Molecular Imaging/Therapy: It's Only Useful If It's Useful—and Available

Advances in imaging technology have made it possible to view molecular pathways within living individuals as never before. However, molecular imaging and therapy have existed for more than a half-century and are based on long-established concepts and methods (see suggested references for support for statements made in this commentary). As molecular techniques come to the forefront in medicine, it has become clear that, just as a diversity of scientists is required to advance basic knowledge in the field, we will need physicians from multiple disciplines, cross-disciplinary training, and a commitment to cooperative exploration if the potential of molecular imaging therapy is to be fulfilled.

In the middle of the last century, scientists capitalized on tracer methodologies using radionuclides to investigate disease. These scientists had a variety of academic backgrounds, and those with medical degrees were from a range of disciplines, including pathology, surgery, internal medicine, pediatrics, and radiology (which included radiotherapy). They shared a common passion to understand health and disease, an understanding of the new field of radionuclide technology, and the access and ability to work with tracer technologies. Recognizing that medical technology should influence patient care, they developed therapeutic and diagnostic methods, some of which continue to be useful today (although often improved by better technology).

To share information, small gatherings were organized. These meetings led to formalization of the Society of Nuclear Medicine (SNM), with its first meeting in 1953 and first journal in 1961. SNM and *The Journal of Nuclear Medicine* became international vehicles for communication of scientific developments in the field. Twenty years later, a remarkable group of individuals identified the need to formalize a medical discipline around clinical and research procedures based on the use of radionuclides for molecular applications. The proposal was met with enthusiasm by organized medicine. Formal support for a new specialty board in nuclear medicine initially came from the American Boards of Internal Medicine (ABIM), Radiology (ABR), and Pathology (ABP) and from SNM. Belated opposition from the American College of Radiology (ACR) and ABR led the American Board of Medical Specialties to approve a compromise: a conjoint board, the American Board of Nuclear Medicine (ABNM), cosponsored by ABIM, ABR, ABP, and SNM. Each of these cosponsoring organizations would appoint 3 individuals to the ABNM board of directors. The initial board, appointed in 1971, included Joseph Kriss, MD, Richard Peterson, MD, and Joseph Ross, MD, from ABIM; Frederick J. Bonte, MD, E. Richard King, MD, and David E. Kuhl, MD, from ABR; Tyra Hutchins, MD, Ralph Kniseley, MD, and W. Newlon Tauxe, MD, from ABP; and Merrill Bender, MD, Paul Harper, MD, and Henry N. Wagner, Jr., MD, from SNM. Nuclear medicine stands on the shoulders of these giants. Scientific pioneers in their own right, they established a board certifying individuals in all aspects of the medical use of radionuclides, including therapy and imaging.

Leaders have visions that extend beyond their own self-interests. The early giants in nuclear medicine envisioned a 3-legged stool contributing to better care for patients. All legs of the stool were deemed important to the integrity of nuclear medicine and included molecular-targeted radionuclide therapy, molecular-targeted radionuclide therapy, molecular imaging, and molecular diagnostics. The seat supported by and uniting these legs was made up of research and development. All were believed to be important and integral to the well being of patients and medicine. With this strong foundation and a growing body of scientific knowledge and professional accomplishment, ABNM became an independent board in 1985.

Shifting Paradigm, Stable Foundation

Today an important paradigm shift to individualized or personalized medicine is occurring. Molecular imaging and therapy are in the forefront of this trend, especially for cancer. For the most part, current cancer therapies are population based; that is, targeted at an "average patient." The goal now is to individualize treatments to improve response and safety. Drugs that work in one individual may be ineffective or cause adverse events in others. Imaging may distinguish responders from nonresponders and promote early changes in management for those who do not respond. The National Cancer Institute's new guidelines for a complete response in lymphoma, now defined by an absence of uptake on imaging in a previously ^{18}F-FDG–avid malignancy, provide an example of the many potential roles of molecular imaging in cancer.

Webster's dictionary defines medicine as "the science and art of diagnosing, treating, curing, and preventing

disease. . .and improving and preserving health." Dorland's dictionary similarly defines medicine as "the art or science of healing diseases; especially the healing of diseases by the administration of internal remedies." Note the emphasis on healing and treating. Molecular imaging and nuclear medicine are almost self-explanatory; the previous focuses on molecules and the latter on atomic nuclei. Groups within our profession have defined nuclear medicine as "the medical specialty that uses the tracer principle, most often with radiopharmaceuticals, to evaluate conditions of the body for the purposes of diagnosis, therapy and research" and molecular imaging as "the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems."

Nuclear medicine is, however, increasingly characterized as merely 1 among many promising molecular imaging approaches. This is despite its position as the stable foundation upon which molecular imaging *and* therapy rest. Although broader in applications for research and development, molecular imaging is and has been essentially radionuclide-based at the clinical level. This is the origin and prototype of technology that has prevailed for more than a half-century. Although imaging combinations may yield additional information, translation for some imaging methods to clinical applications will be difficult. MR imaging provides intrinsic molecular information that can define metabolic pathways and the effect of therapy on these pathways, but it has not progressed in the clinic very far beyond characterization of vessels and vascular spaces. Optical imaging provides a powerful means for research visualization, because it is relatively inexpensive and readily available. But despite substantial enthusiasm from researchers and funding agencies, inherent limitations have prevented either of these imaging methods from translating broadly to the clinic. Both violate the principles of methodology required to accurately trace extrinsically introduced molecules. Tracer methodology requires that: (1) the molecule is not altered by the tracer and (2) the molecular process is not altered by the tracing molecule. Radionuclides are exceptionally well suited for these purposes. Nuclear imaging is highly sensitive, quantitative, and readily translated to human subjects. Radioisotope emissions are not as attenuated as fluorescent signals and, therefore, are less depth dependent. Simply stated, tracer methodologies using radionuclides and radionuclide signal detection are likely to continue to dominate molecular imaging at the clinical level because of their inherent advantages.

Successes and Questions

No other discipline of medicine has proven as continuously exciting over the years as nuclear medicine. As Henry N. Wagner, Jr., MD, has stated, "this is the best-kept secret in medicine." There is long history of an intimate relationship between diagnosis and therapy facilitated by nuclear medicine techniques. Today, the promise of molecular imaging to play an important role in accounting for individual variations of disease and for personalizing the diagnostic strategy is unlikely to be fulfilled in the absence of therapeutic relationships. Although molecular therapy encompasses a much broader range of approaches, molecular-targeted radionuclide therapy provides the most intimate and interdependent relationship of molecular imaging with molecular therapy. The availability and direction of molecular imaging in the future seems likely to depend on current research and successes in molecular therapy.

We have seen some stunning successes. More-effective, less-toxic drugs for lymphoma based on molecular-targeted radionuclide imaging have been approved, with numerous reports of high response rates and favorable long-term outcomes—including reports of cures in otherwise untreatable disease. These drugs compare favorably by almost any standard with competing pharmaceutical regimens, and many believe that these new approaches should be administered earlier in the course of disease progression.

Yet these new molecular-targeted radionuclide-based regimens are markedly underused, even in markets where patients are actively asking for access. Whereas rituximab (Rituxan), a drug for immunotherapy of lymphoma, has been a market success, related drugs ^{90}Y-ibritumomab (Zevalin) and ^{131}I-tositumomab (Bexxar) are so underused that the *New York Times* and other major U.S. newspapers have published articles about the need to expand access. The situation is so counterintuitive to the notion of providing optimal diagnosis and treatment to patients who need it most that we must ask ourselves and our colleagues in other disciplines difficult questions: Why is this so? Is it because there is no longer an advocacy group for molecular-targeted radionuclide therapy? Should we be actively taking the facts to patients and their advocacy groups?

More important and significant for long-range planning is the question of whether nuclear medicine has failed to provide and require adequate therapy training. Have radiation and medical oncology likewise failed to show an interest in molecular-targeted radionuclide-based therapies, so that individuals from these disciplines lack both basic knowledge and defined access? If nuclear medicine focuses solely on molecular imaging, then a vacuum exists and is likely to grow. There is a need for leadership, novel strategies, and partnering with other groups. Oncologists have been accused of "withholding" these treatments for economic and territorial reasons. This is as unacceptable as our failure to ensure that these therapies are readily available to needy patients. Responsible for patient welfare, we can no longer shy away from speaking out.

Going Forward

Nuclear medicine once attracted the best. The future of nuclear medicine and molecular imaging and therapy depends on the long-term availability of talented and passionate scientists and physicians—not on advances in technology. "It is not necessary to change. Survival is not mandatory," wryly noted the efficiency and productivity

expert W. Edwards Deming. If we are to survive, we must have foresight and wisdom. Transformations in patient care can be facilitated by molecular medicine, but only if physicians are trained to provide that care. Organizations already exist with the influence and infrastructure to move forward with training this workforce. In the United States, the SNM's mission is "to improve health care by advancing molecular imaging and therapy." ABNM aims to ensure that physicians meet adequate standards for delivering patient care using nuclear technologies for molecular tracing and therapy. These 2 groups will be looked to as leaders in identifying changes that can lead to the creation of the molecular imaging and therapy workforce of the future.

How will this workforce be different? Given the current challenge of available therapeutics with verified success but limited use, we must ask additional hard questions about the training that nuclear medicine physicians should receive. Do we currently have sufficient focus on the ethical and social responsibilities of each physician and scientist involved in patient care? A therapeutic option is inherent in the definition of medicine and should be seen as an integral part of our field. If molecular tracing (imaging) leads, for example, to a decision that therapy should not be given, then this implies that a therapeutic option exists. We must think like a patient and distinguish that which a physician does from that which a "technocrat" does.

Physician diversity will be required if nuclear medicine is to participate in the full realization of the potential of molecular imaging and molecular-targeted radionuclide therapy. This is a problem that we can and must resolve now. We must identify where and how education in molecular-targeted radionuclide therapy is provided in training programs today, and this effort must not be restricted by traditional discipline boundaries. With additional training, many individuals specializing in medical oncology and radiation oncology—as well as nuclear medicine—have backgrounds that should enable them to engage in molecular-targeted radionuclide therapy. Either new organizations will develop or the existing organizations must embrace this diversity by showing the same willingness as our field's founders to cross boundaries and plan together to adapt to the ever-changing promise of medical progress.

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Gerald DeNardo, MD
Professor Emeritus, Internal Medicine, Radiology, and Pathology
University of California Davis Medical Center
Sacramento, CA

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a number of different types of cancer. After the clinical presentations, Drs. Atcher and McCarthy segued the discussion to the public policy arena by providing an overview of current reimbursement challenges and our regulatory concerns at the U.S. Food and Drug Administration. In addition, they discussed the need to increase patient participation in clinical trials and to remain steadfast in our collective advocacy efforts to boost federal funding for biomedical research at both the Department of Energy and the National Institutes of Health.

Briefing attendees expressed great interest in what was presented and indicated a desire to convene again in the fall for further discussion and information sharing, particularly regarding the expected January release of the revised Centers for Medicare & Medicaid Services National Oncologic PET Registry coverage guidance. Other next steps include exploring ways to work together to increase clinical trials recruitment by educating physicians and nurses about molecular imaging studies. SNM also committed to developing additional materials illustrating the intersection between molecular imaging and comprehensive, quality cancer care. SNM looks forward to expanding upon this initial effort and developing strong working relationships with our colleagues in the cancer community.

Valerie Cronin, CNMT, FSNMTS
SNM/AMI Patient Advocacy Task Force Chair

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a comprehensive view. A standard patient survey instrument has been developed by ABMS for physicians providing direct care. It is likely that a standard brief national survey will be developed for the other groups listed for a 360° survey. The advantage of a standard brief national survey is that the results for each diplomate can be compared with those in a national database. Use of a standard survey also holds the promise of reducing redundancy.

The least-well-understood competency is systems-based practice. The goal of this competency is to have the diplomate understand how other parts of the health care system affect the quality of practice. For example, patient waiting times are often affected by the availability of transporters to bring patients to and from the nuclear medicine facility. The accuracy and timeliness of interpretation are dependent on the accuracy and timeliness of the transcription as well as the method of delivery of the report. Understanding systems-based practice is especially important, because significant improvements in health care usually require changes to systems in addition to changes that individuals can make.

Henry D. Royal, MD
Executive Director, ABNM