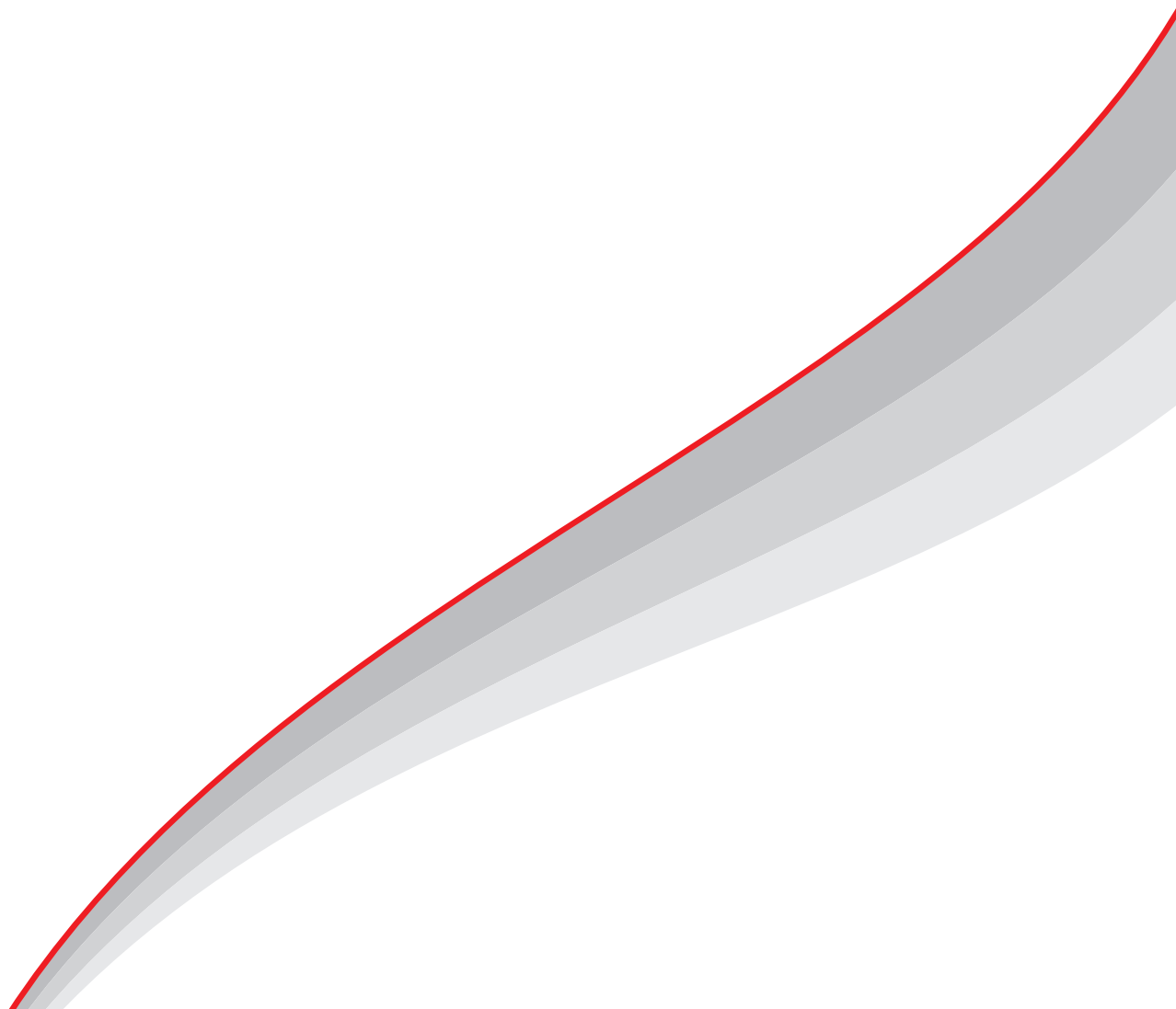


Collaborative Research & Development for Advanced Healthcare



Developing Technology for Current and Future Challenges

— Pioneering Partnerships for Advanced Healthcare —

As society enters an era of aging demographics, there is a growing concern about how to maintain health at these advanced ages.

Maintaining a healthy lifestyle as long as possible involves prevention, ultra-early diagnosis, medical treatment that minimizes the burden on the body and mind, and managing prognosis appropriately.

How can Shimadzu Corporation help?

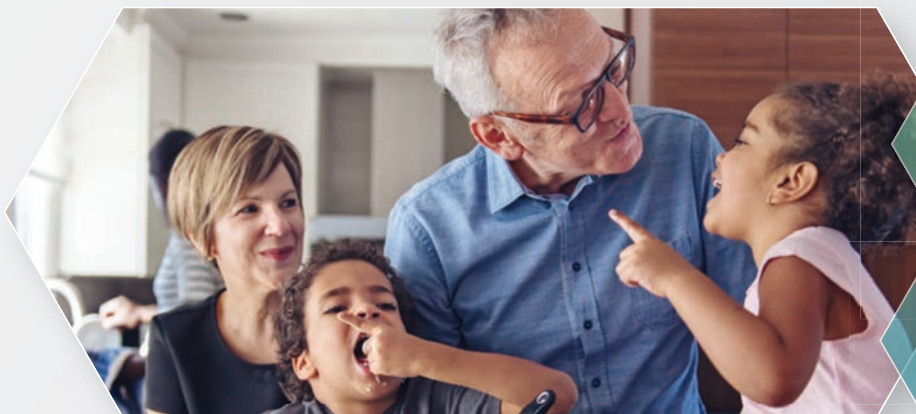
As a pioneer in diagnostic X-ray imaging and a leader in mass spectrometry, Shimadzu has been working daily with researchers to develop solutions that will significantly change the future of healthcare, based on visualization using our medical and imaging technology and quantitative analysis using mass spectrometers.

Moving forward, we will continue to collaborate with pioneering researchers in efforts to develop solutions that extend healthy life expectancies and positively impact the healthcare environment of the future.



Ultra-early
Examination

Diagnosis



Dementia

P. 4 –

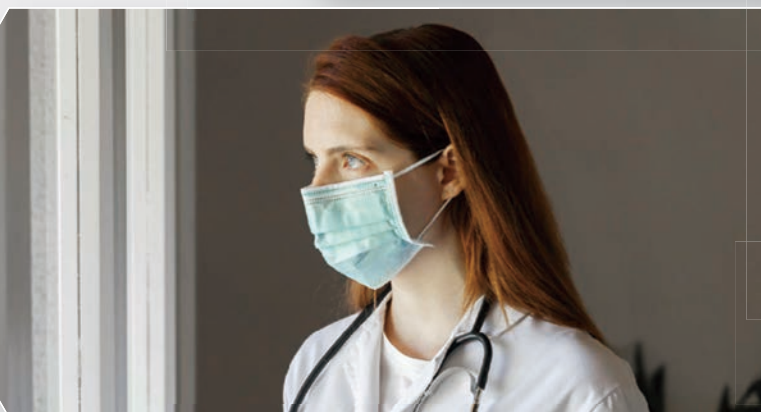
Cancers

P. 6 –



Infection

P. 8 –



Lifestyle
Disease
Bone
Health

P. 10 –



Treatment

Prognostic
Management

From Ultra-early Diagnostics to Prognosis Management of Dementia



Despite the wide variety of research being conducted around the world to determine the causes and mechanisms involved in dementia, most of that research has not resulted in discovering fundamental therapeutics for treating dementia. It is important to discover dementia early, slow its progression, and mitigate its symptoms. For future research, it is essential that patients get examined as early as possible and that symptoms get diagnosed accurately.

Using Shimadzu's analytical science and medical diagnostic imaging technologies, we aim to offer new solutions for the entire healthcare cycle, from ultra-early diagnostics and diagnosis to treatment and prognosis.

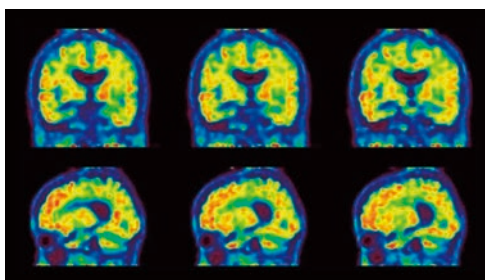
Ultra-early
Examination



Predicting Amyloid-beta Deposition Levels in the Brain from a Blood Test

Shimadzu is developing technology for predicting the accumulation of amyloid-beta deposition in the brain based on results from using mass spectrometry to measure amyloid-beta quantities in a few drops of blood (about 0.5 mL).

Diagnosis



Visualizing Amyloid-beta Deposition in the Brain using PET Imaging

High-performance PET scanning can be used to visualize amyloid-beta deposition in the brain. It contributes to future research of dementia and drug discovery.

Treatment

Prognostic
Management



Evaluating Cognitive Function by Optical Brain Function Imaging

Functional near-infrared spectroscopy (fNIRS) can measure cognitive brain activities in a setting similar to daily life.

Alzheimer's Drug Discovery Support

With Alzheimer's disease, which accounts for more than 60 % of dementia cases, it is said that beta-amyloid starts to accumulate in the brain from about 20 years before the occurrence of symptoms. PET imaging and examination of cerebrospinal fluid (CSF) are used to estimate the extent of accumulation of beta-amyloid. However, there are issues with these tests, such as the limited number of facilities capable of performing them, the high cost of the tests, and the physical burden due to the invasiveness, etc.

Blood Biomarker for Alzheimer's Beta-Amyloid Deposit

Mass spectrometry was used to successfully discover 22 biomarkers, including 8 newly discovered biomarkers. During that process, we also discovered that the ratio between two biomarkers, A β 1-42 and APP669-711, correlates to the progression of Alzheimer's disease.

Mechanism of IP-MS Method

IP-MS combines immunoprecipitation (IP), which achieves selective separation based on an antigen-antibody reaction, with mass spectrometry (MS). In this case, an anti-beta amyloid monoclonal antibody was used to extract beta-amyloids from blood plasma, with the beta-amyloids measured using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF MS).

(1) React the magnetic beads bound to anti-beta amyloid antibodies with the blood plasma sample.

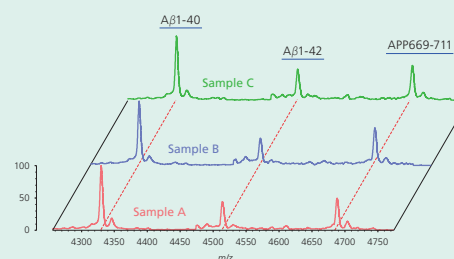
(2) Elute the beta-amyloid in the blood plasma from the magnetic beads.

(3) Analyze the eluate solution in the MALDI-TOF MS system.

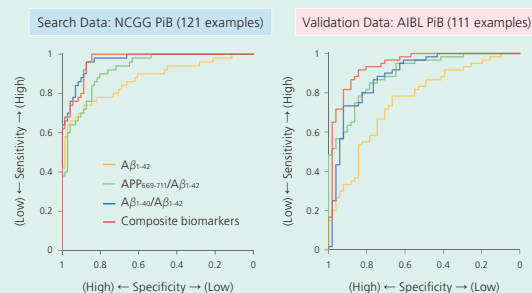
The results of this research were published in Nature volume 554, pages 249 to 254 (2018) "High performance plasma amyloid- β biomarkers for Alzheimer's disease" (doi:10.1038/nature25456).

MALDI-TOF MS for Estimating the Beta-Amyloid Deposition Level in the Brain

This system enables many types of beta-amyloids to be characterized and simultaneously detected with high sensitivity by analyzing only 0.5 mL of blood plasma. Of these beta-amyloids, A β 1-42, A β 1-40, and APP669-711 can be used in combination as biomarkers to estimate the deposition level with high accuracy.



MALDI-TOF MS Mass Spectra



Note: Offered as contract analysis service (only in Japan).
FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.

Joint Research Partner



The Florey Institute,
The University of Melbourne
Prof. Colin L Masters

For more than 30 years, academics have been looking for a test that has high performance in predicting the development of Alzheimer's disease. This is one of the great unmet needs of our society. If a test that only requires taking a few drops of blood with just a minimal invasion really performs well, it will allow the early detection of Alzheimer's disease and assist in developing new therapeutics. SHIMADZU has a long history and a reputation of doing excellent work in developing high performance analytical technology. I'm very confident that this partnership between Industry and Academia is the only way that we can make real progress in this field.

Aiming for Early Detection of Cancer and More Effective Treatment



As people's lives have extended, the number of cancer cases has increased, and the disease has become familiar to everyone. On the other hand, great progress has been made in the diagnosis and treatment of cancer, and the probability of surviving cancer has also increased.

Shimadzu is supporting not only early detection and diagnosis of cancer, but also treatment methods and research using various technologies, such as near-infrared photoimmunotherapy, which is a promising new cancer treatment method.



Early Screening Methods for Colon Cancer (Kobe University and Shimadzu Corporation)

Multi-biomarkers that can be used for diagnosing colon cancer were discovered from metabolomic analysis. The diagnostic predictive algorithms created based on those research-use-only biomarkers have been shown to maintain high sensitivity, even for early-stage colon cancer patients. The ability to measure the biomarkers with minimally invasive blood tests means there is hope for the possibility of screening patients in a clinic, for example, without the effects of bleeding during examinations.

Note: These measures are still currently in research and development.
FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.

Diagnostic Support for Breast Cancer

Using TOF-PET technology, which aims to provide painless examination for breast cancer, the physical burden associated with the examination is reduced, and the information obtained from the high-accuracy detailed images supports the treatment of breast cancer.

Shimadzu's Contributions to the Basic Cancer Treatment Methods

- **Surgical methods**
Near-infrared fluorescence imaging systems are used for visualizing lymph vessels and blood vessels, supporting diagnosis of metastasis and surgical procedures. Also, the technology for analyzing tissue extracted during an operation by ionization mass spectrometry using a probe contributes to rapid pathology diagnosis.
- **Radiotherapy**
Instruments that track the movement of the tumor position due to respiratory motion support X-ray irradiation at the correct position, and together with the treatment system support smooth procedure.
- **Chemotherapy**
Our cutting-edge mass spectrometry technology supports the measurement of anticancer drug levels in the blood and biomarker research.

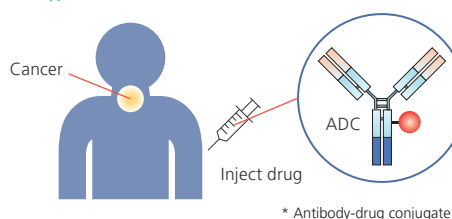
In addition, we are engaged in joint research on near-infrared photoimmunotherapy, a new type of cancer treatment.

Support for Cancer Photoimmunotherapy Research

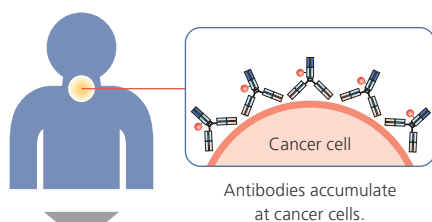
Cancer photoimmunotherapy is a new treatment technique that involves selectively binding the antibody portion of a therapeutic drug to proteins found in excess on the surface of cancer cells and then killing only the cancer cells by irradiating the area with near-infrared light, so that the photosensitive portion of the therapeutic drug reacts with the light. This treatment method also helps the immune system to attack cancer cells by stimulating immune cells, so clinical application to some head and neck cancers has begun. Shimadzu is working with the U.S. National Cancer Institute to conduct R&D on measuring instruments for evaluating and improving the safety and therapeutic effect of the near-infrared photoimmunotherapy for cancer. During the basic research, a near-infrared fluorescence imaging system was used to create a system for evaluating the therapeutic effect in real time.

Mechanism of Cancer Photoimmunotherapy

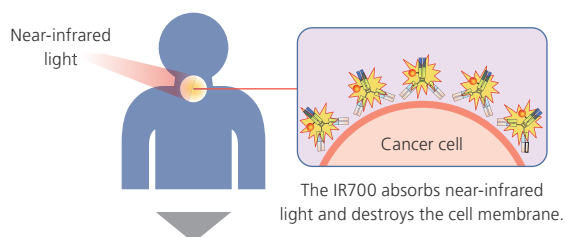
- (1) A therapeutic drug conjugate, with antibodies bound to a photosensitive chemical substance (IR700), is administered.



- (2) The therapeutic drug accumulates only at proteins uniquely present on the surface of cancer cells.



- (3) Near-infrared light irradiation activates the chemical substance, which destroys the cancer cells.



- (4) Excitation light from the chemical substance attenuates.

Near-Infrared Fluorescence Imaging System for Visualizing Progression of Chemical Reaction to Near-Infrared Light

This system creates an image of the chemical reaction to the near-infrared light applied during treatment, and evaluates and records the therapeutic effects.



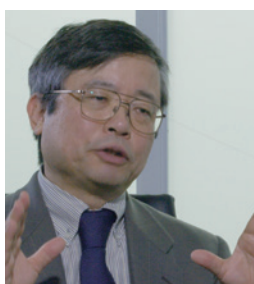
Mass Spectrometer for Confirming Therapeutic Effects Based on Urine and Blood Analysis

We are searching for a metabolomic method of evaluating therapeutic effects.



Note: These measures are still currently in research and development.

Joint Research Partner



U.S. National Cancer Institute,
National Institutes of Health
Dr. Hisataka Kobayashi

Trying to be effective without damaging the body is the concept of NIR-PIT. It can selectively kill cancer cells without damaging or killing many normal cells. Also, this therapy can decrease the number of cancer cells and then increase and activate the host immunity to better fight the cancer. SHIMADZU has the strength in chemistry and we have the strength in biology. That is the reason why we have a very good collaboration in this research.

Confronting Infectious Diseases



The spread of COVID-19 had a great impact throughout the world, and in medical practice, vaccines and therapeutic drugs were rapidly developed through the efforts of many medical practitioners and researchers in testing and treatment. Shimadzu considers the spread of infectious diseases to be a major social issue, and supports all those battling the new infectious disease with science and technology, in order to support those at the frontline and to contribute to bringing the situation to an end. Also, not only do we provide our products, but we also work together with universities, hospitals, and medical institutions, with the aim of creating countermeasures against infectious diseases.

Ultra-early
Examination



Virus Testing

We respond to the demand for PCR testing at local facilities such as clinics, with a simple operation enabling stable data acquisition while preventing human error.

Diagnosis



Diagnosis of Pneumonia

In order to respond to the increased worldwide demand for mobile X-ray systems during the spread of COVID-19, the Shimadzu Group worked together to produce the systems and supply them to the medical institutions that were under strain.

Treatment



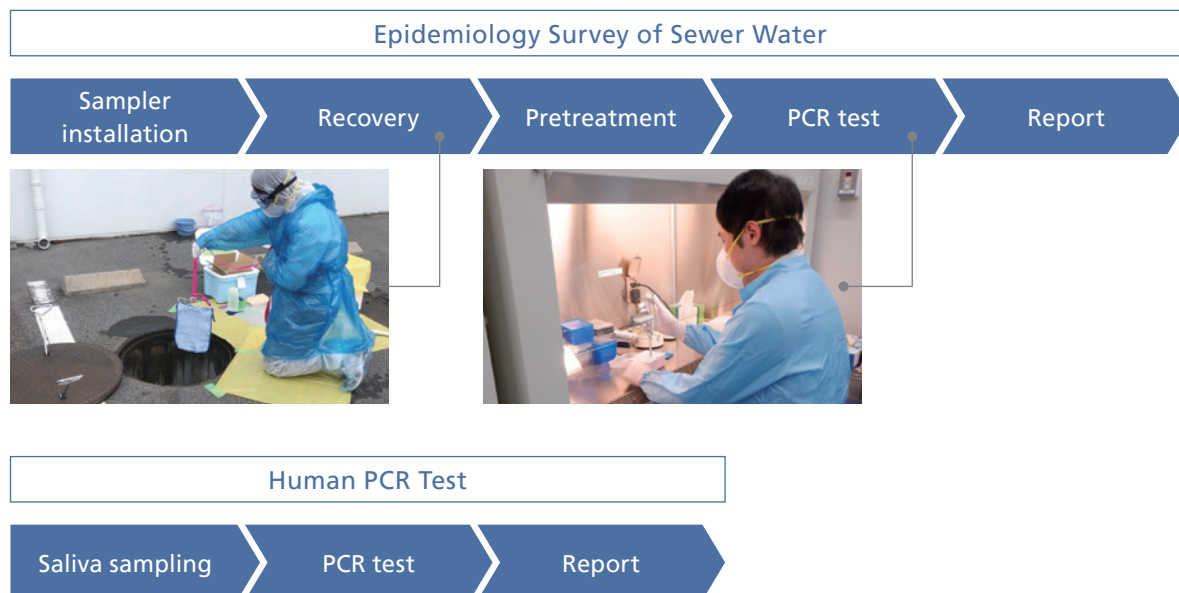
Analysis and Research of Drugs

Alsachim, a Shimadzu Group company in France, developed stable isotope reagents for six types of existing drugs that were candidates for treatment of COVID-19. Stable isotope reagents are used for investigating the effects and side effects of candidate drug compounds, and their relationship to the concentration of the drug in the blood. With these stable isotope reagents and Shimadzu's analytical instruments, in particular liquid chromatograph mass spectrometers, we support the pharmaceutical companies and research institutions working to develop therapeutic drugs.

Prognostic
Management

Public Health Risk Assessment

Shimadzu and Shionogi & Co., Ltd. have established AdvanSentinel, a joint venture for the purpose of assessing public health risks beginning with monitoring sewer water. Sewer (effluent) water is monitored to enable early prediction of COVID-19 clusters in various facilities. In the future, AdvanSentinel will engage in solving other challenges in society by assessing other public health risks, including risks from other infectious diseases, and building a new infrastructure for visualizing public health risks.



Industry-Academia Collaboration on Infectious Diseases

Developing Techniques for Testing for the Novel Coronavirus Using Breath Samples

Through collaborative research with Tohoku University, Shimadzu has succeeded in developing a technique for coronavirus testing via "Breathomics," which uses naturally exhaled breath as a sample.



Researching Technology for Predicting Increased Severity in Coronavirus Cases Based on Blood or Urine Tests

Based on the results of collaborative research with Kumamoto University and AiSTI SCIENCE CO., Ltd., Shimadzu has developed an analysis system and method package* for measuring a group of biomarkers that appear related to the severity of a coronavirus infection.

* A method package contains all the information needed to analyze a sample for a specific application using a Shimadzu liquid chromatograph mass spectrometer.



Creating the Future of Healthcare with Partners



Shimadzu aims to provide total solutions to the healthcare field by strengthening both our technology development capabilities and ability to make these technologies available to the public. For this purpose, we continue to work on the challenges with researchers in Japan and overseas on the frontline of advanced research and development to greatly change future medical treatment.

Shimadzu is working with partners throughout the world to solve the issues in society and to offer a vision for Advanced Healthcare unlike that at present.

Bone Health — Initiatives Regarding Osteoporosis —

Osteoporosis increases with age, and it is one of the reasons why caregiving becomes necessary for the elderly. The conditions of bones can be determined by testing, and by early detection and appropriate intervention, both treatment and bone fracture risk can be reduced. For example, vitamin D, which promotes absorption of calcium and plays a role in bone health, can be measured in blood using mass spectrometry. Also, Shimadzu has developed technology using AI to conveniently realize the DXA method on X-ray images, which has been evaluated to have the highest accuracy for measurement of bone mineral density. In addition, we are providing support for vertebral measurement with the QM method, early detection of osteoporosis, and supporting evaluation of disease risk. Shimadzu has concluded a comprehensive partnership agreement with The Jikei University (Tokyo), aiming at bringing research results into clinical practice through industry-academia collaboration, including the research into bone health.

Flow of Osteoporosis Diagnosis and Shimadzu's Technologies

Blood test

Measurement of vitamin D in blood using a mass spectrometer



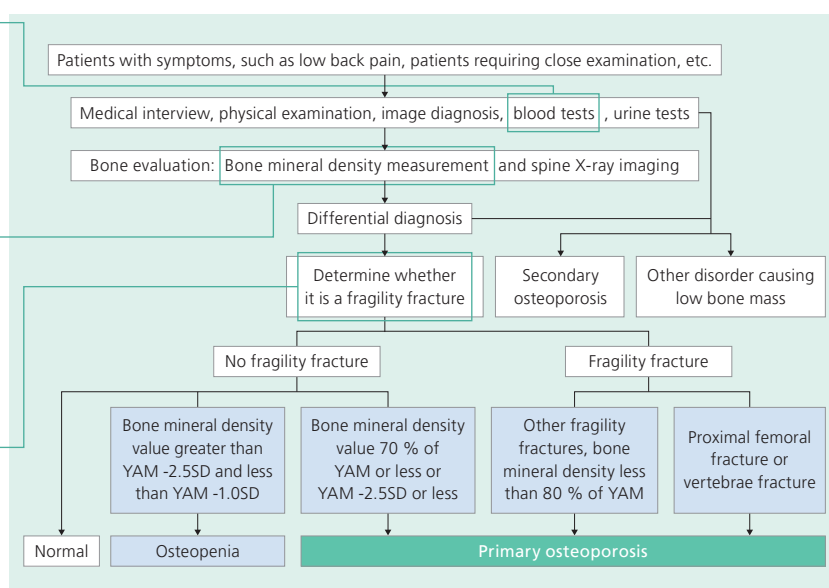
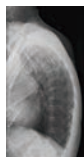
Bone mineral density measurement

Measurement of bone mineral density by the DXA method using a fluoroscopy system



Bone fracture assessment

Vertebral measurement by the QM method using a radiography system



Source: Prepared by Shimadzu based on "Guidelines for the Treatment and Prevention of Osteoporosis, 2015 Edition" (Japan)

New Initiatives Using Analytical and Measuring Technologies

Shimadzu, whose main strengths are medical diagnostic imaging systems and analytical/measuring instruments, is aiming to develop new technologies in clinical testing through synergy between the Group companies, such as Shimadzu Diagnostics Corporation (Japan) and Alsachim SAS (France) whose strengths are in technologies regarding reagents, and Shimadzu Techno-Research Inc. (Japan) which undertakes contract research.

Clinical Testing



We aim to establish new testing methods in clinical research and clinical practice by providing solutions that combine our products and reagents, mainly in the fields of mass spectrometry and genetic analysis.

Microbiological Testing



We aim to create new technologies and improve user-friendliness utilizing our experience in clinical microbiological testing, including supply of culture media for microbiological testing, detection of microorganisms that cause infectious diseases, and identifying effective antibiotic substances for treatment of infectious diseases.

Cell-Related



We provide total solutions in accordance with the culturing process, such as analytical instruments, culturing technologies, and contract analyses, for the necessary cell culturing for manufacture of biopharmaceuticals, regenerative and cellular treatments, and gene therapies.

Shimadzu Techno-Research, Inc. (Japan)

Since its founding in 1972, Shimadzu Techno-Research has actively undertaken contract analysis work using analytical technologies as its basic technologies, such as survey research work for the relevant government ministries and agencies, local public bodies, and public research organizations, environmental analysis and surveys related to company activities, material analysis, and pharmaceutical testing. Great care is taken regarding accuracy control and providing reliable data, which are vital for a contract research organization.



Shimadzu Diagnostics Corporation (Japan)

Shimadzu Diagnostics provides comprehensive services ranging from research and development to manufacture, sales, and contract analysis in fields such as clinical diagnostic drugs, industrial testing chemicals, and cell culturing. Research and development are continuously conducted for expansion of business areas and results, based on accumulated knowledge as the core and searching for new technologies through collaboration with external research organizations, with a mission to investigate advanced fields for the next generation and exploring further possibilities.



Alsachim SAS (France)

Created in 2005, Alsachim is one of the world leaders in the synthesis of stable labeled (^{13}C , ^2H , ^{15}N) internal standards, used in Bioanalysis studies, chemicals, building blocks and metabolites. Based on its expertise, Alsachim develops also Therapeutic Drug Monitoring devices to support hospitals and bioanalyze center to their daily work and routine operation. We supply our products to customers all over the world for more than 15 years, spread across the chemical discipline including the pharmaceutical and biotech industry, clinical and bio-analytical CROs, and research institutions, in areas such as Health, Food and Environment.



KYOLABS: SHIMADZU Healthcare R&D Center for Researching Advanced Solutions

The Healthcare R&D Center uses Shimadzu's technical strengths, including analytical instrument and medical diagnostic imaging technologies, to develop innovative solutions for healthcare applications. We encourage dialogue and joint research with customers in ongoing efforts to address both current and evolving challenges.

In addition to exhibiting core technologies, the Center has also the Cooperation Labs for joint research that serves to create connections between people and between people and intangible objects. Using science and technology, we help extend the healthy life expectancy of people by satisfying unmet needs.



Exhibition Area

This area is used to exhibit Shimadzu measures and technologies, mainly related to healthcare.



Co-working Labs

In these open labs, you can carry out experiments if you have an idea and want to try it out on a small experiment scale.

Gathering Area

We designed this area to offer an environment where people from inside and outside Shimadzu can get together to share activities and interests. It can also be used as an employee co-working space.



Cooperation Labs

This laboratory space is for joint development or research work with non-Shimadzu personnel who are stationed to work at the facility.



KYOLABS is a trademark of Shimadzu Corporation.



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SHIMADZU Advanced Healthcare

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