Title: Positron Emission Tomography (PET) Scanning: Cardiac Applications

See also:
- PET Scanning: In Oncology to Detect Early Response during Treatment
- PET Scanning: Miscellaneous (Non-cardiac, Non-oncologic) Applications of Fluorine 18 Fluorodeoxyglucose
- PET-Scanning: Oncologic Applications

Professional
- Original Effective Date: October 1, 1997
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- Current Effective Date: November 26, 2018

Institutional
- Original Effective Date: September 11, 2004
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- Current Effective Date: November 26, 2018

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<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: Cardiac positron emission tomography perfusion imaging</td>
<td>Comparators of interest are: Coronary angiography Other noninvasive tests for coronary artery disease (eg, stress echocardiography, exercise electrocardiography)</td>
<td>Relevant outcomes include: Test accuracy Disease-specific survival Morbid events Resource utilization</td>
</tr>
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<tr>
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<td>----------</td>
</tr>
</tbody>
</table>
| Individuals:  
- With severe left ventricular dysfunction and are potential candidates for revascularization | Interventions of interest are:  
- Cardiac positron emission tomography scanning to assess myocardial viability | Comparators of interest are:  
- Cardiac magnetic resonance imaging  
- Cardiac single-photon emission computed tomography scanning | Relevant outcomes include:  
- Test accuracy  
- Disease-specific survival  
- Morbid events |
| Individuals:  
- With coronary artery disease and require quantification myocardial blood flow quantification | Interventions of interest are:  
- Quantitative cardiac positron emission tomography perfusion imaging | Comparators of interest are:  
- Coronary angiography with fractional flow reserve  
- Clinical risk models | Relevant outcomes include:  
- Disease-specific survival  
- Morbid events |
| Individuals:  
- With suspected or diagnosed cardiac sarcoidosis who require evaluation | Interventions of interest are:  
- Cardiac positron emission tomography scanning | Comparators of interest are:  
- Clinical evaluation  
- Myocardial biopsy | Relevant outcomes include:  
- Disease-specific survival  
- Test accuracy  
- Morbid events |

**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.

**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.

**Background**

**POSITRON EMISSION TOMOGRAPHY**

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.
Myocardial Perfusion Imaging
For myocardial perfusion studies, patient selection criteria for PET include individual assessment of the pretest probability of coronary artery disease (CAD), based both on patient symptoms and risk factors. Patients at low risk for CAD may be adequately evaluated with exercise electrocardiography. Patients at high risk for CAD typically will not benefit from noninvasive assessment of myocardial perfusion; a negative test will not alter disease probability sufficiently to avoid invasive angiography. Accordingly, myocardial perfusion imaging is potentially beneficial for patients at intermediate risk of CAD (variability defined as 25%-75% disease probability).1,1 Risk can be estimated using the patient’s age, sex, and chest pain quality. Table 1 summarizes patient populations at intermediate risk for CAD.2

Table 1. Individuals at Intermediate Risk for CAD According to Chest Pain Quality

<table>
<thead>
<tr>
<th>Populations</th>
<th>Typical Anginaa</th>
<th>Atypical Anginab</th>
<th>Nonanginal Chest Painc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>30-39</td>
<td>30-70</td>
<td>≥50</td>
</tr>
<tr>
<td>Women</td>
<td>30-60</td>
<td>≥50</td>
<td>≥60</td>
</tr>
</tbody>
</table>

Values are age or age range in years.

CAD: coronary artery disease.
a Chest pain with all of the following characteristics: (1) substernal chest discomfort with characteristic quality and duration, (2) provoked by exertion or emotional stress, and (3) relieved by rest or nitroglycerin.
b Chest pain that lacks one of the characteristics of typical angina.
c Chest pain that has one or none of the typical angina characteristics.

Body habitus can limit SPECT; particularly moderate-to-severe obesity, which can attenuate tissue tracer leading to inaccurate images. In patients for whom body habitus is expected to lead to suboptimal SPECT scans, PET scanning is preferred.

Myocardial Viability
Patients selected to undergo PET scanning for myocardial viability are typically those with severe left ventricular dysfunction who are being considered for revascularization. A PET scan may determine whether the left ventricular dysfunction is related to viable or nonviable myocardium. Patients with viable myocardium may benefit from revascularization, but those with nonviable myocardium will not. As an example, PET scanning is commonly performed in potential heart transplant candidates to rule out the presence of viable myocardium.

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 2 summarizes differences between cardiac SPECT and PET techniques.3

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1 Intermediate-risk ranges used in different studies may differ from the range used here. These pretest probability risk groups are based on a 1995 TEC Assessment and take into account spectrum effect. American College of Cardiology guidelines have defined low risk as less than 10%, intermediate risk as 10% to 90%, and high risk as greater than 90%.
Table 2. Advantages and Disadvantages of Cardiac PET and SPECT

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

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

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 strontium 82/rubidium 82 generator. The half-life of fluorine-18 is long enough that it can be manufactured commercially at offsite locations 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 are also being developed.

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,⁴ and in August 2011, FDA issued similar Current Good Manufacturing Practice guidance for small businesses.⁵ 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 2015.⁶

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 3.

**Table 3. 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>2030 6</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>2211 9</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>1941 4</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.

**POLICY**

A. 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.

B. 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.)

C. 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.

D. Cardiac PET scanning is **experimental / investigational** for quantification of myocardial blood flow in patients diagnosed with coronary artery disease.
RATIONALE
This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through July 9, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Suspected Coronary Artery Disease**

**Clinical Context and Test Purpose**
The purposes of positron emission tomography (PET) scanning in patients with suspected coronary artery disease (CAD) is to confirm a diagnosis and to inform a clinician in disease management decisions such as whether to proceed to invasive procedures in intermediate-risk patients.

The question addressed in this evidence review is: Does the use of PET improve the net health outcome in individuals with suspected CAD?

The following PICOTS were used to select literature to inform this review.

**Patients**
The population of interest is patients with suspected CAD who have indeterminate single-photon emission computed tomography (SPECT) scans.

**Interventions**
The intervention of interest is cardiac PET perfusion imaging.

**Comparators**
The following tests are currently being used to make decisions about managing suspected CAD: coronary angiography or other noninvasive tests for CAD (eg, stress echocardiography, exercise electrocardiography).

**Outcomes**
For patients with suspected CAD, the outcomes of interest are avoidance of unnecessary invasive procedures, cardiac events, and mortality.

**Timing**
For suspected CAD, the timing of the outcome of interest is time to diagnosis.
**Setting**
Cardiac PET perfusion imaging would be administered in an imaging center equipped with a PET scanner.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The sensitivity and specificity of PET may be slightly better than for those for SPECT. Performance characteristics for PET and SPECT based on a 2007 Canadian joint position statement are shown in Table 4.\(^7\)

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>PET</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>89</td>
<td>77</td>
</tr>
<tr>
<td>Estimated positive likelihood ratio(^a)</td>
<td>8.27</td>
<td>3.83</td>
</tr>
<tr>
<td>Estimated negative likelihood ratio(^b)</td>
<td>0.10</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Adapted from Beanlands et al (2007).\(^7\)
PET: positron emission tomography; SPECT: single-photon emission computed tomography.
\(^a\) Estimated positive likelihood ratio = sensitivity/(1 – specificity).
\(^b\) Estimated negative likelihood ratio = (1 – sensitivity)/specificity.

**Diagnostic Performance**

**Systematic Reviews**
Knuuti et al (2018) reported on the results of a meta-analysis of the performance of noninvasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina including publications through April 2017 that included at least 100 patients with stable CAD and either invasive coronary angiography (ICA) or ICA with fractional flow reserve (FFR) measurement as reference standard.\(^8\) A total of 132 studies (28,664 patients) using ICA as the reference standard and 23 studies (4131 patients) using FFR as the reference standard were included. The pooled analysis for the outcome of anatomically significant CAD included 418 patients for PET and the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were as follows: 90% (95% confidence interval [CI], 78% to 96%); 85% (95% CI, 78% to 90%); 5.87 (95% CI, 3.40 to 10.15); and 0.12 (95% CI, 0.05 to 0.29), respectively. The pooled analysis for outcome of functionally significant CAD included 709 patients for PET and the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio (NLR) were as follows: 89% (95% CI, 82% to 93%); 85% (95% CI, 81% to 88%); 6.04 (95% CI, 4.29 to 8.51); and 0.13 (95% CI, 0.08 to 0.22).

Dai et al (2016) conducted a meta-analysis comparing the abilities of the following cardiac imaging modalities to diagnose CAD: SPECT, PET, dobutamine stress echocardiography, cardiac magnetic resonance imaging (MRI), and computed tomography (CT) perfusion imaging.\(^9\) The
reference standard was FFR derived from CT. The literature search, conducted through June 2015, identified 74 studies for inclusion, 5 of which used PET. Study quality was assessed using Standards for Reporting Diagnostic Accuracy and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tools. Pooled sensitivity and specificity for PET were 90% (95% CI, 80% to 95%) and 84% (95% CI, 81% to 90%), respectively. These rates were similar to FFR, the reference standard (sensitivity, 90% [95% CI, 85% to 93%]; specificity, 75% [95% CI, 62% to 85%]).

Jaarsma et al (2012) reported on a meta-analysis comparing the diagnostic performance of noninvasive myocardial perfusion imaging using SPECT, cardiac MRI, or PET. The comparison standard was CAD identified with coronary angiography. A total of 166 articles (N=17,901 patients) met inclusion criteria, with 114 articles on SPECT, 37 on cardiac MRI, and 15 on PET. Sensitivity by patient-level analysis was similar for the 3 tests, with a pooled sensitivity of 88% for SPECT, 89% for MRI, and 84% for PET. Pooled specificity was lower for SPECT (61%) compared with MRI (76%) or PET (81%). The pooled diagnostic odds ratio was 15.31 for SPECT, 26.42 for MRI, and 36.47 for PET. Meta-regression indicated that MRI and PET have a significantly higher diagnostic accuracy than SPECT. Although this analysis was limited by potential publication bias for SPECT and significant heterogeneity in the MRI and SPECT studies, most subgroup analyses have shown a relative superiority of MRI and PET over SPECT.

Another meta-analysis, by Parker et al (2012), compared SPECT with PET stress myocardial perfusion imaging, using coronary angiography as the reference standard. A total of 117 articles met the selection criteria. SPECT was assessed in 113 studies (n=11,212 patients), and PET was assessed in 9 studies (n=650 patients). Patient-level diagnostic accuracy data were pooled in a bivariate meta-analysis, showing significantly better sensitivity for PET (92.6%) than for SPECT (88.3%). The difference in specificity between PET (81.3%) and SPECT (76.0%) was not significant. The pattern of higher sensitivity for PET over SPECT and similar specificity remained when analyses were limited to only high-quality studies.

Takx et al (2015) reported a meta-analysis of studies that compared noninvasive myocardial perfusion imaging modalities (MRI, CT, PET, SPECT, echocardiography) with coronary angiography plus FFR. Literature was searched to May 2014, and 37 studies met inclusion criteria (total N=4698 vessels). Three PET studies of moderate-to-high quality were included (870 vessels); pretest probability of CAD was intermediate to intermediate-high in these studies. NLR was chosen as the primary outcome of interest because ruling out hemodynamically significant CAD is a primary purpose of noninvasive imaging. At the vessel level, pooled NLRs for PET, MRI, and CT were similar and were lower (better) than the pooled NLR for SPECT (PET pooled NLR=0.15 [95% CI, 0.05 to 0.44]; SPECT pooled NLR=0.47 [95% CI, 0.37 to 0.59]). Similarly, at the patient-level, pooled NLRs for PET, MRI, and CT were better than the pooled NLRs for SPECT and echocardiography (PET pooled NLR=0.14 [95% CI, 0.02 to 0.87]; SPECT pooled NLR=0.39 [95% CI, 0.27 to 0.55]). The area under the receiver operating characteristic analyses were similar at both the vessel level (PET, 0.95 vs SPECT, 0.83) and the patient-level (PET, 0.93 vs SPECT, 0.82).

**Retrospective Studies**

Another consideration is that there are fewer indeterminate results with PET than SPECT. Bateman et al (2006) retrospectively matched 112 SPECT and 112 PET studies by sex, body mass index, and presence and extent of CAD, and compared diagnostic accuracy and degree of
interpretative certainty (age, 65 years; 52% male; mean body mass index, 32 kg/m²; 76% with CAD diagnosed on angiography). Eighteen (16%) of 112 SPECT studies were classified as indeterminate compared with 4 (4%) of 112 PET studies. Liver and bowel uptake were believed to affect 46 (41%) of 112 SPECT studies, compared with 6 (5%) of 112 PET studies. In obese patients (body mass index, >30 kg/m²), the accuracy of SPECT was 67% and 85% for PET; accuracy in nonobese patients was 70% for SPECT and 87% for PET. Therefore, for patients with an intermediate pretest probability of CAD, one should start with SPECT testing and only proceed to PET in indeterminate cases. Also, because obese patients are more prone to liver and bowel artifact, PET testing is advantageous over SPECT in these patients.

**Prognostic Performance**

**Systematic Reviews**

Chen et al (2017) published a meta-analysis assessing the prognostic value of PET myocardial perfusion imaging in patients with known or suspected CAD. For inclusion, studies had to have at least one of the following outcomes: mortality, cardiac infarction, or major adverse cardiac event (MACE). The literature search, conducted through June 2016, identified 11 studies for inclusion. Quality assessment was based on: (1) cohort follow-up of 90% or more; (2) blinded outcome assessors; and (3) corroboration of outcomes with hospital records or death certificates. Nine of the studies were of good quality, and two were fair. All 11 studies included cardiac death as the primary or secondary outcome, with a pooled negative predictive value (NPV) of 99% (95% CI, 98% to 99%). Seven studies included all-cause death as an outcome, with a pooled NPV of 95% (95% CI, 93% to 96%). Four studies included MACE as an outcome, with a pooled NPV of 90% (95% CI, 78% to 96%).

Smulders et al (2017) published a meta-analysis comparing the prognostic value of the following negative noninvasive cardiac tests: coronary computed tomography angiography, cardiovascular MRI, exercise electrocardiographic testing, PET, stress echocardiography, and SPECT. Outcomes of interest were annual event rates of myocardial infarction and cardiac death. The literature search, conducted through April 2015, identified 165 studies for inclusion, four of which involved PET. Study quality was assessed using the Newcastle-Ottawa Scale for observational studies. Pooled annual event rates for cardiac death and myocardial infarction for PET were low (0.41; 95% CI, 0.15 to 0.80), indicating that a patient with a negative PET test has a good prognosis.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs comparing outcomes for patients undergoing PET perfusion imaging to patients who did not undergo PET perfusion imaging were identified.
Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Diagnostic utilities of PET and SPECT may be similar in terms of modifying disease risk assessment in a manner that affects subsequent decision making in patients with an intermediate pretest probability of CAD. For example, as shown in Table 5, a patient with a 50% pretest probability of CAD would have a 9% posttest probability of CAD after a negative PET scan compared with 13% probability after a negative SPECT. In either case, further testing may not be pursued.

Table 5. Diagnostic Utility (Effect on Pretest CAD Risk Assessment) of PET and SPECT

<table>
<thead>
<tr>
<th>Pretest Probability</th>
<th>Positive Test</th>
<th>Negative Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PET</td>
<td>SPECT</td>
</tr>
<tr>
<td>30%</td>
<td>78</td>
<td>62</td>
</tr>
<tr>
<td>50%</td>
<td>89</td>
<td>79</td>
</tr>
<tr>
<td>70%</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; PET: positron emission tomography; SPECT: single-photon emission computed tomography.

Meta-analyses have shown that PET is a useful prognostic tool that can be performed successfully in some patients in whom SPECT may be indeterminate due to body habitus or other anatomic factors. Therefore, PET results can be useful in informing clinical decisions in these intermediate-risk patients.

Section Summary: Suspected Coronary Artery Disease
Evidence on the diagnostic accuracy of PET for CAD consists of several systematic reviews and meta-analyses. Meta-analyses comparing PET with reference standards such as ICA and FFR have shown that PET is comparable in diagnostic accuracy. Meta-analyses evaluating the clinical utility of PET have looked at outcomes such as mortality and adverse cardiac events. These meta-analyses have shown that PET is a useful prognostic tool. For some patients in whom SPECT may be indeterminate due to body habitus or other anatomic factors, PET can be performed successfully.

Severe LV Dysfunction Considering Revascularization
Clinical Context and Test Purpose
The purposes of PET scanning in patients with left ventricular (LV) dysfunction who are potential candidates for revascularization is to confirm a diagnosis or to inform a clinician in disease management decisions, specifically regarding revascularization.

The question addressed in this evidence review is: Does the use of PET improve the net health outcome in individuals with LV dysfunction considering revascularization?

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest is patients with severe LV dysfunction who are potential candidates for revascularization.
Interventions
The intervention of interest is PET scanning.

Comparators
The following tests are currently being used to make decisions about managing severe LV dysfunction: cardiac MRI or cardiac SPECT scanning.

Outcomes
For patients with severe LV dysfunction who are potential candidates for revascularization, the intermediate outcome is a viability assessment. If there is sufficient viable myocardium detected, the patient would be a candidate for revascularization. Clinical outcomes of interest are cardiac events.

Timing
For severe LV dysfunction, the timing would be time to cardiac events.

Setting
Cardiac PET would be administered in an imaging center equipped with a PET scanner.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

PET has perhaps been most thoroughly researched as a technique to assess myocardial viability to determine candidacy for a coronary revascularization procedure. For example, a patient with a severe stenosis identified by coronary angiography may not benefit from revascularization if the surrounding myocardium is nonviable. A fixed perfusion defect, as imaged on SPECT scanning or stress thallium echocardiography, may suggest nonviable myocardium. However, a PET scan may reveal metabolically active myocardium, suggesting areas of “hibernating” myocardium that would benefit from revascularization. The most common PET technique for this application consists of N 13 ammonia as a perfusion tracer and fluorine 18 fluorodeoxyglucose (FDG) as a metabolic marker of glucose utilization. FDG uptake in areas of hypoperfusion (referred to as FDG/blood flow mismatch) suggests viable, but hibernating myocardium. The ultimate clinical validation of this diagnostic test is the proportion of patients who experience improvement in LV dysfunction after revascularization of hibernating myocardium, as identified by PET scanning.

SPECT scanning also may be used to assess myocardial viability. Initial myocardial uptake of thallium 201 reflects myocardial perfusion, and redistribution after prolonged periods can be a marker of myocardial viability. Initial protocols required redistribution imaging after 24 to 72 hours. Although this technique was associated with a strong positive predictive value, there was a low NPV; ie, 40% of patients without redistribution nevertheless showed clinical improvement.
after revascularization. NPVs have improved with the practice of thallium reinjection. Twenty-four to 72 hours after initial imaging, patients receive a reinjection of thallium and undergo redistribution imaging.

Studies identified in literature have shown the equivalence of SPECT and PET in their ability to assess myocardium viability. Comparative studies have reported on test accuracy and have not addressed the impact on clinical outcomes. Using a thorax-cardiac phantom with different sized inserts that simulated infarcts, Knesaurek and Machac (2006) tested SPECT and PET images. The investigators concluded that PET was better at detecting smaller defects than SPECT. In this study, a 1-cm insert, not detected by SPECT, was detected by PET.

Slart et al (2005) compared dual-isotope simultaneous acquisition SPECT and PET in the detection of myocardial viability in 58 patients with CAD and dysfunctional LV myocardium. Tracer uptake for PET and SPECT was compared by linear regression and correlation analysis, which showed there was an overall good agreement between SPECT and PET for the assessment of myocardial viability in patients with severe LV dysfunction.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

**Randomized Controlled Trials**

A large RCT, Positron Emission Tomography and Recovery Following Revascularization (PARR-2), evaluated the impact of FDG-PET viability imaging on patients with severe LV dysfunction. Patients from 9 sites were randomized to FDG-PET-assisted physician management (n=218) or standard care management by a physician without PET imaging available (n=212). Management decision options were: revascularization, revascularization workup, or neither. The primary outcome was a composite of cardiac death, myocardial infarction, or recurrent hospital stay for a cardiac cause. Beanlands et al (2007) reported on results after 1 year of follow-up. The intention-to-treat hazard ratio (HR) of a composite event occurring at 1 year was not significant (0.78; 95% CI, 0.58 to 1.1; p=0.15) for PET-assisted management of care compared with standard care. However, among patients in the PET-assisted management of care group who had high or medium myocardium viability and who therefore were recommended to receive revascularization or a revascularization workup, 26% did not ultimately receive the recommended care. Reasons given included symptoms stabilizing, renal failure, multiple comorbidities, and patient refusal. When subgroup analysis included only those patients who received the treatment as recommended based on PET images, the HR for a composite event was significant (0.62; 95% CI, 0.42 to 0.93).

Mc Ardle et al (2016) published long-term follow-up results for PARR-2. Six of the 9 original sites participated in the long-term follow-up study (197 patients in the PET-assisted arm, 195
patients in the standard care arm). Long-term results were similar to the 1-year results. The HR for time to composite event for the whole study population did not differ significantly between the PET-assisted group and the standard care group (0.82; 95% CI, 0.62 to 1.1); however, when analysis was conducted using only the subgroup of patients who adhered to the PET imaging-based recommendations, the HR was statistically significant (0.73; 95% CI, 0.54 to 0.99).

Siebelink et al (2001) performed a prospective randomized study comparing management decisions with outcomes based on PET imaging (n=49) or SPECT imaging (n=54) in patients who had chronic CAD and LV dysfunction and were being evaluated for myocardial viability. Management decisions based on readings of the PET or SPECT images included either drug therapy for patients without viable myocardium or revascularization with either angioplasty or coronary artery bypass grafting (CABG) for patients with viable myocardium. This study is unique in that the diagnostic performance of PET and SPECT was tied to actual patient outcomes. No difference in patient management or cardiac event-free survival was demonstrated between management based on the 2 imaging techniques. The authors concluded that either technique could be used to manage patients considered for revascularization.

Nonrandomized Studies
Srivatsava et al (2016) published a study of 120 patients with LV dysfunction who underwent both SPECT-CT and FDG-PET/CT to determine myocardial viability. If both tests showed defects, the tissue was considered nonviable. If test results were mismatched, the tissue was considered hibernating but viable. If more than 7% of the myocardium was considered viable, patients underwent revascularization by either stenting or CABG (78 patients). Patients assessed as having less than 7% viable myocardium were medically managed (42 patients). The primary outcome was global left ventricular ejection fraction (LVEF). Change in LVEF after 3 months was significantly larger in the surgically managed group (3.5; 95% CI, 2.5 to 4.5) than in the medically managed group (0.7; 95% CI, -0.8 to 2.2).

Section Summary: Severe LV Dysfunction Considering Revascularization
Evidence for the use of PET to assess myocardial viability consists of a large controlled trial that randomized patients with LV dysfunction into 2 groups: one was managed by physicians receiving PET images to inform care decisions, and the other was managed by physicians who did not receive PET images. Follow-up at 1 year and 5 years showed that when patients received care as indicated by the PET images, they were at decreased risk for cardiac death, myocardial infarction, or recurrent hospital stay compared with patients who did not. Available evidence from smaller trials has suggested that the accuracy of PET and SPECT are roughly similar for this purpose. PET may be more sensitive regarding small defects, but the clinical significance of identifying small defects is uncertain.

Myocardial Blood Flow Quantification
Clinical Context and Test Purpose
The purposes of PET scanning in patients with CAD who require myocardial blood flow (MBF) quantification is to inform a clinician in disease management decisions, which would include revascularization decisions, detection of early disease stages to improve preventive measures to reverse risk, or as a tool for monitoring effects of risk factor modification such as lipid-lowering treatment.
The question addressed in this evidence review is: Does the use of PET improve the net health outcome in individuals with CAD in need of MBF quantification?

The following PICOTS were used to select literature to inform this review.

**Patients**  
The population of interest is patients with CAD in need of quantifying MBF.

**Interventions**  
The intervention of interest is quantitative cardiac PET perfusion imaging.

**Comparators**  
The following tests are currently being used to make decisions about quantifying MBF in patients with CAD: coronary angiography with FFR and clinical risk models.

**Outcomes**  
For patients with CAD who require MBF quantification, the intermediate outcome is accurate quantification. The clinical outcome of interest is cardiac events.

**Timing**  
Relevant follow up would be time to cardiac events.

**Setting**  
Cardiac PET perfusion imaging would be administered in an imaging center equipped with a PET scanner.

**Technically Reliable**  
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**  
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Several publications have described the use of PET imaging to quantify both MBF and myocardial flow reserve (MFR; defined as stress MBF/rest MBF).\textsuperscript{22,23} However, as noted in an accompanying editorial\textsuperscript{24} and by subsequent reviewers,\textsuperscript{25} larger prospective clinical trials are needed to understand the clinical utility of these approaches.

**Diagnostic Performance**  
Hsu et al (2017) published a study comparing SPECT with N 13 ammonia PET in blood flow quantitation.\textsuperscript{26} Healthy patients (n=12) and patients with CAD (n=16) underwent both SPECT and N 13 ammonia PET flow scans. MFR measures by SPECT and PET did not differ significantly in healthy patients. The MFR measures were also comparable in patients with CAD. The authors concluded that MFR can be accurately measured by either modality.
Stuijfzand et al (2015) used oxygen 15-labeled water PET imaging in 92 patients with 1-2 vessel disease to quantify MBF, MFR, and “relative flow reserve” (defined as stress MBF in a stenotic area/stress MBF in a normal perfused area). Relative flow reserve was evaluated as a potential noninvasive alternative to FFR on coronary angiography. Using optimized cut points for PET detection of hemodynamically significant CAD (FFR as reference standard), area under the curve analysis showed similar diagnostic performance for all 3 measures (0.76 [95% CI, 0.66 to 0.86] for MBF; 0.72 [95% CI, 0.61 to 0.83] for MFR; 0.82 [95% CI, 0.72 to 0.91] for relative flow reserve; p>0.05 for all comparisons).

**Prognostic Performance**

Juarez-Orozco et al (2017) reported on the results of a systematic review of prognostic studies of quantitative myocardial perfusion evaluation with PET. Eight studies (total N=6804 patients) were included. Risk of bias was assessed using the Quality in Prognostic Studies tool. The risk of bias was rated as low overall with the exception of 1 domain (prognostic factor measurement) with the uncertain risk of bias due to the differences in population characteristics and tracer used. The mean follow-up range was 12 to 117 months for the MACE outcome, 66 to 88 months for the cardiac death outcome, and 43 to 117 months for the all-cause mortality outcome. MFR was independently associated with MACE in all 8 studies with the range of adjusted HRs from 1.19 to 2.93. Pooled analyses for MACE included only 2 studies due to the differences in populations and cutoff values for MFR. There was not enough evidence to establish the prognostic value of MFR for cardiac death or all-cause mortality.

Taqueti et al (2015) evaluated the association between MFR (called coronary flow reserve [CFR] in this study) and cardiovascular outcomes in 329 consecutive patients referred for invasive coronary angiography after stress PET perfusion imaging. Patients with a history of CABG or heart failure, or with an LVEF less than 40%, were excluded. Patients underwent rubidium 82 (Rb-82) or N 13 ammonia PET imaging and selective coronary angiography. MFR was calculated as the ratio of stress to rest MBF for the whole left ventricle. The primary outcome was a composite of cardiovascular death and hospitalization for heart failure. These outcomes were chosen because they are thought to be related to microvascular dysfunction, which impacts PET MBF measures, as opposed to obstructive CAD, which characteristically presents with myocardial infarction and/or revascularization. Patients were followed for a median of 3.1 years (interquartile range, 1.7-4.3) for the occurrence of MACE (comprising death, cardiovascular death, and hospitalization for heart failure or myocardial infarction). During follow-up, 64 (19%) patients met the primary composite end point. In a multivariate model that included pretest clinical score (to determine the pretest probability of obstructive, angiographic CAD), LVEF, left ventricular ischemia, early revascularization (within 90 days of PET imaging), and Coronary Artery Disease Prognostic Index, MFR was statistically associated with the primary outcome (HR per 1 unit decrease in continuous MFR score, 2.02; 95% CI, 1.20 to 3.40). The model used binary classification defined by median MFR, and the incidence of the primary outcome was 50% in patients with low or high CFR. A statistically significant interaction between CFR and early revascularization by CABG was observed: Event-free survival for patients with high CFR who underwent early revascularization was similar in groups who received CABG (n=17), percutaneous coronary intervention (n=72), or no revascularization (n=79); among patients with low CFR who underwent early revascularization, event-free survival was significantly better in the CABG group (n=22) compared with the percutaneous coronary intervention group (n=85; p=0.006) and the no revascularization group (n=57; p=0.001).
Ziadi et al (2011) reported on a prospective study of the prognostic value of MFR with Rb-82 PET in 704 consecutive patients assessed for ischemia. Ninety-six percent (n=677) of patients were followed for a median of 387 days; most (90%) were followed by telephone. The hypothesis tested was that patients with reduced flow reserve would have higher cardiac event rates and that Rb-82 MFR would be an independent predictor of adverse outcomes. The primary outcome was the prevalence of hard cardiac events (myocardial infarction and cardiac death); the secondary outcome was the prevalence of MACE (comprising cardiac death, myocardial infarction, later revascularization, and cardiac hospitalization). Patients with a normal summed stress score but impaired MFR had a significantly higher incidence of hard events (2% vs 1.3%) and MACE (9% vs 3.8%) compared with patients who had preserved MFR. Patients with abnormal summed stress score and impaired MFR had a higher incidence of hard events (11.4% vs 1.1%) and MACE (24% vs 9%) compared with patients who had preserved MFR. Rb-82 MFR was an independent predictor of cardiac hard events (HR=3.3) and MACE (HR=2.4) over summed stress score. Three (0.4%) patients were classified up, and 0 were classified down, with MFR in the multivariate model (p=0.092).

Murthy et al (2011) examined the prognostic value of Rb-82 PET MFR (called CFR in this study) in a retrospective series of 2783 patients referred for rest/stress PET myocardial perfusion imaging. CFR was calculated as the ratio of stress to rest MBF using semi-quantitative PET interpretation. The primary outcome was cardiac death over a median follow-up of 1.4 years. Prognostic modeling was done with a Cox proportional hazards model. Adding MFR to a multivariate model containing clinical covariates (eg, CAD risk factors and CAD history) significantly improved model fit and improved the c index, a measure of discrimination performance, from 0.82 to 0.84 (p=0.02). MFR was a significant independent predictor of cardiac mortality and resulted in improved risk reclassification. In 2012, these authors reported that the added value of PET MFR was observed in both diabetic and nondiabetic patients.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs comparing clinical outcomes for patients undergoing PET to calculate MFR with patients who did not undergo PET were identified.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity and explication of evidence-based decisions informed by the test. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Specificity on how the test would fit into current management guidelines for making treatment decisions is needed to evaluate a chain of evidence.
Section Summary: Myocardial Blood Flow Quantification
Evidence is accumulating on the association between quantitative MBF and MFR and cardiovascular outcomes. Some but not all prospective studies have shown improvements over prognostic models based on clinical risk factors for cardiac events. Editorialists have commented on the potential utility of quantitative perfusion for understanding cardiac physiology and for informing future research. However, because of differences in populations studied, cut points used for classification, covariates used in models, lack of reclassification analyses, and lack of guidance on how decisions are informed by test results, these methods are considered to be in a developmental stage for clinical use.

Cardiac Sarcoidosis
Based on clinical input received in 2011, an additional indication for the workup of cardiac sarcoidosis was added to the evidence review.

There is no standard diagnostic criterion for cardiac sarcoidosis. The latest consensus statement (2014) issued by the Heart Rhythm Society stated that if a histologic diagnosis along with at least 1 clinical symptom (eg, reduced LVEF, heart block, patchy uptake of FDG-PET, late gadolinium enhancement on cardiac MRI, or cardiomyopathy) were present, the patient would have a 50% or greater likelihood of cardiac sarcoidosis. Currently, clinicians are combining clinical data with imaging techniques (cardiac MRI and FDG-PET) to make a diagnosis.

Clinical Context and Test Purpose
The purposes of PET scanning in patients suspected cardiac sarcoidosis is to confirm the diagnosis.

The question addressed in this evidence review is: Does the use of PET improve the net health outcome in individuals with suspected cardiac sarcoidosis?

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest includes patients with suspected cardiac sarcoidosis who cannot undergo MRI.

Interventions
The intervention of interest is PET scanning.

Comparators
The following tests and practices are currently being used to make decisions about managing cardiac sarcoidosis: clinical evaluation and myocardial biopsy.

Outcomes
For patients with suspected or diagnosed cardiac sarcoidosis, the outcome of interest is a diagnosis confirmation or an assessment of disease activity to inform clinical management of the disease.

Timing
For suspected cardiac sarcoidosis, the timing is the time to diagnosis.
Setting
Cardiac PET would be administered in an imaging center equipped with a PET scanner.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Tang et al (2016) published a systematic review on the overall diagnostic performance of FDG-PET/CT in cardiac sarcoidosis, and on subgroups based on the type of patient preparation methods (fasting time, heparin administration, diet).40 The literature search, conducted through August 2014, identified 16 nonrandomized studies (total N=559 patients) for inclusion. Study quality was assessed using QUADAS-2, with most studies having a low risk of bias. Overall sensitivity and specificity, when a large single study with a short fasting duration was excluded, were 81% (95% CI, 76% to 86%) and 82% (95% CI, 77% to 86%), respectively. Subgroup analyses based on the type of patient preparation method showed that the diagnostic odds ratio improved when patients fasted longer (≥12 hours) and heparin was administered. Placing the patient on a high-fat, low-carbohydrate diet before scanning did not affect the diagnostic accuracy of FDG-PET/CT.

A systematic review by Youssef et al (2012) identified 7 studies (total N=164 patients).41 Studies were selected if they used FDG-PET for diagnosis of cardiac sarcoidosis and used criteria of the Japanese Ministry of Health, Labor and Welfare as the reference standard. The pooled sensitivity of PET by random-effects meta-analysis was 89%, and pooled specificity was 78%. The summary area under the receiver operating characteristic was 93%, suggesting a good level of diagnostic discrimination.

A review by Sharma (2009) reported that cardiac MRI was the more established imaging modality in diagnosing sarcoidosis, with an estimated sensitivity of 100% and specificity of 80%.42 Studies using FDG-PET showed high sensitivities; however, the population sizes of the studies were small. The reviewer asserted that imaging studies had incremental value when combined with clinical evaluation and/or myocardial biopsy in the diagnosis of cardiac sarcoidosis.

Nonrandomized Studies
Wicks et al (2018) reported on results of simultaneous PET/MRI to diagnose cardiac sarcoidosis including 51 consecutive patients in the U.K. with known or suspected cardiac sarcoidosis.43 The PET and MR images were analyzed qualitatively in consensus by 2 experienced blinded readers. Using the Japanese Ministry of Health, Labor and Welfare guidelines as the reference standard, the prevalence of cardiac sarcoidosis was 65%. Twenty-eight (55%) patients had abnormal cardiac PET findings. The sensitivity of PET and CMR alone for diagnosing cardiac sarcoidosis was 85% (95% CI, 68% to 95%) and 82% (95% CI, 65% to 93%), respectively. The sensitivity,
specificity, positive predictive value, and NPV for hybrid PET/MR were 94% (95% CI, 80% to 99%), 44% (95% CI, 22% to 69%), 76% (95% CI, 60% to 88%), and 80% (95% CI, 44% to 97%), respectively.

Dweck et al (2018) published a study evaluating the usefulness of a hybrid of cardiac MRI and FDG-PET to diagnose cardiac sarcoidosis.\textsuperscript{44} Patients with suspected cardiac sarcoidosis (N=25) underwent FDG-PET imaging simultaneously with cardiac MRI. The investigators categorized 4 patient groups (MRI+/PET+, MRI+/PET-, MRI-/PET+, MRI-/PET-). The patients with MRI+/PET+ results had increased FDG activity that corresponded with the pattern of injury indicating active cardiac sarcoidosis. The remaining patients, with MRI+/PET-, MRI-/PET+, and MRI-/PET- results, did not show evidence of active cardiac sarcoidosis. Detecting active cardiac sarcoidosis, which is frequently subclinical, is beneficial so that anti-inflammatory therapy can be initiated. The authors concluded that simultaneous assessment of MRI and disease activity with PET permits a more accurate assessment of pattern of injury and disease activity in a single scan, which can impact therapeutic management.

Lapa et al (2016) published a study to determine whether PET/CT using radiolabeled somatostatin receptor ligands for visualization of inflammation would accurately diagnose cardiac sarcoidosis.\textsuperscript{45} Fifteen patients with sarcoidosis and suspicion of cardiac involvement underwent both somatostatin receptor-PET/CT and cardiac MRI. Concordant results between PET/CT and MRI occurred in 12 of the 15 patients.

Yokoyama et al (2015) conducted a study on 92 consecutive patients with suspected cardiac sarcoidosis. The patients underwent FDG-PET/CT following clinical assessment and imaging (electrocardiogram, echocardiography, MRI, perfusion scintigraphy) at the discretion of their physicians. The authors reported an area under the curve of 0.96 for identifying patients with cardiac sarcoidosis using optimized cut points for the maximum standardized uptake value on FDG-PET/CT.\textsuperscript{46}

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies evaluating the clinical utility of using PET or PET/CT in diagnosing cardiac sarcoidosis were identified.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Cardiac sarcoidosis can lead to arrhythmia, heart failure, pericarditis, and heart attacks. There is no criterion standard for diagnosing cardiac sarcoidosis but clinical diagnosis is made through a
combination of clinical evaluations and imaging. Results from meta-analyses and nonrandomized studies have shown that PET can be a useful tool in the clinical diagnostic process.

**Section Summary: Cardiac Sarcoidosis**

Left untreated, cardiac sarcoidosis can lead to serious developments such as arrhythmia, heart failure, pericarditis, and heart attacks. However, there is no criterion standard for diagnosing cardiac sarcoidosis. A combination of clinical evaluations and results from imaging techniques are used in the clinician’s assessment. Results from 2 meta-analyses have shown that PET can be a useful tool in this diagnostic process. Since the meta-analyses, small nonrandomized studies have been published that evaluated variations in PET techniques such as using a radiolabeled somatostatin receptor ligand and adding a simultaneous cardiac MRI. These studies have shown positive results.

**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 SPECT scanning for this purpose. The evidence is sufficient to

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 morbid 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 morbid 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 (eg, 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.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received while this policy was under review in 2011. Input was in general agreement with the medical necessity of positron emission tomography (PET) for myocardial viability or for patients with an indeterminate single-photon emission computed tomography (SPECT) scan. However, reviewers disagreed on using a strict body mass index cutoff to define patients in whom a SPECT scan would be expected to be suboptimal. Therefore, the language of the policy statement was changed to “Cardiac PET scanning may be considered medically necessary to assess myocardial perfusion and thus diagnose coronary artery disease in patients with indeterminate SPECT scan; or in patients for whom SPECT could be reasonably expected to be suboptimal in quality on the basis of body habitus.”

Three reviewers responded to the question whether PET scanning was medically necessary for the workup of patients with suspected cardiac sarcoidosis. All three agreed that PET scanning was medically necessary for this patient group. Two of these reviewers indicated that magnetic resonance imaging (MRI) scanning was the preferred test in the workup of cardiac sarcoidosis but that PET scanning was medically necessary for patients who were unable to undergo MRI. As a result, an additional indication was added to the policy statement for workup of cardiac sarcoidosis: “Cardiac PET scanning may be considered medically necessary for the diagnosis of cardiac sarcoidosis in patients who are unable to undergo MRI scanning. Examples of patients who are unable to undergo MRI include, but are not limited to, patients with pacemakers, automatic implanted cardioverter defibrillators, or other metal implants.”

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). Table 6 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 6. Guidelines for PET and SPECT in Patients at Intermediate Risk of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>Identify extent, severity, and location of ischemia (SPECT protocols vary according to whether patient can exercise)</td>
<td>I</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>IIa</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>IIa</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>
</tr>
</tbody>
</table>

<sup>a</sup> 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).”<sup>47</sup> 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).<sup>48</sup> 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.<sup>49</sup> 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<sup>50</sup> 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.”

<sup>47</sup> Adapted from Klocke et al (2003).
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.\(^{51}\)

ACR does not recommend PET for patients with acute nonspecific chest pain who have a low probability of CAD\(^{52}\) or for asymptomatic patients at risk for CAD.\(^{53}\)

**U.S. Preventive Services Task Force Recommendations**

No U.S. Preventive Services Task Force recommendations for the use of PET in cardiac imaging have been identified.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 7.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01288560</td>
<td>Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) Project I-A of Imaging Modalities to Assist With Guiding Therapy and the Evaluation of Patients With Heart Failure (IMAGE-HF)</td>
<td>1511</td>
<td>Jun 2019</td>
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<tr>
<td>NCT00756379</td>
<td>Randomized Trial of Comprehensive Lifestyle Modifications, Optimal Pharmacological Treatment and PET Imaging for Detection and Management of Stable Coronary Artery Disease</td>
<td>1085</td>
<td>Mar 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

- 78459  Myocardial imaging, positron emission tomography (PET), metabolic evaluation
- 78491  Myocardial imaging, positron emission tomography (PET), perfusion; single study at rest or stress
- 78492  Myocardial imaging, positron emission tomography (PET), perfusion; multiple studies at rest and / or stress
- 0482T  Absolute quantitation of myocardial blood flow, positron emission tomography (PET), rest and stress (List separately in addition to code for primary procedure)
- A9526  Nitrogen N-13 ammonia, diagnostic, per study dose, up to 40 millicuries
- A9552  Fluorodeoxyglucose F-18 FDG, diagnostic, per study does, up to 45 millicuries
- A9555  Rubidium Rb-82, diagnostic, per study dose, up to 60 millicuries
- A9598  Positron emission tomography radiopharmaceutical, diagnostic, for non-tumor identification, not otherwise classified
- G0235  PET imaging, any site, not otherwise specified
A PET scan essentially 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.

There is a new category III add-on code effective January 1, 2018, for absolute quantification of myocardial blood flow (0482T). This code is to be used with the primary PET CPT codes if indicated.

**ICD-10 Diagnoses (Effective October 1, 2015)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A18.84</td>
<td>Tuberculosis of heart</td>
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<tr>
<td>D86.85</td>
<td>Sarcoid myocarditis</td>
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<tr>
<td>I20.0</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>I20.1</td>
<td>Angina pectoris with documented spasm</td>
</tr>
<tr>
<td>I20.8</td>
<td>Other forms of angina pectoris</td>
</tr>
<tr>
<td>I20.9</td>
<td>Angina pectoris, unspecified</td>
</tr>
<tr>
<td>I21.01</td>
<td>ST elevation (STEMI) myocardial infarction involving left main coronary artery</td>
</tr>
<tr>
<td>I21.02</td>
<td>ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery</td>
</tr>
<tr>
<td>I21.09</td>
<td>ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall</td>
</tr>
<tr>
<td>I21.11</td>
<td>ST elevation (STEMI) myocardial infarction involving right coronary artery</td>
</tr>
<tr>
<td>I21.19</td>
<td>ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall</td>
</tr>
<tr>
<td>I21.21</td>
<td>ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery</td>
</tr>
<tr>
<td>I21.29</td>
<td>ST elevation (STEMI) myocardial infarction involving other sites</td>
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<tr>
<td>I21.3</td>
<td>ST elevation (STEMI) myocardial infarction of unspecified site</td>
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<tr>
<td>I21.4</td>
<td>Non-ST elevation (NSTEMI) myocardial infarction</td>
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<td>Acute myocardial infarction, unspecified</td>
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<td>I21.A1</td>
<td>Myocardial infarction type 2</td>
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<tr>
<td>I21.A9</td>
<td>Other myocardial infarction type</td>
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<tr>
<td>I22.0</td>
<td>Subsequent ST elevation (STEMI) myocardial infarction of anterior wall</td>
</tr>
<tr>
<td>I22.1</td>
<td>Subsequent ST elevation (STEMI) myocardial infarction of inferior wall</td>
</tr>
<tr>
<td>I22.2</td>
<td>Subsequent non-ST elevation (NSTEMI) myocardial infarction</td>
</tr>
<tr>
<td>I22.8</td>
<td>Subsequent ST elevation (STEMI) myocardial infarction of other sites</td>
</tr>
<tr>
<td>I22.9</td>
<td>Subsequent ST elevation (STEMI) myocardial infarction of unspecified site</td>
</tr>
<tr>
<td>I24.0</td>
<td>Acute coronary thrombosis not resulting in myocardial infarction</td>
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<tr>
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<td>Dressler's syndrome</td>
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<tr>
<td>I24.8</td>
<td>Other forms of acute ischemic heart disease</td>
</tr>
<tr>
<td>I24.9</td>
<td>Acute ischemic heart disease, unspecified</td>
</tr>
<tr>
<td>I25.10</td>
<td>Atherosclerotic heart disease of native coronary artery without angina pectoris</td>
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<tr>
<td>I25.110</td>
<td>Atherosclerotic heart disease of native coronary artery with unstable angina pectoris</td>
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<td>I25.111</td>
<td>Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm</td>
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<td>I25.118</td>
<td>Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris</td>
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<td>I25.119</td>
<td>Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris</td>
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<td>I25.2</td>
<td>Old myocardial infarction</td>
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<td>Aneurysm of heart</td>
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<td>Coronary artery aneurysm</td>
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<td>Coronary artery dissection</td>
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<td>Ischemic cardiomyopathy</td>
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<td>I25.6</td>
<td>Silent myocardial ischemia</td>
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<td>I25.700</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris</td>
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<td>I25.701</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with angina pectoris with documented spasm</td>
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<tr>
<td>I25.708</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with other forms of angina pectoris</td>
</tr>
</tbody>
</table>
I25.709 Atherosclerosis of coronary artery bypass graft(s), unspecified, with unspecified angina pectoris
I25.710 Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris
I25.711 Atherosclerosis of autologous vein coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.718 Atherosclerosis of autologous vein coronary artery bypass graft(s) with other forms of angina pectoris
I25.719 Atherosclerosis of autologous vein coronary artery bypass graft(s) with unspecified angina pectoris
I25.720 Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris
I25.721 Atherosclerosis of autologous artery coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.728 Atherosclerosis of autologous artery coronary artery bypass graft(s) with other forms of angina pectoris
I25.729 Atherosclerosis of autologous artery coronary artery bypass graft(s) with unspecified angina pectoris
I25.730 Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris
I25.731 Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.738 Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with other forms of angina pectoris
I25.739 Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unspecified angina pectoris
I25.750 Atherosclerosis of native coronary artery of transplanted heart with unstable angina
I25.751 Atherosclerosis of native coronary artery of transplanted heart with angina pectoris with documented spasm
I25.758 Atherosclerosis of native coronary artery of transplanted heart with other forms of angina pectoris
I25.759 Atherosclerosis of native coronary artery of transplanted heart with unspecified angina pectoris
I25.760 Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina
I25.761 Atherosclerosis of bypass graft of coronary artery of transplanted heart with angina pectoris with documented spasm
I25.768 Atherosclerosis of bypass graft of coronary artery of transplanted heart with other forms of angina pectoris
I25.769 Atherosclerosis of bypass graft of coronary artery of transplanted heart with unspecified angina pectoris
I25.790 Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I25.791 Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.798 Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris
I25.799 Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris
I25.810 Atherosclerosis of coronary artery bypass graft(s) without angina pectoris
I25.811 Atherosclerosis of native coronary artery of transplanted heart without angina pectoris
I25.812 Atherosclerosis of bypass graft of coronary artery of transplanted heart without angina pectoris
I25.89 Other forms of chronic ischemic heart disease
I25.9 Chronic ischemic heart disease, unspecified
I42.0 Dilated cardiomyopathy
I42.3 Endomyocardial (eosinophilic) disease
I42.4 Endocardial fibroelastosis

Contains Public Information
I42.5 Other restrictive cardiomyopathy
I42.6 Alcoholic cardiomyopathy
I42.7 Cardiomyopathy due to drug and external agent
I42.8 Other cardiomyopathies
I42.9 Cardiomyopathy, unspecified
I43 Cardiomyopathy in diseases classified elsewhere
I47.0 Re-entry ventricular arrhythmia
I47.1 Supraventricular tachycardia
I49.2 Junctional premature depolarization
I50.1 Left ventricular failure, unspecified
I50.810 Right heart failure, unspecified
I50.811 Acute right heart failure
I50.812 Chronic right heart failure
I50.813 Acute on chronic right heart failure
I50.814 Right heart failure due to left heart failure
I50.82 Biventricular heart failure
I50.83 High output heart failure
I50.84 End stage heart failure
I50.89 Other heart failure
I51.5 Myocardial degeneration
I51.7 Cardiomegaly
I51.89 Other ill-defined heart diseases
I51.9 Heart disease, unspecified

REVISIONS

10-30-2013 Cardiac Applications was originally part of the Positron Emission Tomography (PET) medical policy. Cardiac Applications was pulled out and placed into a separate medical policy, Positron Emission Tomography (PET) Scanning: Cardiac Applications. The medical policy language was unchanged.

Updated Description section.
Updated Rationale section.

In Coding section:
  - Added ICD-10 Diagnosis codes (Effective October 1, 2014)

Updated Reference section.

10-22-2015 Description section updated

In Policy section:
  - In Item A removed the example in the policy statement, “(e.g., obesity)”
  - In Item B added “(See the Policy Guidelines section regarding the relative effectiveness of PET and SPECT scanning.)”
  - In Item C revised wording by removing “the diagnosis of” and adding “diagnosing” to read “Cardiac PET scanning may be considered medically necessary for diagnosing cardiac sarcoidosis in patients...”
  - Added Item D “Cardiac PET scanning is experimental / investigational for quantification of myocardial blood flow in patients diagnosed with CAD.”
  - Policy Guidelines updated to reflect current information on relative effectiveness of PET and SPECT scanning.

Rationale section updated

In Coding section:
  - Removed CPT Code: 78399
  - Added HCPCS Code: A9555
  - Updated Coding notations

References updated
In Coding section:
- Removed ICD Code:  I50.9
- Revised nomenclature of ICD Code:  I50.1


Description section updated

In Policy section:
Updates to the policy section did not change the intent of the policy.
- In Item A added verbiage for "PET" and "SPECT" to read "Cardiac positron emission tomography (PET) scanning...single-photon emission computed tomography (SPECT) scan..."
- In Item B revised "Policy Guidelines" to "Background" to read "...(See the Background Policy Guidelines section regarding the relative effectiveness of PET and SPECT scanning.)"
- In Item C removed "MRI" and replaced with "magnetic resonance imaging" and removed "(AICDs)" abbreviation.
- In Item D removed "CAD" to read "...diagnosed with coronary artery disease."
- Removed Policy Guidelines-myocardial perfusion and myocardial viability definitions.

Rationale section updated

In coding section:
- Added CPT Code:  0482T
- Add HCPCS Code:  A9598, G0235
- Added ICD Code:  D86.85

References updated

REFERENCES


**Other References**

1. Blue Cross and Blue Shield of Kansas, Medical Advisory Committee meeting, April 24, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC-02-03).
2. Blue Cross and Blue Shield of Kansas, Oncology Liaison Committee meeting, February 18, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC-02-03).
3. Blue Cross and Blue Shield of Kansas, Radiology Liaison Committee meeting, February 11, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC-02-03).
4. MCMC, Medical Care Ombudsman Program (MCOP), August 11, 2006, MCOP ID 1071-0720.
6. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee, February 2009.