

## 2014 Cassen Lecture: What Have We Learned from the National Oncologic PET Registry?

*Editor's note: Barry A. Siegel, MD, known for his pioneering work in nuclear medicine and clinical PET imaging, was awarded the Benedict Cassen Prize during the 2014 Annual Meeting of the SNMMI in St. Louis, MO. Siegel is a professor of radiology and medicine and chief of the Division of Nuclear Medicine at Mallinckrodt Institute of Radiology at Washington University School of Medicine in St. Louis. In allowing Newsline to publish his lecture on the National Oncologic PET Registry, Dr. Siegel emphasized the collaborative nature of the registry's success, which he noted "would not have been possible without the efforts of a core group of dedicated participants and the input of physicians from across the nation."*

**B**efore talking about the National Oncologic PET Registry (NOPR) and its efforts to achieve wider reimbursement for PET imaging in clinical practice, I would like to pay tribute to several individuals who have had profound influences on my career. E. James Potchen, MD, was chief of nuclear medicine at Washington University when I was in medical school. As a medical student, I happened to wander into his office looking for a sophomore elective. The next thing I knew I was launched on a nuclear medicine career. Jim pushed me hard to do things very early and taught me never to accept dogma but to look for underlying evidence. Michael J. Welch, PhD (1939–2012), a past SNMMI president and Cassen Prize winner, and I collaborated scientifically for 40 years. I was fortunate to be able to run Mike's translational research laboratory and work with him to advance new discoveries into clinical use. R. Edward Coleman, MD (1943–2012), and I were medical school classmates. He did his nuclear medicine training at Washington University and was the acting director of nuclear medicine while I was in the Air Force. Ed had been quite active in the Institute for Clinical PET, and, about 20 years ago, we launched a number of efforts aimed at enhancing reimbursement for PET procedures. If Ed were here today, we would be sharing this award—he was an absolute partner all the way through.

### Evolution of Clinical PET

PET in its current form was invented at Washington University in the mid-1970s. It was obvious almost immediately that this would be a phenomenal research tool, and research applications rapidly evolved into potential clinical applications as scanners improved and clinical use became more practical. Acceptance of PET into clinical practice, however, occurred very slowly. By 1981 we were performing about 10,000 procedures per year in the United States, with the majority of these in neurology and cardiology (because of the limited field of view of available

scanners). At the end of the next decade, this number had doubled. By 2001 this number had grown to more than 250,000 per year. It was projected at that time that rapid growth would continue, with 3 million scans per year by 2011. The actual number would end up being only about 1.9 million. We had expected not only more rapid expansion of reimbursement but the advent of many new radiopharmaceuticals as PET drivers. This did not come to pass; in fact, growth has been very slow over the technology's 40-year history.

A number of barriers challenged early dissemination of PET. PET was an expensive technology, especially in the beginning, when an in-house cyclotron was needed. Moreover, clinicians did not easily understand the images, which were not as clear as those they were accustomed to seeing (with CT, for example). The supply of radiopharmaceuticals was not reliable, a situation that took many years to remedy. (The coincidence gamma camera, despite the fact that it was not a terribly effective instrument, was actually an important driver in the establishment of a radiopharmaceutical supply chain in the United States.) Radiopharmaceutical production and regulation were problematic, with underlying challenges in variable and restrictive coverage policies by government agencies and private payers. These problems appropriately reflected a general lack of definitive evidence on the utility of this new technology.

### PET Reimbursement in the United States

The process of PET reimbursement in the United States has been complex and slowly evolving. The U.S. Food and Drug Administration (FDA) approved the first New Drug Application for  $^{18}\text{F}$ -FDG in 1994, in part as a result of efforts led by the Institute for Clinical PET. This process was aided by the unique approach implemented through the FDA Modernization Act of 1997, which was supposed to be short-lived but lasted for 14 years, allowing the industry to grow substantially. More challenging was the process of defining reimbursable clinical indications, a process that in the United States has been determined by technology assessment panels of third-party payers and dominated by the Centers for Medicare & Medicaid Services (CMS). The CMS standard is that reimbursement for a medical procedure must be "reasonable and necessary"—qualitative language that is subject to interpretation. In the 1990s, CMS adopted a new evidence-based approach for making coverage determinations, requiring peer-reviewed scientific evidence to document that a new technology leads to changes



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in patient management and to improved health outcomes for Medicare beneficiaries. This change evolved, in part, as a result of perceptions that MR technology had proliferated too rapidly in the 1980s and 1990s after blanket approval without a critical assessment of actual benefits (1). PET became caught in a crossfire situation in which policy-makers were newly wary of high-technology medicine. We faced barriers to reimbursement at every turn.

The nuclear medicine community and the Institute for Clinical PET pushed CMS for broad coverage of PET for oncology. CMS denied this request and asked the community to provide evidence on a cancer- and indication-specific basis. This was problematic, because specific evidence typically had not been very robust. We found ourselves in a classic “Catch-22” situation: we could not get reimbursement because we did not have the evidence, but we could not get the evidence because we did not have reimbursement. Neither the National Institutes of Health nor PET technology manufacturers were prepared to undertake the broad range of clinical trials called for. Most of the PET radiopharmaceuticals of interest were nonproprietary, so the suppliers of these agents were not interested in funding such studies.

At such a difficult juncture, it was important to ask the question: Does PET really improve health outcomes in patients with cancer? This was, frankly, difficult to demonstrate based on the evidence available at the time. The majority of PET clinical trials in the literature were single-institution studies, ranging from pilot studies, with a few patients, up to phase II studies, generally with  $\leq 50$  patients. Only in recent years have we improved on this evidence base, which constituted a major reason for unfavorable technology assessments and limited coverage of PET. In the last few years, we have seen an increase in the number of randomized controlled trials (RCTs; almost all in countries with highly restricted PET coverage). In addition to RCTs, we have also had many observational studies as well as the practice-based evidence compiled by registries. It is important to note that we have largely looked at PET’s effect on health outcomes by assessing change in management as a surrogate for measures of improved outcomes such as survival or quality of life. Change

in management has been especially important in those instances in which PET has led us to avoid therapies that would not have benefited specific patients.

#### Randomized Clinical Trials: $^{18}\text{F}$ -FDG PET in Oncology

Table 1 indicates where we stand with published oncologic RCTs including  $^{18}\text{F}$ -FDG PET. For the most part these have shown that PET does indeed have a benefit, although some trials have yielded conflicting evidence, most notably the recent trial published in the *Journal of the American Medical Association* noting that PET for preoperative staging of patients with liver metastases from colorectal cancer has only a small benefit—quite different from an earlier RCT and from almost all of the nonrandomized trials that have preceded it (2). I would point out that when intention to treat (ITT) analyses have been performed on the results of these trials, no improvement in survival has been documented. One can legitimately ask whether, given the fact that PET is only a small part of the chain in patient diagnosis and management, should a diagnostic test really be expected to be the driver of survival? This has been an ongoing point of discussion with the payer groups for a long time. It would be wonderful if we had RCT results for every tumor and every indication in every location, but no practical mechanisms exist for funding such a comprehensive range of studies, either in the United States or elsewhere in the world.

In addition to applications in staging, restaging, and preoperative planning, the role of  $^{18}\text{F}$ -FDG PET in treatment monitoring has been expanding over the last few years. It is clear that PET is more reliable than anatomic imaging for determining end-of-treatment response. It is now the standard of care in Hodgkin lymphoma and aggressive non-Hodgkin lymphoma at completion of first-line therapy, because it provides a more reliable indication of the state of disease. Interest is also growing in early monitoring during the course of therapy to allow for so-called response adaptation in high- and low-risk patients, as well as more generally allowing us to avoid ineffective (and expensive) treatment. A number of trials are ongoing, and we are awaiting the results of those trials. Two Hodgkin lymphoma response-adaptation trials have now been published at least in partial form, with conflicting results (3,4).

**TABLE 1**  
Randomized Clinical Trials of  $^{18}\text{F}$ -FDG PET in Oncology

Cancer (indication)	No. RCTs	Results
Non-small cell lung cancer (preoperative staging)	5	Mixed but favor reduction in futile thoracotomy
Colorectal cancer (liver metastasis resection)	2	Conflicting results with respect to reduction in futile surgery
Colorectal cancer (recurrence detection)	1	Earlier detection and increased likelihood of complete resection of recurrence
Cervical cancer (treatment of extrapelvic disease guided by PET)	1	No improvement in overall or disease-free survival

Although we are still waiting to hit a home run in this area, I believe it will eventually come.

### **Medicare Coverage of Oncologic PET**

Medicare coverage of PET began in 1998, with reimbursement for evaluation of solitary pulmonary nodules and initial staging of non-small cell lung cancer (NSCLC). Those were the “killer apps” of oncologic PET that really launched its clinical use. The following year, after a public meeting and with considerable restrictions, we managed to get a few more boutique applications added, including suspected recurrent colorectal cancer, lymphoma, and melanoma. In 2001, after a new request for broad coverage and another public meeting, this was expanded to diagnosis, staging, and restaging of 6 prevalent cancers: NSCLC, lymphoma, esophageal cancer, malignant melanoma, colorectal cancer, and head and neck cancer. The central restriction was that PET should be used only to resolve inconclusive results of standard tests or as a replacement for those tests.

In 2002, Ed Coleman and I organized the submission of what ended up being 11 separate petitions to seek coverage for 11 different cancers. This was an unwieldy approach, not only for us in the nuclear medicine community but also for CMS. Therefore, in 2004, while debating what to do with these many petitions and those likely to follow, CMS proposed a mechanism that would allow for expanded coverage: the creation of a national registry. A “snapshot” of Medicare reimbursement of oncologic PET at the time shows that we had reimbursement for diagnosis, staging, and restaging of the 6 prevalent cancers; staging, restaging, and treatment monitoring of breast cancer (treatment monitoring data were not optimal but this was a political decision made at that time); a micromanaged indication for thyroid cancer in thyroglobulin-positive/radioiodine-negative patients; and staging of cervical cancer with negative conventional imaging outside of the pelvis.

### **Coverage with Evidence Development (CED)**

The national registry approach chosen by CMS was based on the concept of coverage with evidence development (CED). This option would allow for coverage of promising drugs, biologics, devices, diagnostics, and procedures that would not otherwise meet Medicare’s evidentiary standards for being “reasonable and necessary.” In a sense, CMS was talking out of both sides of its mouth—but in a good way—saying “We do not think there is sufficient evidence to cover PET, but if you do the following, we will cover it.” CED links coverage to a requirement that patients participate either in a registry or clinical trial. The goal, which is quite logical, is to secure longitudinal data that can document the ways in which technology is being used, as well as results of this use, which may ultimately help to shape policy. CED was first applied to biologic therapies for colon cancer and, at almost the same time, for implantable cardiac defibrillators (a very successful registry) and oncologic PET.

Knowing that this CED determination was coming as part of the National Coverage Determination (NCD) that

related to those 11 petitions we submitted, one Saturday morning Ed and I were on the phone and basically cooked up the idea for NOPR. We were heavily influenced by a paper that had just been published in the *Journal of Clinical Oncology*, a single-institution study written by Bruce Hillner, MD, from the Medical College of Virginia (now Virginia Commonwealth University; Richmond) (5). The cleverest thing that Ed and I did was to recruit Bruce to be the NOPR principal investigator. Ed and I were co-chairs, and we also invited as a co-chair Anthony Shields, MD, PhD, from Wayne State University (Detroit, MI), a medical oncologist and also a medical imager. Based on previous collaborations, we recruited the American College of Radiology Imaging Network (ACRIN) to manage the registry, with statistical support from the group at Brown University (Providence, RI), including Dawei Liu, PhD, Fenghai Duan, PhD, Ilana Gareen, PhD, and Lucy Hanna, MS. The registry was initially funded and launched by the Academy of Molecular Imaging and endorsed by the American College of Radiology, the American Society of Clinical Oncology, and SNM.

### **NOPR Goals**

We worked hand in hand with CMS to develop the registry. Our objective was simple: we wanted to assess the effect of PET on referring physicians’ plans of intended patient management across a wide spectrum of cancer indications for PET not covered by Medicare. Our hypothesis was also relatively simple: that PET would lead to changes in patient management as often for noncovered as for covered cancers.

We also had several important goals that constrained the design of the registry. We did not want to simply perform a clinical trial, publish it, and then move on. We wanted this approach to provide access to PET nationwide, with potential availability in any area of the country. We wanted to do this in a way that would minimize the burden to patients, PET facilities, and referring physicians, while at the same time generating evidence of reasonable and sufficient quality to help CMS decide whether to expand coverage of PET. We also knew that we would need to be financially self-supporting to manage the registry. Although we had some start-up funding, we needed to identify another source of funding. We did this by establishing a per-click charge from PET facilities that would allow them to put patients on the registry and thereby collect from Medicare for the technical component of the PET scan.

Our workflow was quite simple. The referring physician requesting a PET scan was required to fill out a “pre-PET” form answering a series of questions. The pre-PET form asked for the specific reason for the scan, including different categories under the headings of diagnosis, staging and restaging of known cancer, and monitoring of treatment response. The key question on the form asked the referring physician what his or her management strategy would have been had PET not been available. Each patient when arriving for imaging was asked to provide oral consent to have

data used for research purposes. After the PET scan was acquired, interpreted, and reported, the referring physician was asked to complete a second questionnaire (“post-PET” form), which included a mirror version of the key question from the pre-PET form: given the actual PET findings how had intended management changed? The referring physician was also asked to provide informed consent—because, in many ways, these individuals were the subject of this research. It was their behavior that we were studying. Once all these data were sent to the registry, the PET facility was able to submit its claim to Medicare, and, of course, patient management continued with the additional information provided by the PET scan.

### **NOPR Development and Startup**

Eighteen months passed from the time we conceived of the registry to implementation. We had to develop and finalize both a protocol and the capabilities of secure web-based data entry for PET facilities. We also had to address a variety of regulatory requirements, such as whether or not we needed institutional review board (IRB) approval, and ultimately achieving such approval with the help of the Office of Human Research Protection (OHRP) at the U.S. Department of Health and Human Services. We were actually ready to open in February 2006, when, in a conference call 1 week before scheduled opening, all the co-chairs received an e-mail from the OHRP telling us our approach was “illegal” and we could not move forward. With OHRP’s help we were able to solve the problem relatively quickly and open the registry only a few months later. Among many other formal activities, we needed approval from the Office of Management and Budget under the Paperwork Reduction Act and completion of a contract with CMS.

Once we opened and began monitoring incoming data, we identified a number of problems related to education of participants. The first lesson was that no matter how carefully one crafts and tests questions in case report forms, someone will figure out how to answer them illogically. We learned ways to work around this fact of human nature.

### **Key NOPR Results (Before 2009 NCD)**

As a result of Bruce Hillner’s amazing ability to crank out manuscripts, we were able to see initial data published quite quickly, with 3 key papers coming from the registry prior to our 2009 request to CMS to expand coverage. We reported first on the initial year of experience (May 2006 to May 2007) with NOPR (6). This analysis covered use of PET for diagnosis, staging, restaging, and suspected recurrence (but not treatment monitoring), with a consenting cohort of almost 23,000 cases from 1,519 PET facilities. The cohort reflected up-to-date technology; almost 85% of the scans were PET/CT studies. The key finding was that if results were assessed simply as a change from a nontreatment to a treatment strategy (or vice versa), 36.5% of patients experienced a change in management—a figure that was essentially uniform across different indications. That percentage was identical to that reported in similar

PET research. In a subset of patients who were planned to proceed to treatment before PET imaging, ~25% were managed with a nontreatment strategy after PET. When these patients were stratified by pre-PET plans (biopsy, watch, treatment), 25%–48% were assigned either to a new treatment or a major change in therapy after PET.

In a subsequent article, in which we drilled down by cancer type in a total of 40,863 scans, we found that change in management (at 38%) was essentially uniform across cancer types (7). In this paper we also looked at what we called the “imaging-adjusted” change in management. The basic question was: how do we know that PET provides an outcome that is different from one that would have resulted from a CT or MR scan? As a lower boundary of the impact of PET on intended management, we re-analyzed the data assuming no benefit from information provided by PET in cases with alternative pre-PET imaging plans (i.e., we removed all such cases from the numerator but still included them in the denominator). The result was an imaging-adjusted change in management of 14.7%—still 1 in 7 patients received a benefit with PET, even with this very cautious analytic approach.

We looked next at the impact of PET used for treatment monitoring. The construct here was a bit different, and the data were analyzed differently (8). Patients in this cohort were undergoing chemotherapy (82%), chemoradiation therapy (12%), or radiation therapy (6%), and 54% had metastatic disease (ovarian, pancreatic, NSCLC, and small cell lung cancers were the most frequent). We found that PET findings led to a change to another therapy in 26%, adjustment of dose or duration of therapy in 17%, and a switch from therapy to observation/supportive care in 6%. Not surprisingly, management change was seen more often when the post-PET prognosis was judged to be worse rather than improved/unchanged (70% and 40%, respectively).

### **2009 National Coverage Determination**

By April 2009, the date of the first NCD from CMS in response to a NOPR reconsideration request, we had been open for about 3 years, with 1,891 (>90%) U.S. PET facilities participating and 132,946 enrolled patients on whom data entry had been completed. It is my estimate that CMS spent at least \$130 million to cover PET imaging in this first NOPR cohort. To our delight, ~92% of patients and ~96% of referring physicians consented to research use of data, with a resulting 116,952 scans in the research dataset.

On March 25, 2008, the day after online publication of the *Journal of Clinical Oncology* article on initial NOPR results, we made our first request to expand coverage for diagnosis, staging, restaging, and detection of suspected recurrence for all cancers. (We did not ask for coverage of treatment monitoring but for an extension/continuation of NOPR for monitoring. We were being cautious, not entirely sure that the supporting data were sufficiently solid.) The NCD evaluation process was rigorous, included 2 public

comment periods, an Agency for Healthcare Research and Quality technology assessment, and a CMS Medicare Evidence Development and Coverage Advisory Committee public meeting. A draft Decision Memorandum was released on January 6, 2009, followed by a final NCD on April 3.

The new NCD framework divided PET into uses informing initial treatment strategy (previously diagnosis and initial staging) and subsequent treatment strategy (after completion of initial treatment; previously treatment monitoring, restaging, and detection of suspected recurrence). PET coverage for initial treatment strategy was now extended for essentially all cancers (except prostate cancer and cervical cancer diagnosis, as well as exclusions already in place for breast cancer diagnosis and axillary nodal staging and melanoma regional nodal staging). We knew going in to this process that the literature on prostate cancer was such that it might be excluded, so this outcome was not surprising. PET for initial treatment strategy, however, was limited to a single scan per patient per cancer. Later, through another change as the result of a request we made, CMS allowed local Medicare contractors to approve additional scans when there were good reasons for doing so. For subsequent treatment strategy, CMS allowed expanded coverage for PET in all conditions previously covered to include treatment monitoring, with new coverage for cervical and ovarian cancer and myeloma. CED (i.e., NOPR) continued for the remaining noncovered PET studies (~10% of Medicare total).

As we entered the period we refer to as “NOPR 2009”, the registry data collection continued for subsequent treatment strategy of the remaining noncovered cancers (with minor modifications). We collected data on another 155,540 scans. In a paper published in 2012 we compared the results for restaging, suspected recurrence, and treatment monitoring for cancers included in both the NOPR 2006 and 2009 cohorts to identify differences (9). The analysis included data on 41,145 (2006) and 70,358 scans (2009). We found no differences, concluding that “Results strongly suggest it is unlikely that new useful information will be obtained by extending the coverage of certain cancer types and indications only under CED.”

NOPR then submitted another reconsideration request to CMS on July 20, 2012, asking that oncologic  $^{18}\text{F}$ -FDG PET be covered without CED. CMS issued a draft Decision Memorandum on March 13, 2013, agreeing to end the NOPR for  $^{18}\text{F}$ -FDG PET but indicating that this would be limited to a single scan for subsequent treatment strategy, with the rest up to local Medicare administrative contractor discretion, and that prostate cancer would not be covered. Many people believed these were ill-considered decisions. There was a vigorous public response, with more than 200 comments.

The final Decision Memorandum was released on June 11, 2013. In that decision, NOPR was ended for  $^{18}\text{F}$ -FDG PET for all cancers. Up to 3 scans were allowed for subsequent treatment strategy, with additional scans permitted

at Medicare contractor discretion. (Although 3 is better than 1, the number is no more rational, and even today it remains unclear how this decision will be operationalized.) PET was now covered for subsequent treatment strategy in prostate cancer—a change that resulted in part with the help of several influential oncologists. Another important part of this final decision was that CMS defined PET as including standalone PET as well as PET/CT or PET/MR imaging, so that each of these technologies was included in the expanded coverage.

The issue of the limit on scans for subsequent treatment strategy is interesting. Medicare took our data and—to some extent—used it against us. Almost 93% of patients in the NOPR 2006 and 2009 cohorts had  $\leq 3$  scans, which CMS may have as interpreted as meaning “that’s all you need.” The mean number of scans per patient was 1.6, but in this relatively short observation period the range was quite broad (1–29). So in a few places scans may have been used a bit too frequently, but only 4.4% of PET facilities averaged more than 2 scans per patient.

The 3-scan limit is clearly motivated by the CMS concern that PET is widely used for surveillance, which is, under the Medicare law, a noncovered service. Surveillance is the use of imaging to detect disease in the absence of clinical evidence of disease (symptoms, signs, laboratory or other imaging abnormalities). Many medical records show clearly that this is happening. The physician’s note may say “Patient doing well. No evidence of disease. Will see again in 6 mo and get PET scan before next visit.” That PET request is clearly not driven by signs or symptoms in that patient. One might argue that surveillance with PET might provide an advantage by allowing for early detection of recurrent cancer. Unfortunately, virtually no evidence supports the idea that using PET (or other advanced imaging) for surveillance improves patient outcomes. Surveillance is not a trivial undertaking. It generates substantial costs: the cost of the studies themselves, potential complications associated with radiation exposure, the cost and aggravation of downstream testing, and accompanying patient anxiety. As a community we must address the question of surveillance PET, and we should do so either by developing evidence that it is in fact beneficial or changing the behavior of referring physicians and the expectations of patients.

### Contributions, Strengths, and Limitations of NOPR

In addition to securing coverage, one important contribution of NOPR is that the relationship between the nuclear medicine community and CMS has changed from adversarial to collaborative. The NOPR results reflect “real world” data based on very large patient cohorts and had timely relevance to important coverage and clinical issues. Registry data also represented the use of current technology ( $\geq 85\%$  PET/CT).

We are heartened by the fact that good observational studies typically match controlled studies in magnitude and direction of beneficial effects (10–12). One could argue

whether the NOPR was a good observational study, but we believe our results reflect practice. We also are pleased that our results are similar to those of more tightly managed single-institution studies (5) and to several Australian studies with outcome validation (13–17).

In terms of NOPR's limitations, we acknowledge freely that the data had quality problems, because so many people were participating in data gathering and data entry. The potential for bias is always present, given the fact that physicians may have been influenced by the knowledge that future Medicare reimbursement might be affected by their responses. In addition, we had no control group—a fundamental problem with observational studies. Neither historical nor contemporaneous controls would be suitable.

Another limitation was that we collected data only on change in intended, not actual, management. This has now been partially addressed by linking NOPR data with Medicare claims data. In work funded by a National Cancer Institute Grand Opportunity Grant, Dr. Hillner and I, in collaboration with researchers from Dartmouth University (Hanover, NH), linked NOPR data from 2006 to 2008 with Medicare claims. We looked first at restaging/suspected recurrence of the 6 most prevalent cancers and found that 30-day agreement of post-PET plan and claims-inferred action ranged from 27.3% (prostate, surgery only) to 80.9% (kidney, watching) (18). For initial staging the agreement was somewhat better. For the 5 most prevalent cancers, 60-day agreement of post-PET therapy plan and claims-inferred action ranged from 30.4% (ovary, radiation therapy) to 89.5% (small cell lung cancer, systemic therapy) (19). These results are similar to those from Australian studies compiled with formal chart review (13–17). These investigators also used a questionnaire-based approach and reported on the frequency of change in plan and agreement of the plan with actual actions based on follow-up evaluations. The overall agreement ranged from ~50% to ~75%. One of the things I learned in this process is that working with claims can be quite tricky. I am glad we had the experts at Dartmouth and Bruce Hillner to help us through this process.

NOPR results were also limited by the fact that we do not know whether management changes were in the correct direction or improved long-term outcomes. However, using management change in this setting seems logical because of all the information we have from other studies that tell us that the performance of PET and PET/CT is clearly better than that of conventional imaging. Using management change as a surrogate requires a great deal of prior data on test accuracy and value of therapies in these patients. Defining relevant and appropriate long-term outcomes for a diagnostic (as compared with therapeutic) procedure is controversial. The question remains whether overall survival is an appropriate and meaningful metric or whether change in management is adequate. NOPR data also do not tell us anything about whether and when PET should be

used in place of or as a complement to other imaging techniques. Nor does it clarify the optimal sequencing of CT, MR, and PET imaging or which method is best in specific disease settings and patients.

The major problem with our paradigm was that it was possible only to collect limited data and it was difficult to control data quality. This was a consequence of the self-funded model with a large number of nonengaged participants. In such instances, you get what you pay for and can expect only so much. We designed our research approach to strike a balance in the tradeoff between data quantity/quality and access. Possible solutions to this problem in subsequent registries will require more funding of participating sites/referring physicians, more detailed clinical data, and better information about actual management/outcomes. This will also require better educated participants, perhaps with certification before participation and a requirement that referring physicians enter data online with logic checks and “wizards” to help guide responses, along with routine audits/scrubbing of incoming data. These steps will surely increase cost, limit access, and require IRB approval for participating facilities in subsequent registries.

#### **NOPR and <sup>18</sup>F-Sodium Fluoride PET**

On February 7, 2011, NOPR launched another registry for PET with F-18 sodium fluoride used to identify bone metastasis, similar to that in place for <sup>18</sup>F-FDG PET. We have now collected data on more than 27,000 scans with complete data submission. Because the range of clinical information/decisions based on bone scan results is more limited than that from <sup>18</sup>F-FDG PET scans, we have found these data to be a bit more challenging to analyze. We have now published 2 papers and found results quite similar to those with <sup>18</sup>F-FDG PET. In men with prostate cancer, changes in intended management for initial staging, suspected first osseous metastasis, or suspected progression of osseous metastasis ranged from 44% to 52% (with imaging-adjusted percentages of 12%–16%) (20). Similar results were identified with <sup>18</sup>F-fluoride PET in other cancers (21). We submitted a reconsideration request for coverage of <sup>18</sup>F-fluoride PET to CMS on May 15 of this year and just learned in early June that, because of the fall 2013 sequester and funding issues at CMS, it will be a while before they respond.

#### **Additional Coverage**

In March 7, 2013, national noncoverage was removed for new FDA-approved oncologic PET radiopharmaceuticals. Coverage can now be determined at local Medicare Administrative Contractor discretion. The first successful example is <sup>11</sup>C-choline, which was approved in September 2012 for use at a single institution, the Mayo Clinic (Rochester, MN). It remains to be seen whether dealing with multiple contractors will be easier or better than the National Coverage Analysis process.

Although PET/MR imaging is covered by Medicare, other insurers are more reluctant. Obtaining reimbursement levels consistent with the higher costs of this technology

will require convincing data indicating that these increased costs lead to improved outcomes. We have our work cut out for us. Recent payer decisions regarding technologies such as intensity-modulated radiation therapy and proton radiotherapy, with reimbursement at similar rates for techniques with similar clinical outcomes, may set the tone. This means that we must be cautious as we move forward with PET/MR. I know of no related registry currently planned.

### CMS PET Registries: What is Next?

My crystal ball tells me that the next PET registry is likely to be focused on amyloid imaging. The FDA approved  $^{18}\text{F}$ -florbetapir in April 2012,  $^{18}\text{F}$ -flutemetamol in October 2013, and  $^{18}\text{F}$ -florbetaben in March 2014 (effectively as imaging biomarkers of amyloid deposits). In September 2013 an NCD from CMS indicated that 1 amyloid scan per patient would be covered, but only under CED to: develop better treatments or prevention strategies for Alzheimer disease (AD), as a strategy to identify subpopulations at risk for developing AD, or to resolve clinically difficult differential diagnoses (e.g., frontotemporal dementia vs. AD), with a goal of improving health outcomes (including short-term outcomes related to changes in management as well as longer term dementia outcomes).

The NOPR Working Group, the Alzheimer's Association, and SNMMI have been collaborating for a number of months to develop a registry. We have identified many challenges, including the selection of the optimal target population, the absence of established clinical management algorithms based on scan results (unlike the situation for  $^{18}\text{F}$ -FDG PET in cancer), the absence of robust historical control data, the fact that some patient-centered outcomes will take a very long time to be detectable (e.g., slowing of functional decline vs. avoiding futile therapy), and the fact that the NOPR funding model will not work here so that external support will be needed. We have been working on a protocol and plan to meet with CMS. If CMS approves the development of this protocol, we can begin implementation of the infrastructure and, if all goes well, have a registry up and running in 2015.

### Conclusion

NOPR has successfully used one pathway to help achieve coverage for PET in cancer. This pathway has been quite slow and burdensome—not only for us but for the entire community. The takeaway message is that from the outset clinical trials of new molecular imaging tracers and methods must focus not only on what the FDA requires for approval but on obtaining evidence of improved patient outcomes necessary to achieve coverage by Medicare and other third-party payers.

*Barry A. Siegel, MD*  
*Washington University School of Medicine*  
*St. Louis, MO*

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