EDITORIAL

The value and appropriateness of positron emission tomography: An evolving tale

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> The excellence of a gift lies in its appropriateness rather than its value.
>
> Charles Dudley Warner

The extraordinary advances in medical care during the past several decades have impacted both the quality and longevity of an individual's life. However, impressions of modern health care have been adversely impacted by runaway expenses and the high cost of care delivery.[1,2] Medical imaging, including nuclear cardiology, has demonstrated excellent value with regards to diagnosis and risk stratification, but has limited date to support its impact on patient outcome, thereby becoming the focus of public and payer attention due to concerns of overuse.[1,2] This has lead to multiple initiatives to limit test performance and reduce overall spending, including pre-authorization and test substitution.[1] As a response to fiscal pressures and with a goal of optimizing test/patient selection, appropriate use criteria (AUC) have been developed by several organizations, including the American College of Cardiology (ACC) and American Society of Nuclear Cardiology (AS]NC).[3-5] Unfortunately, adoption of these AUC by private and federal health plans has been more limited than desired; many private insurers continue to use radiology benefits managers with their proprietary algorithms for test selection, often lacking consistency with medical literature and expert opinion. However, the AUC were specifically designed to serve as guidance documents for clinicians and others with regards to a variety of cardiac tests and procedures.

Positron emission tomography (PET) MPI has been shown to provide improved image quality, superior interpretative confidence, and higher diagnostic accuracy than SPECT[6-12] and has been considered by many to be a ''gold standard'' of non-invasive testing.[10] In addition to its value as a diagnostic study, the independent and incremental value of myocardial perfusion PET has also been demonstrated in multiple studies, including a multicenter registry involving more than 7,000 patients.[11] PET possesses a greater discriminatory power than other non-invasive modalities with regards to cardiac events.[12] Furthermore, rubidium-82 perfusion PET is associated with a lower radiation burden and more rapid test performance, making this procedure an attractive test for the evaluation of known or suspect ischemic heart disease.[10,12] However, the costs associated with this procedure are high, as is the level of reimbursement,[13] which although justifiable based on procedural costs, places additional strain on an already financially overburden health system.

The AUC for radionuclide imaging that were initially published in 2005 were revised and expanded in 2009[3] as a result of technologic advances in nuclear cardiology, feedback from ASNC and individual providers, and improvements in the development of AUC. All of the indications for radionuclide imaging (RNI) are intended for application for both SPECT and PET, unless specifically identified as being germane only to SPECT. The only stipulation regarding the AUC indications impacting PET is that exercise testing is the preferred stress modality for RNI. As exercise PET myocardial perfusion imaging is currently not an option in most centers, this preference is not applicable to PET, although the development of new PET perfusion agents, such as F-18 flurpiridaz, will make exercise testing an option in the future.[14] Notably, there are no ''pure'' PET AUC, largely due in part to the similar applications of

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both techniques and the modest amount of PET literature, other than for the detection of ischemic heart disease. However, it is highly likely that these criteria are well suited for both SPECT and PET; the advantages of PET, as noted above, would not likely impact the classification of appropriate use.

In this issue of the Journal, Winchester et al[15] report the findings of a retrospective analysis regarding the appropriate use of PET imaging. This unique study is the first report specifically designed to evaluate the AUC for PET and examined not only the categories of appropriate use but also the frequency of abnormal perfusion findings stratified by the level of appropriateness. The authors also describe the relationship of appropriateness to subsequent clinical events.

This study utilized the 2009 RNI AUC,[2] which have now been largely replaced by the AUC for stable ischemic heart disease, published in 2013 as part of the new multimodality approach.[3] These new AUC provide an update based on the newest literature but importantly, reflect a number of methodological changes, including new terms for the categories of appropriate use.[4] The newer terms of ''may be appropriate'' and ''rarely appropriate'' are similar to the older terminology of ''uncertain'' and ''inappropriate'' but should not be used interchangeably. The new multimodality AUC should replace the 2009 RNI criteria whenever possible. There were 43 indications present in the multimodality AUC that were consistent to those of the RNI AUC, with 35 (81%) rated in a similar appropriateness category, although the definitions and nomenclature for some of the indications contain minor changes. Changes in appropriate categories between the two sets of AUC are noted in Table 1. Although these differences in AUC may somewhat modify the results presented in the current paper, it is doubtful that these will alter its overall impact.

Winchester et al[15] found that appropriate and uncertain indications for PET were present in 79.5% and 10.4%, respectively, with an inappropriate rate of 10.2%. As shown in Table 2, these categorizations for PET appropriate use are similar to those found in the majority of reports with SPECT,[16-31] although there are some reports of SPECT MPI with higher frequency of inappropriate studies.[19,27] For evaluation of the scintigraphic findings and outcomes, the authors have combined ''appropriate'' with ''uncertain'' categories, which although somewhat controversial, is consistent with the intent of these AUC—''uncertain is assumed to not provide grounds for denial of reimbursement.''[5]

A key finding in the current report is the presence of abnormal PET perfusion among all classes of appropriateness, although only 7.7% of studies performed with an inappropriate indication had abnormal perfusion. However, this low rate of abnormal findings was present even among appropriately indicated studies (28%). Similarly, abnormal perfusion has been noted in multiple reports of SPECT AUC, even among inappropriate indications, although the frequency of abnormal SPECT findings appears greater than those found in the present PET trial (Table 3). Of note, no ischemia was detected in any of the inappropriate PET examinations in the present report. These overall low rates of abnormal scintigraphic findings may be related to the cohort studied and temporal factors, as there has been a declining rate of abnormal SPECT findings during the several decades, from >40% abnormal studies to <10%.[32]

The next critical and evolutionary step for imaging AUC is to compare outcomes of patients with appropriate vs inappropriately performed procedures. For example, even if an inappropriate test yields abnormal results, is it

Table 1. Differences between the appropriateness categorization based on the 2009 radionuclide imaging (RNI) AUC and the 2013 multimodality (MM) AUC

Indication	2009 RNI[2]	2013 MM[3]
High CHD risk asymptomatic	A	M
Low CHD risk syncope	I	M
Worsening symptoms, normal prior study	U	A
High CHD risk, Agaston score 100-400	A	M
Agaston score > 400	A	M
Preop assessment, intermediate risk surgery, ≥1 risk factor with poor functional capacity	A	M
s/p CABG, asymptomatic, <5 years	U	R
s/p CABG, asymptomatic, ≥5 years	A	M

A, Appropriate; *M*, may be appropriate; *R*, rarely appropriate; *U*, uncertain; *I*, inappropriate; Agaston score refers to CT-derived calcium scoring.

Table 2. Classification of appropriate use for SPECT myocardial perfusion imaging

Study	Year	n	Appropriate (%)	Uncertain (%)	Inappropriate (%)
Mehta et al[16]	2008	1,209	80	5	13
Gibbons et al[17]	2008	284	64	11	14
Hendel et al[18]	2010	6,351	71	15	14
Carryer et al[19]	2010	281	60	16	24
Gibbons et al[20]	2010	284	66	15	7
Gholamrezanezhad et al[21]	2011	291	75	5	14
Druz et al[22]	2011	585	63	20	14
Koh et al[23]	2011	1,623	82	5	10
Gupta et al[24]	2011	314	84	5	11
Aldweib et al[25]	2013	1,199	62	20	18
Doukky et al[26]	2013	1,511	52	3	46
Khawaja et al[27]	2013	280	63	14	24
Moralidis et al[28]	2013	3,032	73	7	19
Medolago et al[29]	2014	2,134	84	9	7
Lalude et al[30]	2014	420	77	10	13
Singh et al[31]	2014	328	88	6	7

Percentage may not add to 100% due to unclassified studies or rounding errors.

Table 3. Abnormal SPECT results and event rates based on appropriate use categories

	Year	n	A (%)	U (%)	I (%)
Abnormal results					
Mehta et al[16]	2008	1,209	55	47	32
Gholamrezanezhad et al[21]	2011	291	33	47	11
Koh et al[23]	2011	1,623	40	21	27
Doukky et al[26]	2013	1,511	40	21	18
Khawaja et al[27]	2013	280	15		7
Medolago et al[29]	2014	2,134	58	-	33
Events					
Druz et al[22a]	2011	585	12	7	2
Koh et al[36b]	2011	176	6	-	1
Aldweib[25c]	2013	1,199	10	4	5
Khawaja et al[27d]	2013	280	14	0	3
Medolago et al[29d]	2014	2,134	9		3

[a]MI, death, revascularization, admission.
[b]Perioperative 90-day major cardiac events.
[c]Death.
[d]Cardiac catheterization.

predictive of subsequent events? To date, we have limited information to answer this type of question, as few SPECT studies have attempted to correlate appropriateness category and scintigraphic findings with patient outcomes (Table 3). Aldweib et al[25] demonstrated that SPECT studies done for inappropriate indications had an overall low cardiovascular risk and favorable outcomes when compared with uncertain or appropriately performed examinations. Khawaja et al[26] revealed that an inappropriately performed test is less likely to be abnormal but also showed that these patients were less likely to undergo coronary angiography and revascularization. Although 18% of these patients had an abnormal SPECT study, only 3% of patients with inappropriate SPECT examinations underwent angiography and none had coronary revascularization. In a large trial of 1,511 consecutive patients, Doukky et al[27] demonstrated that inappropriate use of SPECT MPI was associated with

reduced prognostic value. The hazard ratio for cardiac events, including death and/or myocardial infarction, among patients undergoing SPECT for appropriate or uncertain indications was 3.1-3.7, while those who had SPECT for an inappropriate indication failed to demonstrate discriminatory power with regards to these ''hard'' endpoints. However, all abnormal SPECT findings were associated with increased rates of coronary revascularization, irrespective of the level of appropriate use. Therefore, an abnormal SPECT MPI, when appropriate, was associated with death and/or MI or other major cardiac events, but if performed for inappropriate indications, the SPECT study did not predict events.

Similar to the SPECT reports describing the prognostic value of AUC, the current report by Winchester et al[15] demonstrated that an abnormal PET study or one which possesses significant ischemia (summed difference score >5) is associated with a hazard ratio for events of 4.5 and 5.1, respectively. Inappropriate PET scans were associated with low angiography rates and the clinical value of these studies appears negligible. The SPECT reports, along with the current paper, provide support for the prognostic implications of RNI AUC, as using radionuclide imaging in an inappropriate fashion fails to detect patients at increased risk for subsequent cardiac events.

However, the literature examining the association of appropriate use with outcomes has major limitations with regards to endpoint selection. The selection of diagnostic catheterization as an endpoint in the investigation by Winchester et al[15] and others[27] is flawed, as physicians were likely biased in their decision to refer a patient for coronary angiography based on scan findings and does not represent a meaningful change in outcome to the patient. Coronary revascularization, while still somewhat subjective, might have been a preferable endpoint except that PCI and CABG were also infrequently performed in the current trail [34 subjects (6.5%)], in keeping with the overall low-risk nature of the study cohort. In fact, only 26.1% had an abnormal study and far fewer had significant ischemia (12.5%). The selection of objective endpoints, such as death or myocardial infarction, would have been ideal, but these were infrequent events and would have required far more patient to be included in the trial. Not withstanding these limitations, the hypothesis that inappropriate PET (or SPECT) utilization fails to detect patients at increased risk of events or who require additional diagnostic testing/therapeutic intervention is highly thought-provoking and merits additional research.

Few would question the outstanding diagnostic and prognostic utility of PET MPI, with medical evidence not only supporting these applications but also demonstrating cost-effectiveness.[10,12] The development of new agents, including F-18 flurpiridaz, will likely strengthen the potential value and clinical use of this method, especially given the likelihood of unit dose availability and the further evolution of hybrid imaging. Enthusiasm for widespread clinical application of PET MPI, however, must be tempered with the need for any non-invasive test to have the capacity to impact care management and patient outcomes as well as the recognition of the current fiscal environment in health care. Earlier this year, the United States Congress passed legislation that mandates the use of AUC for advanced medical imaging, including PET, slated to begin in 2017.[33] Therefore, the evaluation of appropriate use has moved beyond an academic exercise into the mainstream of clinical practice.

The current work is the first to examine the use of AUC for PET imaging and demonstrates that inappropriate PET is infrequently associated with abnormal findings and rarely leads to cardiac catheterization. This further supports the need for the medical community to embrace peer-developed AUC as guidance documents, in order to optimize how we order PET scans and other tests/procedures. It is becoming increasingly evident that the performance of inappropriate radionuclide imaging is far less likely to achieve care goals but when performed appropriately may limit downstream unnecessary clinical consequences, such as angiography and revascularization. The development and now validation of AUC for PET and other methods must move beyond statistical correlations to direct patient impact. Fortunately the ACC/ASNC AUC for radionuclide imaging are ideally suited to an algorithmic approach and are now being embedded into web-based tools[34] and clinical decision support instruments.[35] Placing the AUC into the clinical realm for use at the time of ordering will hopefully allow practitioners to optimize their use of cardiac imaging, emphasizing clinical value, with recognition of cost. Studies to date have been encouraging with this approach, especially when coupled with additional educational initiatives.[33,34] Through continued efforts to optimize use of PET MPI, the true promise of this remarkable technique will be realized.

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