

Practice-Based Evidence of the Beneficial Impact of Positron Emission Tomography in Clinical Oncology

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The unexamined life is not worth living.
—Attributed to Socrates, 5th century BCE

This issue of the *Journal of Clinical Oncology* contains a landmark article by Hillner et al¹ that reports the results of a Center for Medicaid & Medicare Services (CMS)-sponsored trial of the National Oncology PET Registry (NOPR) study in patients with a variety of tumors. I have used the term “landmark” because it is the first time that CMS has used the mechanism of coverage with evidence development (CED) for the study of a diagnostic imaging methodology as a step toward a national coverage decision (NCD).

Medicare has an obligation to provide its beneficiaries with technology advances that may result in improved health care, using the standard of “reasonable and necessary.” At present, the combination of positron emission tomography (PET) and the radiotracer [18F]fluorodeoxyglucose (FDG) is recognized to meet this standard; resulting in reimbursement by Medicare for nine oncology tumor types: non-small-cell lung cancer (NSCLC); breast, head and neck (including thyroid), colorectal, cervical, and esophageal cancers; melanoma and lymphoma (Hodgkin’s disease and non-Hodgkin’s lymphoma), for diagnosis, staging tumor extent and restaging recurrent tumor. Because the insurance industry as a whole follows the lead of the federal government in reimbursement decisions, PET is widely used in clinical oncology for the tumor types on the “approved” Medicare list.

The decision to reimburse is referred to as an NCD, and CMS is responsible for this process. In making the positive PET reimbursement decision for these nine tumor types, CMS used the standard “that all evidence currently available must be adequate to conclude that the item or service is reasonable and necessary.” Of course, clinical oncology deals with many more than nine tumor types, and some major human diseases, such as pancreatic, ovarian, and prostatic cancers were not included; patients with these tumors and a variety of others were potentially being denied the benefits of PET imaging.

For this reason a group of professional organizations concerned with imaging in oncology petitioned CMS for a broader NCD to include additional tumor types for PET reimbursement. These organizations argued that sufficient evidence would be unlikely to be developed for additional tumor types, because there was little support for this type of clinical trial with a substantial number of patients. Also, for a number of the tumor types that are uncommon or rare, it would be impossible to provide sufficient evidence from the literature related to patient outcomes. CMS agreed to work with these groups using a highly innovative mechanism, CED, to develop sufficient data so that a meaningful NCD could be made. Essentially, CMS and the investi-

gators agreed on the study population, methods, and key study end points, and CMS agreed to provide covered services for PET scans performed as part of this clinical trial. The investigators agreed to establish the registry (NOPR) and oversee data collection and reporting. The study that was ultimately developed met the CMS criteria for such a trial, namely that there was no evidence that the procedure would cause harm, and there was a potential for patient benefit. In keeping with CMS policy, a particular emphasis was placed on evaluating evidence of an influence on clinical practice as a way to help Medicare beneficiaries and providers make appropriate diagnostic and therapeutic decisions. (CMS has spent a great deal of effort to make the entire process participatory and transparent; interested reader is referred to Federal Register, Vol 68, No 187, Friday Sept 26, 2003, 55,634, as well as several guidance documents on NCD available through the CMS website, <https://www.cms.hhs.gov>.)

The goal of the study by Hillner et al was to assess the impact of PET on patient management in a group of tumors that are not generally reimbursed by Medicare. A total of 22,975 PET cases from 1,178 PET centers, or nearly 80% of the PET centers in the United States, were collected and entered into the NOPR registry in 1 year. Questionnaires were used to compare pre-PET management plans with post-PET management plans. The main finding was that PET was associated with a 36.5% change in decisions to treat or not treat. In addition, there was a significant reduction in the use of additional types of diagnostic images and in biopsy application with the use of PET. The investigators concluded that, in more than one third of older patients undergoing PET for one of the cancer types covered under this CED policy, there was a major change in the intended management including type of treatment.

This study has major strengths, particularly in its scale, with more than 22,000 cases collected during the course of 1 year. This is no small feat, and reflects the power of Medicare data when used for this type of focused clinical trial. The rapidity of data collection is an important positive feature because of changes that rapidly occur in diagnostic imaging technologies over time. Generating such large numbers in such a short time helps assure the relevance of the information. It is important to note that, during this interval, more than 400,000 PET scans were performed on Medicare beneficiaries for the nine approved tumor indications. Thus, although PET scans in the unapproved indications were performed with a frequency less than 10% of the total Medicare patients studied with PET, the sample size of the unapproved PET scans was more than adequate to cover the management question posed. Also, more than 80% of all PET centers in the United

States participated in the trial; thus, the data can be considered representative across PET centers from groups that are small and large, major and minor, academic and private practice. As such, the findings are relevant to policy setting in a way that single-institution studies may not be because of possible sampling bias in patient population, equipment, or experience of PET readers.

The main limitation of this study is probably in the primary end point, intended patient management, rather than the actual management. There is also no certainty that the management proposed is correct. Although it is not the role of the diagnostic tests to dictate a management plan, there can be no doubt from the study that statistically PET had a major impact on primary physicians' intended management across the spectrum of clinical sites and practicing caregivers.

CMS will use this data in making an NCD. CMS may include conditions restricting coverage, as they have in the past. Still, on the basis of the strong message from this study and CMS's role in planning it, it seems likely that the indications for PET in oncology will be broader in the future. In this way this study, is an important step in the long process of establishing clinical acceptance and insurance reimbursement for PET as a routine diagnostic imaging modality.

Evidence-based medicine (EBM) is a commonly used phrase that has become a mantra for how to pursue the optimal practice of medicine. From the clinical point of view, EBM usually means basing clinical practice exclusively on those diagnostic tests and treatments for which there is solid evidence of efficacy. The EBM approach is most often founded in randomized trials and meta-analysis. Oftentimes, what is required is a prospective randomized controlled trial with sufficient power to enable a clear-cut answer. EBM may be a useful gold standard for practice, especially when the clinical question is well defined in all its parameters.

Recently, the deficiencies of EBM have been recognized. Unfortunately, much of clinical practice can not be subjected to this kind of rigorous assessment. Another obvious disadvantage is that a randomized clinical trial may take years to accumulate the necessary data, and a further amount of time to analyze it completely and then teach the medical community how to properly use the information obtained. By the time the process is complete, the results may be antiquated, as a result of ongoing progress with better agents which themselves must be introduced in clinical trials.

Practice-based evidence study designs are being proposed as a more practical alternative to randomized trials or meta-analysis for many clinical practice questions including relative effectiveness of drugs, diagnostic agents, and procedures.² The approach often depends on knowledge of the clinicians and caregivers to define topics for study as part of a multidisciplinary team, with "What works?" "When?" and "At what cost" among the typical types of questions posed. A component of ongoing practice is the subject of close examination and analysis. There is immediacy to results obtained, and there

is often rapid feedback so that the findings can be rapidly introduced to improve practice.

The concept of CED could be considered an example of how practice-based evidence study design can be used to rapidly answer an important clinical question, in terms of how a performance measure that is adopted for a Medicare beneficiary influences clinical outcomes. In the study by Hillner et al, a properly performed PET scan was the performance measure, and the change in management plan was the outcome. The key advantages seen were the speed of development of the evidence and the relevance of the findings across all 50 states.

Socrates, seeker of truth, is a good model for those of us who are in clinical practice, whether in a diagnostic specialty or a therapeutic one. Our clinical practice needs to be critically examined and re-examined, if possible in an ongoing way, so that we can continually make corrections and refine our skills in choosing diagnostic or therapeutic approaches for optimized patient care. Now that maintenance of competence is a requirement for maintaining licensure in many states, as individuals we are reminded that "life-long learning and self-assessment" and "evaluation of performance in practice" are two of the four core competencies. I think Hillner et al and CMS are to be commended for using a highly relevant practice-based clinical trial approach to assess an important question in diagnostic oncology. This is a good example of cooperation between the professional sector and government, to get to the "truth." Socrates would have been proud. One can only hope that this approach by CMS will be expanded to other aspects of diagnostic imaging practice in oncology.

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