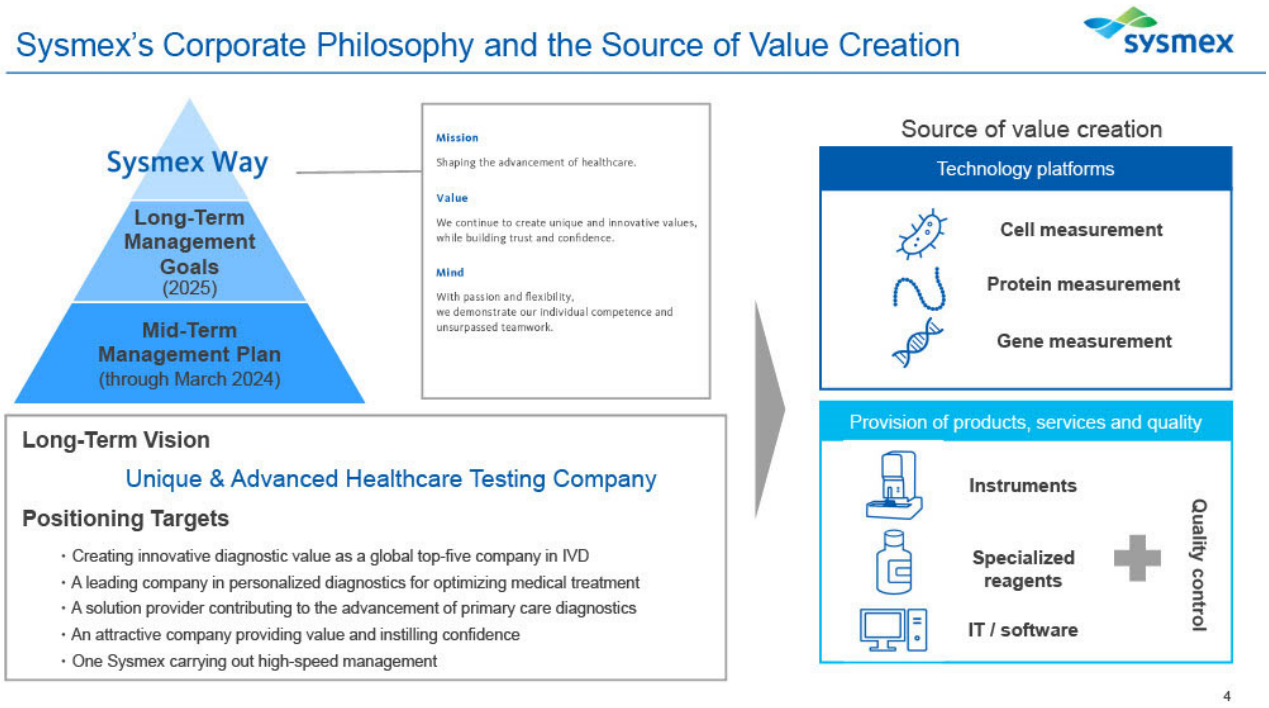
Presentation



Ietsugu: Good morning. I am Ietsugu of SYSMEX.

Our R&D meeting has been skipped several times due to COVID-19, although it has been held online. Thank you for joining us today.

Okay, next, please. Here is SYSMEX's corporate philosophy and source of value creation.

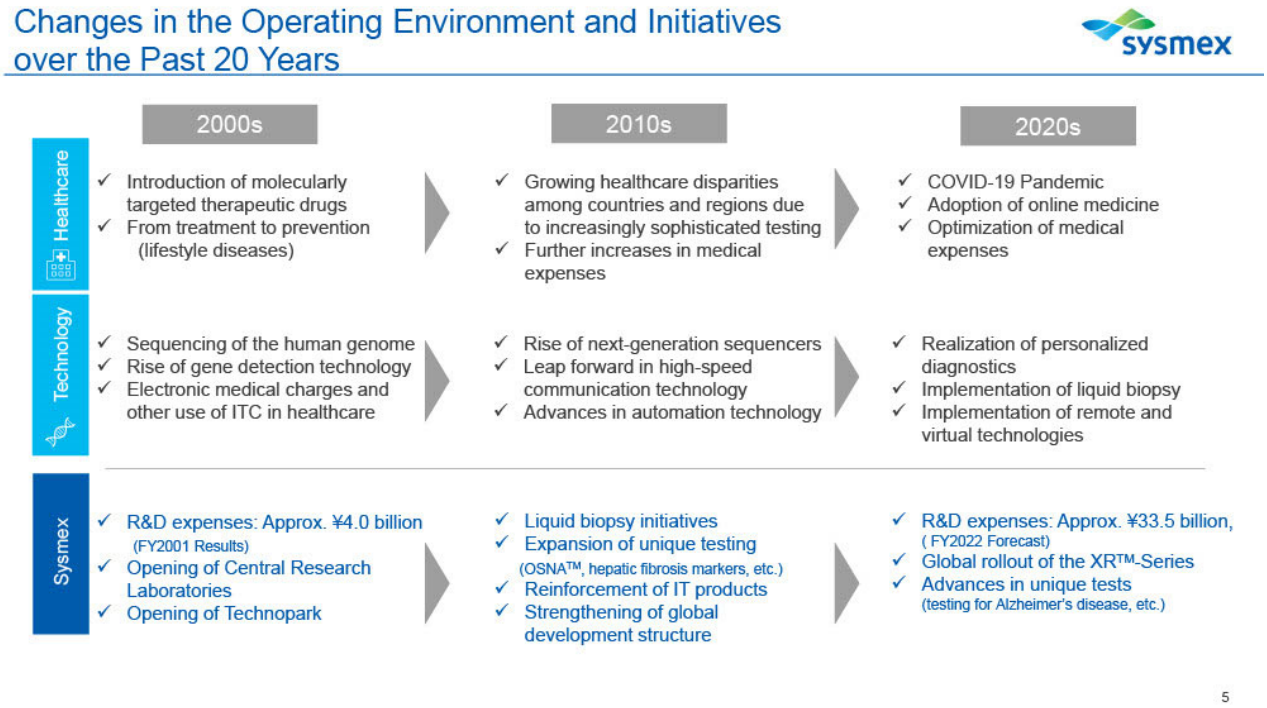
Our corporate philosophy is the Sysmex Way, which consists of Mission, Value, and Mind, and our most important mission is "Shaping the advancement of healthcare." The theme of how we can further promote healthcare is very important to us, and in a sense, it is our purpose.

Our long-term vision is to become a unique and advanced healthcare testing company. In addition to being advanced, it is also very important to be unique. We originally started out in hematology and have been expanding our portfolio.

As you can see here, we have three technology platforms as sources for value creation. Cell measurement starts with blood testing. Then we move on to protein measurement and gene measurement, which gradually become more and more precise.

To advance this technology, we provide products, services, and quality with analytical instruments and specialized reagents. SYSMEX also manufactures its own IT software.

In addition, it is very important to guarantee the accuracy of the data of our tests, especially for those of us involved in medical care. The establishment of such a system is accuracy control.



Next, please. This is a change in the environment and our efforts over the past 20 years.

In the year 2000, molecularly targeted drugs were introduced in the medical field, and the most important topic of the 2000s was the decoding of the human genome, which was a major change in the world. We established Central Research Laboratories in 2000, and at the time, everyone was against the opening of Central Research Laboratories. However, we challenged them, and in a sense, we developed this kind of research with the genome in mind.

In the 2010s, there is an increase in the sophistication of testing, and the other major point is how to control the cost of medical care, which is becoming very large.

And, technically speaking, NGS. In fact, sequencers were on the rise. With that, now we are in an era where the entire genome can be read for USD1000. Also, the very technology of high-speed communication has evolved very much in the form of 4G and 5G.

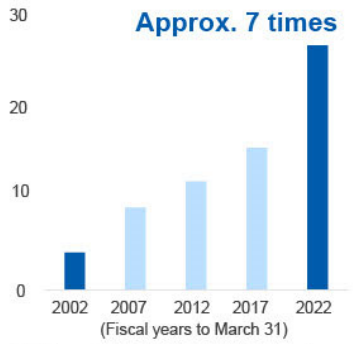
On the other hand, SYSMEX is developing a liquid biopsy approach. We have also created a global research system.

Although the pandemic occurred in 2020, we are developing personalized diagnosis and liquid biopsy. We plan to spend JPY33.5 billion on research and development for this purpose in the fiscal year ending March 31, 2023.

R&D Investment Trends

R&D Expenses

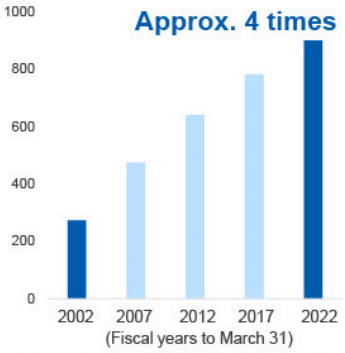
(Billions of yen)



Total investment over the past 20 years: Approx. ¥300 billion
- Advances in the hematology field (XE-Series→XN™-Series→XR-Series)
- Expansion of the immunochemistry and life science fields

R&D Personnel*

(People)



Expansion to around 1,000 people over the past 20 years
- Acquisition and development of diverse specialized human resources to enhance competitiveness (mechanics, biology, software, etc.) *only S-Corp employees

R&D Locations

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

Opening of bases in six countries in the past 20 years
- Ascertaining leading-edge technologies and customer needs globally

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Next, please. Research and development investments.

Our R&D investment has increased 7-fold over the past 20 years, and the number of employees has quadrupled to over 1,000. On the other hand, although we originally started our R&D activities in Japan, we now have bases in 6 countries around the world, including Germany, the US, the UK, Singapore, and China.

Sysmex's Objectives

Core Competencies

No. 1 share of the global market in hematology field

Global sales and service structure

R&D capabilities (Instruments, Reagent, IT)

Production structure

Diverse human resources

Materiality and Contributing SDGs

Mission : Shaping the advancement of healthcare.

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

Diagnosis + patient management
- Personalized medicine (cancer, dementia)
- Rare diseases (such as hereditary diseases)

Digital transformation
- Caresphere™
- Digital medicine

Challenges in new domains
- Regenerative medicine
- Medical robotics

Extend healthy lifespans | Improve accessibility to healthcare | Increasingly sophisticated healthcare | Optimization of medical expenses

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Next, please. This is the objectives of SYSMEX.

One of our core competencies and strengths is in the field of hematology, where we are number one in the world with a market share of over 50%. As an IVD company, we probably have the most clients. We are developing this through our global sales and service system, which is basically a direct sales system, and in this sense, we are directly connected to our customers.

Then, how do we focus on R&D capabilities? We focus on instruments, reagents, and IT, but another important factor is the production system. How we can supply our customers with high efficiency is very important actually. Instruments production base is mainly in Japan. However, as China is promoting a "buy China" policy, we are also implementing knockdowns in some instruments. Reagent production bases are expanded to all over the world. We also have a diverse workforce.

In order to “Shaping the advancement of healthcare,” we have been developing our diagnostics business, diagnostics plus patient management, digital transformation, and challenges in new domains, and as you can see, we are now also involved in medical robotics.

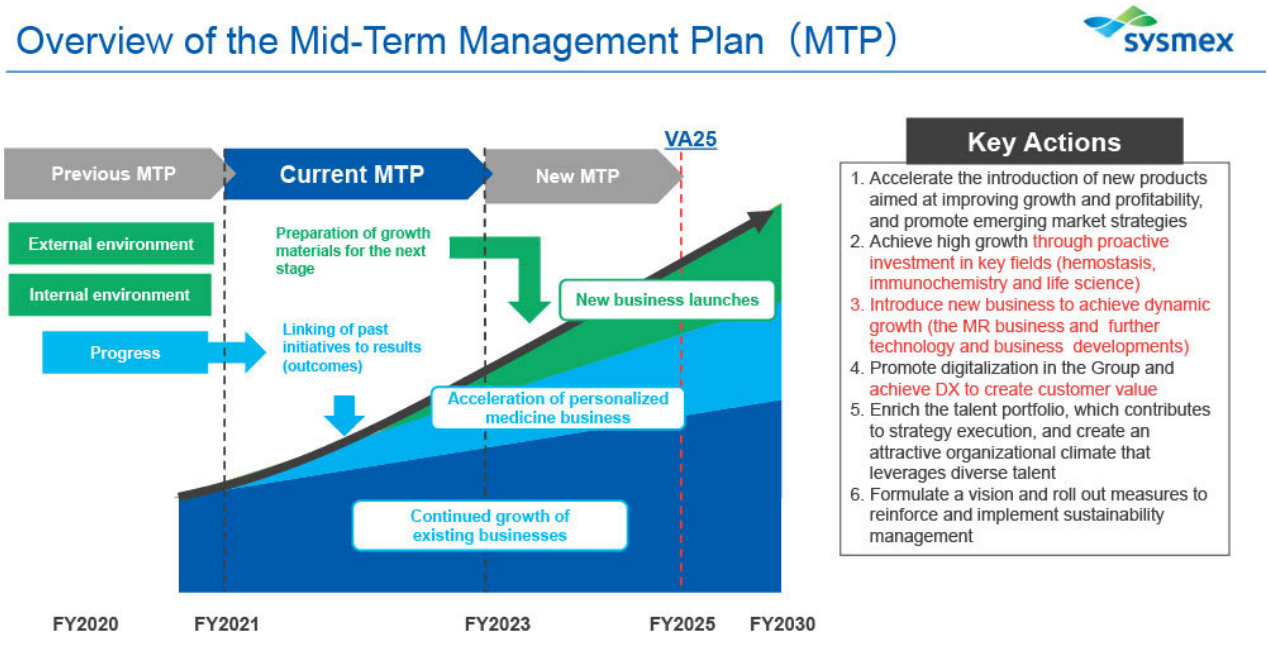
We are now working toward the SDGs of extending healthy life expectancy, improving access to medical care, upgrading medical care, and optimizing medical costs.

That concludes my presentation. Thank you for your attention.

Moderator: Mr. Ietsugu, please be seated.

Now, Mr. Asano, please.

Asano: Good morning. This is Asano. Thank you very much for your attendance at today's R&D Meeting and for your participation online. I am very pleased to be able to hold our R&D Meeting in this manner after four years.

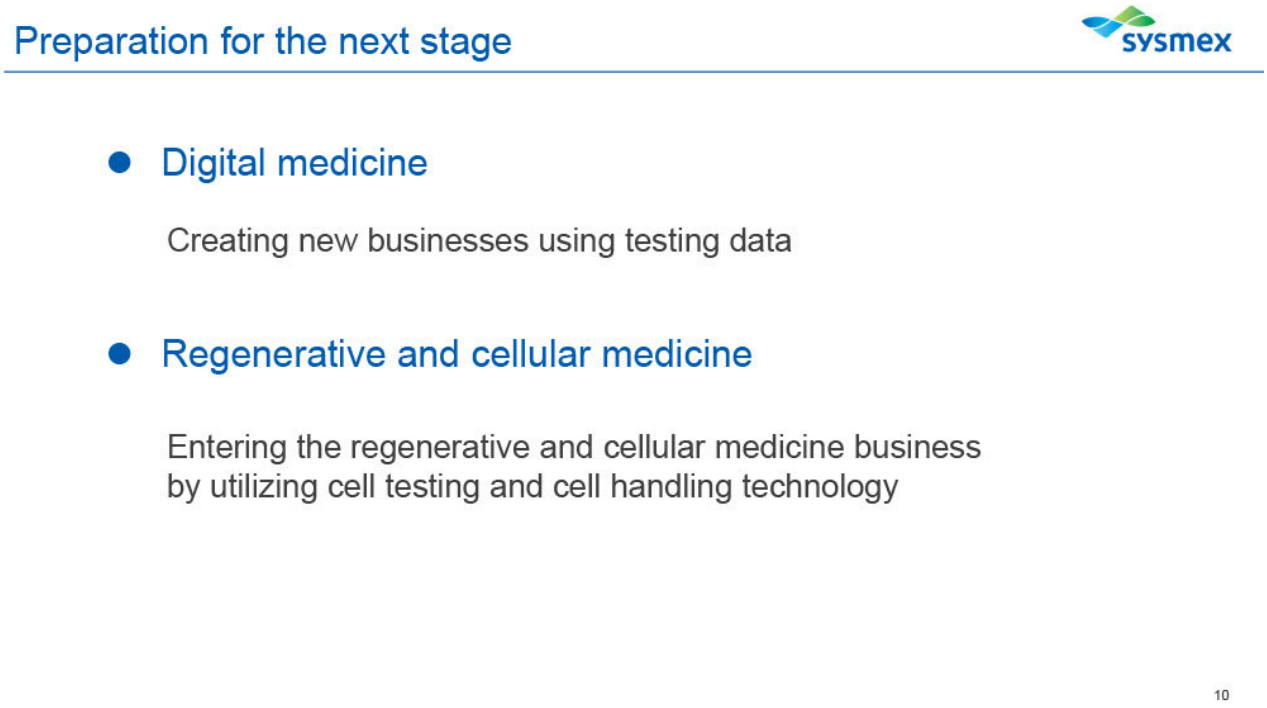


Next slide, please. We are currently in the process of completing the second year of our Mid-Term Management Plan, and today I will be reporting on the results of that plan.

As shown on this slide, our R&D efforts are based on three pillars: product development for the continued growth of existing businesses; R&D for the commercialization of personalized medicine centering on liquid biopsy; and the preparation of new growth materials for medium- to long-term growth.

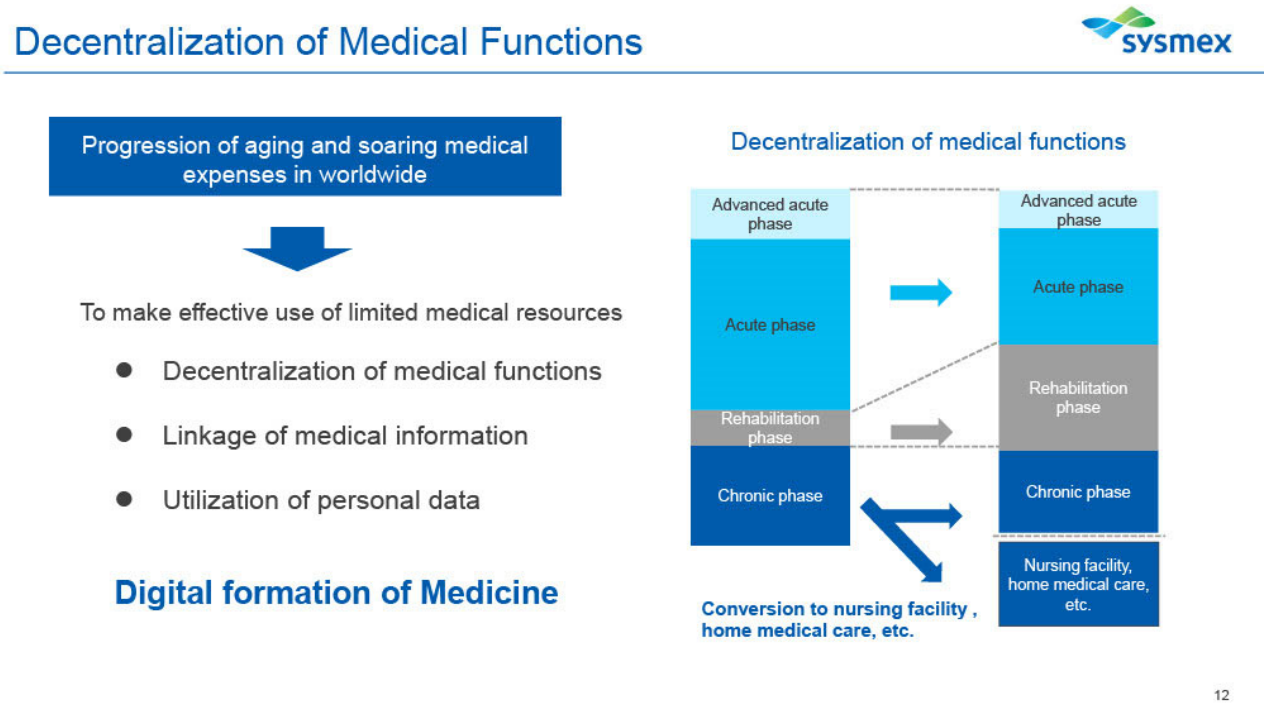
As for the existing business, I explained about hematology last year, so Mr. Ohashi will be explaining about the immunochemistry field later this year. In the area of personalized diagnostics, Mr. Ohashi will talk about our efforts in the life science field, and Mr. Yoshida will give a detailed explanation of the Alzheimer's disease test that was approved for production and marketing in Japan at the end of last year. I would like to explain the green part of this slide, the part about the preparation for the next stage.

Since each of our Mid-Term Management Plans is implemented over a span of two years, FY2023 is the final year of the current medium-term plan and also the year in which a new medium-term plan will be launched. I would like to take another opportunity to explain the new medium-term plan.



Next slide, please. Now, we are moving forward with two areas for new growth: digital medicine and regenerative and cellular medicine.

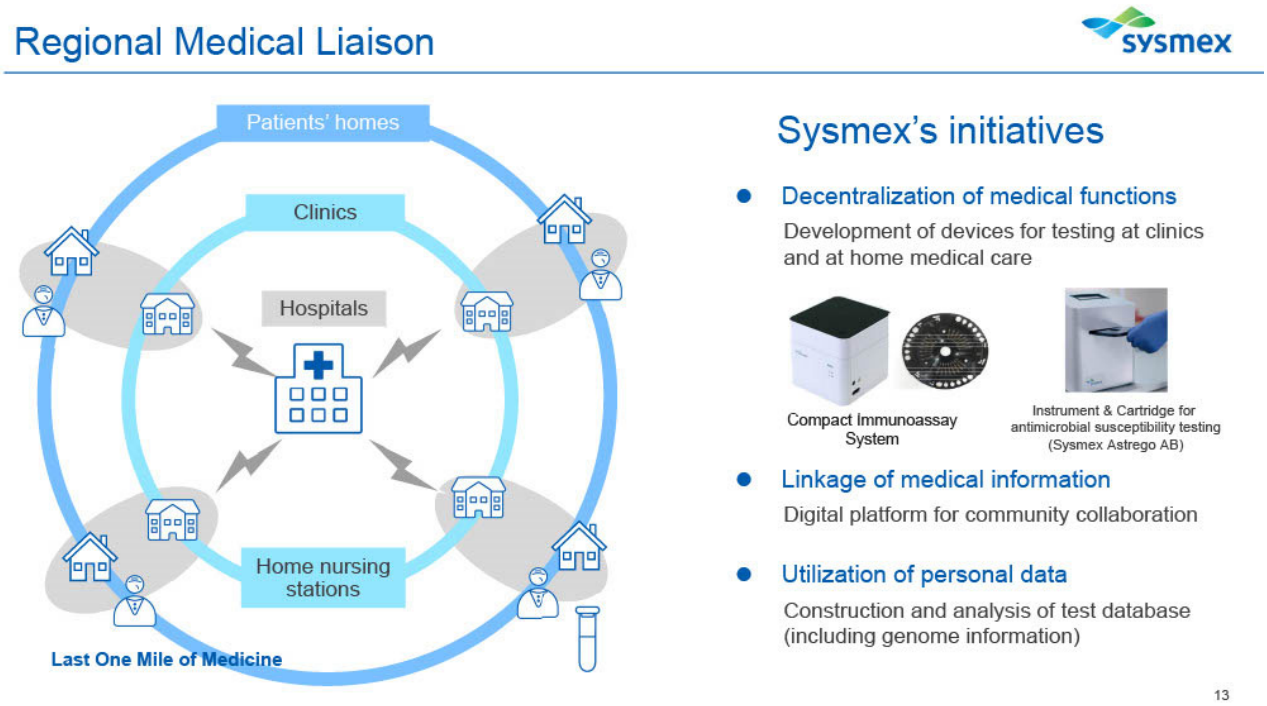
In order to accelerate development in these two areas, both are being promoted through open innovation in collaboration with partner companies.



Next slide, please. So, let's start with digital medicine.

We believe that digital medicine, or the digital transformation of healthcare, will be the most impactful factor in the future of healthcare. In order to make effective use of limited medical resources in an aging global society, we believe that medical functions will be decentralized in the direction of more core hospitals for the acute phase and more specialized regional medical services for chronic and rehabilitation phases, as shown in the diagram on the right.

The decentralization of medical functions can create inefficiencies due to information disconnection, so information linkage among medical functional institutions is a necessity. Conversely, as such coordination of medical information progresses, medical information will accumulate, and the challenge will now be how to utilize this data to contribute to better healthcare. In any case, we believe that the use of digital technology is the key to reforming the structure of healthcare.



Next slide, please. We look at this from the perspective of regional healthcare.

After completing acute care, patients return home and enter chronic care. Chronic care is crucial to improving a patient's quality of life and requires solid medical care at home. In fact, the number of patients receiving home medical care has increased significantly in recent years, and the number of clinics and home nursing stations that provide such care is on the rise.

Under these circumstances, SYSMEX's first task is to provide inspection instruments that are compatible with home healthcare and deliver solid results. When you think of home medical care and medical testing, you inevitably get the impression of wearables and micro blood collection testing. Since it is still difficult to provide accurate medical care with only that, we believe that a thorough examination with blood sampling and other tests is necessary even in the home setting.

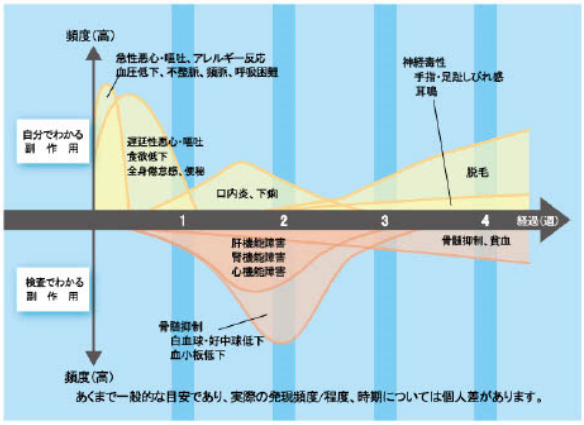
The next need is to be able to share medical data, including laboratory data. We believe it is important to provide such a digital platform, which we will discuss later.

The next step is to develop solutions that provide more effective care to individual patients by accumulating and utilizing medical data or more advanced personalized medicine. We have begun to work on both issues.

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

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

■ Side effects after administration of cancer drugs



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

■ Issues with hospital and community care

Outpatient hospitals

Patient concerns about daily side effects of anticancer drugs

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

Home nursing

Home nurses' concerns

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

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Next slide, please. This is for your reference, but it shows the actual situation in anticancer drug treatment in hospital outpatient clinics. I will not go into details, but it has become clear through hearings and other means that patients suffer from side effects when there is a lack of information coordination between hospitals and home care nurses. We hope to improve this situation through digital technology and inspection.

Introduction of D'PULA Medical Solutions

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

sysmex × OPTiM

D'PULA Medical Solutions Corporation

Corporation Philosophy

Connecting Lives, Connecting Healthcare

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

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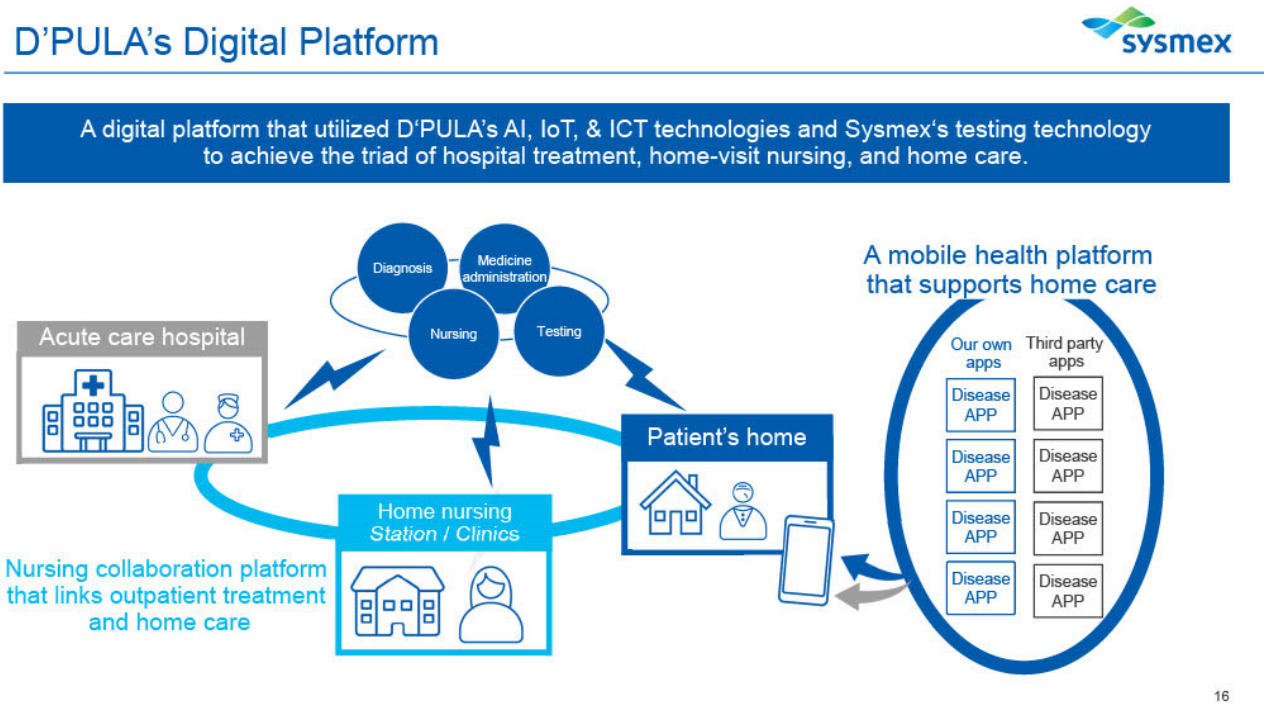
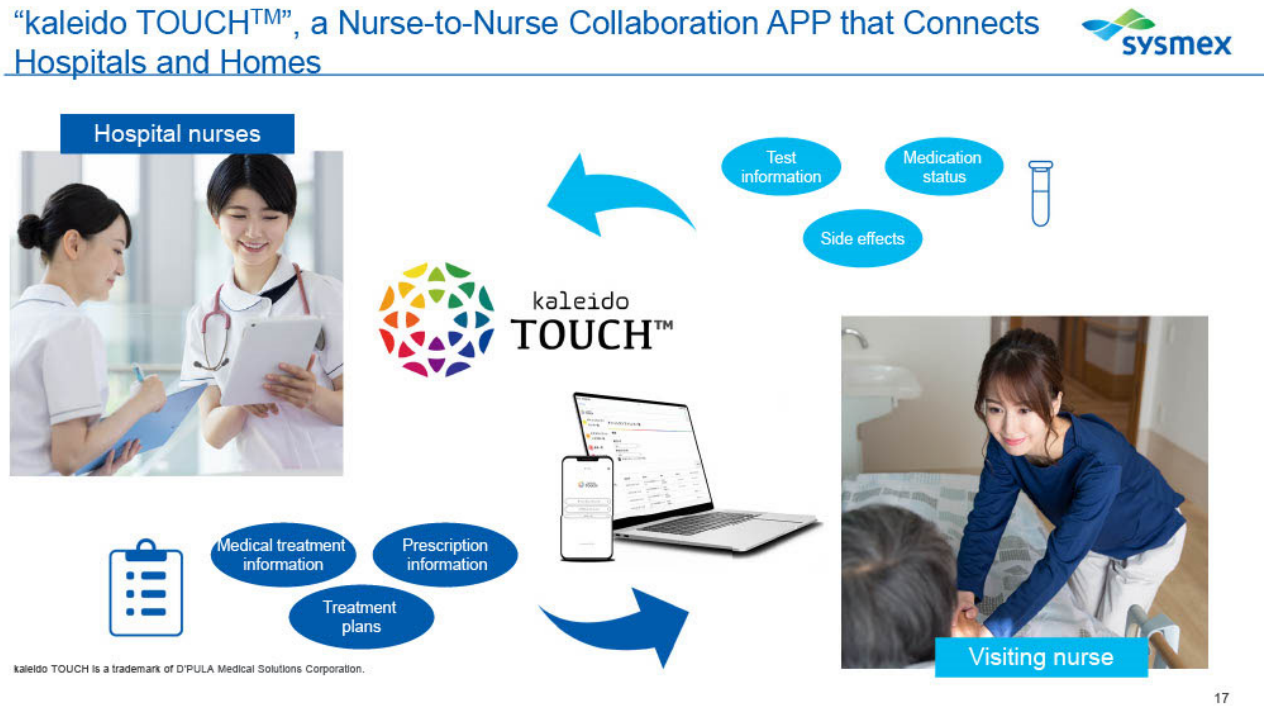
Next slide, please. To accelerate our efforts in this area of digital medicine, we established a joint venture with OPTiM, a leading IT and AI company, in 2020. The name of the Company is D'PULA Medical Solutions Corporation. The origin of company name is a coined word from the Greek D'PULA,

which stands for digital or data and bridge, and together they connect lives and medicine through digital business.

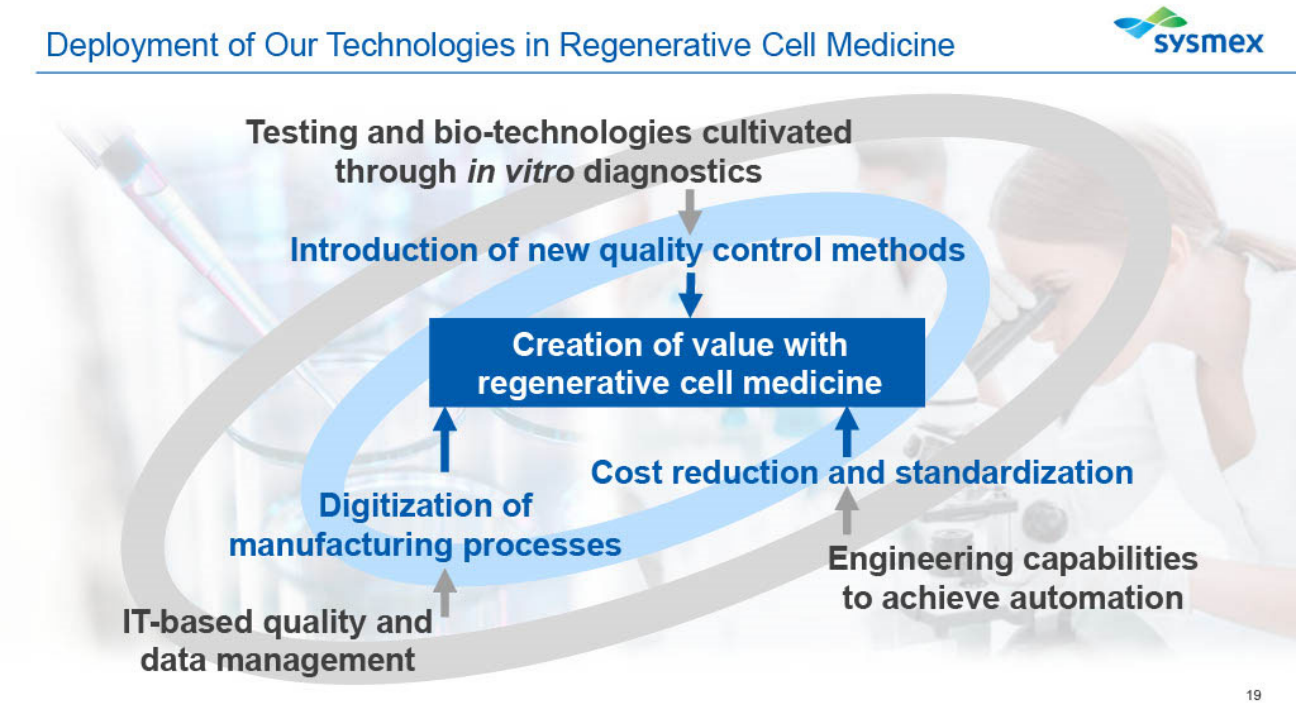


Next slide, please. This D'PULA is currently developing a digital platform to realize the trinity of hospital treatment, home nursing, and home care.

This platform is designed to provide a means of regional collaboration and to link with so-called digital medicine, and data can also be stored via this platform.



Next slide, please. As the first step, we have launched kaleido TOUCH, an app that links hospitals and home care providers. We would like to take kaleido TOUCH as our first step, incorporate home inspections into the system, and further enhance the digital platform to launch it as a new business in the future.

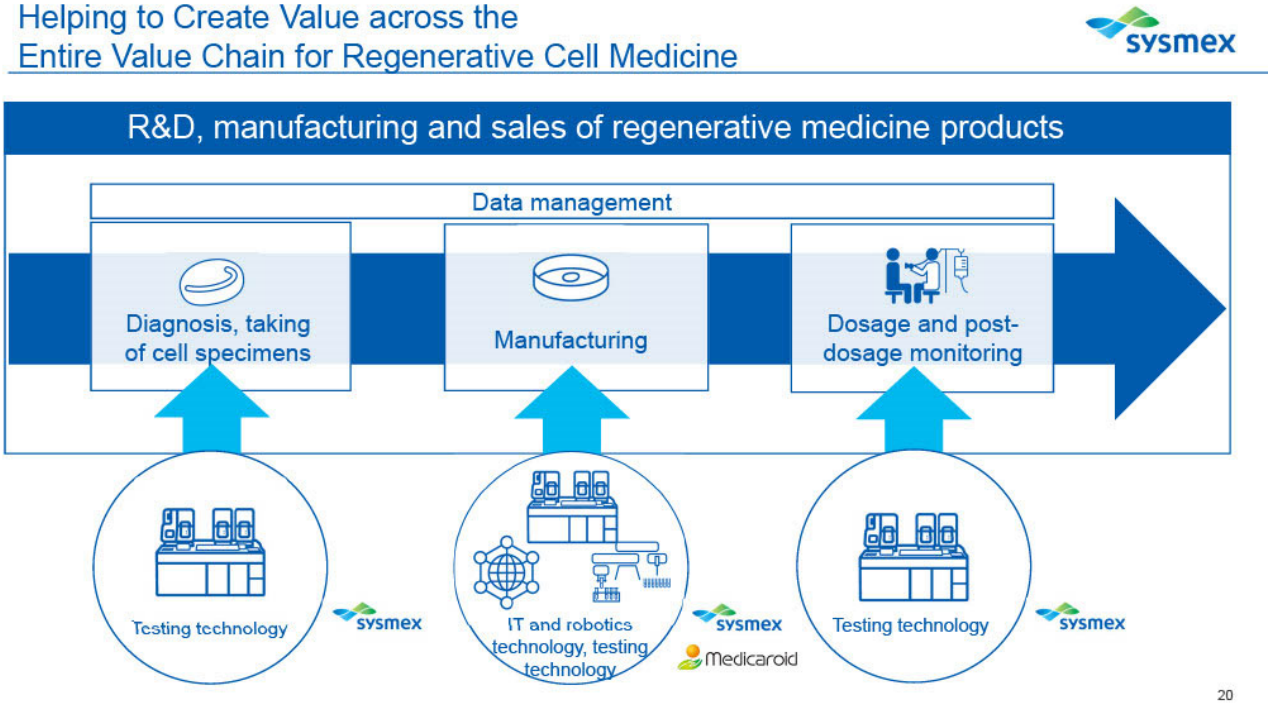


Now, let me talk about the second initiative, regenerative and cellular medicine.

Regenerative and cellular medicine, hereafter simply abbreviated as regenerative medicine, is currently undergoing a lot of research and development, and the market is starting to emerge. However, quality control and cost issues in the manufacture of regenerative medicine products remain.

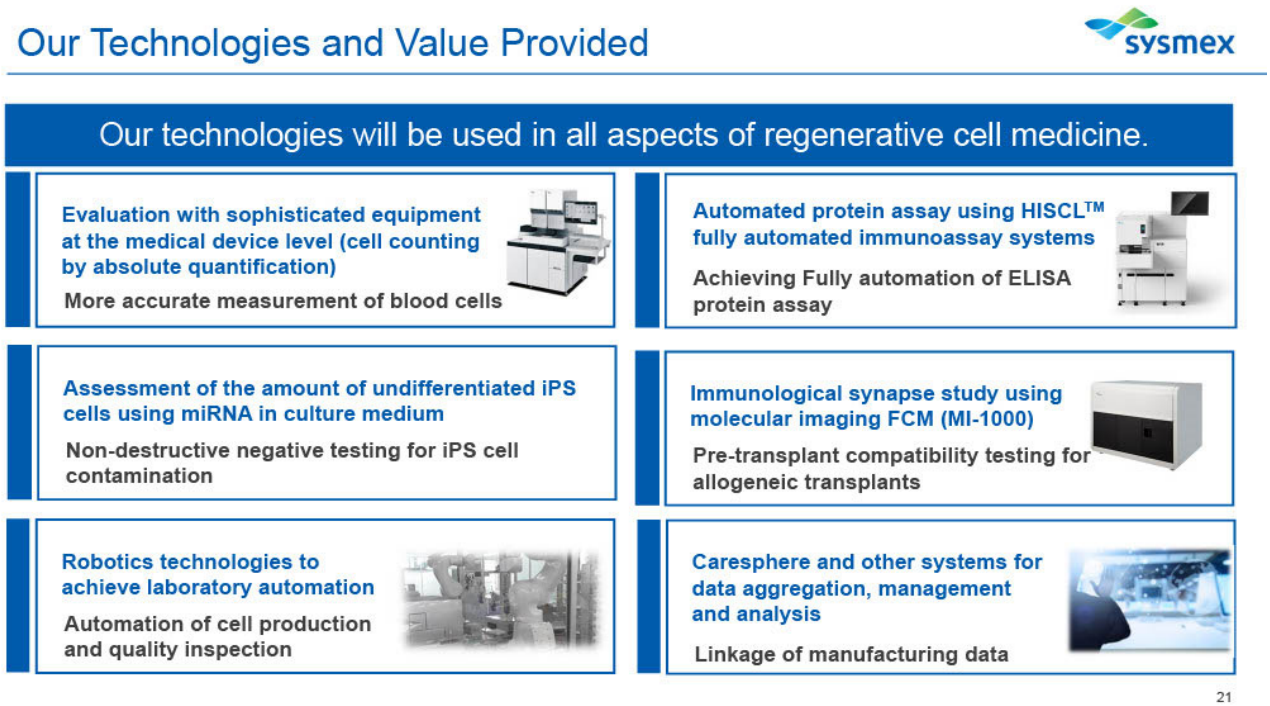
We have developed a quality control method for the manufacturing process of regenerative medicine products by utilizing the testing technology we have cultivated in our diagnostics business, and we are providing this method to companies engaged in regenerative medicine.

In addition, we have developed a PCR system together with Kawasaki Heavy Industries and Medicaroid for automation systems using robots, so the technology can be converted to other applications. In addition, IT technology for process management can be developed, including by affiliated companies.



Next slide, please. Thus, we have the elemental technologies for the manufacture of regenerative medical products in place.

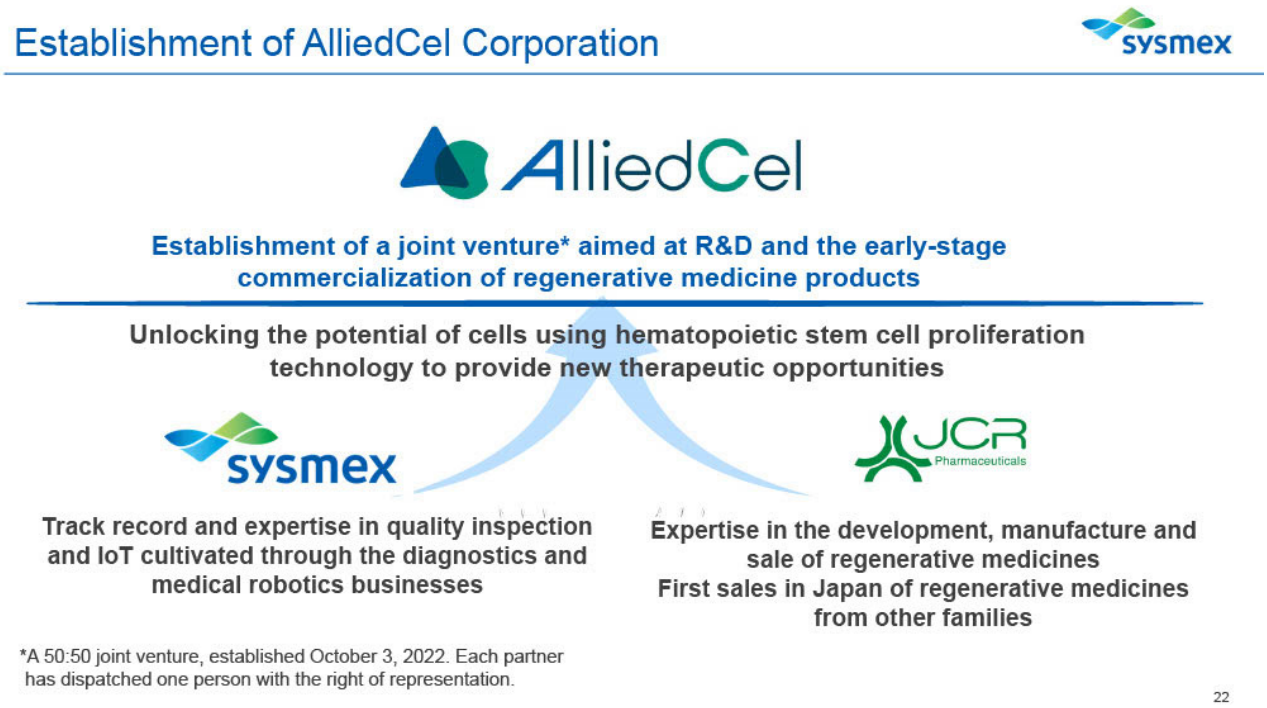
We also believe that regenerative medicine as a whole is an area where our technologies can be utilized throughout the entire value chain of regenerative medicine, including testing from the stage of taking cell specimens prior to product manufacture and monitoring after transplantation.



Next slide, please. Specifically, I would like to briefly introduce what kind of technologies we have developed so far.

From the top of the left column, there are products that use our hematology and flow cytometry technology, technology to measure cells, technology to examine the differentiation status of iPS cells by measuring microRNAs in culture medium using genetic testing, and robotization.

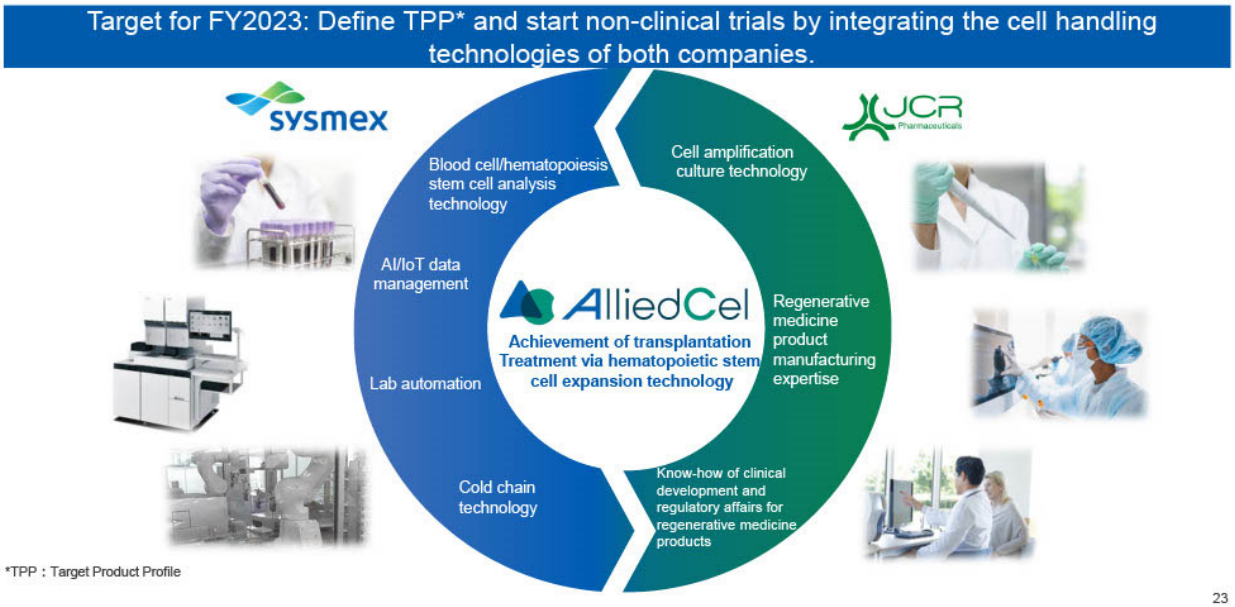
Moving to the right, we have technology that uses HISCL to measure cell differentiation function, cytokines that are indicators of differentiation and function, technology that uses molecular imaging FCM to test the suitability of transplants, and IT technology.



Next slide, please. We believe that these technologies can be used to develop a certain business in the field of regenerative medicine, but we have determined that it would be difficult to commercialize a major business by ourselves, as we have no experience in the development of regenerative medicine products. Therefore, we decided to collaborate with JCR Pharmaceuticals and established AlliedCel last year.

As you may know, JCR is a pharmaceutical company headquartered in Ashiya City, Hyogo Prefecture, and has developed some very unique products. In particular, Temcel, a regenerative medicine product developed by the Company to suppress GVHD after hematopoietic stem cell transplantation, has already been used in a very large number of patients.

Contribution to Hematopoietic Stem Cell Transplantation Implemented by AlliedCel



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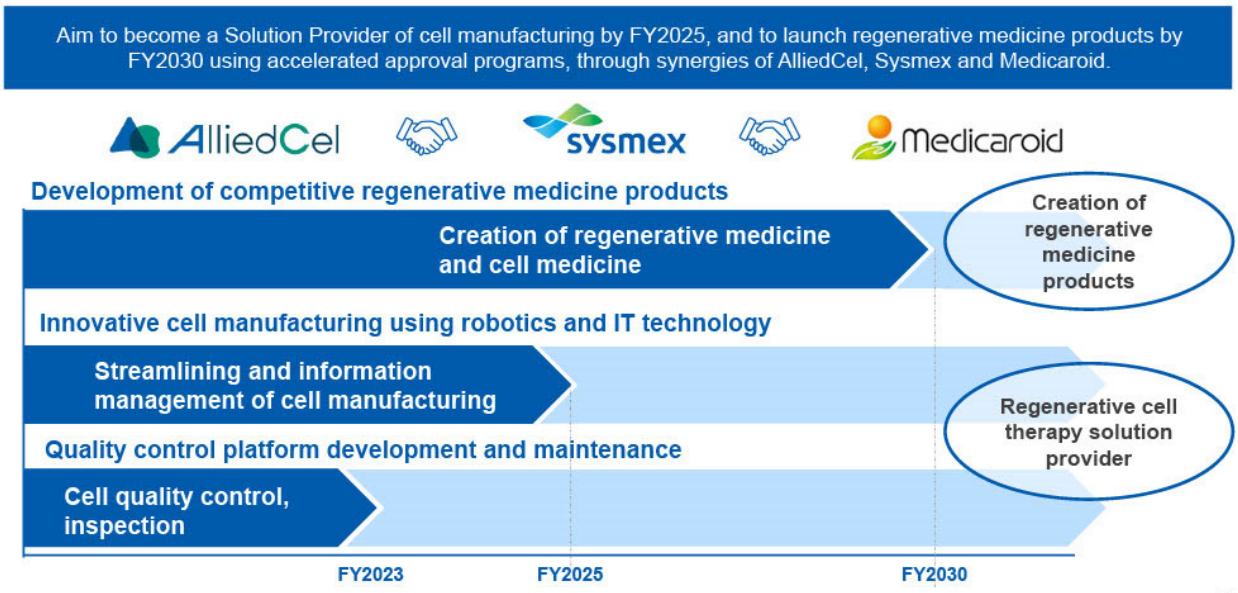
Next slide. This slide is a bit repetitive, but as I explained earlier, our technology and JCR's knowledge and expertise in the development and manufacture of regenerative medicine products, clinical trials, and pharmaceutical affairs are comprehensive, and we expect that there will be good synergies between the two companies. Regarding AlliedCel's specific initiatives, we believe that our first target is a regenerative medicine product using hematopoietic stem cells, and we hope to finalize the product image at an early stage and begin non-clinical trials by the end of FY2023.

Timeline in the Area of Regenerative Cell Therapy Business



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Next slide. This is my last slide.

AlliedCel ultimately aims to develop regenerative medicine products, but we believe that the quality testing methods, automation, or information systems themselves that will be established in the process will be valuable, and we are considering making them a separate business.

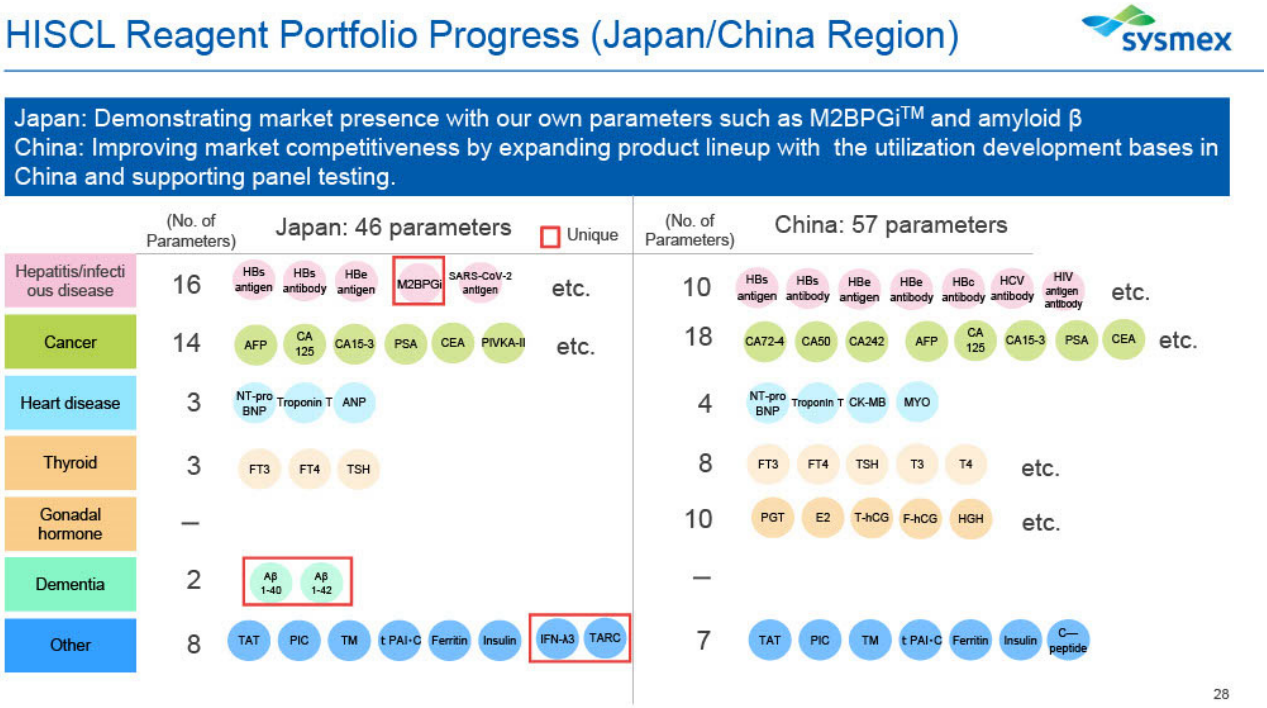
That is all from me. Thank you for your attention.

Moderator: Mr. Asano, please be seated.

Now then, Mr. Ohashi, please start.

Ohashi: My name is Ohashi from the Reagent Engineering Division. Thank you for joining us today.

I would like to explain our efforts in the field of immunochemistry and our efforts in life sciences with regard to the creation of testing value in our priority areas.

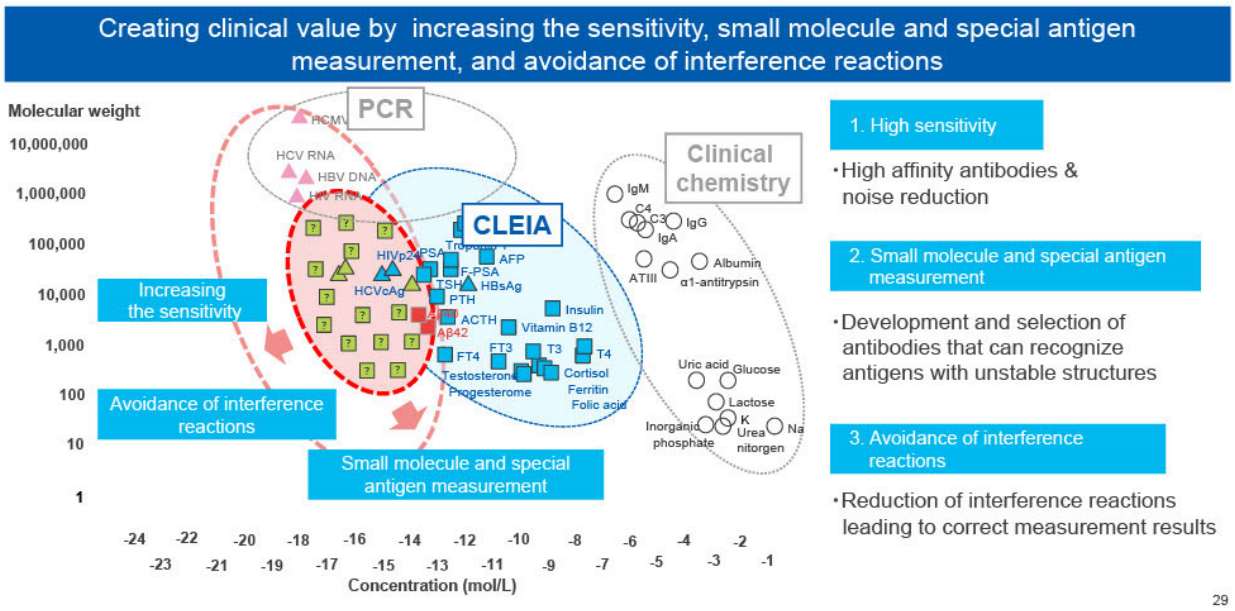


First, we are working in the field of immunochemistry.

This slide shows the current status of our portfolio in Japan and China.

We are currently up to 46 parameters in Japan and 57 parameters in China. However, its contents are unique. China currently has 57 parameters to accommodate panel testing, mainly tumor markers. In Japan, we are promoting the development focusing on infectious disease parameters used to deal with COVID-19, parameters, such as interferon lambda used to predict the severity of the disease, and, as I will explain later today, unique parameters such as Aβ40 and 42 in the field of dementia.

Expanding the Strength of HISCL with Technology



Next, please. I will use this diagram to explain how HISCL's strength will be expanded in the future.

In this figure, the lower horizontal axis is the concentration, and the vertical axis is the molecular weight. The molecular weight is the molecular weight of the protein target. Clinical testing has historically started with biochemistry, that is, with high concentrations, and has gradually moved to the left in terms of how accurately to measure low concentrations in the blood. Currently, the light blue area, written as CLEIA, is the large area of HISCL.

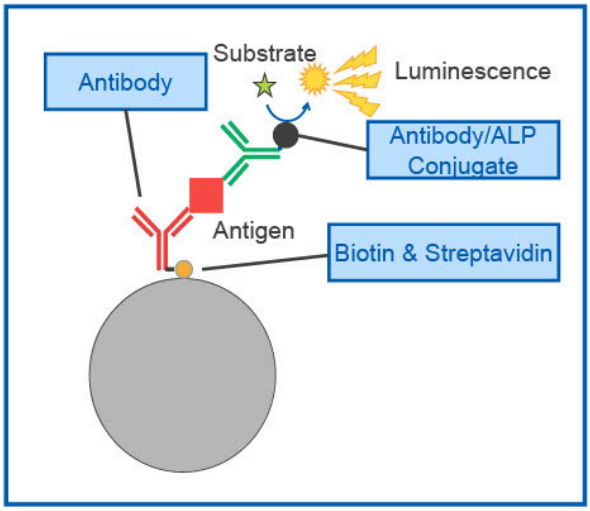
Naturally, in order to increase clinical value, it is important to move forward more to the left. It is necessary to avoid interfering substances, etc., not only to increase sensitivity but also to promote accurate diagnosis. In addition, we would like to make HISCL more useful by developing a system to measure special antigens and unstable antigens that have been difficult to measure in the past, and by making it possible to measure better small molecules that could only be measured by mass spectrometry.

Therefore, today I would like to go through these points: one, two, and three, in order.

Core Technology: Key Points for Improving Immunochemistry Reagent Performance

sysmex

Immunochemistry reagent performance is determined by high-performance raw materials



Antibody

Antibodies with confirmed disease specificity in addition to basic performance

Antibody/ALP Conjugate

Increasing the sensitivity by using uniform molecules via genetic engineering

Biotin & Streptavidin

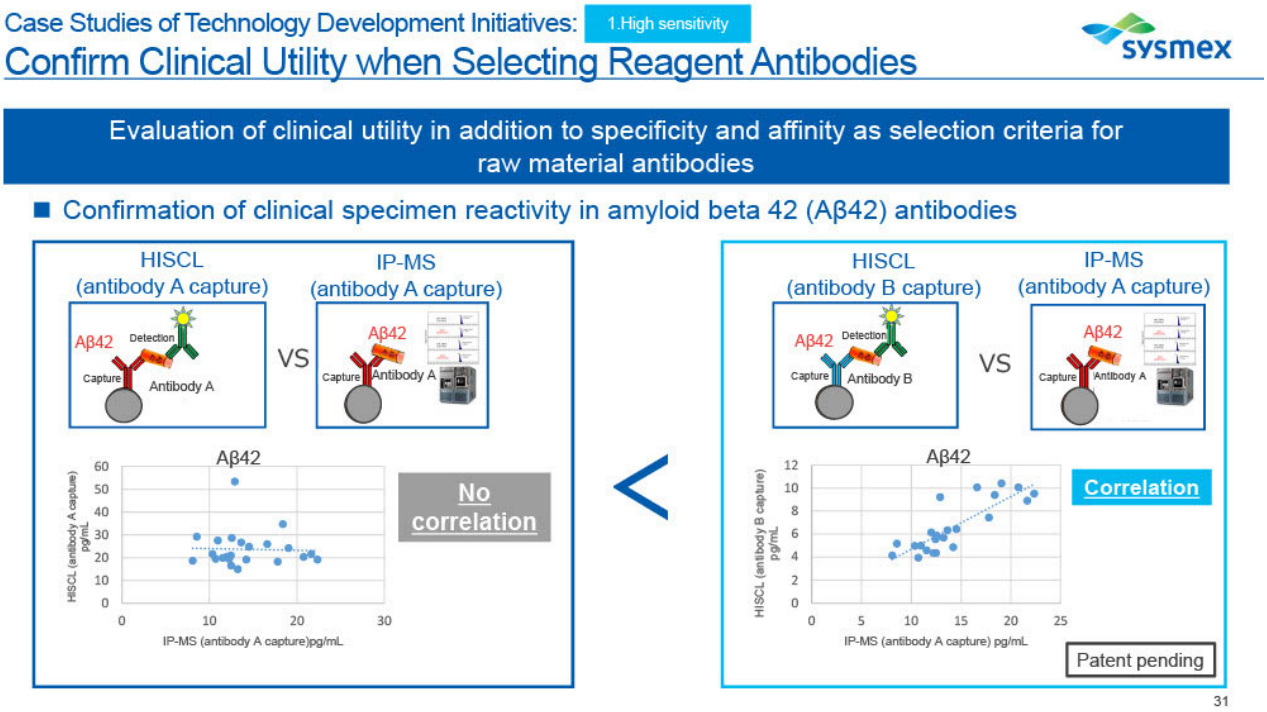
Avoiding interference by developing highly original new substances

Next, please. In this figure, we will first explain the system of HISCL measurements.

The large gray balls are magnetic particles. The antibodies are then bound to them using streptavidin and biotin. The information we want to know is how much the red square, antigen, is.

To determine this information, a green Y-shaped antibody called a secondary-labeled antibody is enzymatically reacted with alkaline phosphate attached to the antibody to emit light. Then, the mechanism is that the luminescence correlates with the amount of antigen (red square) and proceeds to quantification.

So, I would appreciate it if you could keep this diagram in mind as the words antibody, secondary-labeled antibody, biotin, and streptavidin will be used in the following slides.



Next, please. First, let me explain about antibodies with high clinical utility.

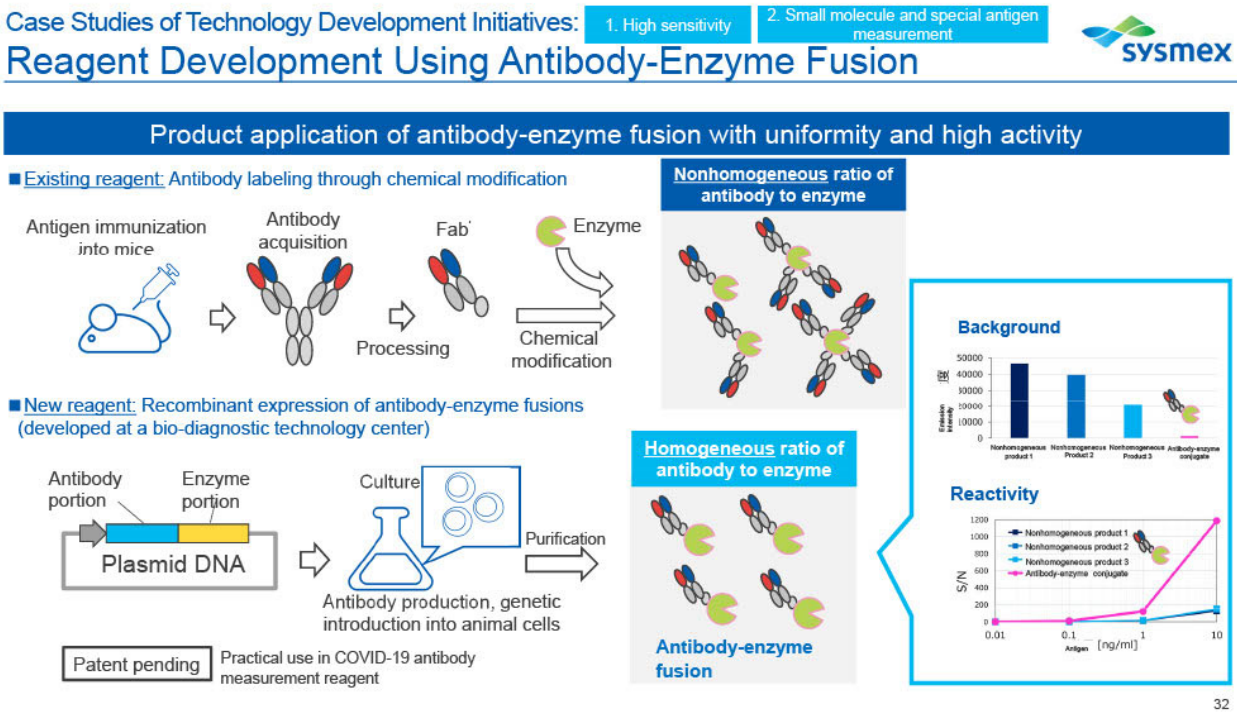
Antibodies are very important raw materials for the production of reagents.

Look at the left side of this figure, enclosed in the gray border. Each magnetic particle has an antibody attached to it. The target here Aβ42 is captured. Since the environment in the HISCL is different from that in the patient's specimen, the clinical usefulness depends on how well the antibodies that can capture the target in the HISCL machine are captured and used.

In this sense, in the mass spectrometry, written as IP-MS, it is important to select an antibody that correlates well with the immune response to Aβ42 in the patient's sample, as indicated by the star marks.

In the figure on the left, the lines are straight, which means there is no correlation. On the other hand, when the correlation improves, the slope becomes 45 degrees, and the dots converge. In the figure on the right, this is close to that state. You can see that it is important to select antibodies carefully from the early stage of the disease.

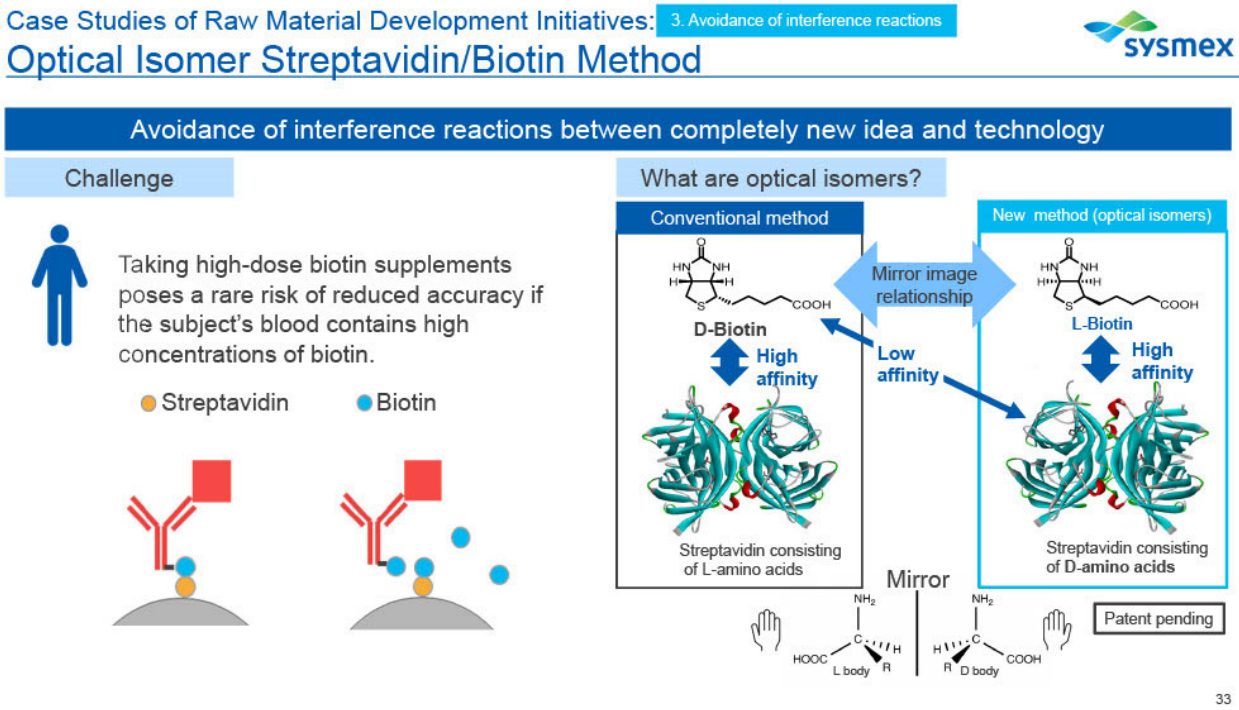
In the development of HISCL, we are screening to capture antibodies with high clinical utility from an early stage.



Next, please. In this figure, I will explain the upper part of the immunization, the secondary-labeled antibody, which is the upper part drawn in the shape of a sandwich.

In existing reagents, monoclonal antibodies obtained from mice were enzyme-digested and combined with enzymes to make secondary-labeled antibodies. However, this method produces a variety of molecular species. In addition, the enzyme may be damaged during the reaction, resulting in a high background.

To avoid this, we have established the technologies at our Bio-Diagnostics Technology Center, which opened in 2019. This technology is based on genetically engineering a reaction between a reactive part of an antibody and an enzyme, and then producing a protein from the plasmid vector. This technology produces a single molecule and lowers the background, leading to higher sensitivity of the HISCL reagent and reduced background noise.



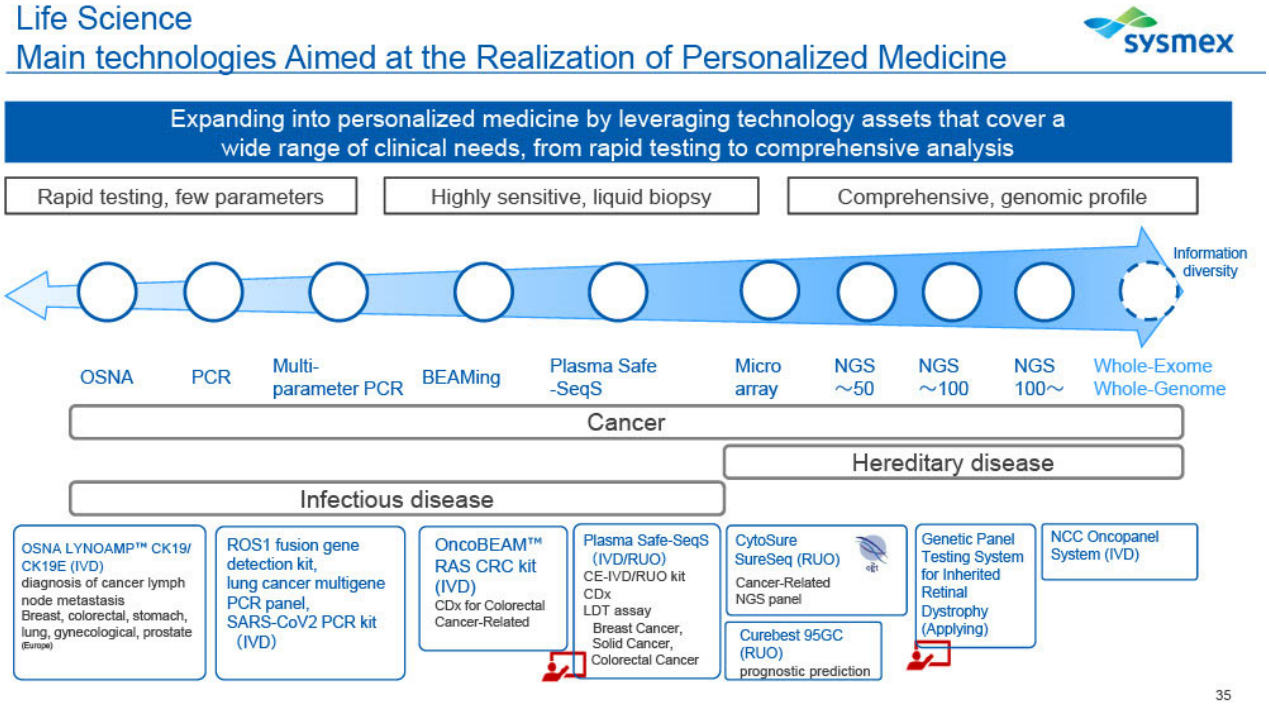
Next, please. Finally, this is a slide I prepared to let you know about a very dreamy story.

It is a difficult slide to understand, so let me explain it with a little topic as well. On February 17, I think, Hayabusa2 brought back a sample from Ryugu that contained many organic molecules, including a 1-to-1 ratio of D- and L-bodies of amino acids.

In nature, amino acids D and L usually exist in a normal 1-to-1 ratio. However, all living organisms on earth are supposed to use this L-body. I'll leave for another time the question of whether that represents what biological evolution has done on earth, but anyway, everything from Escherichia coli to humans uses this L-body.

For example, if a patient is taking a high concentration of a supplement, biotin, there will be biotin in the specimen. If there is a large amount of light blue biotin on the left side of the antibody, the antibody may be removed, resulting in a false-negative result at the point where the color should normally appear. To avoid this problem, we have developed a biotin and streptavidin method using D-amino acids, as depicted on the right side.

This technology is made possible by chemically synthesizing streptavidin from D-amino acids in total synthesis and developing an environment in which this is carefully folded. Using this technique, it is possible to create a reaction system with exactly the same molecules and with the same mechanism of unaffectedness.



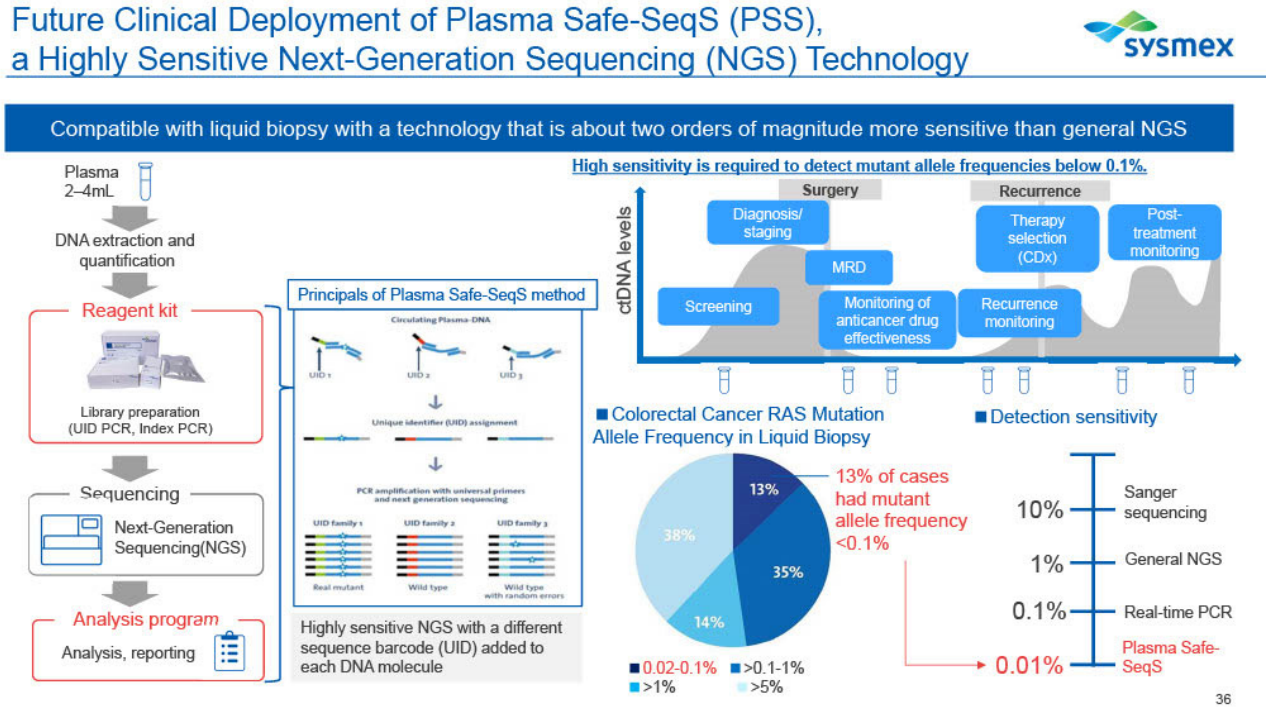
Next, please. Next, I would like to explain our life science initiatives.

In explaining gene technology, I first explained immunity in terms of molecular weight and concentration, but now I would like to explain genes in terms of information content.

The arrow on the leftmost side of the document is light-colored, which means that the amount of information is small. For example, the OSNA method for diagnosis of cancer lymph node metastasis, which we have been working on, and the PCR for COVID-19 have a small number of items and targets, but it is important to provide results quickly and with high sensitivity.

However, in liquid biopsy, for example, high sensitivity is required. To meet this need, BEAMing, using flow cytometry and digital PCR technology, or on the right side, the Plasma Safe-Seq system is required.

Furthermore, in the area of genetic diseases, where we need to look at genetic information in a more comprehensive manner, microarrays and NGS are needed as platforms. Today, I would like to explain about the Plasma Safe-Seq system, which is marked in red at the bottom, and the genetic panel testing system for IRD.



Next, please. First, I will explain about the high-sensitivity NGS technology, Plasma Safe-Seq sequencing.

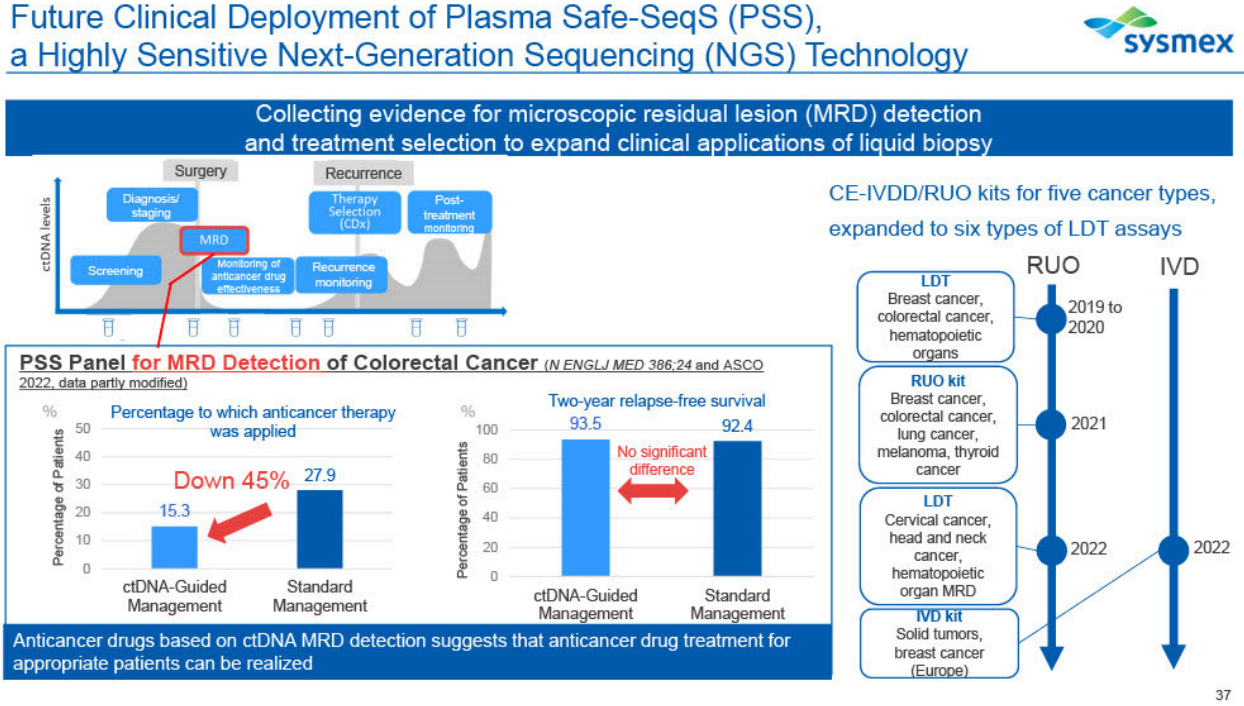
This document shows that how this system can be used for treatment and postoperative monitoring of cancer patients, here today we are showing colorectal cancer.

I will talk mainly about this MRD on the right side of the surgery. The key point is whether cell-free DNA that flows out of micro lesions that were not surgically removed after surgery can be detected properly.

The key to our technology is that we can extract DNA using 2 mm to 4 mm crystals, quantify it, and then use reagent kits to detect it with certainty. Compared to previous NGS methods, the Plasma Safe-Seqs system (bottom right) can detect with a sensitivity two orders of magnitude higher, 0.01%.

Let me go back to the principle of Plasma Safe-Seq. When we look at a gene, we use various tags called UIDs. This is a special system that allows us to understand if the mutation is simply a PCR error or if the mutation is really present in the patient. This is the reason for the high sensitivity of the system.

The important point is that using this method, we are now able to detect alleles at the 0.01% level for the 13% of cases where we could not detect alleles at the 0.1% level or lower.



Next, please. Here is the actual clinical data reported at a conference.

Top left, at the micro lesions called MRD. According to ASCO data from last year, 2022, in the PSS panel for MRD detection of colorectal cancer, standard treatment guidelines required anticancer drugs to be administered to 27.9% of patients, while using our system, the percentage was reduced to 15.3%, a 45% reduction.

In fact, when we compared whether the patients relapsed or not for two years, there was no significant difference as shown on the right side, which leads us to the fact that we were able to avoid unnecessary administration of anticancer drugs.

Today, I talked about colorectal cancer, but we are currently developing the CE-IVDD/RUO kit for five types of cancer and 6 types of LDT assays, and we are planning to announce them overseas as we obtain more clinical data.

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

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

Inherited retinal dystrophy (IRD)

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

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

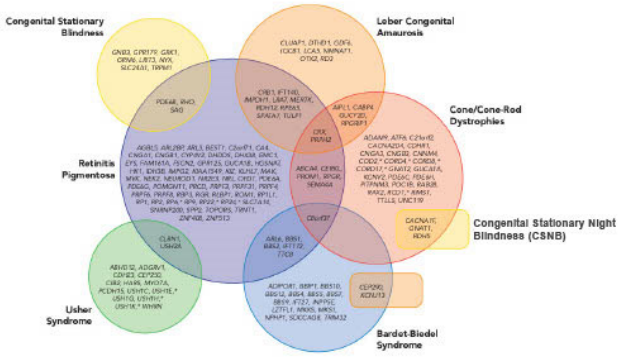
Field of vision of a normal person

Field of vision of an IRD patient

Resource; NIH National Eye Institute

Need for a multigene panel

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



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

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Next, please. Finally, I will discuss the development of genomic medicine for inherited retinal dystrophy.

IRD, inherited retinal dystrophy, is an inherited, intractable disease that causes gradual narrowing of the visual field. There are approximately 300 known causative genes, and the disease differs depending on the combination of these genes. Therefore, it is important to have comprehensive genetic information on what mutations are present in order to develop low vision care plans, etc.

Under PMDA review : JAPAN

Genetic Panel Testing System for Inherited Retinal Dystrophy

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

Existing gene panel testing assets

Gene mutation analysis set (for cancer genomic profiling)

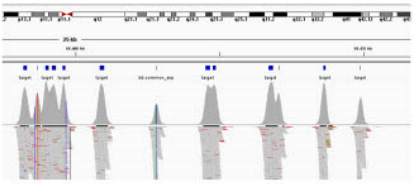
OncoGuide™ NCC Oncopanel System

CytoSure SureSeq

rikengenesis

Expert panel support system OncoGuide™ NET

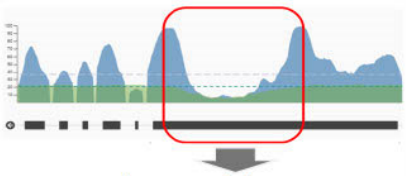
Panel system for inherited retinal dystrophy



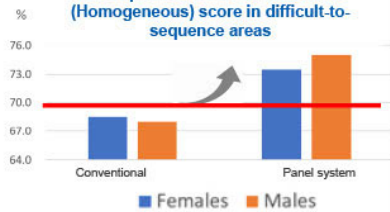
Extraction and mutation analysis of **about 80 genes** associated with disease

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

difficult-to-sequence regions with whole-exon testing



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



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Next, please. One of our gene panel assets is the NCC OncoPanel system. We will use this asset to further extract about 80 genes that will be needed.

In addition, we have a gene capture system, a machine learning technology called boosting, and a technology called tiling, in which primers are carefully arranged like tiles to eliminate unreadable areas. By using these technologies, we have been able to further improve the uniformity of the product compared to conventional products, and this picture shows that we have been able to bring the product to a level that meets the expectations of patients.

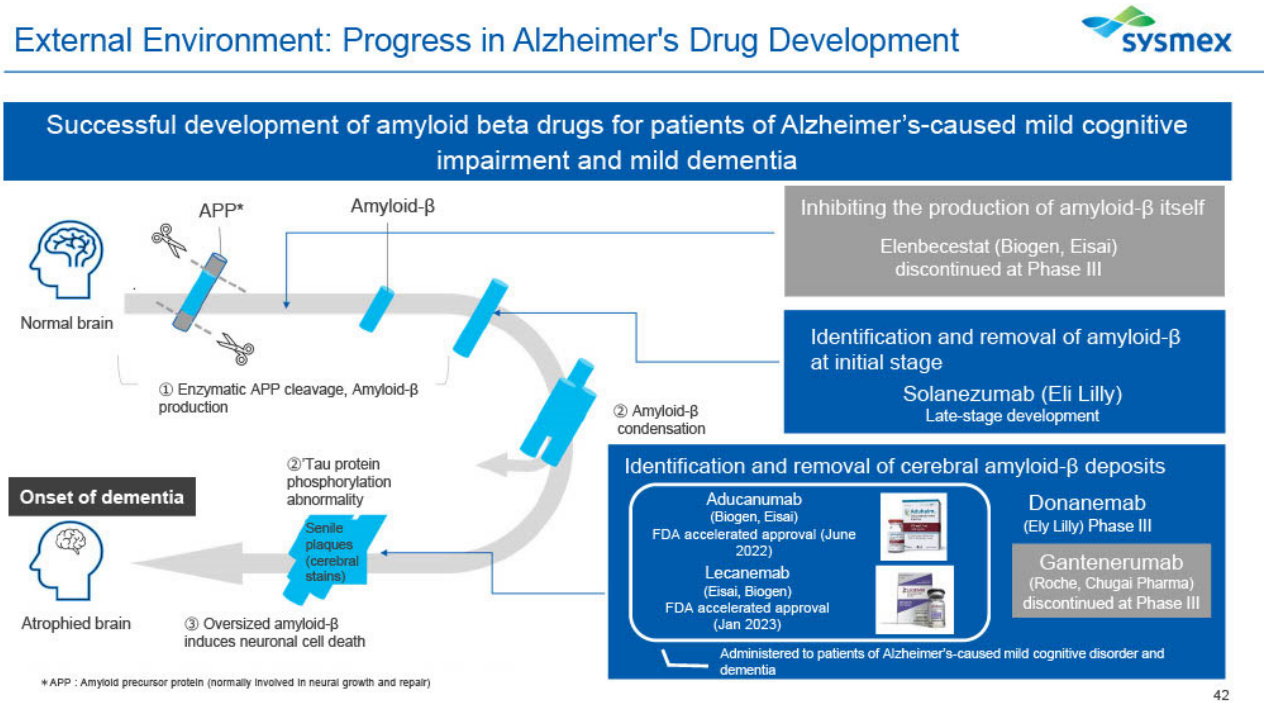
In the areas of immunochemistry reagents, genetic technology, and reagents that I have explained, we are always working on cutting-edge technologies and hope to capture the market by striving to make these technologies useful to patients. That is all. Thank you very much.

Moderator: Mr. Ohashi, please be seated.

Now then, Mr. Yoshida, please start.

Yoshida: Hello, everyone, I am Yoshida.

I would like to explain the amyloid-β test reagents that have been approved for production, especially for the diagnosis of diseases of the central nervous system, as introduced by Mr. Asano, and how they will change with the enhancement of treatment methods, as well as the future approach to liquid biopsy in a larger sense.



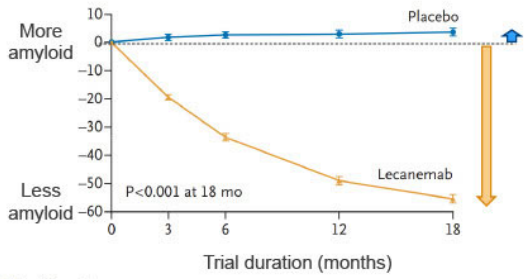
Next, please. First is this slide of the external environment.

As you all know, one of the factors in the development of Alzheimer's disease is known to be the progression of abnormal aggregation of amyloid-β. Drugs targeting each have been developed and researched, and there has been controversy over whether those drugs really work or not.

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

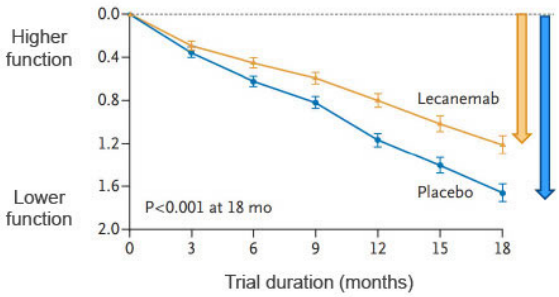
Early and accurate detection of the state of cerebral amyloid-β deposits is important for treatment

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



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

■ Relation between cognitive function and trial duration



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

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

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Next slide, please. As shown on the left side of the slide, disease-modifying drugs that target Aβ can reduce Aβ in the brain. Furthermore, data have shown that such things inhibit cognitive decline.

The data suggest that how early and accurately the state of amyloid-β accumulation in the brain is found is critical for treatment.

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

Blood (plasma): Aβ42, Aβ40, Aβ composite, p-Tau181, p-Tau217
- Mass spectrometry systems : C2N, Shimadzu Corporation
- Fully automated immunoassay systems : **Sysmex（HISCL）**、Roche* FUJIREBIO*

*Research stage

Sensitivity, specificity, quantitativity

Minimal invasiveness, convenience, standardization

Minimal invasiveness, convenience

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

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

Quantitativity, objectivity

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

Minimal invasiveness, convenience

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

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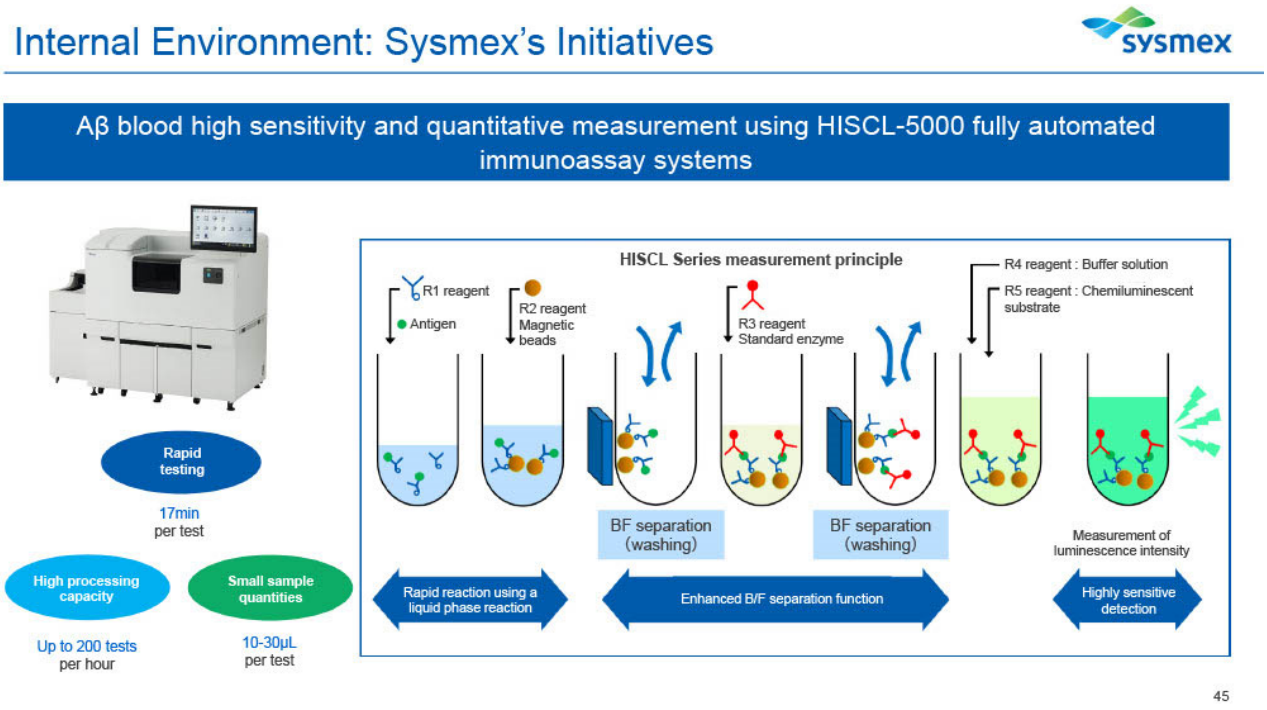
Next slide, please. On the other hand, along with research on the development of such therapeutic agents, methods for testing Aβ in the brain have been developed and studied. As you can see in the middle of the slide, imaging tests such as amyloid PET and tau PET have been developed.

In addition, there are also video analysis, and tests of functions such as verbal cognitive function analysis, as well as component tests centered on spinal fluid.

For the past several years, we have been researching methods to properly measure these biomarkers of dementia in blood, as highlighted in blue in the upper part of the slide, and, of course, we have been comparing them with those developed by other companies.



Next slide, please. This is a description of the principle of HISCL, a fully automated immunoassay system that can be used in our clinical laboratories, as I have explained.

As shown here, HISCL has a high throughput of 17 minutes per test and uses a small sample volume, approximately 10 to 30 microliters of crystals per test.

As shown in the illustration on the right side of the slide, we have been able to obtain and prove high sensitivity and quantification of Aβ in blood by, as Mr. Ohashi explained earlier, adding innovations to obtain higher sensitivity in existing molecules and reduce background noise.

Internal Environment: Performance and HISCL Series Technological Features

Manufacturer or University	Specimen type	Measurement principle / markers	AUROC	Sensitivity	Specificity
Shimadzu Corporation*1	Blood	Mass spectrometry Aβ40, 42, APP669-711 combination	0.91	0.86	0.82
Washington University*1	Blood	Mass spectrometry Aβ42/40 ratio	0.88	0.88	0.76
C2N Diagnostic*1	Blood	Mass spectrometry Aβ42/40 ratio	0.81	-	-
Roche*1	Blood	Immunoassay Aβ42/40 ratio	0.77	0.75	0.72
FUJIREBIO*1	CSF	Immunoassay Aβ42/40 ratio	0.86	0.82	0.82
Sysmex*2	**Blood**	**Immunoassay Aβ42/40 ratio**	**0.86**	**0.88**	**0.72**

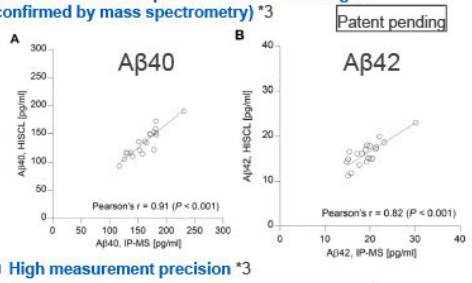
HISCL Series Technological Features

■ Unique antibody combination

■ Fully automated

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

Patent pending



■ High measurement precision *3

	Measurement precision(%)
Aβ40	< 4.6
Aβ42	< 5.3

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

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Next slide, please. This is a list of the results of the study up to that point.

The upper part shows the results of other companies and the results reported in papers. The performance of SYSMEX's HISCL in terms of the ratio of Aβ42 and Aβ40 is almost comparable to that of other companies, and we have also compared these technical characteristics in various ways.

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

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

News

Press Release

Dec. 22, 2022

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

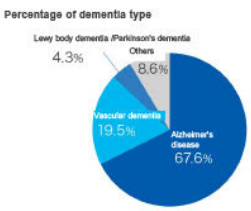
– Measurement of Plasma Aβ Using Automated Immunoassay System HISCL™-5000/HISCL™-800 –

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

Unprecedented experience in challenging research and product development process

Contribution to progress in healthy life, and aging society

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



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

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Next, please. As a result, we were able to obtain manufacturing and marketing approval for Aβ40 and 42 reagents in December of last year.

This was a challenging technical trial for SYSMEX, and in the product development process, with the help of doctors from various medical institutions and our partner companies, we were able to prove this by utilizing many clinical specimens.

As shown on the right side of the slide, we believe that this is a major first step in contributing to the advancement of healthy life expectancy and to the aging society that we are facing on a global scale.

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

Eisai Biogen

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

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

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

Eisai Biogen

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

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

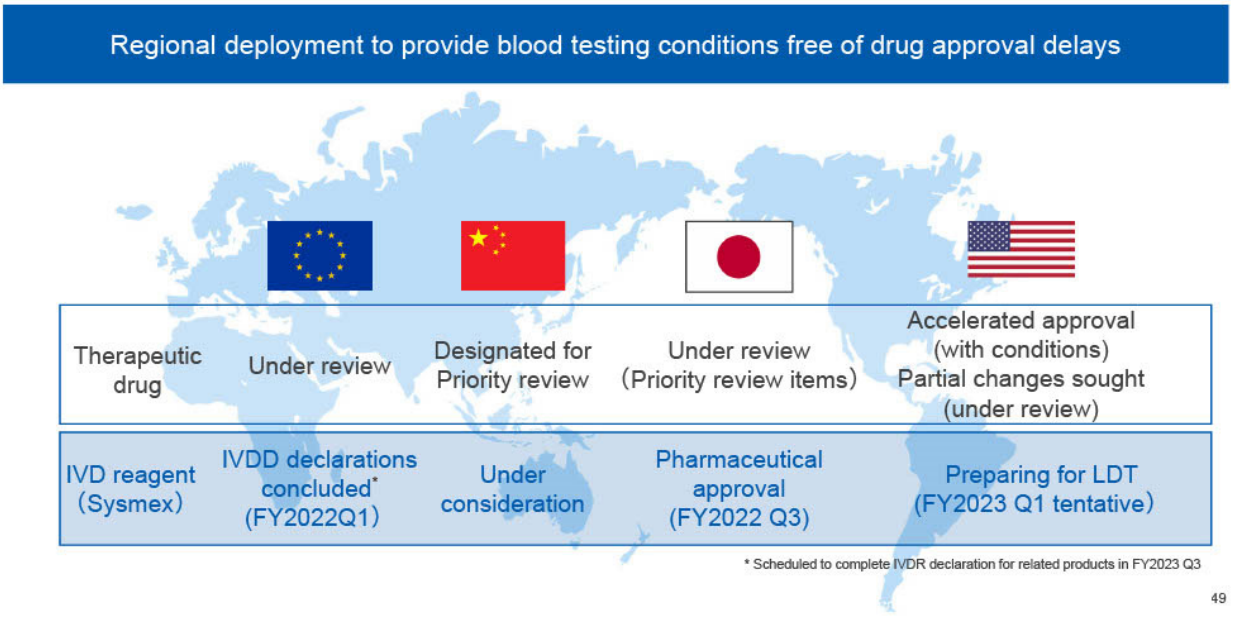
This application is based on the results of the Phase III Clarity AD study and Phase IIb clinical study (Study 201), which demonstrated the lecanemab treatment showed a reduction of clinical decline in early AD. Prior to submitting this application, Eisai utilized the prior assessment consultation system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

Resource: Eisai Co.,Ltd website

Next, please. Also, about two weeks after we received the manufacturing approval, there was big news for us and for all of you. The clinical implementation of the drug has been steadily moving forward.

These are the Eisai press releases; FDA related press release on the left side of the slide, and then the status in Japan on the right side of the slide.

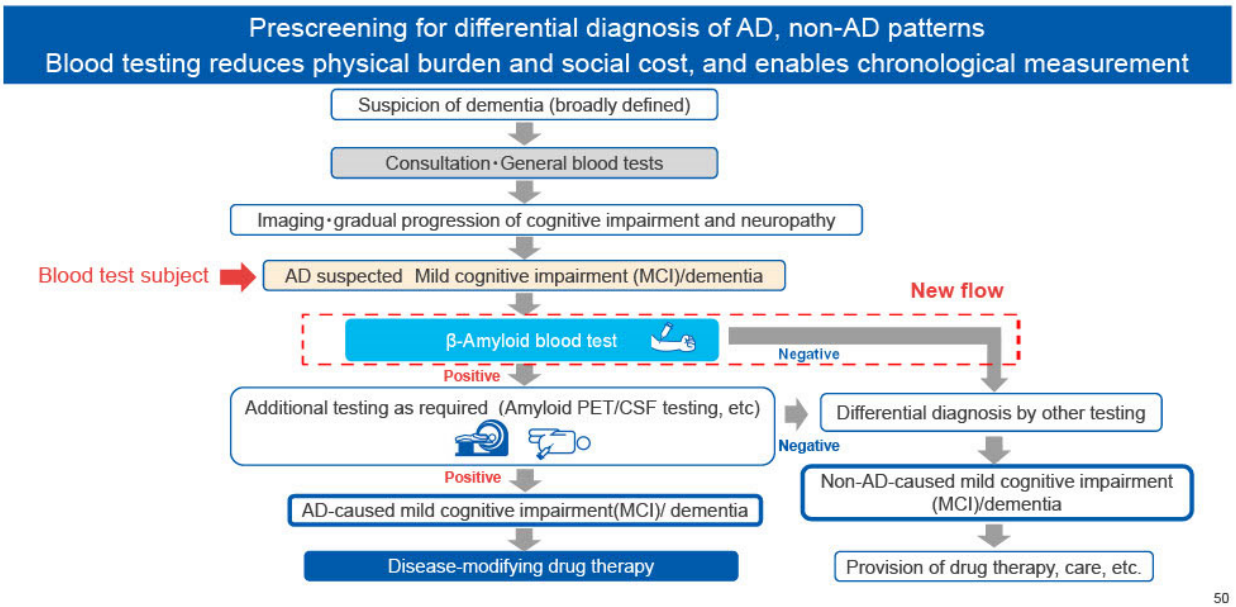
Global Status of Dementia Treatment and Diagnosis



Next slide please. In these areas, global development of treatment and diagnosis of dementia is expected. Here is an example.

It is said that, after expedited approval in the US, the review process will proceed with priority in Europe, China, and Japan. SYSMEX will promote early market introduction measures tailored to the characteristics of each region in order to provide this blood test environment without delay in the approval of therapeutic drugs.

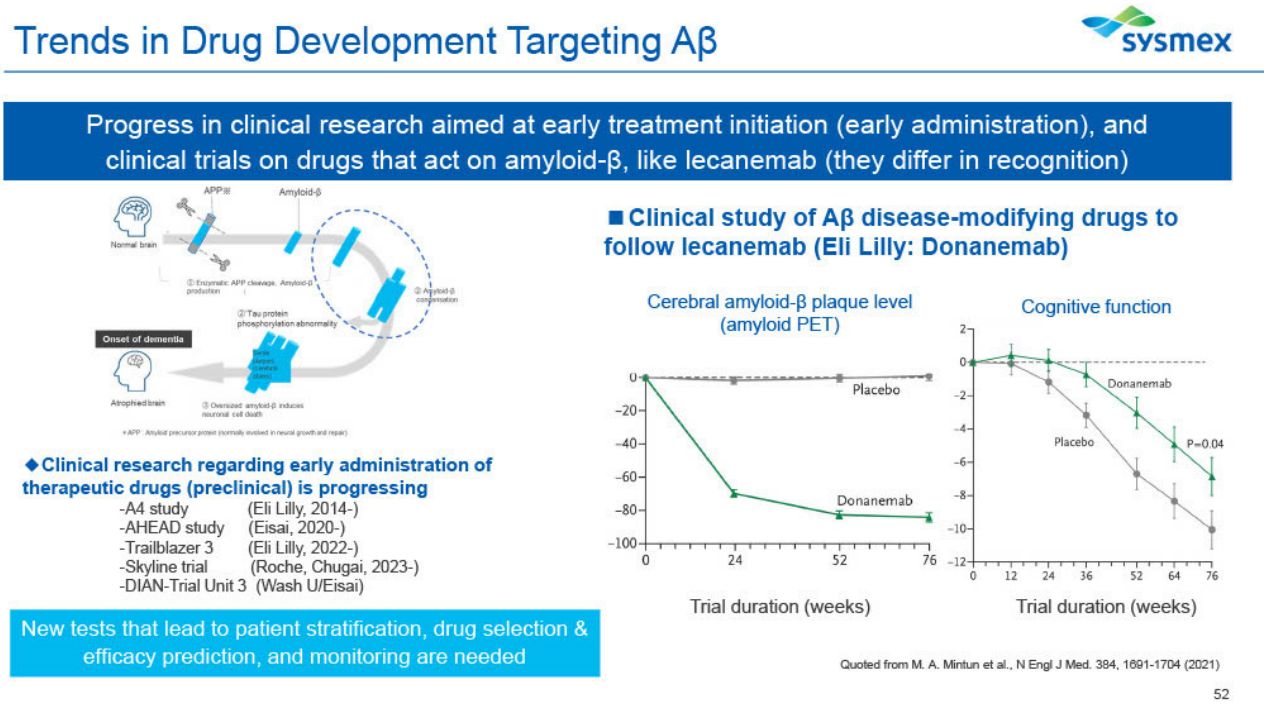
Image of the Flow of Alzheimer's Disease (AD) Diagnosis Using Aβ Blood Test



The next slide shows how these treatments are used.

If the diagnosis of Alzheimer's disease is made using the Aβ blood test, and finally, if treatment with disease-modifying drugs, which has not been available until now, becomes available, we would like to offer this blood test to patients with mild dementia or suspected dementia who are suspected of having AD.

We believe that by proceeding to the more precise tests afterwards, such as amyloid PET, it will be possible to reduce the physical burden and social costs. In addition, we believe that the disease status of those who test negative can be monitored over time.



Next, please. After the provision of medical care that complements and satisfies the diagnosis and treatment of dementia, the next step is envisioned.

The blue dotted circle on the left side of the slide indicates that clinical research is underway to develop Aβ-targeting drugs for the treatment of early-stage disease without subjective symptoms, in other words, for the prevention of malignant transformation.

In other words, we believe that new tests will be necessary for stratification of patients, selection of therapeutic agents, and predictive monitoring of efficacy. Also, as you can see on the left side of the slide, the Aβ disease-modifying drugs that will follow Lecanemab will require some kind of indicator of amyloid-β accumulation in the brain, as well as improvement in cognitive function.

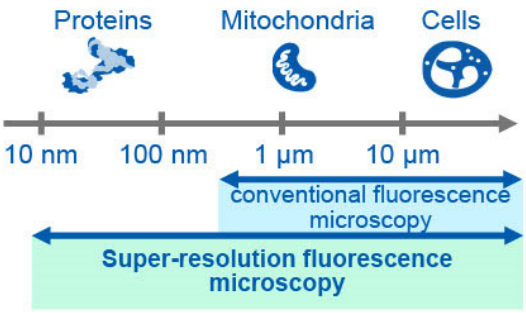
Undertakings Utilizing Treatment Research

sysmex

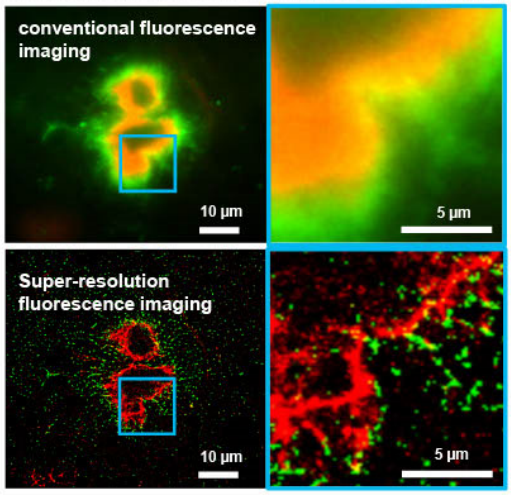
Devising a measurement system that enables detailed evaluation of Aβ aggregates (oligomers and protofibrils), which are targets of disease-modifying drugs

Single Molecule Fluorescence Microscope For Research Use
HM-1000

Image resolution (spatial resolution)



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



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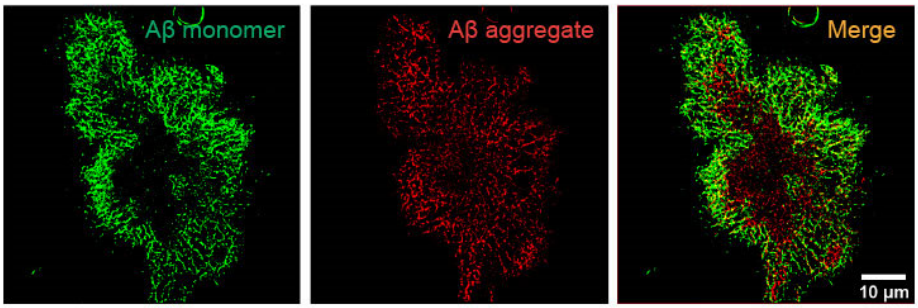
Next, please. In order to link the subject to such a therapeutic agent to a diagnosis, it is important to know what kind of Aβ is being captured in the brain.

This is an image of each of the super-resolution microscopes we have developed so far, and we have constructed a system that can measure which antibodies reflect the state of the brain under which conditions.

Visualization of Aβ Aggregate Distribution in Mouse Brain Amyloid Plaques

sysmex

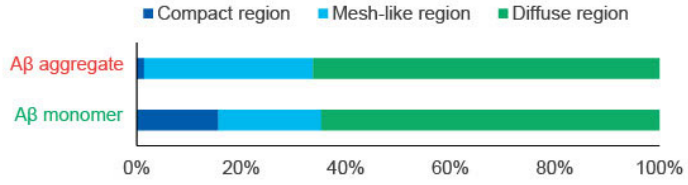
Difference in staining and aggregation density between Aβ monomers and Aβ aggregates confirmed. Enables detailed analysis of the characteristics of new therapeutic drugs for future approval



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

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

Diffuse region:
The area other than above.



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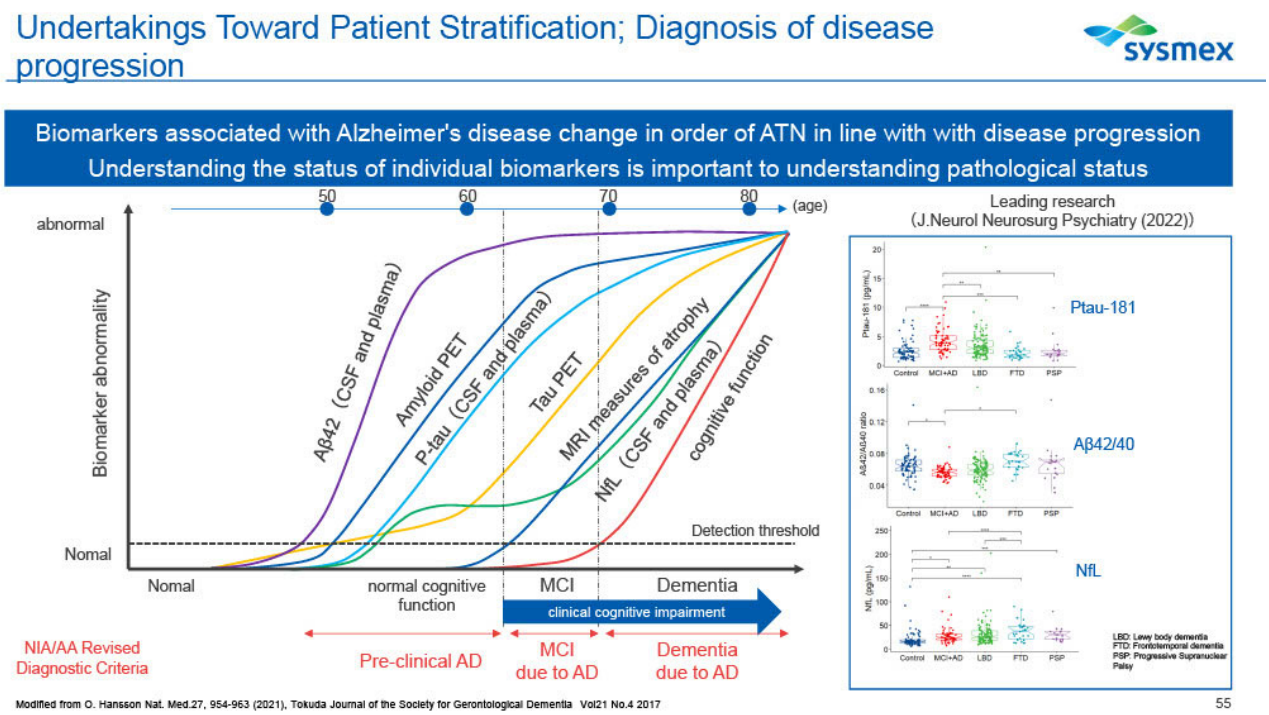
Next, please. This is the latest data available. These monomers of Aβ are present.

In addition to this green signal, we believe that our system can also be used to study how Aβ aggregates are distributed within the aggregates and how such symptoms develop.

We also believe that this kind of imaging analysis will be possible for our antibodies, antibodies developed by other companies, and antibody drugs.

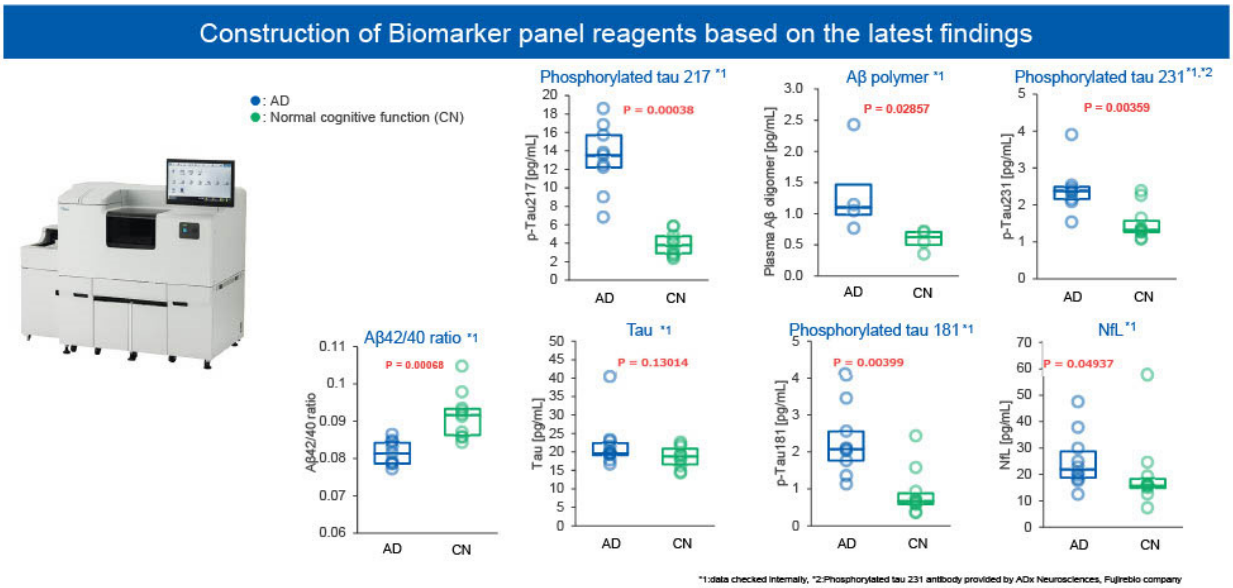


Next slide, please. These studies lead to patient stratification, which is, in other words, the state of progression of the disease. We believe that this will help us understand how the patient is in the situation.

On the left side of this slide is a hypothetical model, in which various tests and studies have been conducted to determine what to look for when Alzheimer's disease develops, with or without symptoms, at the ages of 50, 60, 70, and 80 years old, respectively.

As an example, on the right side of the slide, you can see the results of studies on phosphorylated tau, Aβ40 and Aβ42 ratios, and cranial nerve loss proteins such as NfL. These classifications have been validated in a variety of diseases.

Expansion of Blood Biomarker Panel Items



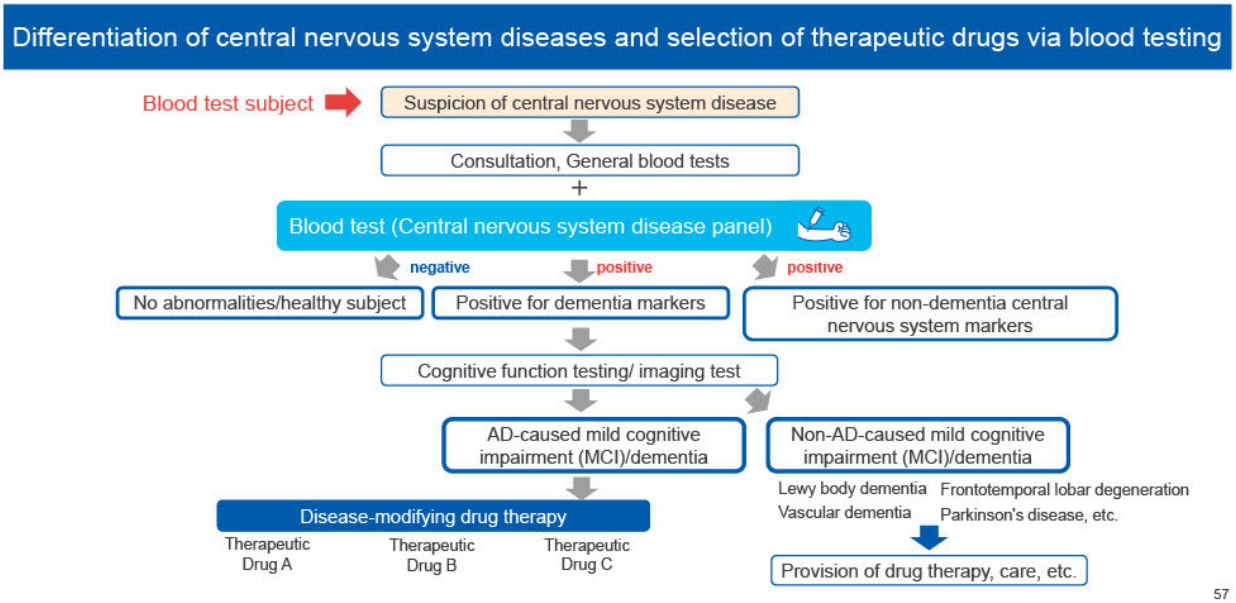
Next slide, please. In order to respond to such a situation, we still have to consider blood biomarkers as a panel.

In addition, it is necessary to understand how to incorporate the latest findings and the significance of each molecule in future research and clinical conditions. We believe that HISCL can be used for this purpose.

As I explained earlier in the characteristics of HISCL, we envision the development of these panelized reagents based on the concept of how to detect a large number of seemingly small substances in the blood plasma of patients.

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

sysmex

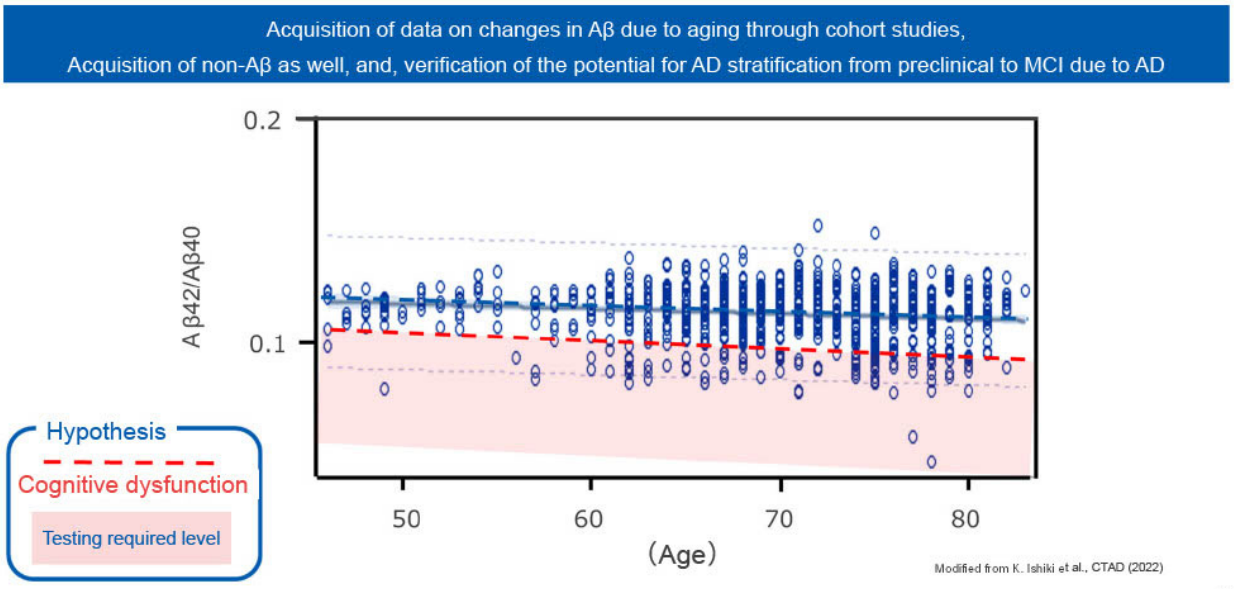


Next slide, please. As research on diagnostic reagents, therapeutic agents, and pathophysiology progresses, and more disease-modifying drugs become available, we can offer this blood test to patients who are suspected of having a disease.

We still have a lot of work to do in terms of research on the mechanism of therapeutic drugs and the development of panel, but we are confident that this is what we are aiming for.

Age-Associated Changes in Biomarkers; Understanding what Is Normal

sysmex

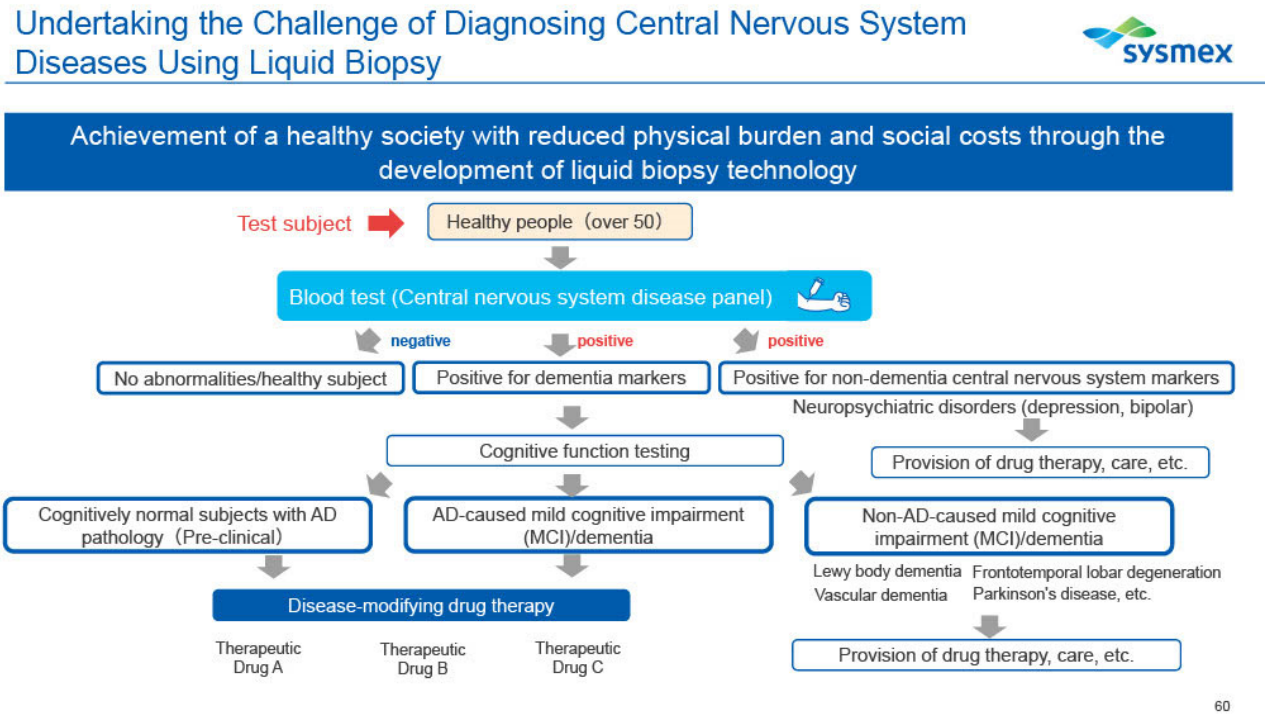


Next slide, please. I have just introduced what we are working on, but I would like to explain our efforts in anticipation of what is to come in the future.

This is the latest results from the cohort study, which was conducted in joint research. We received blood samples from 822 men aged 50 to 60, 70, and 80 years old, each of whom was considered normal. We took the data in order to understand how Aβ42 and 40 behave in these people.

Hypothetically, we believe that patients who need to be tested can be selected from the dotted line where we have drawn a dotted line indicating cognitive dysfunction. Of course, we still need to continue to look at this, but we are beginning to get a clearer picture of these points.

Furthermore, each point, each one shows a different patient, and we need to follow these people to see how they change. We also believe that we can look at normal aging points in the 50s, 60s, 70s, and 80s.



Next slide, please. Finally, I would like to discuss liquid biopsy.

We believe that by developing research to understand the state of the brain, we will be able to offer testing to healthy people. In other words, blood tests can be used to assess risk, of course. Furthermore, for those who are diagnosed as having no abnormalities, the test can be used to monitor their risk.

Naturally, we can also provide appropriate treatment for patients who test positive for those dementia markers. And we could also provide monitoring with respect to that treatment effect as well.

Furthermore, by adding biomarkers that have been obtained through this kind of research, we can also add to the list of neuropsychiatric disorders, as you can see on the right side of this slide. We would like to deploy the blood-based liquid biopsy technology for depression and bipolar disorders, which are the next social issues to be addressed.

Thank you for your attention.

[END]