FEP 6.01.20 Cardiac Applications of Positron Emission Tomography Scanning

Effective Date: January 15, 2019

Description
Positron emission tomography (PET) scans use positron-emitting radionuclide tracers, which simultaneously emit 2 high-energy photons in opposite directions. These photons can be simultaneously detected (referred to as coincidence detection) by a PET scanner, comprising multiple stationary detectors that encircle the thorax. Compared with single-photon emission computed tomography (SPECT) scans, coincidence detection offers greater spatial resolution. PET has been investigated as an option to diagnose and evaluate patients with cardiac conditions such as coronary artery disease, left ventricular dysfunction, and cardiac sarcoidosis.

Comparison between PET and SPECT
A variety of studies have suggested that PET scans are only marginally more sensitive or specific than SPECT scans. Therefore, the choice between a PET scan (which may not be available locally) and a SPECT scan presents another clinical issue. Table 1 summarizes differences between cardiac SPECT and PET techniques.3

Table 1. Advantages and Disadvantages of Cardiac PET and SPECT3

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>Superior diagnostic capability, particularly for obese patients and patients with multivessel disease&lt;br&gt;Quantifiable blood flow evaluation&lt;br&gt;Integration of functional and anatomic information&lt;br&gt;Better spatial and contrast resolution&lt;br&gt;Lower frequency of artifacts</td>
<td>Higher equipment cost&lt;br&gt;Cyclotron or rubidium generators required&lt;br&gt;Radiotracers with short physical half-life do not permit exercise stress testing</td>
</tr>
<tr>
<td>SPECT</td>
<td>Wide availability&lt;br&gt;Well-established through published studies and familiar worldwide&lt;br&gt;Lower equipment cost&lt;br&gt;Less expensive radiotracers&lt;br&gt;Combined with dynamic exercise stress testing</td>
<td>Longer acquisition duration&lt;br&gt;Lower resolution images due to artifacts and attenuation&lt;br&gt;Higher radiation burden</td>
</tr>
</tbody>
</table>

PET: positron emission tomography; SPECT: single-photon emission computed tomography.

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A variety of radionuclide tracers are used for PET scanning, including fluorine 18, rubidium 82, oxygen 15, nitrogen 13, and carbon 11. Most tracers have a short half-life and must be manufactured with an on-site cyclotron. Rubidium 82 is produced by a stronitium 82/rubidium 82 generator. The half-life of fluorine-18 is long enough that it can be manufactured commercially at offsite and shipped to imaging centers. Radionuclides may be coupled with a variety of physiologically active molecules, such as oxygen, water, or ammonia. Fluorine 18 is often coupled with fluorodeoxyglucose to detect glucose metabolism, which in turn reflects metabolic activity, and thus viability, of the target tissue. Tracers that target the mitochondrial complex also are being developed.

**OBJECTIVE**

The objective of this evidence review is to determine whether positron emission tomography scanning improves the net health outcome in individuals with suspected or diagnosed coronary artery disease, severe left ventricular dysfunction, and cardiac sarcoidosis.

**POLICY STATEMENT**

Cardiac positron emission tomography (PET) scanning may be considered **medically necessary** to assess myocardial perfusion and thus diagnose coronary artery disease in patients with indeterminate single-photon emission computed tomography (SPECT) scan; or in patients for whom SPECT could be reasonably expected to be suboptimal in quality on the basis of body habitus.

Cardiac PET scanning may be considered **medically necessary** to assess myocardial viability in patients with severe left ventricular dysfunction as a technique to determine candidacy for a revascularization procedure. (See the Background section regarding the relative effectiveness of PET and SPECT scanning.)

Cardiac PET scanning is **investigational** for quantification of myocardial blood flow in patients diagnosed with coronary artery disease.

Cardiac PET scanning may be considered **medically necessary** for diagnosing cardiac sarcoidosis in patients who are unable to undergo magnetic resonance imaging. Examples of patients who are unable to undergo magnetic resonance imaging include, but are not limited to, patients with pacemakers, automatic implanted cardioverter defibrillators, or other metal implants.

**POLICY GUIDELINES**

A positron emission tomography (PET) scan involves 3 separate activities: (1) manufacture of the radiopharmaceutical, which may be manufactured on site or at a regional center with delivery to the institution performing PET; (2) actual performance of the PET scan; and (3) interpretation of the results.

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

A number of PET platforms have been cleared by the U.S. Food and Drug Administration (FDA) through the 510(k) process since the Penn-PET scanner was approved in 1989. These systems are intended to aid in detecting, localizing, diagnosing, staging, and restaging of lesions, tumors, disease, and organ function for the evaluation of diseases and disorders such as, but not limited to, cardiovascular disease, neurologic disorders, and cancer. The images produced by the system can aid in radiotherapy treatment planning and interventional radiology procedures.

PET radiopharmaceuticals have been evaluated and approved by FDA for use as diagnostic imaging agents. These radiopharmaceuticals are approved for specific conditions.
In December 2009, FDA issued guidance for Current Good Manufacturing Practice for PET drug manufacturers, and in August 2011, FDA issued similar Current Good Manufacturing Practice guidance for small businesses. An additional final guidance document issued in December 2012 required all PET drug manufacturers and compounders to operate under an approved new drug application (NDA) or abbreviated NDA, or investigational new drug application, by December 2015.

To avoid interruption of the use of PET radiotracers already in use in clinical practice, before the issuance of specific guidance documents, FDA made determinations of safety and effectiveness for certain uses of PET radiotracers. The following radiopharmaceuticals used with PET for cardiac-related indications were reviewed in this manner and subsequently had approved NDAs as summarized in Table 2.

### Table 2. Radiopharmaceuticals Approved for Use with PET for Cardiac Indications

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Manufacturer</th>
<th>NDA</th>
<th>Approved</th>
<th>Cardiac-Related Indication With PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorine 18 fluorodeoxyglucose (F-18-FDG)</td>
<td>Various</td>
<td>20306</td>
<td>2000</td>
<td>CAD and left ventricular dysfunction, when used with myocardial perfusion imaging, to identify left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function</td>
</tr>
<tr>
<td>Ammonia N 13</td>
<td>Zevacor Pharma</td>
<td>22119</td>
<td>2000</td>
<td>Imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing CAD</td>
</tr>
<tr>
<td>Rubidium 82 chloride</td>
<td>Bracco Diagnostics</td>
<td>19414</td>
<td>1989</td>
<td>Assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; NDA: new drug application; PET: positron emission tomography.

### RATIONALE

#### Summary of Evidence

For individuals with suspected coronary artery disease and an indeterminate SPECT scan who receive cardiac PET perfusion imaging, the evidence includes several systematic reviews and meta-analyses. Relevant outcomes are test accuracy, disease-specific survival, morbid events, and resource utilization. Meta-analyses of studies in which PET results were compared with results from coronary angiography and fractional flow reserve have shown that PET is comparable in diagnostic accuracy to these referent standards. In meta-analyses of studies that included clinical outcomes such as mortality and adverse cardiac events, results have shown that PET is a useful prognostic tool. Subgroup analyses have shown that PET can be useful in patients whose body habitus is likely to result in indeterminate SPECT scans (eg, patients with moderate-to-severe obesity). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with left ventricular dysfunction who are potential candidates for revascularization who receive cardiac PET scanning to assess myocardial viability, the evidence includes a large randomized controlled trial with long-term follow-up and several small trials comparing SPECT with PET. Relevant outcomes are test accuracy, disease-specific survival, and morbid events. In the large controlled trial, patients with left ventricular dysfunction were randomized to care from physicians who would make management decisions based on PET images or to care from physicians who would make management decisions without PET images. At 1- and 5-year follow-ups, patients who received care indicated by the PET images were at decreased risk for cardiac death, myocardial infarction, and recurrent hospital stays compared with patients who did not. The trials comparing SPECT with PET showed that both modalities were useful in managing patients considering revascularization. Evidence-based recommendations from specialty societies have concluded that PET scanning is at least as good as, and likely superior, to
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SPECT scanning for this purpose. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with coronary artery disease who require myocardial blood flow quantification who receive quantitative cardiac PET perfusion imaging, the evidence includes observational studies. The relevant outcomes are disease-specific survival and morbidity events. Studies adding PET-derived quantitative myocardial blood flow and myocardial flow reserve to prognostic models of clinical risk factors for cardiac events have reported inconsistent results, indicating that these methods are in a developmental stage for clinical use. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with suspected or diagnosed cardiac sarcoidosis who require evaluation who receive cardiac PET scanning, the evidence includes systematic reviews and meta-analyses. The relevant outcomes are disease-specific survival, test accuracy, and morbidity events. Currently, there is no criterion standard for diagnosing cardiac sarcoidosis. A combination of clinical evaluations and results from imaging techniques, usually MRI, are used during the clinician’s assessment. The pooled results from meta-analyses have shown good sensitivity, specificity, and area under the curve estimates. Several small studies have evaluated variations in PET techniques such as using a radiolabeled somatostatin receptor ligand and adding a simultaneous cardiac MRI. Reported results were positive in these small studies, but larger samples are needed to confirm the usefulness of these changes. While MRI is the technique most often used to evaluate cardiac sarcoidosis, for patients who are unable to undergo MRI (e.g., patients with a metal implant), evidence supports PET scanning as the preferred test. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Cardiology et al
The American College of Cardiology, American Heart Association, and American Society for Nuclear Cardiology (2003) updated their joint guidelines for cardiac radionuclide imaging, including cardiac applications of positron emission tomography (PET).7 Table 3 summarizes the guidelines for PET and single-photon emission computed tomography (SPECT) imaging in patients with an intermediate risk of coronary artery disease (CAD).

Table 3. Guidelines for PET and SPECT in Patients at Intermediate Risk of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Indication</th>
<th>Classa</th>
<th>SPECT</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify extent, severity, and location of ischemia (SPECT protocols vary according to whether patient can exercise)</td>
<td>I</td>
<td>I</td>
<td>Ila</td>
</tr>
<tr>
<td>Repeat test after 3-5 y after revascularization in selected high-risk asymptomatic patients (SPECT protocols vary according to whether patients can exercise)</td>
<td>Ila</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>As initial test in patients who are considered to be at high risk (ie, patients with diabetes or those with a &gt;20% 10-y risk of a coronary disease event) (SPECT protocols vary according to whether patients can exercise)</td>
<td>Ila</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myocardial perfusion PET when prior SPECT study has been found to be equivocal for diagnostic or risk stratification purposes</td>
<td>Not appropriate</td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Klocke et al (2003).6

a Class I is defined as conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class IIa is defined as conditions for which there is conflicting evidence or a divergence of opinion, but the weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb is similar to class II except that the usefulness/efficacy is less well-established by evidence/opinion.

PET: positron emission tomography; SPECT: single-photon emission computed tomography.
These guidelines concluded that PET “appears to have slightly better overall accuracy for predicting recovery of regional function after revascularization in patients with left ventricular dysfunction than single-photon techniques (ie, SPECT scans).” However, the guidelines indicated that both PET and SPECT scans are class I indications for predicting improvement in regional and global left ventricular function and natural history after revascularization; therefore, the guidelines did not indicate a clear preference for PET or SPECT scans in this situation.

The American College of Cardiology Foundation and American Heart Association (2009) collaborated with 6 other imaging societies to develop Appropriate Use Criteria for cardiac radionuclide imaging (RNI). Their report stated:

“...use of cardiac RNI for diagnosis and risk assessment in intermediate- and high-risk patients with coronary artery disease (CAD) was viewed favorably, while testing in low-risk patients, routine repeat testing, and general screenings in certain clinical scenarios were viewed less favorably. Additionally, use for perioperative testing was found to be inappropriate except for high selected groups of patients.”

American College of Radiology
The American College of Radiology (ACR) Appropriateness Criteria (2011) considered both SPECT and PET to be appropriate for the evaluation of patients with a high probability of CAD. ACR indicated that PET perfusion imaging has advantages over SPECT, including higher spatial and temporal resolution. Routine performance of both PET and SPECT are unnecessary. The 2017 update stated:

“Hybrid PET scanners use CT [computed tomography] for attenuation correction (PET/CT) following completion of the PET study. By coupling the PET perfusion examination findings to a CCTA [coronary computed tomographic angiography], PET/CT permits the fusion of anatomic coronary arterial and functional (perfusion) myocardial information and enhances diagnostic accuracy. The fused examinations can accurately measure the atherosclerotic burden and identify the hemodynamic functional significance of coronary stenosis. The results of the combined examinations can more accurately identify patients for revascularization.”

The ACR Appropriateness Criteria (2012) also recommended PET for the evaluation of patients with chronic chest pain and the low-to-intermediate probability of CAD.

ACR does not recommend PET for patients with acute nonspecific chest pain who have a low probability of CAD or for asymptomatic patients at risk for CAD.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Beginning 2002, Medicare began to cover fluorine 18 fluorodeoxyglucose (FDG)-PET for the determination of myocardial viability as a primary or initial diagnostic study before revascularization and continued to cover FDG-PET when used as a follow-up to an inconclusive SPECT. However, if a patient only receives FDG-PET with inconclusive results, a follow-up SPECT is not covered. Full and partial ring PET scanners approved or cleared by the U.S. Food and Drug Administration (FDA) are covered.

“Limitations: In the event that a patient receives a SPECT with inconclusive results, a PET scan may be performed and covered by Medicare. However, SPECT is not covered following a FDG PET with inconclusive results....

Frequency: In the absence of national frequency limitations, contractors can, if necessary, develop reasonable frequency limitations for myocardial viability.”
A national coverage determination for PET for perfusion of the heart (220.6.1) states that “PET scans performed at rest or with pharmacological stress used for noninvasive imaging of the perfusion of the heart for the diagnosis and management of patients with known or suspected coronary artery disease using the FDA-approved radiopharmaceutical Rubidium 82 (Rb 82) are covered.” The following criteria are required:

- “The PET scan, whether at rest alone, or rest with stress, is performed in place of, but not in addition to, a single photon emission computed tomography (SPECT); or
- The PET scan, whether at rest alone or rest with stress, is used following a SPECT that was found to be inconclusive. In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the patient. (For purposes of this requirement, an inconclusive test is a test(s) whose results are equivocal, technically uninterpretable, or discordant with a patient's other clinical data and must be documented in the beneficiary's file.)"

REFERENCES

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45. Lapa C, Reiter T, Kircher M, et al. Somatostatin receptor based PET/CT in patients with the suspicion of cardiac sarcoidosis: an initial comparison to cardiac MRI. *OncoTarget.* Nov 22 2016;7(47):77807-77814. PMID 27780922


54. Centers for Medicare & Medicaid Services (CMS). Coverage and Related Claims Processing Requirements for Positron Emission Tomography (PET) Scans – for Breast Cancer and Revised Coverage Conditions for...
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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>December 2011</td>
<td>New Policy</td>
<td></td>
</tr>
<tr>
<td>December 2012</td>
<td>Update Policy</td>
<td>Policy updated with literature review, references updated, policy statements unchanged.</td>
</tr>
<tr>
<td>September 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, References 4, 11, 12, and 17 added and some reordered, No change in policy statements.</td>
</tr>
<tr>
<td>September 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review, adding references 1, 2, 4, 19, 24, and 25. No change to the policy statement.</td>
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<tr>
<td>December 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through July 9, 2018; references 8, 28-29, 31-35, and 43 added. Policy statements unchanged except Cardiac PET scanning for quantification of myocardial blood flow policy statement corrected from “not medically necessary” to “investigational” due to FDA 510 clearance.</td>
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