FDA Clears Breast Cancer–Specific Molecular Prognostic Test

The U.S. Food and Drug Administration (FDA) announced on February 6 marketing clearance for a microarray analysis test that determines the likelihood of breast cancer returning within 5–10 years after an initial cancer. The MammaPrint is the first FDA-cleared molecular test that profiles genetic activity. MammaPrint was developed by Agendia (Amsterdam, The Netherlands), where the product has been on the market since 2005.

"Clearance of the MammaPrint test marks a step forward in the initiative to bring molecular-based medicine into current practice," said FDA Commissioner Andrew C. von Eschenbach, MD. "MammaPrint results will provide patients and physicians with more information about the prospects for the outcome of the disease. This information will support treatment decisions."

Agendia compared the genetic profiles of a large number of women suffering from breast cancer and identified a set of 70 genes with activities that confer information about the likelihood of tumor recurrence. The MammaPrint test measures the level of activity of each of these genes in a sample of a breast tumor and then uses a specific algorithm to produce a score that determines low or high risk for spread to another site.

The MammaPrint is the first cleared in vitro diagnostic multivariate index assay device. Earlier in 2007 the FDA issued a draft guidance document indicating that these complex molecular tests would need to meet premarket review and postmarket device requirements even when such tests are developed and used by a single laboratory. Although FDA regulates diagnostic tests sold to laboratories, hospitals, and physicians, it uses discretion when regulating tests developed and performed by single laboratories. On February 8, the FDA held a public meeting to discuss draft guidance describing its regulatory approach to this type of test.

"There have been rapid advances in microarrays and other pioneering diagnostics, and a corresponding increase in the use and impact of these complex tests. This has prompted FDA to take a closer look at the potential risks as well as the benefits associated with such tests when they are developed and used in laboratories," remarked Steven Gutman, MD, director, Office of In Vitro Diagnostic Device Evaluation. "This test clearance takes into account the development of these innovative technologies and ensures public health by carefully evaluating their performance."

U.S. Food and Drug Administration

NRC Addresses ^{131}I Multicapsule Vial Errors

The Office of Federal and State Materials and Environmental Management Programs of the Nuclear Regulatory Commission (NRC) on February 2 issued a broad alert to medical use licensees and radiation control program directors about events in which patients were administered dosages of sodium iodide ^{131}I that were less than the prescribed dosages. In September 2006, 1 licensee performed administrations incorrectly on 2 separate occasions. In each case, only 1 sodium iodide ^{131}I capsule was administered to the patient, rather than 2 capsules containing the total dose. Consequently, the patients did not receive the dosages prescribed in the written directives. Before these events, the licensee had received the total prescribed dose in a single capsule. In this case instead of the expected single capsule, the commercial radiopharmacy split the prescribed dose between 2 capsules delivered in a single vial. The licensee measured the radioactivity in each vial before administration to ensure the proper dosage. When the vials were emptied for administration, 1 of the 2 capsules remained in each vial, which was placed back into its shipping container and returned to the pharmacy. The 2 patients were released, having received only a portion of the prescribed dosage. Over the last 10 years, 12 events of this type have been reported. In some of these cases, patients were administered 1 of multiple capsules contained in a single vial. In other cases, patients were administered 2 of 3 capsules, where 2 capsules were placed in 1 vial by the commercial pharmacy, and the third capsule was placed in a separate vial. In a few instances, the errors were discovered shortly after the patients were released, and the patients returned to the licensees to receive the remaining portions of the prescribed dosages.

NRC regulations (10 CFR 35.63) do not require licensees to perform a direct measurement of a unit dosage in a dose calibrator before administration if the unit dosage is corrected for decay based on the activity determined by an appropriately licensed manufacturer, preparer, or licensee (e.g., commercial pharmacy). However, as a measure for prevention of these types of medical events, a licensee could assay the vial containing ^{131}I capsules after administration of the dosage to assure that no capsules remain in the vial. To keep occupational doses as low as reasonably achievable, assay measurement of the vial postadministration is preferred over visual verification of the content of the vial. Precautions can also be taken before administration and include reviewing the packing slip before administration to verify the number of capsules shipped by the pharmacy. In addition, assaying the activity before administration could identify that the total dose was not in the vial and that

a missing capsule(s) may, for example, have been placed in another vial of the shipment.

The NRC noted that another negative consequence of a capsule remaining in a vial is that the licensee may incorrectly mark and label the vial for transport back to the commercial radiopharmacy. For example, the vial may be placed back into the original container and shipped back to the commercial pharmacy with the marking and labeling of a package that is assumed to be empty when, in fact, it is not. This could result in a violation of the requirements in 10 CFR 71.5, "Transportation of Licensed Material." Another example of an adverse consequence of a capsule remaining in the vial is that this might result in the inadvertent disposal of a vial containing ^{131}I in nonradioactive waste, in violation of the requirements for waste disposal or for storage and control of licensed material in 10 CFR Part 20.

Although recipients of this alert were urged to review the information for applicability to their facilities, no specific action or written response was required.

Nuclear Regulatory Commission

Environment, Exercise Affect Mouse Study Results

Results of a study released on February 20 from the University of Arizona may have implications for the thousands of scientists worldwide, including those investigating nuclear and molecular imaging, who use "knockout" mice in their research. In "Knockout Mice: Is it Just Genetics? Effects of Enriched Housing on Fibulin-4+/− Mice," appearing in the online journal *PLoS One* and available at http://dx.doi.org/10.1371/journal.pone.0000229, lead researcher Ann Baldwin, PhD, suggested that environmental factors may play a large part in research findings that investigators assume are attributable to genetic differences. Moreover, the study indicated that optimal environments for animal handling may serve to obscure and/or counteract the effects of some genetic deficiencies.

Baldwin, a professor of physiology and psychology at the University of Arizona College of Medicine, developed a study focusing on heterozygous fibulin-4 knockout mice (mice with only 1 copy of a gene that encodes for fibulin-4, which is localized in the aortic media and is essential for maintaining arterial integrity). She wanted to determine whether these mice showed arterial defects on a microscopic scale, despite outward normal appearance. Using electron microscopy, she found small areas of disorganized tissue (gaps) in the aortas of the knockout mice, approximately 100 times the number found in control (wild-type) mice.

The researchers then asked whether these differences could be offset by enriched housing conditions. One group of test mice were housed 4-per-cage in standard cages ($26 \times 16 \times 12$ cm) containing only bedding. Another group was housed 2-per-cage in larger cages ($33 \times 25 \times 25$) equipped with a shelf, ladder, exercise wheel, and plastic tube. Observed at night on specific occasions during the testing period, the animals housed in the larger cages spent approximately 40% of the observation time exercising in the wheel, while mice housed in the standard cages remained relatively stationary. The mice housed in the standard cages grew heavier than those in the larger cages (about twice the weight at the same age) and showed large quantities of adipose tissue around the aorta. The mice in the larger cages showed virtually no fat around the aorta and showed far fewer regions of disorganized tissue in the aorta than those housed in standard cages.

The evidence suggests that although the knockout mice were genetically predisposed to arterial damage, simply housing them in an enriched environment reduced the number of gaps occurring in the aorta. Baldwin suggested that research findings that are assumed to be attributable simply to genetic differences might be affected by environment. In addition, environments may counteract the effects of some genetic deficiencies.

University of Arizona

IAEA/ISO Create New Radiation Danger Symbol

The International Atomic Energy Agency (IAEA) and the International Organization for Standardization (ISO) on February 15 released the design of a new radiation warning symbol intended to supplement the traditional radiation trefoil symbol. With radiating waves, a skull and crossbones, and a running person, the new symbol was designed "to help reduce needless deaths and serious injuries from accidental exposure to large radioactive sources."

"I believe the international recognition of the specific expertise of both organizations will ensure that the new standard will be accepted and applied by governments and industry to improve the safety of nuclear applications, protection of people, and the environment," said Eliana Amaral, director of the IAEA Division of Radiation, Transport, and Waste.

The IAEA and ISO expressed hope that the new symbol, the result of a 5-year project conducted in 11 countries, will be useful in alerting individuals to the potential dangers of proximity to large sources of ionizing radiation. The symbol was developed by human factor experts, graphic artists, and radiation protection experts and was tested by the Gallup Institute on a total of 1,650 individuals in Brazil, Mexico, Morocco, Kenya, Saudi Arabia, China, India, Thailand, Poland, Ukraine, and the United States.

"We can't teach the world about radiation," said Carolyn MacKenzie, an IAEA radiation specialist who helped develop the symbol, "But we can warn people about dangerous sources for the price of a sticker." The symbol is intended for IAEA Category 1, 2, and 3 sources defined as dangerous sources capable of causing death or serious injury, including food irradiators, teletherapy machines for cancer treatment, and industrial radiography units. The symbol is to be placed on the device housing the source, as a warning not to dismantle the device or to get any closer. It will not be visible under

normal use but will be apparent if an individual attempts to disassemble the device. The symbol will not be located on building access doors, transportation packages, or containers.

"The new ionizing radiation warning symbol (ISO 21482) is the latest successful result of long-standing cooperation between the IAEA and ISO. We encourage the symbol's rapid adoption by the international community," said ISO Secretary-General Alan Bryden. Strategies to apply the symbol on existing large sources are being developed by the IAEA.

International Atomic Energy Agency

Femtoscience a Focus at AAAS

A special session titled "Femtoscience: From Nuclei to Nuclear Medicine," was held on February 16 at the annual meeting of the American Association for the Advancement of Science in San Francisco, CA. Organized by Bradley Sherrill, PhD, of Michigan State University (MSU; East Lansing), the session provided an overview of current efforts to create new materials on the femtoscale, the scale of the atomic nucleus (roughly 1 million times smaller than the scale of measures used in nanotechnology). Research at the forefront of this field studies new forms of nuclei with a large excess of either neutrons or protons compared with normal atomic nuclei. These studies provide critical insight into the nature of atomic nuclei and promise to assist in major advances in understanding mesoscopic systems, where aspects of quantum mechanical, single-particle motion, and many-body phenomena coexist. These studies on the tiniest of scales have a link to astrophysics, where similar processes are governed by exotic isotopes. The ability to fabricate new isotopes (a kind of femtotechnology) also promises to play a significant role in providing new tools for medicine and nuclear data for energy and national security. Among the presenters and topics were David Dean, PhD, (Oak Ridge National Laboratory, TN) on "Atomic Nuclei and Mesoscopic Science"; Hendrik Schatz, PhD, (MSU) on "Ashes to Ashes, Dust to Dust"; Larry Ahle, PhD, (Lawrence Livermore National Laboratory (CA) on "Atomic Nuclei and the National Need"; and Tom Ruth, PhD (TRIUMF, Vancouver, BC) on "Designer Nuclides for Nuclear Medicince."

American Association for the Advancement of Science

Fisher Appointed to ACMUI

The Nuclear Regulatory Commission (NRC) announced on February 26 the appointment of Darrell R. Fisher, PhD, as the patient's rights advocate on its Advisory Committee on the Medical Uses of Isotopes (ACMUI). The ACMUI was established in 1958 and advises the NRC on policy and technical issues related to the regulation of the medical use of radioactive material. Fisher, an SNM member and medical physicist with experience in dosimetry and health effects of radionuclides and radiopharmaceuticals, is currently a senior scientist with 28 years experience at the Pacific Northwest National Laboratory (Richland, WA). He leads the radioisotopes research program and serves as scientific director of the U.S. Department of Energy isotope production program. He previously served as an assistant to the director of the American Association of Cancer Patients. A survivor of childhood cancer, he has also worked with other patient advocate organizations as a counselor to patients evaluating cancer treatment options. He was a science advisor to U.S. Customs and Border Protection, in Washington, DC, and previously served as science advisor to the Secretary of Energy's human radiation experiments investigative study. Fisher is an adjunct member of the radiology faculty at the University of Washington and of the environmental sciences, pharmaceutical sciences, and English and humanities faculties at Washington State University.

Nuclear Regulatory Commission

Nursing Workforce Expands, Ages

The number of licensed registered nurses (RNs) in the United States grew by almost 8% between 2000 and 2004 to a new high of 2.9 million, while the average age of the RN workforce also continued to increase, according to a report released by the Health Resources and Services Administration (HRSA) on February 20. The report, "The Registered Nurse Population: Findings from the March 2004 National Sample Survey of Registered Nurses," found that real earnings for RNs grew significantly for the first time in more than a decade. The average age of RNs climbed to 46.8 years in 2004, the highest since the first comparable report was published in 1980. More than 40% of RNs were 50 years of age or older in 2004, a dramatic increase from 33% in 2000 and 25% in 1980. Only 8% of RNs were younger than 30 in 2004, compared with 25% in 1980. The survey also found that more than 83% of RNs with active licenses were employed in nursing in 2004, the highest employment rate since 1980; the average annual earnings for RNs in 2004 were $57,785; and the number of RNs with master's or doctoral degrees rose to 376,901 in 2004, an increase of 37% from 2000.

Published every 4 years by HRSA's Bureau of Health Professions, data in the survey cover educational background, practice specialty areas, employment settings, position levels, job satisfaction and salaries, geographic distribution, and personal demographics, such as sex, racial/ethnic background, age, and family status. Copies of the survey results are available at http://ask.hrsa.gov.

Health Resources and Services Administration

CMS to Provide Physician Performance Data

The Centers for Medicare & Medicaid Services (CMS) announced on February 15 subcontracts for management of regional collaboratives that will combine Medicare data with data from other insurers to produce information on the performance of health care providers for the benefit of Medicare beneficiaries. The Delmarva Foundation for Medical Care, one of the

CMS quality improvement organizations, has entered into subcontracts as part of the Better Quality Information to Improve Care for Medicare Beneficiaries (BQI) Project with the: Indiana Health Information Exchange, Massachusetts Health Quality Partners, Minnesota Community Measurement, and Wisconsin Collaborative for Healthcare Quality. The results of the BQI Project will be used to provide performance information to physicians that will assist them in improving the quality of care for Medicare beneficiaries and to give physician performance information to Medicare beneficiaries to assist them with physician selection.

"This is an important advancement," said CMS Acting Administrator Leslie V. Norwalk. "The BQI project will give Medicare beneficiaries a broad overview of provider performance resulting in better choices in meeting their health care needs. The regional collaboratives, spurred by great leadership from physicians and others in the health care community, will also provide critical information to physicians and Medicare on the best practices for data collection, aggregation, and reporting."

The quality measures to be used in the BQI project are national consensus-based measures that have been adopted by AQA (an alliance of health care providers, health plans, senior groups, employers and unions that also played a role in the establishment of the subcontracting collaboratives). The BQI project also aims to provide methods to aggregate Medicare claims data with claims data from other payers, including employers, health insurance plans, and in some case Medicaid programs, to produce more accurate measures of the quality of services being provided by physicians to Medicare recipients.

CMS plans to announce 2 additional BQI subcontractors in the near future. Additional information on each regional collaborative as well as the Department of Health and Human Services Value-Driven Health Care Initiative is available at www.hhs.gov/transparency.

Centers for Medicare & Medicaid Services

(Continued from page 28N)

Being Inclusive: To ensure the long-term viability of molecular imaging and nuclear medicine, SNMTS approved bylaws to encourage not only nuclear medicine technologists but also those in related fields to join the Technologist Section. Pending a vote by the general membership, this action would allow practitioners from emerging technologies to become members.

Virginia Pappas, CAE
Chief Executive Officer, SNM