

# AMDD *Vol.12*

## NEWSLETTER

December 2012

English translation of Japanese newsletter

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### **“Companion Diagnostics” to Support “Personalized Medicine”**

Ever since the sequencing of all human genes (the human genome) was accomplished, research into “personalized medicine,” which enables the provision of medicine tailored to the needs of each patient, has been in progress, and the results of this research have begun to be exerted on the clinical front of cancer treatment. The key are test kits called “companion diagnostics,” which are similar to in-vitro diagnostics (IVD). They are distributed along with specific anticancer agents and offer advantages in optimizing dosage based on the predicted effects and safety of such anticancer agents.

#### **The Hercep Test, Conducted Prior to Drug Administration**

One example of this is the Hercep Test, an immunostaining test conducted prior to the administration of the anticancer agent Herceptin, a drug that is effective against breast cancer. The test is conducted before the administration of the drug to determine the overexpression of HER2 protein, the HER2 oncogene product, on the cell surface. For patients without overexpression, another anticancer agent should be selected, as Herceptin is not effective in these patients.

These kinds of personalized medicine are expected to improve the quality and safety of medical care and facilitate the efficient use of healthcare resources in the future. While molecular target drugs such as Herceptin have been developed in the U.S. and Europe, “Poteligeo,” which was developed in Japan, finally made its long-awaited debut last March. Poteligeo is a potent anticancer agent against adult T-cell leukemia (ALT virus), which is endemic in Kyushu and Shikoku.

It was not until the development of the new drug Vemurafenib in the U.S. that a truly effective drug for malignant melanomas was found for patients with developed metastasis. This drug is particularly effective in individuals with mutations in a biomarker called BRAF. Crizotinib has also been launched as a molecular target drug for non-small-cell lung cancer,

covering almost 5% of patients with this type of cancer. IVD for Vemurafenib and Crizotinib were developed at the same time and simultaneously approved, along with their respective drugs, by the U.S. Food and Drug Administration (FDA) in August 2011. This raised global awareness of the significance of companion diagnostics, creating a wave of simultaneous approval around the world.

### **The Likelihood of Recurrence and Prognostic Predictions**

There used to be a time when a pathologist would examine the appearance of a cancer cell microscopically to determine whether it was cancerous or not. However, the spread of the clinical application of biomarkers has led to consideration of their usage to determine treatment methods and response evaluation. In the future, the examination of thousands of genes and their patterns will allow the likelihood of recurrence to be determined and the patient's prognosis to be predicted.

However, genetic tests are not a panacea. Although basic researchers who administer the anticoagulant warfarin, which is used to prevent stroke and heart attacks, may say they can identify the likelihood of efficacy after examining two genes, genetic tests are only relevant for approximately 40% of Caucasians and 24% of Asians. The reality is that clinicians must still seek the optimum dosage through the careful diagnosis and treatment of their patients.

### **A Ray of Hope in the Face of Expensive Kits**

The downside of personalized medicine is insurance coverage: health insurance only contributes 25,000 yen toward the cost of a genetic test kit. Not every patient can afford to pay out of pocket for an IVD, which costs approximately 400,000 yen. While initially hesitant, the Ministry of Health, Labour and Welfare has set the price of ALK genetic tests for lung cancer patients to 65,200 yen per test. Also, with a high drug price of 100,000 yen approved for the test conducted prior to the administration of Poteligeo, it appears there may be a ray of hope.

Meanwhile, the question of how expensive companion diagnostics for genome information, which will be introduced in the future, will be as incorporated into the universal health insurance system, remains a momentous challenge.

\* This is a summary of a lecture by Dr. Fujiwara prepared by the editorial desk.

Dr. Yasuhiro Fujiwara  
Chairman, Department of Breast and Medical Oncology, National Cancer Center Hospital

Dr. Fujiwara graduated from the Faculty of Medicine, Hiroshima University in 1984. He became an internal medicine resident at the National Cancer Center Hospital in 1986, and started working for the Pharmaceuticals and Medical Devices Evaluation Center under the Pharmacology Division of the National Cancer Center Research Institute in 1989. He became an assistant at the Division of General Medicine, Hiroshima University Hospital in 1992. After serving at the Institute of Health Sciences, he became the chief doctor at the National Cancer Center in 2002. He served as the director of both the Clinical Laboratory Department and the Department of Clinical Trial Coordination and Developmental Therapeutics, and was appointed to his current post as Deputy Director of the National Cancer Center Hospital (Management) in 2010. He assumed the position of executive officer at the same center (Office of Planning and Strategies) in 2012.

## **PMDA's Activities to Develop Innovative Medical Devices**

### **Regulatory Science**

The Pharmaceuticals and Medical Devices Agency (PMDA) offers three services: “Reviews,” “Safety Measures,” and “Relief for Adverse Health Effects.” These services represent a wonderful mechanism unique to Japan, called the “Safety Triangle,” covering all aspects of the industry, from the development to the use of pharmaceutical products and medical devices. Under this mechanism, the PMDA performs its daily operations, publicizes its mission and establishes its philosophy, pledging to single-mindedly work toward its goals, for the benefit of patients waiting for more effective and safer medical devices.

In order to foster services based on scientific decisions, the PMDA is working to promote “regulatory science.” This is an area of study that promotes social harmony and contributes to society by adapting academic science to the real world. The PMDA seeks to develop regulatory science and nurture human resources through the promotion of regulatory science research, the establishment of agreements with 13 university-affiliated graduate schools, and cooperation with the Ministry of Health, Labour and Welfare on a project called the “Initiative for Accelerating Regulatory Science in Innovative Drug, Medical Device, and Regenerative Medicine,” as well as through the exchange of opinions via academic conferences and presentations.

### **Response to the Creation and Review of Innovative Medical Devices**

In order to link seeds of innovative drugs and medical devices to applications for approval, the PMDA launched its “Pharmaceutical Affairs Consultation” service during the last fiscal year to offer advice to universities and research institutions, as well as venture companies, on the trials that must be conducted from the early development stage. This service enjoys a high reputation among users. We seek to make this consultation service more widely known and enhance our provision of services, as needed, to promote its further use.

We also need to collaborate with academia to nurture reviewers capable of contributing to the application of state-of-the-art technology. Therefore, this fiscal year, the PMDA established the Science Committee, consisting of external experts in medicine, pharmacology, dentistry, and engineering. The Science Committee discusses and proposes strategies, including proposals on the creation of policies and guidelines for products that incorporate cutting-edge science and technology, to improve reviews from a scientific perspective, and set up subcommittees that specialize in fields such as pharmaceuticals, medical devices, and regenerative medicine, in order to examine different issues.

In addition, the PMDA launched a horizontal standards project to advance product development, promote the international coordination of review standards, and expedite reviews through the clarification of scientific views regarding the review of medical devices and the like. In this project, relevant departments in the PMDA conduct activities in a horizontally-integrated manner in order to systematize review information and the results of regulatory science studies, and to develop standards and guidelines. The companion diagnostics project was launched as a part of the horizontal standards project to sort out problems related to companion diagnostics and create necessary guidelines. The Five-Year

Strategy for Medical Innovations developed in 2012 emphasizes the importance of efficient medical care with fewer side effects tailored to individual patients (personalized medicine), and we hope that the outcomes of this program will contribute to medical innovations in the future.

We expect that these efforts by the PMDA will also lead to the revitalization of the medical devices industry and, as a result, not only contribute to the industrial sector, but also improve the health and safety of the Japanese people.

### **Pharmaceutical and Medical Ethics**

The judgments we make in our operations at the PMDA are grounded in pharmaceutical affairs, and we believe that the most basic foundation for a correct understanding of the purpose and means of pharmaceutical affairs is found in Article 1 of the Pharmaceutical Affairs Law: “The objective of this law is to implement regulations necessary to ensure the quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, and medical devices, while taking measures related to the regulation of designated drugs and measures necessary to promote the research and development of drugs and medical devices, particularly those for which there is a pressing medical need, and thereby improve health and hygiene.”

Pharmaceutical affairs fundamentally assure the three elements of “quality,” “efficacy,” and “safety.” Based on my experience as a clinician, medical treatment provided at the medical front always overlaps with these three elements in pharmaceutical affairs. In the medical world, doctors strive to provide the best possible medical care, tailored to the needs of each individual, in accordance with the medical ethics described in the Oath of Hippocrates. According to this oath, doctors are required to actively provide ever-improving medical care, never provide any care that could be disadvantageous to their patients, and, in the case of unforeseen circumstances, always respond with their best efforts. In the pharmaceutical world as well, reviewers are required to approve drugs and medical devices that will be useful in the treatment of a wide variety of patients, and to respond promptly and appropriately when a problem occurs. While medical ethics in the world of medical care involves the establishment of a one-on-one relationship of trust between doctor and patient, ethical relationships in the world of pharmaceutical affairs are located in the multiple and vast relationships of trust among medical personnel and patients within Japan and throughout the world. I believe it is pharmaceutical affairs, with its large-scale relationships of trust, which best represent the ultimate form of medical ethics.

Providing patients with devices that are medically necessary in a prompt manner is a big mission that has been imposed on the institutions of industry, government and academia. Collaboration among all three institutions is essential to fulfill this mission. Your continued support and cooperation are greatly appreciated.

Dr. Tatsuya Kondo  
Director  
Pharmaceuticals and Medical Devices Agency (PMDA)

Dr. Kondo was born in Tokyo in 1942. He graduated from the Faculty of Medicine at the University of Tokyo and entered the Department of Neurosurgery as a doctor at the same faculty and university in 1968. After working for the Department of Neurosurgery at the First Tokyo National Hospital (now the National Center for Global Health and Medicine), he studied at the Max-Planck Institute in what was

then West Germany in 1977. He started working for the Department of Neurosurgery at the National Medical Center Hospital (now the National Center for Global Health and Medicine) in 1978. After serving in positions such as Chief Neurosurgeon, Director of the Department of Surgery and Director of the Second Department of Specialized Outpatient Services at the hospital, he became the director of the hospital in 2003. He was appointed to his current post in 2008.

## **Patient's Voice**

### **Breast-Conserving Operations Up to 60%**

By Ms. Ikuko Nakazawa  
Idea Four

Idea Four is an organization for breast cancer patients, founded in 1989 by women who had undergone breast-conserving therapy themselves. It is a council organization run by around ten caretakers with no appointed chairperson, and currently has about 350 members all across the country.

The 2010 edition of the survey of medical institutions and patients on breast cancer therapy marked the sixth time the survey has been conducted since the organization's establishment. The survey started when the implementation rate of breast-conserving surgery was less than 5 percent. However, it topped 50 percent in 2003, and the rate hit its peak at 60 percent in 2010. This is due to an increasing number of cases in which the focus is no longer on "simply preserving the breast," but rather "preserving the breast with a better postoperative shape," where a method is chosen for reconstructing the breast in a better shape if there is a large degree of deformity after removing the cancer. The dark era in which patients were asked, "Which do you value more, your life or your breast?" seems to have come to an end.

With a large number of patients around the world, breast cancer therapy is constantly advancing. A large dissection of the lymph nodes under the arm used to be made, but the advent of "sentinel lymph node biopsy" has enabled doctors to identify the first lymph nodes to which the fluid flows, reducing the need for dissection, and thus decreasing the number of patients at risk for lymphedema. In terms of postoperative medication, breast cancer has taken the lead over other cancers for the development of various new drugs.

The first molecular target drug, Herceptin, has been found to be effective against types of high-grade breast cancer that were considered difficult to live with in the event of recurrence, and was heralded as a breakthrough drug with fewer side effects. While its efficacy is limited to cancer cells on which a particular protein is found, it does seem to enable patients to live a longer, healthier life.

Recently, it has been said that gene profiling enables breast cancer to be sorted into different types of properties, allowing different treatment policies depending on the subdivided types. On the other hand, there is growing concern whether this kind of profiling is capable of making a correct assessment.

Furthermore, it is difficult to avoid thinking about the cost of medicine. How many patients can afford to continue paying 10 million yen a year no matter how good the medicine is?

Advanced medical treatment and costs are a critical issue for both individuals and the nation. Nonetheless, a new therapy represents “hope” for patients with multiple-organ metastases. They can live with cancer with the belief that “If I survive one more year, another new therapy will be developed.”

**Idea Four, an organization for breast cancer patients:**  
<http://www.ideafour.org/index.html>

## **Medical Journalist Viewpoint**

### **What Personalized Medicine Can Give to You**

By Mr. Mitsuru Miyata  
Special Editor, Nikkei BP

Although many people may feel reassured when they receive medicine from their doctor, medicine these days is actually not that potent. Except in the case of medicines like antipyretic analgesics for symptomatic therapy, the ratio of patients who respond well to medicine is surprisingly small. According to a book published in 2000 called *Pharmacogenomics*, 70–100% of all patients with cancer, 40–70% of those with asthma, and 45–75% of those with diabetes do not respond to existing medicines. The situation is not much different for a wide range of other diseases, from psychiatric disorders and osteoarthritis to high blood pressure and hyperlipidemia.

Biotechnology has contributed to the elucidation of disease induction mechanisms at the molecular level, and innovative medicines, including molecular drugs and antibody drugs launched in the 21st century, are becoming actual drugs that are therapeutically effective. However, Xalkori, a specific cure for pneumonia launched in Japan last May, is effective in only 4% of lung cancer patients. Its efficacy is limited to those with a specific genome of the ALK-EML4 fusion gene. This is because Xalkori is a drug which inhibits the EML4-ALK fusion protein that is abnormally activated in this type of lung cancer. Herceptin, the world’s first breast cancer therapeutic agent that proved effective against cancer, only works in cases of HER2-positive breast cancer, which affects 25–30% of breast cancer patients. However, the data to date demonstrates that it works in only 25–30% of HER2-positive patients. In short, the reality is that Herceptin is only effective for 5–10% of all breast cancer patients.

Breast cancer, in fact, is caused by various factors. Thus, the irony is that the more efficacious a molecular target drug or anti-body drug is, the fewer the number of patients who respond to it. From the viewpoint of pharmaceutical companies, this does nothing but shrink the market. Conversely, no therapeutic effects can be expected when these expensive molecular target medicines and antibody drugs are administered to patients who do not respond to them, and such patients end up being exposed to the risk of side effects. Meanwhile, in advanced countries, medical expenses keep rising at a skyrocketing pace due to aging populations and technological innovations. No country can afford to administer medicine to patients for whom its efficacy is not clear. Personalized medicine resolves all these contradictions that have arisen in the creation of drugs during the 21st century. The



simultaneous development of new drugs and diagnostic agents, which identify patients who will respond well and have fewer side effects to a given drug prior to its administration, is the key to making personalized medicine a reality.

In addition, companies drunk on the success of blockbuster drugs and awash in extravagance must revise their R&D and business models. The shift to a personalized medicine business model has started in Japan as well.

## **AMDD 4th Annual General Meeting Held**

The 4th annual general meeting of the American Medical Devices and Diagnostics Manufacturers' Association (AMDD) was held on September 13, 2012, at the Imperial Hotel (Sakura-no-Ma) in Uchisaiwai-cho, Tokyo. Mr. Takashi Shimada (President of Medtronic Japan Co., Ltd.), who was appointed the third Chairman of the AMDD in April, said in his opening address, "AMDD continues to seek to improve medical care for Japanese people through the provision of advanced medical technology."

Following the approval of the budget for the next fiscal year and amended articles of incorporation, the chairpersons of each committee reported on their activities over the past year, with a report from the RAQA Committee attracting special attention. The summary is as follows:

Over the past year, there were various occasions for dialogue about the revision of the Pharmaceutical Affairs Law. In July 2011, AMDD submitted its "Proposals Regarding Revisions to the Pharmaceutical Affairs Law for Medical Devices" to the Minister of Health, Labour and Welfare, in cooperation with the PA Committee and Advocacy Committee, and demanded that "medical devices and drugs be treated separately," without amending the content of QMS (ISO 13458). In June, the New Growth Strategy was endorsed by the Cabinet, and the "creation of innovative drugs and medical devices" and "resolutions for the drug lag and device lag" were specified for the Life Innovation Project, changing current trends in the development of medical devices. Concurrently, at the hearing on the medical devices industry held by Diet members, there was an opportunity to deliver the industry's opinions on "how pharmaceutical regulations should be." During the event, the then-Minister of Health, Labour and Welfare Ms. Komiyama stated, "I think it would be good to have regulations suited to the special characteristics of medical devices." In the future, these regulations may be legally divided into regulations for "drugs, quasi-drugs and cosmetics" and for "medical devices."

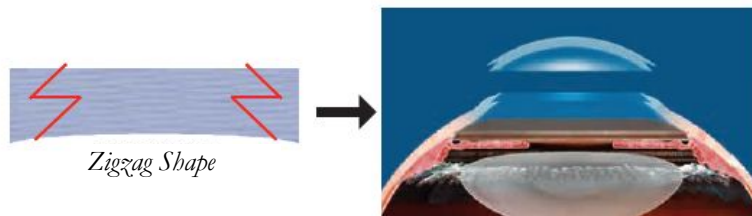
A special lecture entitled "Health Policy for the Near Future, Enacting Two-Stage Basic Principle" was delivered by Dr. Ichiro Innami, Professor at the Faculty of Policy Management, Keio University. "In order to solve problems in medical care, we need to operate a comprehensive system incorporating the medical care delivery system, the medical insurance system and the medical fee system," said Dr. Innami. "The enactment of a basic medical care act that can act as a unified philosophy of these three pillars is essential."

## The Value of Medical Technology (Ophthalmic Materials) Laser Corneal Transplant

The cornea contributes most of the eye's optical power, and even slight distortion or opacity can have a major impact on vision. The corneal function may be lost due to external injury, infection or genetic disease, in which case a corneal transplant would be the only way to regain corneal transparency.

Manual operation using special tools made it impossible to render corneal tissues of a donor (cornea provider) and a recipient (patient) in the exact same shape. Such differences in shape result in postoperative wound dehiscence or astigmatism.

A femtosecond laser, like the iLASIK introduced last time in this column, is capable of forming a corneal graft. Resection of the corneal tissues of the donor and recipient in the same, complex shape, as shown below, enables the wound to be more stable.



Furthermore, if the opacity is limited to the corneal surface, only the superficial layer is resected and transplanted with the donor's cornea, cut in the same shape. According to one report, a lamellar keratoplasty was performed without sutures. Lasers maximize the options and effectiveness of corneal transplants in cases of partial corneal opacity.

(By Junko Kodama AMO Japan K.K.)



## Media Seminar Co-hosted with the Japan Association of Clinical Reagents Industries

The American Medical Devices and Diagnostics Manufacturers' Association (AMDD) co-hosted an IVD media seminar, entitled “The Prospects for Personalized Medicine in Japan,” at the Mitsubishi Building M Plus in Marunouchi, Tokyo, on August 27.

First, Dr. Isao Ikeda (Chief Executive Officer and President, Abbott Japan Co., Ltd.) made an opening address on behalf of both associations. Ms. Miwa Nishida (Manager, Regulatory & Clinical Development Department, Roche Diagnostics K.K.), then described the development of IVD, personalized medicine, and companion diagnostics.

Next, Dr. Yasuhiro Fujiwara, Chairman, Department of Breast and Medical Oncology, National Cancer Center Hospital (and Deputy Director, Promotion of Medical Innovation Promotion Office, Cabinet Office) delivered a lecture, “Necessary Provisions for the Development and Execution of Clinical Test,” and explained about “personalized medicine,” in which the optimum treatment is selected based on the individual patient’s genetic information. He discussed the molecular target drug Trastuzumab (product name: Herceptin), effective in the treatment of some breast cancers, as one example. He also pointed out the significance and challenges of companion diagnostics, such as their ability to predict therapeutic efficacy through the use of the biomarker HER2 and prevent serious side effects.

(The lecture provided by Dr. Fujiwara is summarized on page 1.)

### **Value of Medical Technology**

Our mission is to make more people understand the unlimited potential of advanced medical technology and its contribution to the reformation of the Japanese medical care system

Note: All opinions in this newsletter are the personal opinions of the authors, and do not necessarily represent the opinions and activities of AMDD.