AMDD Vol.30

NEWSLETTER

May 2019

English translation of the Japanese newsletter

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Toward an Era when a Drop of Blood or Urine can be Used to Detect Cancer

Developing First-in-Japan New Technology with MicroRNA

How can Japan save its people from an increasing number of cancers in this rapidly aging society? Amid the various efforts to address this issue, there is a research project on body fluid diagnosis, titled, "Development of Diagnostic Technology for Detection of microRNA in Body Fluids" for the "early detection of cancer," in which I served as a project leader. This national project includes nine research and development institutions led by the National Cancer Center Japan and joint research with eight universities.

With about 8 billion yen of research funding from the government, the project we have been working on comprises a group of over 100 experts with a mission to detect 13 types of Stage 1 and Stage 2 cancers. Another noteworthy characteristic of the project is that four companies: Toray, Toshiba, Arkray, and Precision System Science participated to expedite commercialization of the diagnostic technology.

Body fluid diagnostics is a new dream technology launched in Japan that detects cancer in its early stages using only a drop of body fluid such as blood, saliva, urine, or tears. It detects and analyzes microRNA (consisting of about 20 nucleotides) in body fluids to diagnose cancers.

The biggest benefit of this diagnostic technology is that cost is dramatically reduced to one-tenth that of a conventional needle biopsy, which samples part of the tissue from a lesion for testing. Another benefit is its minimal invasiveness to patients. It protects patients from health damage due to CT scans, which pose radiation risks.

MicroRNA is encapsulated in a particle, called an exosome, and circulates in body fluids. It has been known that exosomes are involved in the intercellular exchange of information secreted by cancerous cells, and deeply involved in the progression and metastasis of cancer.

There are 2,655 types of microRNA, but we were able to decode all of them by using Toray's "3D-Gene" DNA chips, which are made in Japan. We completed the analyses of 53,000 samples by February 2019, including 2,400 cases of breast cancer, 3,300 cases of colon cancer, 3,200 cases of gastrointestinal cancer, and 2,700 cases of lung cancer.
The results demonstrated our high detection rates: 97% for breast cancer and 99% for ovarian cancer, and we were also able to differentiate other types of cancers from healthy cells at high rates. It is safe to say that this is an extremely effective testing method for detecting cancer.

However, some issues still remain: while it can accurately differentiate cancerous cells from healthy cells, it is difficult to differentiate benign diseases from borderline tumors. Overdiagnosis is also a problem. Thus, further refinement of the diagnostic technology is necessary.

MicroRNA has great potential, enabling stratified treatment to examine which medications work for which patient. It may be applied not only for cancers, but also for various diseases including dementia.

Future Prospects

The five-year project concluded in March 2019, and now the process to develop its practical application will start.

Japan is ahead of the rest of the world in this field, but the National Institutes of Health (NIH) in the United States has invested a massive amount of its budget in this area (over 10 billion yen) and is in hot pursuit. In Japan, four companies have been collaborating on commercialization, and microRNA is expected to be approved soon as an in vitro diagnostics (IVD). In the not-so-distant future, microRNA will be practically applied as an approach to perform primary screening in comprehensive medical checkups.

We would like to collect data from long-term follow-up on large-scale groups and verify the research results. Fukui prefecture, among others, has offered its cooperation, but it remains to be seen how the results will be verified.

Dr. Takahiro Ochiya
Ph.D. in Medicine from Osaka University Graduate School in 1988. Postdoctoral fellow at La Jolla Cancer Institute of America (now the Sanford-Burnham Medical Research Institute) in 1991. Chief Scientist at National Cancer Center Japan in 1993. Head of the Division of Molecular and Cellular Medicine, National Cancer Center Research Institute in 2010, and Project leader in 2018. Professor at Institute of Medical Science, Tokyo Medical University from April 2018 to present.

Social Security and Healthcare up to 2040

Year 2040 Problem

The year 2025 is when baby boomers will reach 75 years old or older. The government undertook comprehensive tax and social security reforms with this "Year 2025 problem" in mind by raising the consumption tax this year.

Now that the 2025 problem has been addressed, we must overcome another challenge, which is the Year 2040 problem.

Looking at changes in the demographic pyramid of Japan, the working-age population was large in the 1960's while the elderly population was small (large supporting group). In 2010, about 50 years later, two or three working-age people support one elderly person (small supporting group).

Since reaching its peak, the population of Japan has plunged into a nosedive. We are living in an era of dramatic change that we have never experienced before.

Japan's demographic composition shows the elderly population of those aged 65 years or older continues to increase despite a consistent decrease in the overall population and working-age population. The population supporting the elderly is decreasing while the elderly population is increasing. This trend will peak in 2042. For Japanese social security, the period up to 2042, when the imbalance between service demand and supply reaches a maximum, will a very challenging time. This is the "Year 2040 problem".

Looking at the ratio of social security benefits versus GDP, the growth of financial resources is expected to slow compared with the pace to date. But we can weather this slowdown by managing the economy. The most serious concern is how to secure human resources.

In an estimate of workers in 2040, the human resources needed in the area of healthcare/welfare account for nearly 19% in all areas. However, the working-age population is falling sharply, and there is a great shortage of manpower on the supply side. It is indispensable, therefore, to develop service offerings more efficiently with limited manpower.

The government put forward three pillars to tackle this issue: (1) Diversifying employment/social participation, (2) Extending the healthy lifespan, and (3) Providing Healthcare/welfare services. Of these, (2) and (3) are closely associated with healthcare/welfare. For (2), medical institutions and private businesses (sports clubs, etc.) must cooperate to alleviate the onset and aggravation of lifestyle-related diseases, and focus on the health management of citizens by providing exercise programs, extending venues available for exercise, and implementing anti-frailty measures. Pillar (3) includes training personnel to promote robots, AI, practical applications of ICT, data health reform, and task shifting; and promoting the development and active use of senior personnel.

Workstyle Reform for Physicians

Improved productivity is vital for promoting healthcare/welfare service reform. Among the major developed countries, Japan's working-age population has continued to decrease. In developed countries with higher per-capita GDP than Japan, total working hours are shorter than in Japan. Long working hours in Japan imply that productivity is low. In other words, Japanese work too much but do not work efficiently.

Such a working style, peculiar to Japanese, is prominent in the healthcare industry. Physicians are at the top of the list of occupations where weekly overtime exceeds 60 hours. Some house staff physicians work over 75 hours per week. Physicians are also workers if they are employed by hospitals. If their own health is at risk, they cannot provide reliable healthcare. Among the especially hard-working medical departments is gynecology, followed by emergency and surgery. Such hard-working physicians are concentrated in university hospitals and medical institutions with emergency care functions.

This prompted us to tackle workstyle reform for physicians: promoting physicians' health while providing the medical services needed in the region; and introducing an upper limit and restriction of working hours after reviewing years of conventional practice sustained by long working hours.

If overtime is suddenly limited to 960 hours per year in line with the general rules, it may devastate emergency healthcare. Thus, we provided a grace period of five years, during which time the upper limit of working hours is set at 1,860 hours per year. During the grace period, continuous work is limited and there should be an obligatory 9-hour interval between work shifts. If overtime exceeds the monthly upper limit, interview guidance is provided. In some cases, "doctor's orders" will be issued. Based on these proposals, we will first prioritize reducing the estimated 20,000 physicians nationwide who perform 1,860 hours of overtime to zero physicians over the next 5 years.

Streamlining work is indispensable in promoting reform. For example, surgeons, who must perform operations, should be able to delegate tasks such as outpatient care or hospital ward management to other staff. In promoting this shift to task-sharing, we recommend streamlining meetings, properly supervising attendance and absences, and strongly promoting shortened working hours. The key is to allow physicians to focus on the work that only they can perform.

At the same time, peoples' awareness must change along with workstyle reform for physicians. A patient cannot make a midnight visit to a hospital and demand a briefing for an operation on the following day; decent manners on the part of patients is also needed.

Using this opportunity of workstyle reform for physicians, I would like to overhaul the way healthcare is provided to society.

Councillor, Health, Labour and Welfare Minister's Secretariat
(In charge of health policy, industrial development of pharmaceutical products, mental healthcare, and disaster control.)
(Holding joint appointments with Health and Welfare Bureau for the Elderly, and Health Insurance Bureau)
Mr. Sakoi Masami

Graduated from Tokyo University School of Medicine in 1989. Surgeon clinician. Joined the Ministry of Health, Labour and Welfare in 1992. After studying at Harvard School of Public Health, took offices of Manager of Hiroshima Prefectural Health and Welfare Department in 2006, Health Insurance Bureau Planning Counselor, Head of Division of the Heath for the Elderly, and Head of Regional Medical Care Planning Division. Became Head of Medical Economics Division of Health Insurance Bureau in 2016. Took office in 2018 as Councillor, Health, Labour and Welfare Minister's Secretariat (incumbent).

Patients Voice:
Addressing the Status of Patients with Dystonia/Dyskinesia and Our Current Challenges

Advocate Group for Improving the Environment of Patients with Dystonia/Dyskinesia
Mr. Shuichi Kawashima
Representative

The Advocate Group for Improving the Environment of Patients with Dystonia/Dyskinesia, founded in October 2017, has been working to improve the treatment, daily living, and working environments of such patients. Dystonia is characterized by the sudden contraction of muscles, and dyskinesia, the involuntary movement of specific muscles. Both symptoms are due to abnormalities in the cerebral motor command system, resulting in uncontrolled movement of the body.

In either disease, the sites, scopes, and severity of symptoms vary depending on patients. Patients need a broad-range of related information since there are many types of symptoms in dystonia: genetic, occupational, drug-induced, secondary to other diseases, traumatic, and psychogenic; while most symptoms of dyskinesia are drug-induced. The advocate group

addresses the requests of these patients by setting up platforms on social networking sites (SNS) and mixi so that everyone can freely exchange information, and continuing to disseminate a variety of information on its website, Facebook, and Twitter. As the group communicates extensively with specialists and related parties, it has begun the process for planning and executing lobbying campaigns to related companies.

Therapies for the two diseases include discontinuation/change of causative drugs, botulinum toxin treatment, drug therapy, surgery, and acupuncture, but all of these are symptomatic therapies. Only some patients experience dramatic improvements. Botulinum toxin treatment benefits a considerable number of patients with a relatively high rate of improvement. However, the guideline promoting an increased therapeutic effect with the concomitant use of needle electromyography and ultrasonography has not been fully implemented in clinical practice, and this is one of the issues.

Of all surgical procedures, deep brain stimulation (DBS) and intrathecal baclofen therapy (ITB) benefit several hundreds of patients. However, problems seem to remain in the durability and size of implantable devices, as well as foreign-body reactions. These are some of the reasons that surgeons have refocused their attention on coagulation as it leaves no device in the body.

Amid significant technological progress in the fields of brain science and regenerative medicine, coupled with totally new and organic understanding of the human body, there is a ray of hope that such progress may bring about a dawn when innovative therapies are implemented for dystonia and dyskinesia, "diseases of the cranial nerve network."

Advocate Group for Improving the Environment of Patients with Dystonia/Dyskinesia
https://www.dys-kaizen.org

Supporting patients with a clinical team: Volume 2
Clinical Laboratory Technologists

Japanese Association of Medical Technologists
Yoshifumi Miyajima,
Representative Director

Team-based healthcare in Japan was developed to provide patients with safe, quality medical service. Its principle is that physicians, nurses, and professionals in other job categories make the best use of their respective specialties, in-depth knowledge, and high technological skill

to tackle diseases together with patients. Team-based healthcare initially started out as infection control and nutrition support at medical institutions.

In 2009, the government began to overhaul the assignment of roles for physicians and nurses to promote team-based healthcare. In 2014, it established a training system for nurses performing certain designated procedures and revised the law concerning sample collection by clinical laboratory technologists. The government is about to discuss further reducing the burdens on physicians and nurses at the review meeting of workstyle reform for physicians so that some of their tasks can be delegated to professionals in other job categories.

The Japanese Association of Medical Technologists (JAMT) views the scope of work for clinical laboratory technologists as a series of processes (including explaining laboratory tests to patients, collecting samples, accurate analysis/measurement, and data aggregation and evaluation). Against this backdrop, we promote training to our members and work on related laws and their revisions to help facilitate the practical application of such processes in clinical settings.

In recent years, we are on the cusp of the Fourth Industrial Revolution. In the manufacturing industry, innovations expected to come will include altering production technologies with AI and robots, product development in new markets, and reforms to organizational operations. Likewise, innovations expected in the healthcare industry, particularly in the area of laboratory tests, may shift simple tasks (such as operation and monitoring of testing devices developed in the future) from human hands to future devices. As a result, task-shifting before and after analyses by clinical laboratory technologists is expected to accelerate.

Furthermore, by streamlining analytical tasks as well as the aggregation, evaluation, and interpretation of test results by clinical laboratory technologists, it is urgently necessary for us to develop devices that can be actively used to provide information, build operational systems, and train personnel.

Japanese Association of Medical Technologists
http://www.jamt.or.jp

AMDD Holds 2019 New Year's Party/Annual General Meeting

The American Medical Devices and Diagnostics Manufacturers' Association (AMDD) held a New Year's party on January 11, 2019 at the Imperial Hotel in Tokyo. Kosuke Kato, Chairman of AMDD (also Managing Director, Edwards Lifesciences Limited) provided a greeting followed by congratulatory speeches from Yoshinori Oguchi, Vice Minister of Health, Labour and Welfare, and Masaya Watanabe, Chairman of The Japan Federation of Medical Devices Associations (Executive Officer, Hitachi, Ltd.). Kenichi Matsumoto (Chairman and CEO, Sakura Global Holding Co., Ltd.) proposed a toast, and the New Year celebration began with distinguished guests from various circles.

AMDD held an annual general meeting on March 12, 2019. Following the opening remarks by Kosuke Kato, the 2019 budget proposal and four new directors were approved and adopted with a unanimous vote. Masami Sakoi, Councillor, Health, Labour and Welfare Minister's Secretariat was invited to give a special lecture on workstyle reform to improve

social security and productivity under the title, "Social Security and Healthcare up to 2040". (See page 2 for an abstract of Mr. Sakoi's lecture.)

Kosuke Kato
Chairman of AMDD

Yoshinori Oguchi
Vice Minister of Health, Labour and Welfare

8th Media Seminar Jointly Hosted by JACRI and AMDD
— Possibility of cancer diagnosis with microRNA in body fluids —

The 8th Media Seminar jointly hosted by the Japan Association of Clinical Reagents Industries (JACRI) and the American Medical Devices and Diagnostics Manufacturers' Association (AMDD) was held on March 22, 2019 at Trust City Conference in Marunouchi, Tokyo.

Takahiro Ochiya, Project Leader of the Division of Molecular and Cellular Medicine, National Cancer Center Research Institute was invited as a lecturer. He gave a lecture on a technology that allows the diagnosis of 13 types of cancer at one time by analyzing microRNA in body fluids including urine and blood and shared the latest research data and the development status towards its practical application. (See page 1 for an abstract of Mr. Ochiya's lecture.)

Value of Medical Technology:
<Diagnosis/Treatment of Heart Disease>
Small Implantable Ventricular Assist Device Designed to Improve Circulation and QOL of Patients with Severe Cardiac Failure

A heart transplant is the final therapeutic approach for patients with severe cardiac failure, including dilated cardiomyopathy and ischemic cardiomyopathic disease who are hospitalized for a long time or repeatedly admitted to hospitals. There were 55 cases of heart transplants performed in Japan in 2018, while over 700 patients were registered on the waiting list for a heart transplant as of February 2019. The waiting period is about three years and tends to be longer in Japan than in other countries.

An implantable ventricular assist device is a medical device implanted in patients on the heart transplant waiting list for the bridging period until transplantation. It assists some cardiac functions by operating a pump implanted in the left ventricle with an extracorporeal battery.

The treatment with implantable ventricular assist devices has been covered by health insurance in Japan since April 2011. But there was demand for much smaller pumps that allow a full flow rate of circulatory assistance as Japanese patients are often of smaller body types. Health insurance started covering this smaller implantable ventricular assist device in January 2019. The device is easier for operators to implant and reduces the burden on the patients' bodies. The device is expected to contribute to better QOL for patients as a treatment that improves patients' symptoms and to help patients return to daily life at home and in society.

(Text provided by Naoko Ono, Medtronic Japan Co., Ltd.)

Implantable ventricular assist device system

Commemorative Project for the 10th Anniversary of AMDD

This year marks the 10th anniversary of AMDD. AMDD was established as an independent body in 2009 to continue the activities of the Medical Devices and Diagnostics Subcommittee of the American Chamber of Commerce in Japan (ACCJ), and became a general incorporated association in 2016. Under a new mission statement: "Providing

valuable medical technology and information to your loved ones today, so that they may live in good health," we have been expanding our activities.

AMDD appreciates your immense support, and intends to continue working on various activities to contribute to healthcare and well-being in Japan.

As part of the commemorative project, we plan to issue a 10th anniversary publication that summarizes AMDD's 10-year history and its directions for the future, as well as a third volume of essays, "Good to have Met You!," by patients who have experience with medical devices and in vitro diagnostics (IVD). Additionally, we will organize a contest to collect ideas on communicating the value of future medical devices and IVD to as many people as possible.

I look forward to your continued support of AMDD.