Molecular Imaging INSIGHT

BY JONATHAN BATCHELOR

Evidence-Based MEDICINE

Points to Wider Role for Molecular Imaging in Patient Care

Evidence-based medicine, the practice of healthcare interventions guided by or based on supporting scientific evidence, is a topic of great interest among payors and clinicians. The combined pressures of rising medical costs, longer life expectancy, and a demographic spike in patients 50 years and older has led to the charge that healthcare policy planners have embraced its practice as method to rein in increased expenditures. Public health officials' counter that evidence-based medicine ensures that patients receive the best resources for their care, without unnecessary and wasteful procedures.

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"Some fear that evidence-based medicine will be hijacked by purchasers and managers to cut the costs of healthcare," observed David L. Sackett, MD, and colleagues more than a decade ago (*British Medical Journal*, Jan. 1996). "This would not only be a misuse of evidence-based medicine but suggests a fundamental misunderstanding of its financial consequences. Doctors practicing evidence-based medicine will identify and apply the most efficacious interventions to maximize the quality and quantity of life for individual patients; this may raise rather than lower the cost of their care."

A healthcare area that has seen an unprecedented surge in utilization in the recent past is that of diagnostic imaging. It is perhaps the fastest rising medical expenditure in the United States, with an annual growth rate of 9 percent, nearly one-half more than the annual increase in general medical expenditures (approximately 6 percent). As such, policy-makers and payors are increasingly demanding that evidence-based data justify the utilization of imaging procedures.

Although evidence-based medicine has been the focus of work by many healthcare researchers (nearly 30,000 citations on the term are available on the National Library of Medicine's PubMed web site), imaging has received scant attention in this arena. When it comes to scholarly research on evidence-based nuclear medicine imaging and molecular imaging, the data become clearer still with approximately 27 citations returned on these search criteria.

According to Bruce E. Hillner, MD, professor and eminent university scholar in the department of internal medicine at Virginia Commonwealth University in Richmond, Va., evidence-based medicine research in molecular imaging has been hamstrung by its failure to perform prospective data collection and sufficiently randomized patients. He said this may be due to a lack of tradition in the imaging community to follow the paradigma similar model as the therapeutic community that does clinical trials.

R. Edward Coleman, MD, professor of radiology and chief of the division of nuclear medicine at Duke University School of Medicine in Durham, N.C., points to a lack of funding from the same governmental and private-payor organizations that are demanding the evidence-based data. Further complicating this is the fact that the number of nuclear medicine physicians to do the research is declining.

"The challenges [to conducting evidence-based medicine research in molecular imaging] are getting the funding to get the studies performed, actually getting the studies performed, getting government approval, and then getting reimbursement from the third-party payors," Coleman noted.

Meta-evidence for metabolic imaging

One of the primary limitations for achieving robust evidence-based medicine studies in molecular imaging, and diagnostic imaging in general, has been a lack of prospective studies with a

NOPR Delivers Evidence for Expanded PET Use in Oncology Imaging

Diagnostic findings from FDG-PET imaging changed the intended care of more than one in three cancer patients, according to a study of first-year data from the National Oncologic PET Registry (NOPR), published in May in the *Journal of Clinical Oncology*. NOPR was launched in May 2006 in response to the Center for Medicare and Medicaid Services' (CMS) Coverage with Evidence policy to collect data through a clinical registry to inform the Center's FDG-PET coverage determination decisions for currently non-covered cancer indications. The registry is comprehensive, including data from 23,000 patients.

''The NOPR working group sought to measure the impact of PET findings on patient management in a manner minimally intrusive to care providers," said Bruce E. Hillner, MD, lead author for the study and professor and eminent university scholar in the department of internal medicine at Virginia Commonwealth University in Richmond, Va. "This was critical for successfully collecting the large amount of data required for a robust analysis."

Hillner, currently chair of one of the guideline panels within the American Society of Clinical Oncology (ASCO), is also chair of the NOPR working group. NOPR is sponsored by the Academy of Molecular Imaging (AMI) and managed by the American College of Radiology (ACR) and the ACR Imaging Network (ACRIN); ASCO and SNM also have played key roles in guiding the project's development.

NOPR is a prospective data registry that collects information from a PET facility, from the physician requesting a PET scan, and from the interpreting physician's PET report for cancers not currently covered by CMS. The registry was designed to meet CMS criteria for evidence development; therefore, all patients are Medicare beneficiaries. PET studies performed on Medicare beneficiaries for CMS-approved indications in breast, cervical, colorectal, esophageal, head and neck, non-small-cell lung, and thyroid cancers, or lymphoma or melanoma are not eligible.

Cancer types that Medicare currently reimburses for only through NOPR include those of the ovary, uterus, prostate, pancreas, stomach, kidney and bladder. The NOPR web site, www.cancerpetregistry.org, has

sufficiently randomized cohort, as Hillner noted. However, meta-analysis of research from single-site and multisite studies, are providing indications for a wider role in the utilization of molecular imaging.

Rahain Hussain, MD, of the Institute of Nuclear Medicine and Ultrasound in Dhaka, Bangladesh, and John Buscombe, MD, of the department of nuclear medicine, at Royal Free Hospital in London, used an on-line, literature-based approach to the evidence basis for scintimammography.

Their results, published in the journal *Nuclear Medicine Communications* (July 2006), reviewed outcomes for 2,424 patients from single-center trials and 3,049 patients from multicenter trials on scintimammography conducted with 99mTc MIBI-labeled isonitriles. They only included studies conducted after 1997, to ensure that the data were from exams conducted after the procedure had become mature.

They found that the procedure had an overall sensitivity of 85 percent and a specificity of 84 percent. They were not able to determine patient outcomes or management changes as a result of the scintimammography procedure, due to the retrospective nature of their analysis. However, they do believe that the multinational review indicates use of the procedure.

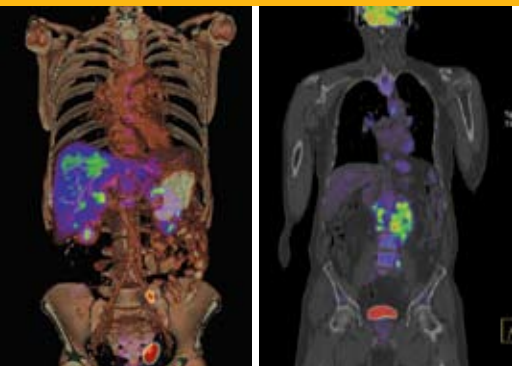
"There is evidence that this is a robust imaging technique delivering high sensitivities and specificities in patients studied in both single-center and multicenter trials and, as such, can be relied on as an adjunctive method for the investigation of primary breast cancer," they wrote.

Evidence-based justification for nuclear cardiology procedures also has used the literature meta-analysis approach in lieu of instituting a multisite clinical registry. Myocardial perfusion scintigraphy (MPS) data were presented to the UK National Institute of Clinical Excellence by the British Nuclear Cardiology Society and British Nuclear Medicine Society and discussed in the *European Journal of Nuclear Medicine and Molecular Imaging* (Feb. 2004).

"In patients presenting with stable or acute chest pain, strategies of investigation involving MPS are more cost-effective than those not using the technique," the authors wrote. "MPS also has particular advantages over alternative techniques in the management of a number of patient subgroups, including women, the elderly and those with diabetes, and its use will have a favorable impact on cost-effectiveness in these groups."

They noted that the technique was being underutilized in the UK, based on wait time for the procedure (20 weeks) and by comparison with the numbers of revascularizations and coronary angiograms performed. The researchers found that the current number of MPS studies performed in the UK was 1,200 per million residents; they estimated that the real need was for 4,000 MPS procedures per million residents.

Another study, published in the *European Journal of Nuclear Medicine and Molecular Imaging* (Jan. 2006) and *Journal of*



Ovarian and abdominal cancers are two of the cancer types for which Medicare currently reimburses only through the National Oncologic PET Registry (NOPR). At left is an ovarian carcinoma in a PET with contrast CT angiography (Biograph 16 PET•CT; courtesy of the University of Tennessee Medical Center, Knoxville). Image at right shows a malignant lymphoma in the abdomen (Biograph 16 PET•CT; courtesy of Beijing Hospital, Beijing, China).

a complete list of the covered cancer types for the registry.

The study analyzed data regarding nearly 23,000 patients contributed to NOPR by more than 1,200 facilities in the United States that provide PET scans. The mean patient age of the patients was 72.6 years; 9.7 percent were younger than 65 years and 5.2 percent were 85 years or older.

The primary end-point of the study was the impact of PET on physicians' intended management. The study authors assessed a change in management in four ways:

- Intended management was stratified as either treatment or non-treatment.
- The intent of planned therapies was determined to be either curative or palliative, which allowed the researchers to assess if a meaningful change included a change in intent, even if the specific therapy did not change.
- Changes in the type or number of clinical actions were defined as minor or major; a major change was defined as a switch in treatment type and a minor change was defined as the addition or deletion of treatments, but where one type remained constant in the pre- and post-PET plan.
- The data also were scored as to whether therapy intensity increased, decreased, or was unchanged by comparing the number of modes in the pre- and post-PET plans.

Analysis of data collected found that FDG-PET utilization is associated with a 36.5 percent change in the decision of whether or how to treat a patient's cancer. The study also found that PET is associated with a management change in almost 75 percent of patients when the addition or deletion to specific modes of therapy was

Nuclear Medicine (Nov. 2006), deemed multislice CT and SPECT "complementary rather than overlapping" technologies in coronary artery disease detection. The authors concluded that "although a relationship exists between the severity of CAD on multislice CT and myocardial perfusion abnormalities on SPECT, analysis on a regional basis showed only moderate agreement between observed atherosclerosis and abnormal perfusion."

The Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD (SPARC) multicenter trial currently underway (50 sites; 2,800+ patients enrolled; goal: 3,700) is seeking to define the clinical value of myocardial perfusion (stress SPECT, stress PET), CT coronary angiography (CTA) and combined myocardial perfusion-anatomy (PET/CT) imaging on post-test resource utilization. It also looks to determine the incremental prognostic value of stress SPECT, stress PET, CTA and PET/CT for predicting cardiac death and nonfatal myocardial infarction following a procedure.

The Biostructure and Bioimaging Institute of the National Council of Research in Naples, Italy, utilized a literature-based review of different clinical applications of nuclear medicine procedures in cardiology. Their work, published in the *Quarterly Journal of Nuclear Medicine* (Dec. 2002), advocated specific instances for the utilization of cardiac molecular imaging.

"Radionuclide imaging techniques appear to be appropriate in risk assessment, prognosis and evaluation of therapy in patients after myocardial infarction," the authors wrote. "In patients with unstable angina, radionuclide testing is indicated in the identification of ischemia within the distribution of the 'culprit' lesion or in remote areas. Exercise and pharmacological cardiac perfusion imaging are appropriate and useful in the diagnosis and prognosis of chronic coronary artery disease. Nuclear medicine procedures are also useful in the assessment of myocardial viability in patients with left ventricular dysfunction, in the assessment of interventions for the evaluation of patients after percutaneous transluminal coronary angioplasty and coronary artery bypass grafting."

In 2006, Johannes Czernin, MD, and colleagues from the department of molecular and medical pharmacology in the Ahmanson Biological Imaging Clinic/Nuclear Medicine and David Geffen School of Medicine at the University of California, Los Angeles, performed a literature-based evidence review of improvements in cancer staging with PET/CT. Their findings, published in the *Journal of Nuclear Medicine* (Jan. 2007, supplement), determined that reliable evidence had emerged in support of the notion that PET/CT offers diagnostic advantages over its individual components for the major cancers.

"Although the value of PET/CT over PET alone for treatment monitoring has yet to be determined, improvements in the staging and restaging accuracies of PET/CT over PET or CT alone for

NOPR Delivers Evidence for Expanded PET Use in Oncology Imaging, *cont'd*

"These data confirm what we have known for some time: molecular imaging is a powerful tool in diagnosing, treating, and monitoring disease and is capable of dramatically changing the course of patient care. For oncologists, we're getting a much better idea of how to use this technology in patients with cancer."

SNM President Alexander J. McEwan, MD, professor and chair of the department of oncology, faculty of medicine, at the University of Alberta and director of oncologic imaging at Cross Cancer Institute in Edmonton, Canada

included. In addition, the NOPR data revealed that for patients with a pre-PET plan of biopsy, the post-PET plan had a significant impact on care, with these patients avoiding biopsy in about 75 percent of the cases analyzed.

NOPR working group co-chair R. Edward Coleman, MD, professor of radiology and chief of the division of nuclear medicine at Duke University School of Medicine in Durham, N.C., and study author, observed, "We were especially surprised by the impact of the PET findings on patients who were originally planned to have a biopsy."

Oncologist, NOPR working group co-chair and study author Anthony F. Shields, MD, professor of medicine and oncology at the Karmanos Cancer Institute at Wayne State University in Detroit and chair of ACRIN's Oncology Committee said of the research findings, "These results confirm what we suspected from increasing experience with PET. However, we lacked the significant data required to prove the benefit of PET for many uncovered indications. It's very encouraging that oncologists and other clinicians may have access to the valuable information PET affords for ensuring the best patient care."

"These data confirm what we have known for some time: molecular imaging is a powerful tool in diagnosing, treating, and monitoring disease and is capable of dramatically changing the course of patient care," commented SNM President Alexander J. McEwan, MD, professor and chair of the department of oncology,

different cancers are now established," the authors wrote. "These improvements are frequently statistically significant and average about 10 to 15 percent."

The push for prospective

"The kinds of studies that radiologists and nuclear medicine physicians have been used to doing look at the sensitivity and specificity of diagnostic tests and are very uncommonly linked to outcomes; but it's hard to look at outcomes when you're only one tiny piece in the chain," said Barry A. Siegel, MD, professor of radiology and chief of the division of nuclear medicine at the Mallinckrodt Institute of Radiology at Washington University in St. Louis.

"Randomized, controlled trials are very hard to do in diagnostic imaging," he noted. "Clinicians are reluctant to have patients participate in those trials and patients are reluctant to participate in those trials."

An effort to address the lack of prospective, randomized studies in nuclear medicine imaging was launched in November 2005, with the creation of the National Oncologic PET Registry (NOPR). (See sidebar starting on page 4.) NOPR was developed in response to the Centers for Medicare and Medicaid Services (CMS) proposal to expand coverage for positron emission tomography with ^{F18}FDG PET to include cancers and indications not presently eligible for Medicare reimbursement.

The NOPR working group is chaired by Hillner, and co-chaired by Siegel, Coleman, and Anthony F. Shields, MD, professor of medicine and oncology at the Karmanos Cancer Institute at Wayne State University in Detroit.

Diagnostic findings from FDG-PET imaging changed the intended care of more than one in three cancer patients, according to a study of first-year data from NOPR, recently published in the *Journal of Clinical Oncology* (May 2008). The registry is still open and continues to accept patients, according to Shields.

"As of late March this year, we had 75,000 patients enrolled," he said. "We are currently running about 200 patients a day; I don't think any of us expected that we would see this amount of participation when we began."

SNM president Alexander J. McEwan, MD, professor and chair of the department of oncology, faculty of medicine, at the University of Alberta and director of oncologic imaging at Cross Cancer Institute in Edmonton, Canada, believes that the NOPR model holds great promise as a structure for future evidence-based molecular imaging indications.

"The NOPR trial has shown that you can, on a multicenter basis, collect the type of change of management leading to change of outcomes data that we have to build into imaging trials," McEwan said. "I think as a base skeleton, with a bit more refinement depending on the complexity of procedure, we can use this model as a starting point for future evidence-based molecular imaging trials." MII

faculty of medicine, at the University of Alberta and director of oncologic imaging at Cross Cancer Institute in Edmonton, Canada.

"For oncologists, we're getting a much better idea of how to use this technology in patients with cancer," McEwan said. "The NOPR study demonstrates that PET has a role in a number of cancers for which we now have evidence we didn't have before."

To further a better understanding of the NOPR results and their meaning for clinical practice, as well as the appropriate use of PET technology in cancer imaging, McEwan said that SNM is closely working with both ASCO and the American Society for Therapeutic Radiology and Oncology (ASTRO) to develop more teaching courses for their members as well as ongoing involvement in one another's conferences.

On the basis of its research findings, NOPR has formally asked CMS to reconsider its current National Coverage Determination (NCD) on FDG-PET and requested that it provide Medicare coverage of FDG-PET for diagnosis, staging and restaging across all oncologic indications. CMS is expected to issue a formal response to the NOPR request by October this year.

"The NOPR Working Group was careful to consider the impact of including or excluding in their analysis cases where the pre-PET treatment plan was already imaging," said AMI president Timothy McCarthy, PhD, in a letter to Steve Purrough, MD, CMS director, coverage and analysis group. "Yet, even assuming that PET provided no advantages for those patients with pre-PET imaging plans, the NOPR Working Group's 'worst-case estimate' [in their words] was that PET would nevertheless be associated with a major change in treatment in nearly 20 percent of patients."

"NOPR afforded oncologists and nuclear medicine physicians a unique opportunity to make PET available to Medicare beneficiaries and to improve our understanding of the role of PET in oncology practice," said study author Barry A. Siegel, MD, professor of radiology and chief of the division of nuclear medicine at the Mallinckrodt Institute of Radiology at Washington University in St. Louis, chair of ACRIN's PET Imaging Core Laboratory, and NOPR working group co-chair. "Based on these data, Medicare should strongly consider opening up the coverage to include diagnosis, staging and restaging for all cancers."