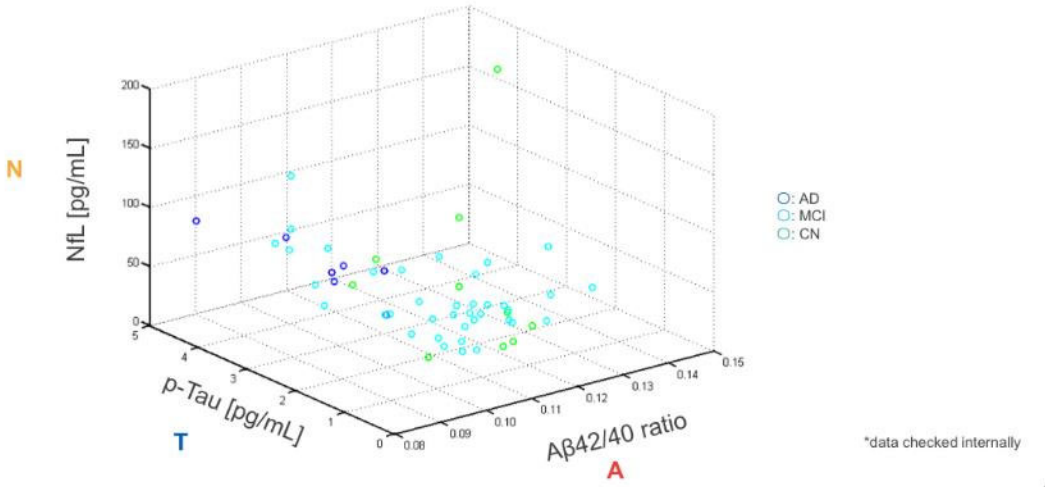


In fact, in light of the scientific, medical, and social recognition, we are working to prepare a panel that will play a leading role in properly quantifying the phosphorylated tau and Aβ polymers described here, as well as the Aβ42/40 ratio, tau, phosphorylated tau 181, and NfL that are released when nerves are damaged, which have been studied so far.

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

sysmex

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



*data checked internally

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We are currently working on a three-dimensional classification using the three biomarkers with each patient.

Sysmex's Initiatives

sysmex

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

Blood testing

System advantages
- Automated medical testing systems
- Quantitative/rapid

Clinical research advantages
- Low level of invasiveness (frequency)
- Multi-marker (Therapeutic target molecules, etc.)

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

Screening/ patient stratification

Selection of treatment and prevention methods

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

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

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

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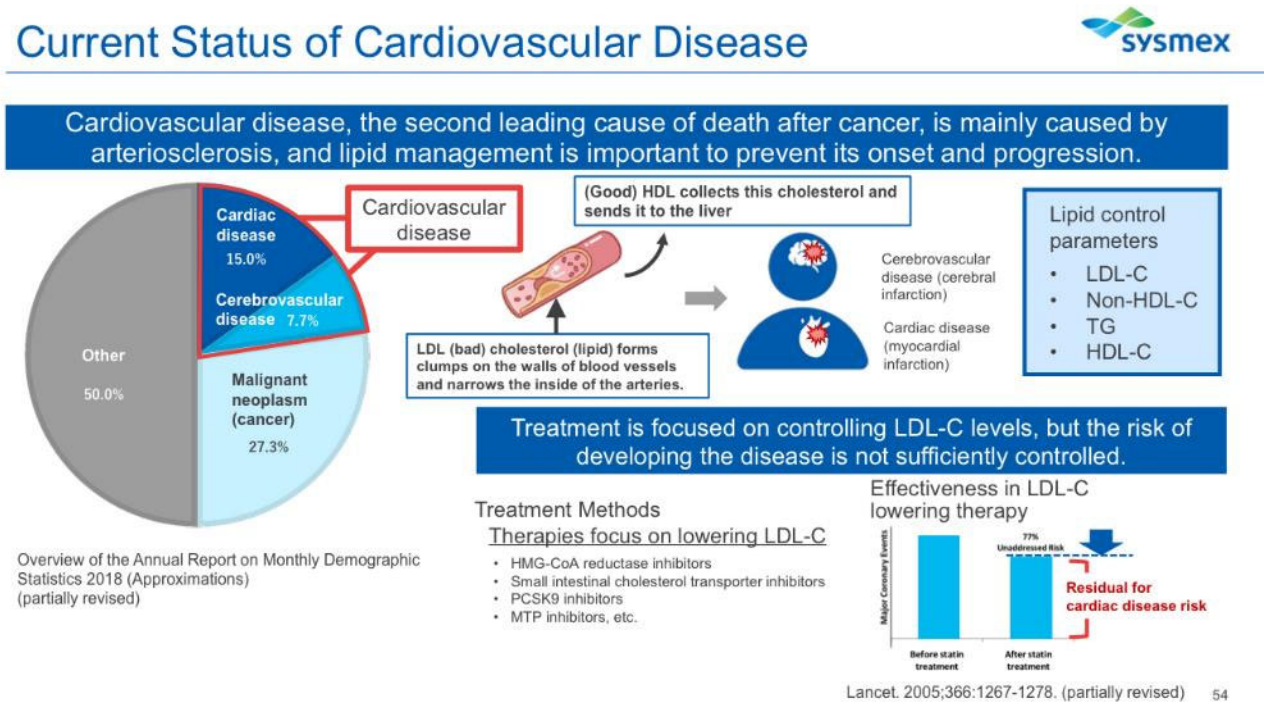
Using these studies to date, we would like to be the first to establish a global testing system in conjunction with treatment approval activities.

First of all, as you all know, we have submitted an application for approval in the field of assisting in understanding the state of amyloid accumulation in the brain in japan. In the US, we have also started preparations for a pharmaceutical application using the breakthrough device method, in order to obtain approval at an earlier date.

In addition, we are also working on the development of a method that will allow this type of technology to be used in the world, verified, and utilized in research as early as fiscal year ending March 31 2023, including in the US.

In this way, we are receiving inquiries and offers for joint research on dementia from related organizations not only in Japan, but also in the US, Europe, and China, so we would like to further develop HISCL's technology accordingly.



Next, I would like to explain another initiative, the cardiovascular disease initiative.

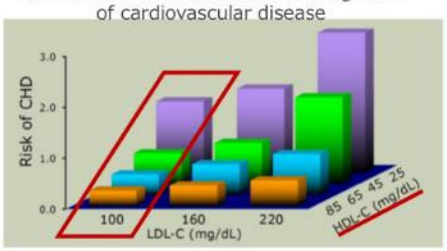
As you all already know, this is a major problem as the second leading cause of death after cancer. On the other hand, it is becoming clear that controlling blood pressure and blood fats alone is not enough to reduce the risk of cardiac disease.

As you can see on the lower right side of the slide, LDL is controlled to a certain level, and even though it is now under control, it is known that the risk of developing heart disease remains even in such patients.

Current Status of Therapeutic Drugs and Test Targeting HDL

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

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



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

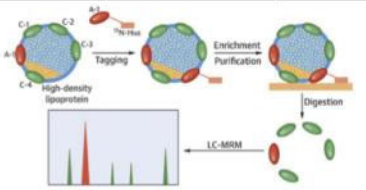
Drugs to increase HDL-C do not reduce risk of cardiac disease, so development has been halted.

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

Examples of clinical applications of HDL function tests

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

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



55

In developing therapeutic drugs, as focusing on measuring HDL-C function, it has been found that such therapeutic drugs promote functional changes, not quantitative changes.

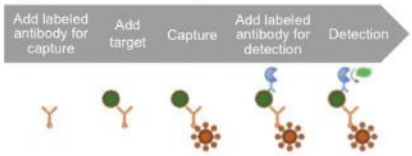
This is the case in the US, but a test to evaluate the risk of cardiac disease by examining the constituent proteins of HDL has been implemented from 2020.

Sysmex's Initiatives: HI-1000

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

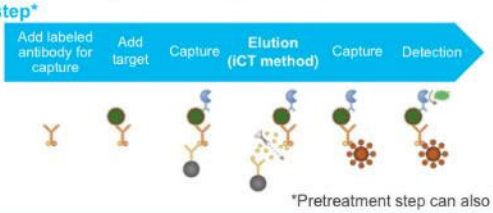
Flexible, highly sensitive and automatic measurement possible using the HI-1000

Typical Immunoassay



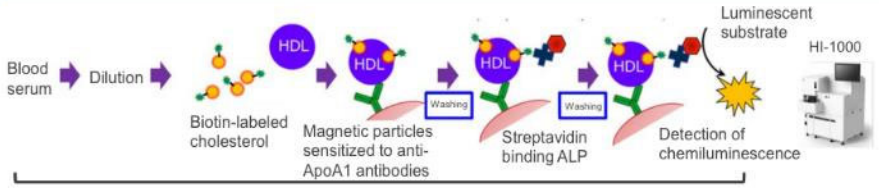
HI-1000

Immunoassay incorporating the iCT (immune complex transfer) step*



*Pretreatment step can also be added

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



All processes in the equipment.

Characteristics

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

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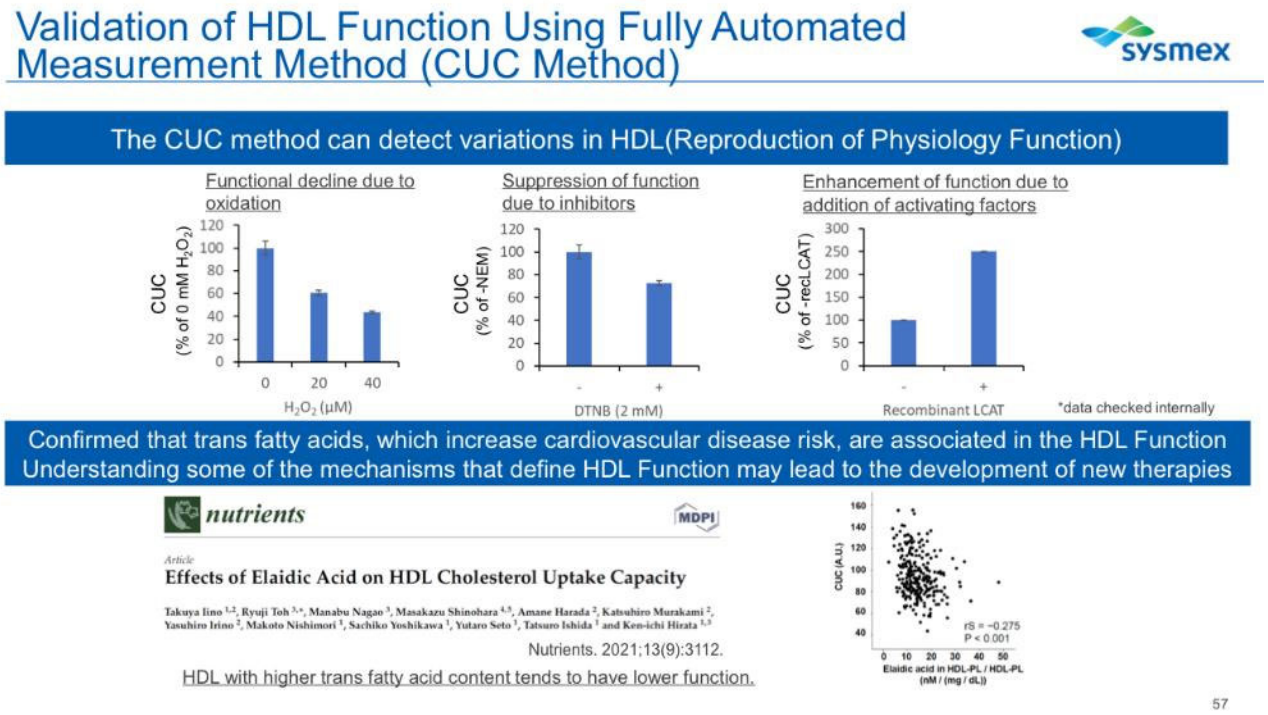
In light of this situation, we have been developing a flexible type of HISCL called HI-1000 to measure such functions.



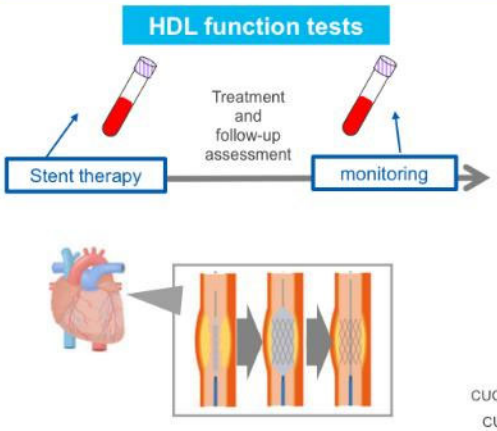
In this context, we have continued to verify chemically and medically whether the function of HDL really reproduces the physiology function.

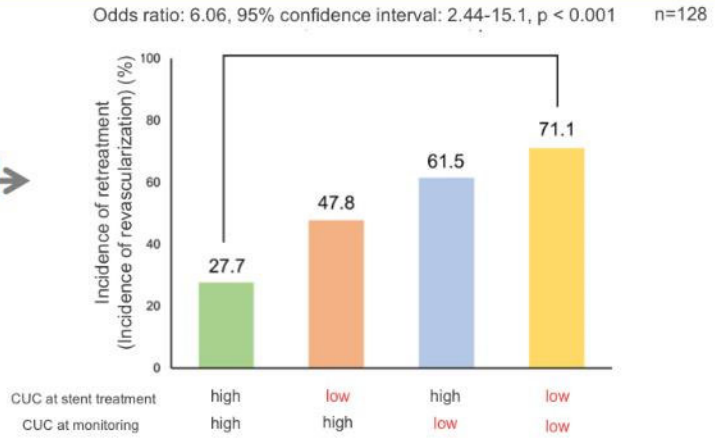
As you can see in the upper part of the slide, it is a little difficult to understand, but we have found that we can reproduce the function of HDL as it responds in vivo using the method we have used. In collaboration with Kobe University, we have also shown that trans fatty acids, which are believed to increase the risk of cardiovascular disease, are involved in the regulation of HDL.

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

sysmex

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





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

Atherosclerosis. 2022 Jan 24

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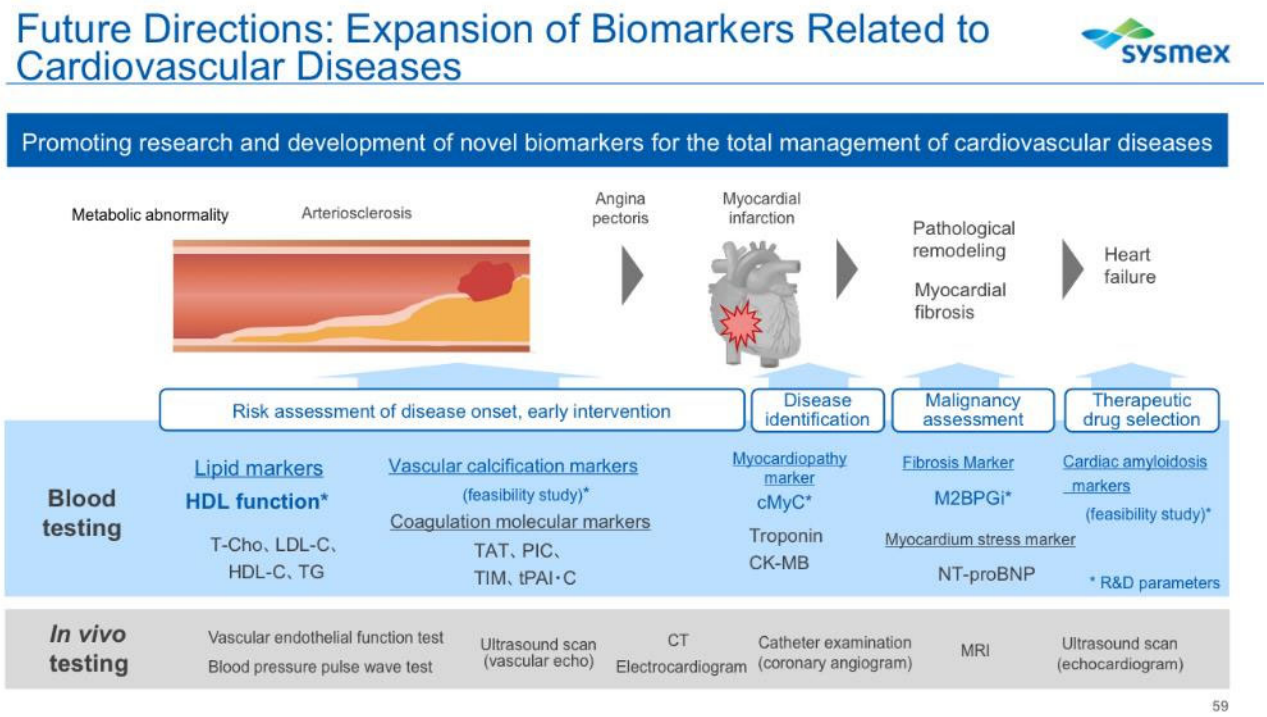
In fact, we have obtained data that our HDL function test can be used for follow-up after cardiac catheterization.

This test involves obtaining blood samples from patients who have undergone stenting for follow-up. By comparing the HDL function values of the blood with the test values at that time, we have learned that we can find cases in which patients are at risk of recurrence based on the situation at the time of re-testing.



Using this information, SYSMEX offers biomarkers, such as coagulation molecules, platelet, and blood cell counts, which are related to lipids in blood tests.

In addition, we will also resolve such metabolic abnormalities in accordance with the progression of pathological conditions, such as atherosclerosis, angina pectoris, and myocardial infarction.

We also identify the risk of early onset of disease, early intervention, disease differentiation, and grade of disease to determine what kind of treatment should be provided. Furthermore, when choosing therapeutic drugs, by using and combining our HISCL and hemostasis testing systems, as well as combining them with biological tests, we would like to expand our portfolio for the system and also our portfolio of novel biomarkers towards the total management of cardiovascular diseases.

This is the end of my explanation. Thank you very much for your attention.

[END]