Nuclear Medicine: Trailblazing Imaging Practice and Sciences for More than a Century

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Nuclear medicine has been a trailblazer in imaging sciences and practice for more than a century. Since Marie Curie, the first woman in nuclear medicine, discovered radioactive elements and was awarded the Nobel Prizes for Physics in 1903 and for Chemistry in 1911, nuclear medicine has evolved through an extraordinary series of collaborations among basic and translational scientists, visionary inventors, government agencies, industry investors, and physicians working well beyond the "see it/say it" bounds of traditional radiology. In doing so, nuclear medicine has often pioneered paths to new modalities, such as cross-sectional imaging, hybrid imaging, molecular imaging, imaging biomarkers, and theranostics, introduced models of cooperative research and development, and been an innovator and "first adopter" of techniques and approaches that are now common in medical imaging practice and beyond.

Nuclear medicine pioneered a combination of diagnosis and therapy long before the portmanteau term "theranostics" was coined. The availability of isotopes of iodine in the 1930s and early 1940s led to the first diagnostic use of ^{131}I and subsequent companion therapeutic applications in thyroid cancer. Our field—even before it was routinely called nuclear medicine—was using imaging to both pinpoint the site of metabolic disease and target it with injectable internal radiation. Successes in identifying twinned diagnostic and treatment agents that work together has continued through today's ^{68}Ga-labeled PET/CT agents and ^{177}Lu-prostate-specific membrane antigen therapies. These innovations have saved and extended many lives and have changed the way that medicine as a whole looks at targeted therapeutic approaches. The success of radioimmunotherapy, including with ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan, are a continuation of long nuclear medicine traditions.

"Scanning" had its medical origins in nuclear medicine, which pioneered cross-sectional imaging and novel machine-driven techniques for recording activity within the body. In 1951 Benedict Cassen and collaborators automated Cassen's prototype rectilinear detector so that it could scan the distribution of radioiodine within the thyroid. The results were revolutionary (even if they also prompted the first skeptical comments calling the field "unclear" medicine). Numerous investigators were soon working to refine Cassen's detector and create other methods for scanning in medical imaging. David Kuhl, MD, a nuclear medicine physician and radiologist at the University of Pennsylvania (Philadelphia), in 1954 invented a photorecording system for radionuclide scanning that brought more clarity to the images. Hal O. Anger's scintillation (gamma) camera, developed in 1958 at Berkeley (CA), made it possible to collect dynamic real-time date on activity within the body. By 1962, Kuhl had introduced with colleagues emission reconstruction tomography, which would evolve into SPECT and, later, through research at Washington University (St. Louis, MO), into PET. Kuhl extended the idea to transmission scanning by 1966, which was immediately extended to research in radiology on transmission X-ray scanning (CT), that is used in everyday practice now. These and other scanning innovations in nuclear medicine, including the early introduction of color images and cine mode, provided a template for cross-sectional imaging and for dynamic scanning that have become common not only in the larger world of medical imaging but across medical practice.

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Nuclear medicine has also led the way in quantitative assessment of imaging data. With the need for assessment of biodistribution and dosimetry and the means to automate data capture, our field has emphasized the crucial role of quantitative data in research and clinical practice. The introduction of SUVs for PET and SPECT made (semi)quantitative assessment of imaging data a routine part of practice. More important, quantitative metrics in nuclear medicine have enabled more reliable comparison of imaging results across institutional and geographic boundaries, facilitating large multi-institutional studies and more standardized procedures. Nuclear medicine has also been an early adopter of artificial intelligence (AI) and machine learning, including efforts in nuclear cardiology, oncology, and neurology. *The Journal of Nuclear Medicine* published AI papers in the early 1990s. Moreover, we have been and remain open to working with other imaging areas and medical disciplines to optimize the potential of our technologies by combining them in hybrid forms in PET/CT, SPECT/CT, PET/MRI, and others under current development.

More than any other discipline, nuclear medicine has led the way in forming effective and productive collaborations with government agencies. By the end of World War II, the U.S. government's capabilities for reactor production

of radionuclides were greater than those of the few universities with cyclotrons. The Atomic Energy Agency (later the Nuclear Regulatory Commission) was created in 1946 to oversee military and peace-time applications of radiation and underlined the need for wide government support for related medical research. Inherent in this movement was the need to regulate complex issues such as transportation of radioactive substances, exposure of employees and the general public, onsite preparation of imaging and therapeutic agents, and access to difficult-to-acquire radioisotopes. In the intervening years, nuclear medicine has created models for interactions with regulators, government scientists and agencies, and legislators that have resulted in greater availability of tracers, funding that has moved the field forward, and encouragement of private sector companies and industries to invest in our efforts.

What seems most remarkable about the way in which nuclear medicine continues to pioneer these advances is that—unlike Curie's early work with her husband Pierre and only one laboratory assistant—every development in nuclear medicine has been the result of broad collaboration. These successful collaborations have depended on luck and dedication: the availability of the right radioisotopes at the right time, the ingenuity shown by men and women who work together (sometimes across great distances) to create imaging agents that pair in optimal ways with new techniques, the willingness to jump modality lines to create new technologies, the cooperation of the U.S. and other governments in producing research isotopes and encouraging the availability of supplies for imaging, the support of professional societies in encouraging public acceptance and understanding, and the confidence of inventors and investors who are willing to promote novel approaches.

Perhaps this is the most important pattern characterizing nuclear medicine: working together, both within the field and reaching out for collaboration, to advance and develop techniques that continue to benefit patients worldwide.

NEWSBRIEFS

SNMMI/ACR Clinical Data Registry for Nuclear Medicine

SNMMI and the American College of Radiology (ACR) announced in April a new collaborative clinical data registry to support high-quality practice and patient care. The registry will allow collection and analysis of data on nuclear medicine procedures and is intended to support continuous improvement in patient care. "This synergistic partnership reaffirms the commitment of both organizations to provide the highest level of nuclear medicine care for our patients," said Phillip Koo, MD, chair of the SNMMI Quality Committee. "The initiative will support that goal through evidence-based practice improvements born from a data-rich registry." The initiative will also facilitate reporting of quality performance to the federal government.

"Intersociety collaboration between the SNMMI and the ACR will be key to the future of nuclear medicine and practice improvements in the U.S.," said Don Yoo, MD, chair of the ACR Commission on Nuclear Medicine and Molecular Imaging. "Both organizations are committed to this important data registry."

The diagnostic interventional radiology/nuclear medicine component of the registry will be piloted this year. Participating pilot sites will have access to the data for the duration of the pilot, including deidentified data from other participating sites, allowing practices to compare and assess the quality of care provided to patients. A joint Registry Committee will review requests for access to and use of registry data for research, publication, quality improvement, or other purposes. The registry will initially focus on PET/CT imaging data. In the future, the collaborative registry may expand to include quality measures focused on therapeutic aspects of nuclear medicine. For information about participating, contact Sukhjeet Ahuja, MD, MPH, at sahuja@snmmi.org.

SNMMI

Effects of Alcohol on Brain Energy Patterns

Shokri-Kojori et al. from the National Institute on Alcohol Abuse and Alcoholism (NIAAA; Bethesda, MD) and the National Institute on Drug Abuse (Rockville, MD) reported in the February 11 issue of *Nature Communications* (2019;10:690) on a study using ^{18}F-FDG PET and functional MR imaging to determine the correspondence between cerebral glucose metabolism (indexing energy utilization) and synchronous fluctuations in blood oxygenation (indexing neuronal activity). In a March 4 news release, NIAAA focused on findings in the study expanding knowledge about the ways in which alcohol affects the brain and described potential applications in neuropsychiatric disease. "The brain uses a lot of energy compared to other body organs, and the association between brain activity and energy utilization is an important marker of brain health," said George F. Koob, PhD, director of NIAAA, which funded the study. "This study introduces a new way of characterizing how brain activity is related to its consumption of glucose, which could be very useful in understanding how the brain uses energy in health and disease."

Using PET, the researchers found that alcohol significantly affects brain glucose metabolism (which the authors termed "power"). Functional MR showed that alcohol also had significant effects on energy use as well as regional

brain activity (which the authors termed "cost"). "We measured power by observing to what extent brain regions are active and use energy," said Ehsan Shokri-Kojori, PhD. "We measured cost of brain regions by observing to what extent their energy use exceeds their underlying activity." In a group of healthy volunteers, the researchers showed that different brain regions that serve distinct functions have notably different power and cost. They then investigated the effects of alcohol on these new measures by assessing a group of people that included light and heavy drinkers and found that both acute and chronic exposure to alcohol affected power and cost in brain regions. "In heavy drinkers, we saw less regional power, for example, in the thalamus, the sensory gateway, and frontal cortex of the brain, which is important for decision making," said Shokri-Kojori. "These decreases in power were interpreted to reflect toxic effects of long-term exposure to alcohol on the brain cells."

Also identified was a decrease in power in visual regions during acute alcohol exposure, which was related to disruption of visual processing. At the same time, visual regions had the most significant decreases in cost of activity during alcohol intoxication, which is consistent with the reliance of these regions on alternative energy sources such as acetate, a byproduct of alcohol metabolism.

The authors concluded that despite widespread decreases in glucose metabolism in heavy drinkers compared to light drinkers, heavy drinking shifts the brain toward less efficient energetic states. They pointed to the need for future studies to investigate the mechanisms contributing to this relative inefficiency. "Studying energetic signatures of brain regions in different neuropsychiatric diseases is an important future direction, as the measures of power and cost may provide new multimodal biomarkers for such disorders," said Dr. Shokri-Kojori. Nora Volkow, MD, senior author of the study, said "The findings from this study highlight the relevance of energetics for ensuring normal brain function and reveal how it is disrupted by excessive alcohol consumption."

National Institute on Alcohol Abuse and Alcoholism
Nature Communications

U.S. Dementia-Related Deaths Double

In an article published in the March 14 issue of *National Vital Statistics Reports* (2019;2:1–29), Kramarow and Tejada-Vera from the Centers for Disease Control and Prevention (CDC) surveyed CDC data on mortality attributable to dementia in the United States from 2000 to 2017. They reported that the rate of dementia-associated deaths almost doubled during this period. The article presented data for dementia as an underlying cause of death, including tabular breakouts for selected characteristics such as age, sex, race, Hispanic origin, and state of residence. Trends in dementia deaths overall and by specific cause were also featured, including reporting of dementia as a contributing cause of death. Data were gathered from information from all death certificates filed in the 50 states and the District of Columbia, with dementia-related deaths defined as those attributed to unspecified dementia, Alzheimer disease, vascular dementia, and other degenerative diseases of the nervous system. Among the findings was a total of 261,914 deaths attributable to dementia as an underlying cause of death in the United States in 2017, with 46% as a result of Alzheimer disease. The age-adjusted rate for dementia as an underlying cause of death was 66.7 deaths per 100,000 U.S. population, and age-adjusted death rates were higher for women (72.7) than for men (56.4). Death rates increased with age from 56.9 per 100,000 among individuals aged 65–74 y to 2,707.3 deaths per 100,000 individuals aged ≥85. Age-adjusted death rates were higher among the non-Hispanic white population (70.8) than the non-Hispanic black population (65.0) or the Hispanic population (46.0). Death rates attributable to dementia varied by age, sex, race, and Hispanic origin across states. The authors concluded that "understanding patterns and trends in dementia mortality is an important component of addressing this public health challenge," pointing to projections that suggest that by 2060 nearly 14 million individuals in the United States could be living with Alzheimer disease and related dementias.

National Vital Statistics Reports

PLANET Onco Dose Receives 510(k) Clearance

On March 7, the U.S. Food and Drug Administration (FDA) announced 510(k) clearance to DOSIsoft (Villejuif, France) to market its PLANET Onco Dose software platform for oncology and ^{90}Y microsphere selective internal radioembolization therapy (SIRT) and for 3D dosimetry components. In a March 12 press release announcing the decision, DOSIsoft described the 2 main elements of the PLANET Onco Dose modular software suite: (1) an oncology module with core system features, comprehensive reviewing of multimodal molecular image series (CT, MR, PET, and SPECT), fusion and registration, automatic and semiautomatic contouring of regions of interest, tumor segmentation, quantification, tumoral activity monitoring, and therapy response assessment; and (2) a dosimetry module including 3D personalized voxel-based internal dosimetry computation dedicated to molecular radiotherapy, including a personalized 3D dosimetry solution for ^{90}Y-based SIRT. To support SIRT, the software suite provides 3D liver–lung shunt assessment, voxel-based dosimetry based on ^{90}Y-microsphere PET (or SPECT Bremsstrahlung) series, dose computation models, analysis down to any liver subregion, advanced and interactive dosimetry quantification, the ability to scale to known activity, and compatibility with PET images acquired with another radioisotope (correction of branching ratio and decay parameters). "The current 510(k) FDA clearance of PLANET Onco Dose is a great achievement and recognition of our technology and solution," said Jean-Elie Kafrouni, DOSIsoft Americas CEO. "As a dosimetry expert company well-established in Europe, we will be bringing more

innovation to the U.S. centers with software versions supporting other radionuclide-based therapies in the near future."

U.S. Food and Drug Administration
DOSIsoft, Inc.

Almost Half of Global Childhood Cancers Not Diagnosed

On February 26, *The Lancet Oncology* issued a press release highlighting a modeling study in its current issue that estimated that almost 400,000 new cases of childhood cancer occur around the world annually but that current methods count only around 200,000 of these children. The simulation-based analysis was e-published on the same day by Ward et al. from Harvard University/Harvard Medical School (Boston, MA), St. Jude's Children's Research Hospital (Memphis, TN), and the Dana-Farber/Boston Children's Cancer and Blood Disorders Center (Boston, MA). The model made predictions for 200 countries and estimated that undiagnosed cases could account for more than half of the total in Africa, South Central Asia, and the Pacific Islands. In North America and Europe only 3% of cases remain undiagnosed. The authors estimated that without significant improvements 2.9 million cases will be missed in the next decade.

"Our model suggests that nearly 1 in 2 children with cancer are never diagnosed and may die untreated," said Zachary Ward, MPH, from the Harvard T.H. Chan School of Public Health. "Accurate estimates of childhood cancer incidence are critical for policy makers to help them set health care priorities and to plan for effective diagnosis and treatment of all children with cancer. While underdiagnosis has been acknowledged as a problem, this model provides specific estimates that have been lacking."

Previous estimates for the total incidence of global childhood cancer were based on data from cancer registries, which identify cases in defined populations. Sixty percent of countries, however, do not have such registries, and those that do cover only a small fraction of the overall population. As a result, many patients are not diagnosed and their cancers not recorded. The Global Childhood Cancer microsimulation model developed for this study incorporated data from cancer registries, combining it with data from the World Health Organization (WHO) Global Health Observatory, demographic health surveys, and household surveys developed by UNICEF.

The study provided data on underdiagnosis for each of 200 countries, estimating that in 2015 397,000 new childhood cancer cases occurred globally, compared to 224,000 that were recorded as diagnosed. This suggests that 43% (172,000 cases) of global childhood cancer cases were undiagnosed. The authors noted substantial regional variation, ranging from 3% in Western Europe (120 undiagnosed cases out of 4,300 total new cases) and North America (300 of 10,900 cases) to 57% (43,000 of 76,000 new cases) in Western Africa. In most regions of the world, the number of new childhood cancer cases is declining or stable. The authors estimated, however, that 92% of all new cases occur in low- and middle-income countries.

The most common childhood cancer in most regions of the world in 2015 was found to be acute lymphoblastic leukemia, with 75,000 new cases globally (including, among others, 700 in Northern Europe, >1,500 in West Africa, >3,500 in East Africa, and almost 30,000 in South Central Asia). In East and West Africa, Burkitt lymphoma was more common (>4,000 cases in East Africa and >10,000 in West Africa). "Health systems in low-income and middle-income countries are clearly failing to meet the needs of children with cancer. Universal health coverage, a target of United Nations Sustainable Development Goals, must include cancer in children as a priority to prevent needless deaths," said senior author Rifat Atun, MBBS, MBA, from Harvard University.

The authors found that barriers to access and referral in health systems result in substantial underdiagnosis of childhood cancer in many countries. They also emphasized that their results might be affected by limited data availability in some countries and by the model assumption that all diagnosed cases were accurately recorded in cancer registries. In commentary published in the same issue of *The Lancet Oncology*, Eva Steliarova-Foucher, PhD, from the WHO International Agency for Research on Cancer (Lyon, France), said "Where national data are available and used in the presented model, the proposed estimates should be robust. Yet the only way to validate these new estimates is for countries to ensure efficient provision of representative data....Increasing registration coverage and improving the data quality of existing registries would help to reduce the estimation error, which is equivalent to 21,000 cases globally....Developing efficient vital statistics systems would help to ensure registration completeness and unveil the magnitude of underdiagnosis of cancer. Currently, some mortality statistics are available in only 4 of 34 low-income countries and in 21 of 47 lower-middle income countries."

The Lancet Oncology