

## Impact of Positron Emission Tomography/Computed Tomography and Positron Emission Tomography (PET) Alone on Expected Management of Patients With Cancer: Initial Results From the National Oncologic PET Registry

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### ABSTRACT

#### Purpose

Under Medicare's Coverage with Evidence Development policy, positron emission tomography (PET)/computed tomography (CT) and PET became covered services for previously noncovered cancer indications if prospective registry data were collected. The National Oncologic PET Registry (NOPR) was developed to meet these coverage requirements and to assess how PET affects care decisions.

#### Methods

The NOPR collected questionnaire data from referring physicians on intended patient management before and after PET. After 1 year, the cohort included data from 22,975 studies (83.7% PET/CT) from 1,178 centers. The numbers of scans performed for diagnosis of suspected cancer (or unknown primary cancer), initial cancer staging, restaging, and suspected cancer recurrence were approximately equal. Prostatic, pancreatic and ovarian cancers represented approximately 30% of cases.

#### Results

If PET data were not available, the most common pre-PET plan would have been other imaging. In these patients, the post-PET strategies changed to watching in 37% and treatment in 48%. In patients with planned biopsy before PET, biopsy was avoided in approximately 70%. If the pre-PET strategy was treatment, the post-PET strategy involved a major change in type in 8.7% and goal in 5.6%. When intended management was classified as either treatment or nontreatment, the post-PET plan was three-fold more likely to lead to treatment than nontreatment (28.3% v 8.2%; odds ratio = 3.4; 95% CI, 3.2 to 3.6). Overall, physicians changed their intended management in 36.5% (95% CI, 35.9 to 37.2) of cases after PET.

#### Conclusion

This large, prospective, nationally representative registry of elderly cancer patients found that physicians often change their intended management on the basis of PET scan results across the full spectrum of its potential uses.

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### INTRODUCTION

The Centers for Medicare & Medicaid Services (CMS) and commercial insurers face recurring challenges in determining what constitutes sufficient evidence to support coverage for new tests and treatments.<sup>1-3</sup> In 2005, CMS established a new approach to coverage policy called coverage with evidence development (CED) for selected promising technologies.<sup>4,5</sup> The CED policy offered a novel, formal approach for coverage of evolving diagnostic and treatment methods that would not otherwise meet CMS's evidentiary standards.<sup>6</sup>

Among the first technologies to be covered under CED were positron emission tomography-

(PET)/computed tomography (CT) and PET (hereinafter collectively referred to as PET), specifically an expansion of payment for PET for previously noncovered cancer types and indications. PET with [<sup>18</sup>F]fluorodeoxyglucose (FDG) in oncology is based on the observation that most cancers exhibit increased glucose utilization compared with normal tissues.<sup>7,8</sup> Between 1998 and 2005, CMS approved Medicare reimbursement for PET for specific indications for patients with nine malignancies.<sup>9</sup>

The National Oncologic PET Registry (NOPR) was developed to meet the CED coverage requirements and to assess how FDG-PET affects care decisions. Herein, we report the first-year results from

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NOPR on the overall impact of PET on intended patient management for previously noncovered cancers.

## METHODS

The NOPR is a prospective data registry that collects information from the PET facility, from the physician requesting the PET scan, and from the interpreting physician's PET report. Data submission to the registry is required by CMS as a condition for coverage. All data are entered by participating facilities via a secure Web-based interface and stored at the American College of Radiology (ACR) in Reston, VA, accessible online at [www.cancerPETregistry.org](http://www.cancerPETregistry.org).

A description of NOPR's operations and human subject protection procedures has been reported.<sup>10,11</sup> In brief, the PET facility is responsible for collecting information from the referring physician on Pre-PET and Post-PET Forms. The Pre-PET Form collects (1) the study indication, (2) the cancer type (if known) and provisional stage, (3) the patient's performance status, (4) whether the referring physician will be the treating physician, and (5) the referring physician's planned management if PET were not available. When the PET scan is completed, the PET facility uploads the PET report to the database. The final step is completion of a Post-PET Form by the referring physician. There are several Post-PET Forms, specific to study indication; all assess the referring physician's planned management in light of the PET findings.

Data collection is conducted in accordance with an ACR institutional review board–approved protocol. The PET facility documents on the PET Report Submission Form whether the patient gives oral consent for research use of the data. The physician is asked on the Post-PET Form for consent to use the data for research. The research database consists of only cases for which both patient and physician gave consent.

## Outcomes

The primary end point is the impact of PET on physicians' intended management. A change in management is assessed in four ways. The first dichotomizes intended management as either treatment (eg, surgery, chemotherapy, radiation, or other treatment, alone or in combination) or nontreatment (watching, noninvasive imaging, biopsy, or supportive care). The second approach dichotomizes the intent of planned therapies as either curative or palliative. In this approach, a meaningful change includes a change in intent, even if the specific therapy does not change.

The third and fourth approaches consider a change in type or number of clinical actions. Changes were defined as minor or major. A major change was defined as a switch in treatment type (eg, from surgery to chemotherapy) where the original mode of treatment was not included in the post-PET plan even if the treatment goal remained constant. A minor change was defined as the addition or deletion of treatments, but where one type remained constant across the pre- and post-PET plan. Figure A1 (online only) shows a grid indicating which changes were classified as major or minor. The final approach scored therapy intensity as increased, decreased, or unchanged by comparing the number of modes in the pre- and post-PET plans. For example, a change from surgery to surgery plus chemotherapy was scored as an intensity increase, and a change from radiation and chemotherapy to only chemotherapy as a decrease.

## Statistical Analysis

The change in intended management after PET was modeled as a binary variable after a binomial distribution. The changes were defined at the PET scan level, and were assumed independent for different patients, cancer types, or indications. Approximately 6% of patients had two or more scans; however, because almost all of these multiple scans were performed for different indications in the cancer care continuum, they were treated as independent.

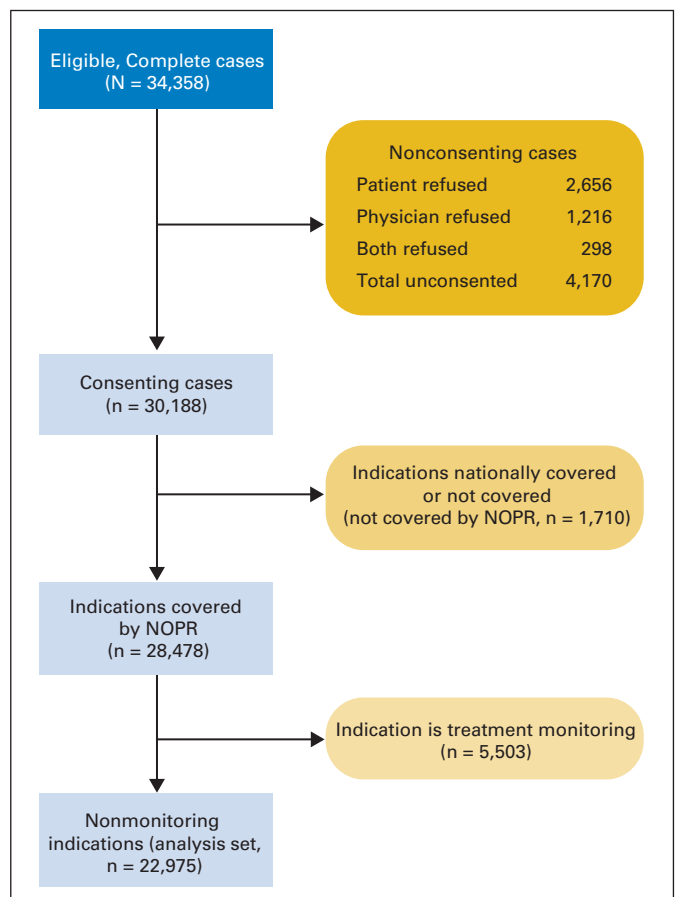
The changes in the intended management plan were analyzed for each indication and in different dichotomizations of patient management plans. All CIs are two-sided and calculated with a Gaussian approximation. Odds ratios (ORs) were calculated to quantify the association between two binary variables. All statistical analyses were carried out with SAS version 9.1 (SAS Institute, Cary, NC).

## RESULTS

### Defining the Cohort

The registry was designed to meet CMS criteria for evidence development; therefore, all patients are Medicare beneficiaries. PET studies performed on Medicare beneficiaries for the specifically approved indications in breast, cervical, colorectal, esophageal, head and neck, non–small-cell lung, and thyroid cancers, or lymphoma or melanoma were not eligible.<sup>9</sup> An estimated 400,000 PET or PET/CT studies were performed for covered oncologic indications in Medicare beneficiaries during the study interval (D. Babish, personal communication, September 2007).

The NOPR began accepting patients on May 8, 2006. As of May 7, 2007, 34,358 PET studies were registered, had complete data submitted, and were potentially eligible for inclusion (Fig 1). A total of 4,170 (12.1%) were excluded because either the patient or the physician did not consent to research use of the data. Of the remaining 30,188 eligible cases, 1,710 cases (5.7%) were excluded because the PET scan seemed to have been requested for a cancer type and indication already covered or specifically not covered by Medicare. Accordingly, 28,478 cases, representing 82.9% of registered PET studies, formed the study cohort. PET studies performed for treatment monitoring (ie, during a planned course of chemotherapy or radiation therapy when a change



**Fig 1.** Development of the National Oncologic Positron Emission Tomography Registry (NOPR) data set under the Medicare coverage with evidence development policy.

in such therapy was being considered) were excluded and will be reported separately (n = 5,503). We elected to do this because treatment monitoring is a less well-established indication for PET and is associated with rather different options for change in management.

This report is based on the remaining 22,975 PET studies performed in 21,419 patients, 93.8% of whom underwent one PET scan and 6.2% of whom underwent two or more PET scans. All together, 1,178 centers contributed from all 50 states. The mean and median numbers of PET studies per center were 19.5 and 10, respectively; the 25<sup>th</sup> to 75th quartile range was four to 25, and the maximum was 594.

### Cohort Profile

Table 1 summarizes the cohort's characteristics. The mean patient age was 72.6 years; 9.7% were younger than 65 years and 5.2% were 85 years or older. Cases were classified into distinct cancer indications. Approximately one quarter of patients underwent PET to diagnose a suspected cancer or to find the primary cancer in a patient with metastatic disease of unknown origin. In patients with known cancer, nearly equal numbers were performed across the natural history spectrum: 28.1% for initial staging, 24.4% for restaging after completion of therapy, and 23.5% for suspected recurrence. The provisional cancer summary stages at the time of PET are summarized in the table. In 28.3% of cases, the physicians were unwilling to provide a summary stage estimate. Prostatic, pancreatic, and ovarian cancers represented approximately 30% of cases. Seventeen different cancer types had a prevalence of at least 1%. The vast majority of scans were performed using a PET/CT scanner (83.7%) that was in a fixed, non-hospital-based location.

### Outcome Results

Table 2 summarizes the impact of PET on intended management classified as either treatment or nontreatment. The difference between the pre- and post-PET plan (rows) is compared with the original indication for the scan (columns). Changes from an intended nontreatment to a treatment plan occurred in 28.3% of cases, whereas 8.2% of cases changed from treatment to nontreatment (OR = 3.4; 95% CI, 3.2 to 3.6). The change from intended nontreatment to treatment was consistently three to four times more frequent than changing from treatment to nontreatment across the spectrum of cancer indications. Overall, there was a change in 36.5% (95% CI, 35.9 to 37.2) of cases by this criterion.

Changes in intended management were slightly more frequent with PET/CT versus PET (range, 0.6% to 4.8% by indication). However, a logistic regression model found that the impact of scan type was not statistically significant ( $P = .13$ ).

### Curative Versus Palliative Intent of Planned Therapeutic Management

Table 3 shows the associated changes in management when the goal of treatment, either curative or palliative, also is considered. Overall, there was a 42.2% change in intended management after provision of the PET results. In 5.6% of all cases, representing 16.7% of cases whose pre-PET plan was treatment, there was a change in therapeutic goal.

PET was associated more frequently with upstaging (or showing a greater extent of cancer) than with downstaging. The ratio of changing to a palliative versus curative goal was similar for cases of suspected

**Table 1.** Cohort Demographic, Clinical, and PET Characteristics (n = 22,976)

Characteristic	No. of Patients	%
<b>Age, years</b>		
Mean		72.6
Interquartile range (25-75)		68-79
< 65	2,238	9.7
> 85	1,187	5.2
65-85	19,550	85.1
<b>Sex</b>		
Female	11,455	49.9
Male	11,520	50.1
<b>Race or ethnicity</b>		
Hispanic or Latino	1,003	4.4
Not Hispanic or Latino	10,019	43.6
Ethnicity unknown	11,953	52.0
Asian	232	1.0
African American	912	4.0
White	10,924	47.5
Other	639	2.8
Unknown	10,268	44.7
<b>ECOG performance status</b>		
0	9,212	40.1
1	10,831	47.1
2	2,181	9.5
3	683	3.0
4	68	0.3
<b>Cancer indication</b>		
Diagnosis		
Suspected primary	3,366	14.6
Unknown primary tumor	1,929	8.4
Suspected paraneoplastic syndrome	221	1.0
Initial staging	6,464	28.1
Restaging	5,607	24.4
Suspected recurrence	5,388	23.5
<b>Pre-PET summary stage</b>		
No evidence of disease	2,131	9.3
Localized only	4,438	19.3
Regional by direct extension or lymph node involvement	2,973	12.9
Metastatic disease: single suspected site	3,077	13.4
Metastatic disease: multiple suspected sites	3,847	16.7
Unknown or uncertain	6,509	28.3
<b>Cancer type</b>		
Prostate	2,692	11.7
Ovary and uterine adnexa	2,096	9.1
Pancreas	2,068	9.0
Bladder	1,615	7.0
Kidney and other urinary tract	1,600	7.0
Unknown primary	1,579	6.9
Stomach	1,412	6.1
Lung, small cell	1,403	6.1
Uterine	1,198	5.2
Liver and intrahepatic bile ducts	819	3.6
Myeloma	701	3.1
Connective or other soft tissue	576	2.5
Cervix	434	1.9
Gallbladder and extrahepatic bile ducts	429	1.9
Thyroid	312	1.4
Primary brain	271	1.2
Retroperitoneum	265	1.2
All others	1,612	7.0

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**Table 1.** Cohort Demographic, Clinical, and PET Characteristics (n = 22,976) (continued)

Characteristic	No. of Patients	%
Scan type		
PET	3,747	16.3
PET/CT	19,228	83.7
PET facility location		
Hospital based	6,583	28.7
Not hospital based	16,392	71.3
Fixed scanner	17,449	75.9
Mobile scanner	5,526	24.1

Abbreviations: PET, positron emission tomography; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography.

cancer or initial staging, but shifted predominantly to palliative treatment in patients evaluated for restaging and suspected recurrence.

### Major and Minor Changes in Management

Figure 2 shows the associated change in management with PET when major and minor changes in the mode of therapy or when changes between nontreatment strategies are considered. The bars represent the different cancer imaging indications. Overall, the agreement between the pre- and post-PET plans was 26.3%, ranging from 23.4% to 30.7% across indications. A major change in intended management occurred in 30.3% to 39.7% depending on the indication. A major change in the mode of therapy, such as from pre-PET surgery to post-PET radiation, occurred in 2% to 4% of cases for each indication. In one sixth of initial staging cases, there was a minor change in the treatment plan.

### Changes by Action Type

Table 4 summarizes the changes in intended management when stratified by the specific intended action. If PET were not available, the pre-PET plans were classified as imaging, biopsy, watching or supportive care, and treatment. The post-PET treatments were classified as new or a major change from the pre-PET plan, a minor change, or the same treatment.

The most common strategy if PET had been unavailable, accounting for 41% of cases, would have been alternative imaging. In these cases, the post-PET plan remained additional imaging in only 6%. In slightly less than one half, treatment would be initiated, and approximately one third of patients would subsequently be watched.

In the 15% of cases where biopsy would have been the intended management in lieu of PET, the post-PET plan continued to include biopsy in only one quarter of these (3.8% overall). After PET, subsequent management was nearly equally distributed between subsequent treatment and watching. Among the cases having a pre-PET watch or supportive care plan, the post-PET plan was treatment in 24% and biopsy in another 9%.

Among all of the cases with an initial treatment plan, the post-PET treatment plan remained the same in 42.4%, and involved a minor addition or deletion in one quarter and a major change in 8.7%. Minor changes in the treatment plan occurred in more than 50% of cases where the plan included two or more types of therapy (data not shown). Using the number of modes of therapy as an indicator of treatment intensity, the pre- and post-PET intended management was unchanged in approximately two thirds of cases, whereas 10% had an increase and 22% had a reduction in intensity. On the post-PET form, referring physicians indicated that the results of PET enabled them to avoid additional tests or procedures in 76.9% of cases (range, 71.5% to 82.0% by indication).

## DISCUSSION

Several prospective and retrospective single-center studies have examined changes in management after PET was used for the evaluation of patients with cancer. Reported frequencies of change ranged from 30% to 40%.<sup>12-18</sup> These reports assessed the value of PET in aggregate or focused on cancer indications currently covered by Medicare. For cancer types included in our study, small single-center reports found that PET/CT was associated with changes in management in 16% to 52% of patients.<sup>19-21</sup> We found a change in intended management in our cohort of previously noncovered cancers similar to that reported in single-institution studies evaluating patients with covered cancers.

Historically, assessments of imaging technologies have focused on image quality and test performance (eg, sensitivity and

**Table 2.** Change in Management Associated With PET Stratified As Treatment Versus Nontreatment

Management Plan	Pre-PET	Post-PET	PET Indication				All Patients
			Diagnosis	Initial Staging	Restaging	Recurrence	
No. of scans per indication			5,516	6,464	5,607	5,388	22,975
%	Treatment	Treatment	16.0	46.5	15.8	20.4	25.5
	Nontreatment	Nontreatment	52.9	14.0	48.0	40.7	37.9
	Nontreatment	Treatment	23.2	31.6	28.6	29.2	28.3
	Treatment	Nontreatment	7.9	7.9	7.5	9.7	8.2
Change in management			31.1	39.5	36.1	38.9	36.5
95% CI			29.9 to 32.3	38.3 to 40.7	34.9 to 37.4	37.6 to 40.2	35.9 to 37.2
Odds ratio for pre- and post-PET plan			2.94	4.00	3.81	3.01	3.45
95% CI			2.62 to 3.26	3.61 to 4.39	3.49 to 4.22	2.71 to 3.31	3.27 to 3.63

Abbreviation: PET, positron emission tomography.

**Table 3.** Change in Management Plan When Therapeutic Intent Is Considered

Management Plan	Pre-PET	Post-PET	Pre-PET Indication				All Patients
			Diagnosis	Initial Staging	Restaging	Suspected Recurrence	
No. of scans			5,516	6,464	5,607	5,388	22,975
%	Nontreatment	No change	52.9	14.0	48.0	40.7	37.9
		To curative	10.2	16.7	9.2	8.4	11.4
		To palliative	13.0	15.0	19.4	20.8	16.9
	Curative	No change	5.2	25.7	4.4	5.2	10.8
		To palliative	2.3	7.2	2.6	3.4	4.0
		To nontreatment	4.8	5.6	3.8	4.4	4.7
	Palliative	No change	7.3	10.9	7.6	10.4	9.1
		To curative	1.1	2.8	1.2	1.3	1.6
		To nontreatment	3.1	2.3	3.7	5.3	3.6
Overall change			34.5	49.5	39.9	43.6	42.2

Abbreviation: PET, positron emission tomography.

specificity) rather than impact on patient management. During the last 30 years, this focus has led to inconsistent adoption of CT, magnetic resonance imaging, and most recently PET and PET/CT for specific clinical applications.

There are many unanswered questions regarding the role of PET in the management of patients with cancer, especially in those with relatively uncommon cancers. The CED policy is a novel approach to expand the prospectively collected evidence base for specific clinical situations. The CED policy for diagnostic technologies shifts the research focus from test performance to a broader focus addressing the impact of a specific test on patient care decisions. In contrast, prospective treatment registries or large practical clinical trials will predominantly have patient survival as their most relevant end point.<sup>2,22</sup>

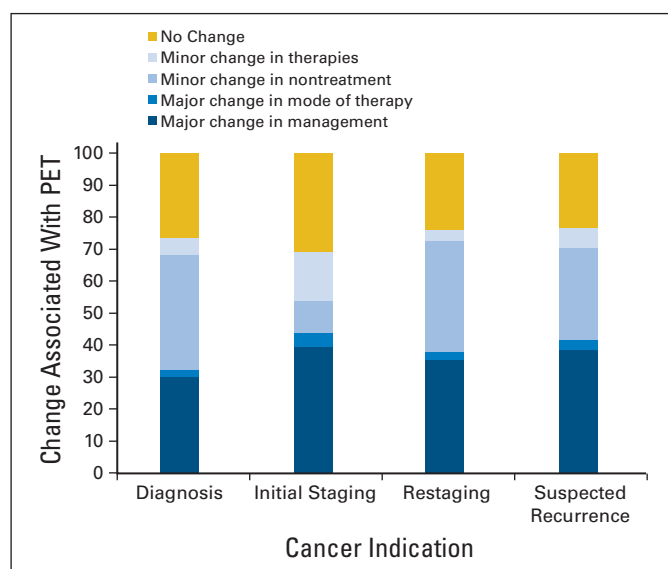
We believe the data collected by NOPR fulfils an unmet need with its primary scientific aim of measuring the impact of PET on

patient management in a manner that is minimally intrusive to care providers. We believe our findings are representative of Medicare patients for whom PET would be ordered if it were covered by CMS for the expanded indications. Patient eligibility was determined solely by a request for PET that was presumably motivated because the referring physician's needed the information to guide patient management. As of May 2007, 1,519 PET facilities in all 50 states, representing approximately 80% of all US facilities, had registered to participate in NOPR (G. Prochaska, personal communication, September 2007). At least one NOPR case in our cohort was contributed by 78% of registered facilities.

Our main finding is that PET is associated with a 36.5% change in the treatment or no-treatment decision. Within NOPR, the impact of PET on decisions varied minimally by the specific cancer indication. The impact of PET seems to be greater than the impact of body CT when it was introduced 30 years ago.<sup>23-25</sup> In aggregate, PET was associated more commonly with delineation of greater cancer burden or more sites of disease than with downstaging. When specific changes between nontreatments and the addition or deletion of specific modes of therapy are included, PET was associated with a management change in almost three quarters of patients.

The most common pre-PET strategy would have been some other form of imaging. Our data show that, on the basis of the PET findings, the requesting physician usually acted as though the patient evaluation was complete after the PET study and intended either to start therapy or to watch the patient.

The inclusion of cases where the pre-PET plan was imaging may overestimate the impact of PET. Specifically, it is possible that, if these patients had alternatively undergone other imaging, the same postimaging pattern of management that was observed post-PET would have occurred. However, even when these cases, representing 41% of the total cohort, were excluded, PET was associated with a major change in management in 33% of the remaining cases. As a worst-case estimate, if no benefit from PET was assumed for cases with a pre-PET imaging plan, then PET still would be associated with a major change in 19% of patients.



**Fig 2.** Change in intended management associated with positron emission tomography (PET) stratified by cancer indication.

**Table 4.** Changes in Intended Management Plan Associated With PET Stratified by Strategy

Post-PET Plan	Pre-PET Plan			
	Image (n = 9,518)	Biopsy (n = 3,552)	Watching or Supportive Care (n = 2,199)	Treatments (n = 7,706)
<b>Nontreatment</b>				
Image	5.8	6.0	4.6	3.0
Biopsy	9.5	24.0	9.0	6.8
Watching or supportive care	37.2	33.6	62.3	15.6
<b>Treatment</b>				
Same treatment	NA	NA	NA	42.4
New or major* change in treatment(s)	47.6	36.3	24.1	8.7
Minor† change in treatment	NA	NA	NA	23.5

Abbreviations: PET, positron emission tomography; NA, not applicable.

\*A major change in treatment strategy was defined as a change where the pre- and post-PET plan did not have one or more types of treatment in common (Fig A1)

†Minor changes include one or more types of treatment that remained constant.

We were surprised by the impact of PET on patients with a pre-PET intended management of biopsy. In approximately three quarters of these patients, a biopsy was avoided. Failure to follow through with a tissue biopsy in patients with a negative PET study may reflect overconfidence in PET results.

Major strengths of the NOPR data are the large sample size, the completeness of the data, and the national scale. Assessing the change in intended patient management as the primary end point is not as scientifically satisfying as would be documentation of actual management. Yet, using actual management may also be flawed or compromised because the planned patient management may not be performed.

A major limitation of our data is the inability to determine whether the intended changes in management were in the correct direction or confer benefit in long-term outcomes. Large registries for evaluating patient outcomes cannot replace prospective studies that avoid spectrum and verification biases.<sup>26,27</sup> Furthermore, from the registry data, we cannot document that the physicians actually completed the planned management changes.

Another limitation is that NOPR does not address whether PET should be used in lieu of other imaging techniques or is complementary to them. A prior study using a similar pre- and post-PET questionnaire design found that one key benefit of PET was the referring physician's impression that all noninvasive diagnostic options had been exhausted.<sup>14</sup> In our study, referring physicians, in more than three quarters of cases, indicated that PET enabled them to avoid additional tests and procedures.

Prospective comparisons of different sequencing approaches of CT and PET or PET/CT in cancer patients are needed. A recent Dutch prospective trial randomized patients being staged for non-small-cell lung cancer to traditional work-up or to initial PET.<sup>28</sup> The investigators found that staging accuracy and overall costs were similar in the two arms, but that fewer invasive procedures were performed in the early-PET arm. Another report suggests that PET/CT along with colonoscopy is sufficient for initial staging of colorectal cancer.<sup>29</sup> Given the increasing attention to the growth in imaging procedures, PET/CT may be more expensive as a single study, but its use could, in aggregate, markedly reduce overall cancer imaging costs.<sup>30</sup>

In conclusion, more than one third of older patients undergoing PET for one of the cancer types covered under Medicare's CED policy had a major change in intended management, including type of treat-

ment. The relative impact of PET on intended management was observed across the spectrum of indications of its potential uses in cancer patients.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

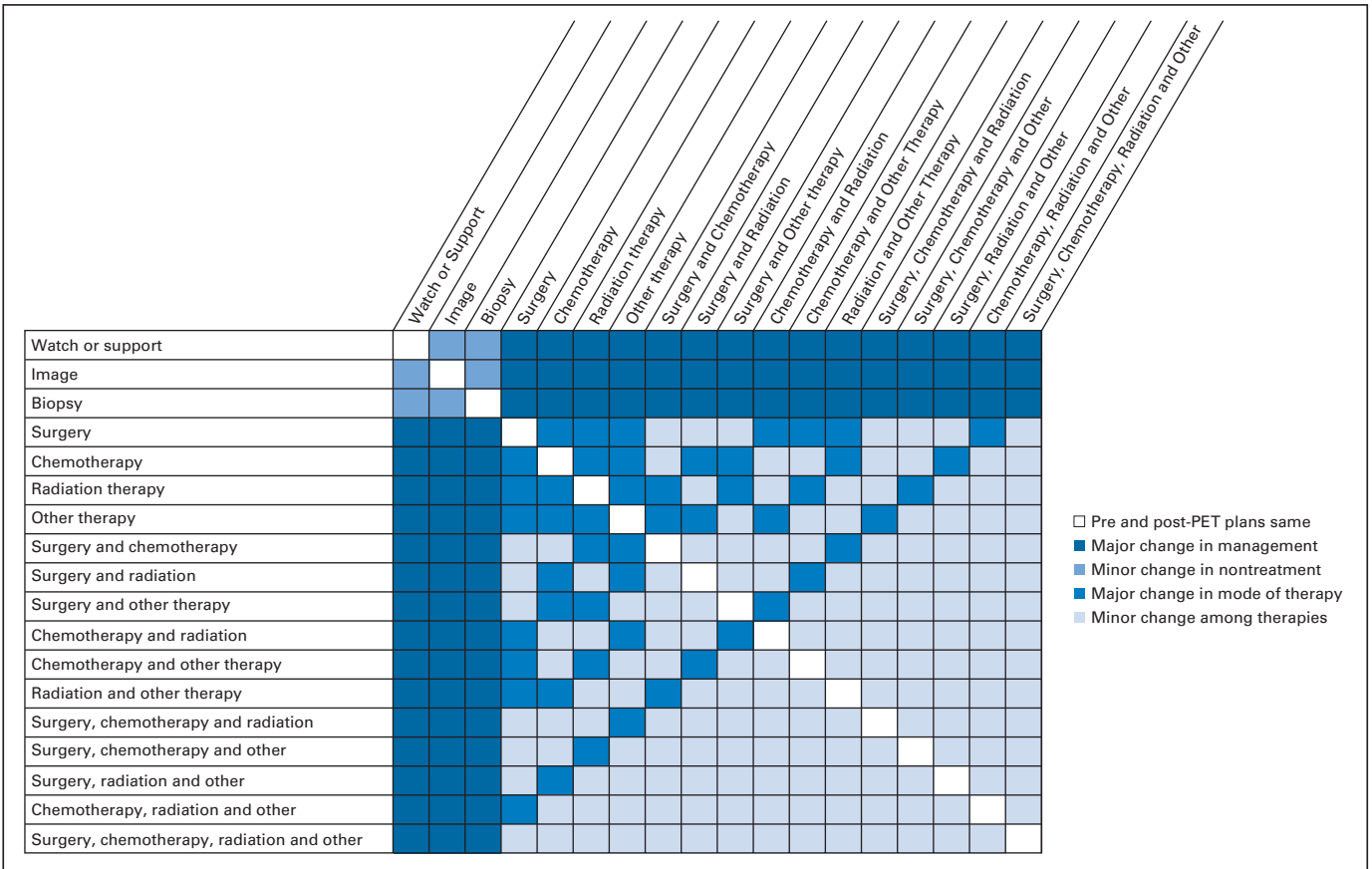


Fig A1. Definition of minor and major changes in intended management. PET, positron emission tomography.