Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/01/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Positron Emission Tomography (PET) Miscellaneous Applications is addressed separately in medical policy 00104.

Note: Positron Emission Tomography (PET) Oncologic Applications is addressed separately in medical policy 00105.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of positron emission tomography (PET) scanning to assess myocardial perfusion and thus diagnose coronary artery disease (CAD) to be eligible for coverage when patient selection criteria are met.

Patient Selection Criteria
Coverage eligibility for the use of positron emission tomography (PET) scanning assessment of myocardial perfusion and diagnosis of coronary artery disease (CAD) will be considered when ANY of the following are met:
- Single photon emission computed tomography (SPECT) study is unavailable or inconclusive; OR Patients who may be prone to artifact, such as severely obese patients (body mass index [BMI] ≥ 35 kg/m²); OR
- Patients who have had a breast implant; OR
- Conditions associated with high risk for morbidity (e.g., allergy to contrast medium, poor arterial access, renal dysfunction for which angiography increases the likelihood of renal failure).

Based on review of available data, the Company may consider the use of positron emission tomography (PET) scanning to assess the myocardial viability in patients with severe left ventricular (LV) dysfunction as a technique to determine candidacy for a revascularization procedure to be eligible for coverage.

Based on review of available data, the Company may consider the use of cardiac positron emission tomography (PET) scanning for the diagnosis of cardiac sarcoidosis in patients who are unable to undergo magnetic resonance imaging (MRI) scanning to be eligible for coverage. Examples of patients who are unable to undergo magnetic resonance imaging (MRI) include, but are not limited to, patients with pacemakers, automatic implanted cardioverter-defibrillators (AICDs), or other metal implants.
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When Services Are Considered Not Medically Necessary
Based on review on available data, the Company considers the use of positron emission tomography (PET) scanning for cardiac application to be not medically necessary** when patient selection criteria are not met or for conditions not indicated in the policy statement.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of positron emission tomography (PET) scanning for quantification of myocardial blood flow in patients diagnosed with CAD to be investigational.*

Background/Overview
Cardiac PET scanning is used in two key clinical situations: 1) myocardial perfusion scanning as a technique of identifying perfusion defects, which in turn reflect CAD; and 2) assessment of myocardial viability in patients with LV dysfunction as a technique to determine candidacy for a revascularization procedure. A third potential clinical use related to CAD is being evaluated, use of cardiac PET in the measurement of myocardial blood flow and blood flow reserve.

Positron emission tomography scans use of 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, consisting of multiple stationary detectors that encircle the thorax. Compared to SPECT scans, coincidence detection offers greater spatial resolution.

A variety of 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. The radionuclides may be coupled to a variety of physiologically active molecules, including oxygen, water and ammonia. Fluorine-18 is often coupled with fluordeoxyglucose (FDG) to detect glucose metabolism, which in turn reflects the metabolic activity, and thus viability, of the target tissue. Tracers that target the mitochondrial complex are also being developed.

Note: This policy only addresses the use of radiotracers detected with the use of dedicated PET scanners. Radiotracers such as FDG may be detected using SPECT cameras, a hybrid PET/SPECT procedure that may be referred to as FDG-SPECT or molecular coincidence detection. This technique is not discussed in this document.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The FDA issued a Federal Register notice on March 10, 2000, summarizing the regulatory history of PET radiotracers and highlighting its decisions on safety and effectiveness for certain uses of certain PET
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radiotracers. With regard to PET radiotracers used for cardiac indications, the FDA has approved the following uses:

- **F-18-FDG for evaluation of myocardial hibernation.** The FDA concluded that “a 10-mCi dose (for adults) of FDG F-18 injection produced under conditions specified in an approved application can be found to be safe and effective in PET imaging of patients with CAD and LV dysfunction, when used together with myocardial perfusion imaging, for the identification of LV myocardium with residual glucose metabolism and reversible loss of systolic function.”
- **N-13-ammonia for evaluation of myocardial blood flow/perfusion.** The FDA concluded that “a 10-mCi dose (for adults) of ammonia N-13 injection produced under conditions specified in an approved application can be found to be safe and effective in PET imaging of the myocardium under rest or pharmacological stress conditions to evaluate myocardial perfusion in patients with suspected or existing CAD.”
- **In addition, rubidium-82-chloride injection for evaluation of myocardial perfusion** (NDA-19-414) was previously approved in 1989 “for assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction.”

Furthermore, the Federal Register notice stipulates that due to safety concerns stemming from various manufacturing practices, “the agency cannot conclude that these PET drugs are generally recognized as safe and effective for the above-noted indications and therefore needs to review information on how each drug product is formulated and produced at each manufacturing site. Because these PET drugs are not generally recognized as safe and effective, they are new drugs for which approved NDA’s [New Drug Application] or ANDA’s [Abbreviated New Drug Application] are required for marketing.”

On December 10, 2009, FDA issued guidance for Current Good Manufacturing Practice (CGMP) for PET drug manufacturers, and in August 2011, FDA issued similar CGMP guidance for small businesses. Compliance with PET CGMP regulations is required 2 years from the date of the earlier guidance that is, beginning December 10, 2011. As FDA develops new regulations, and reviews radiotracer safety and effectiveness, implementation of Plan policies regarding PET scans may need to focus on the following:

- Whether or not an individual PET radiotracer manufacturer facility meets current good manufacturing practices (CGMP) as established by FDA;
- Whether or not the radiotracer is FDA-approved and is being used for a specific indication that has been FDA-approved; and
- Whether or not evidence demonstrates improvement in net health outcome with PET scanning for the clinical indication for an individual patient.

Centers for Medicare and Medicaid Services (CMS)
Beginning October 1, 2002, Medicare will cover FDG PET for the determination of myocardial viability as a primary or initial diagnostic study before revascularization and will continue to cover FDG PET when used as follow-up to an inconclusive SPECT. However, if a patient received FDG PET with inconclusive results, a follow-up SPECT is not covered. FDA-approved or FDA-cleared full and partial ring PET scanners are covered.
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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 after FDG PET with inconclusive results.

Frequency: In the absence of national frequency limitations, contractors can, if necessary, develop reasonable frequency limitations for myocardial viability.

Rationale/Source
This policy has been updated periodically using the MEDLINE database. The most recent literature review was performed for the period through June 24, 2015. Following is a summary of the key literature to date.

Myocardial Perfusion Imaging
In a patient with symptoms suggestive of CAD, an important clinical decision point is to determine whether invasive coronary angiography is necessary. A variety of noninvasive imaging tests, including PET, using rubidium-82 and SPECT scans have been investigated as a means of identifying reversible perfusion defects, which may reflect CAD and thus identify patients appropriately referred for angiography.

Sensitivity and specificity of PET may be slightly better than SPECT. For example, the performance characteristics for PET and SPECT based on the 2007 Canadian Joint Position Statement is shown in Table 1 below.

Table 1 Performance Characteristics of PET and SPECT Scanning Based on the 2007 Canadian Joint Position Statement

<table>
<thead>
<tr>
<th></th>
<th>PET</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.91</td>
<td>0.88</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.89</td>
<td>0.77</td>
</tr>
<tr>
<td>Estimated positive likelihood ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.27</td>
<td>3.83</td>
</tr>
<tr>
<td>Estimated negative likelihood ratio&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10</td>
<td>0.16</td>
</tr>
</tbody>
</table>

PET: positron emission tomography; SPECT: single-photon emission computed tomography.
<sup>a</sup> Estimated positive likelihood ratio = sensitivity/(1 – specificity).
<sup>b</sup> Estimated negative likelihood ratio = (1 – sensitivity)/specificity.

However, diagnostic utilities of PET and SPECT may be similar, i.e., in terms of altering disease risk assessment in a manner affecting subsequent decision making among patients with intermediate pretest probability of CAD. For example, as shown in the table below, a patient with a 50% pretest probability of CAD would have a 9% post-test probability of CAD following a negative PET scan compared to 13% after a negative SPECT. In either case, further testing would not likely be pursued.

Table 2 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>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>70%</th>
<th>95%</th>
<th>90%</th>
<th>19%</th>
<th>27%</th>
</tr>
</thead>
</table>

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

In 2012, Jaarsma et al reported a meta-analysis comparing the diagnostic performance of noninvasive myocardial perfusion imaging using SPECT, cardiac magnetic resonance imaging (MRI) or PET. The comparison standard was CAD identified with coronary angiography. A total of 166 articles (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%) and PET (81%). Pooled diagnostic odds ratio was 15.31 for SPECT, 26.42 for MRI, and 36.47 for PET. Metaregression indicated that MRI and PET have a significantly higher diagnostic accuracy than SPECT. Although this analysis is limited by potential publication bias for SPECT and significant heterogeneity in the MRI and SPECT studies, most subgroup analyses showed a relative superiority of MRI and PET over SPECT.

A second 2012 meta-analysis by Parker et al compared SPECT and PET stress myocardial perfusion imaging, using coronary angiography as the reference standard. A total of 117 articles met selection criteria. SPECT was assessed in 113 studies (11,212 patients), and PET was assessed in 9 studies (650 patients). Patient-level diagnostic accuracy data were pooled in a bivariate meta-analysis, showing significantly better sensitivity for PET (92.6%) compared with SPECT (88.3%). There was no significant difference in specificity between PET (81.3%) and SPECT (76.0%). The pattern of higher sensitivity for PET over SPECT and similar specificity also was found among higher quality studies.

Takx et al (2014) reported a meta-analysis of studies that compared noninvasive myocardial perfusion imaging modalities (MRI, CT, PET, SPECT, echocardiography) with coronary angiography plus fractional flow reserve (FFR). Literature was searched to May 2014, and 37 studies met inclusion criteria (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. Negative likelihood ratio (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]). Area under the receiver operating characteristic (AUC) 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).

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

Merhige et al (2007) reported on noncontemporaneous patients who had similar probabilities of CAD and were evaluated by SPECT or PET. In this single-center study comparing PET with SPECT, patients who received PET scans had lower rates of angiography (13% vs 31% SPECT) and revascularization (6% vs 11% SPECT) with similar rates of death and myocardial infarction at 1-year follow-up. These results are viewed as preliminary, and additional comparative studies showing impact on outcomes are needed.

Section summary
Evidence on the diagnostic accuracy of PET for myocardial perfusion imaging establishes that PET is at least as good as SPECT in terms of sensitivity and specificity. However, the modest difference in accuracy may not translate to clinically meaningful differences in diagnosis or management, and SPECT remains the first line test in most instances. There are some patients in which SPECT is indeterminate due to body habitus or other anatomic factors, PET can be performed successfully.

Myocardial Viability
Positron Emission Tomography 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 indeed 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 left ventricular (LV) dysfunction after revascularization of hibernating myocardium, as identified by PET scanning.

Single Photon emission computed 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 (PPV), there was a low negative predictive value (NPV); ie, 40% of patients without redistribution nevertheless showed clinical improvement after revascularization. NPV has 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.
Further supporting the equivalency of these two testing modalities, Siebelink et al (2001) performed a prospective randomized study comparing management decisions and outcomes based on either PET imaging or SPECT imaging in 103 patients who had chronic CAD and LV dysfunction and were being evaluated for myocardial viability. Management decisions included drug therapy or revascularization with either angioplasty or coronary artery bypass grafting. This study is unique in that 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 two imaging techniques. The authors concluded that either technique could be used for management of patients considered for revascularization who have suspicion of jeopardized myocardium.

Studies identified in literature updates continued to show the equivalence of SPECT and PET. Comparative studies reported on test accuracy and did not address impact on clinical outcomes. As one example, Slart et al (2005) concluded that there was overall good agreement between SPECT and PET for the assessment of myocardial viability in patients with severe LV dysfunction. Using a thorax-cardiac phantom, Knesaurek and Machac (2006) concluded that PET was better at detecting smaller defects. In this study, a 1-cm insert was not detectable by SPECT, yet it was detectable by PET.

Section Summary
Positron emission tomography and SPECT can both be used to assess myocardial viability. The available evidence supports that both have roughly similar accuracy for this purpose. Positron emission tomography may be more sensitive for small defects, but the clinical significance of identifying small defects is uncertain.

Quantified Myocardial Blood Flow
Several publications describe the use of PET imaging to quantify both myocardial blood flow and MFR. However, as noted in an accompanying editorial and by subsequent reviewers, larger prospective clinical trials are needed to understand the clinical utility of these approaches. For example, Stuifzand et al (2015) used 15-O[\(H_2O\)] PET imaging in 92 patients with 1-2 vessel disease to quantify myocardial blood flow, myocardial flow reserve (MFR, defined as stress myocardial blood flow/rest myocardial blood flow), and “relative flow reserve” (defined as stress myocardial blood flow in a stenotic area/stress myocardial blood flow 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), AUC analysis showed similar diagnostic performance for all 3 measures (0.76 [95% CI, 0.66 to 0.86] for myocardial blood flow; 0.72 for MFR [95% CI, 0.61 to 0.83]; and 0.82 [95% CI, 0.72 to 0.91] for relative flow reserve; p>0.05 for all comparisons).

Taqueti et al (2015) evaluated the association between MFR (called coronary flow reserve in this study) and cardiovascular outcomes in 329 consecutive patients referred for invasive coronary angiography after stress PET perfusion imaging. Patients with a prior history of coronary artery bypass grafting (CABG) or heart failure, or with left ventricular ejection fraction (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 myocardial blood flow 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...
myocardial blood flow 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 major adverse cardiovascular events (MACE, comprising death, cardiovascular death, and hospitalization for heart failure or myocardial infarction). During follow-up, 64 patients (19%) 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 (hazard ratio [HR] per 1 unit decrease in continuous MFR score, 2.02 [95% CI, 1.20 to 3.40]). Using binary classification defined by median MFR, 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) or percutaneous coronary intervention (PCI; 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 PCI group (n=85; adjusted log-rank test, p=0.006) and the no-revascularization group (n=57; adjusted log-rank test, p=0.001).

In 2011, Ziadi et al reported a prospective study of the prognostic value of myocardial flow reserve (MFR) with rubidium-82 (Rb-82) PET in 704 consecutive patients. Ninety-six percent of patients (n=677) were followed for a median of 387 days; most (90%) were followed up 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. Primary outcome was the prevalence of hard cardiac events (myocardial infarction and cardiac death); secondary outcome was prevalence of major adverse cardiac events (MACE; comprising cardiac death, myocardial infarction, later revascularization, cardiac hospitalization). Patients with a normal Summed Stress Score (SSS) and 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 a preserved MFR. Patients with an abnormal SSS and MFR less than 2 had a higher incidence of hard events (11.4% vs 1.1%) and MACE (24% vs 9%) compared with patients who had a preserved MFR. Rb-82 MFR was an independent predictor of cardiac hard events (hazard ratio [HR]=3.3) and MACE (HR=2.4) over SSS. Three patients (0.4%) were classified up and 0 classified down with MFR in the multivariate model (p=0.092).

Murthy et al (2011) examined the prognostic value of Rb-82 PET coronary flow reserve (CFR) in a retrospective series of 2,783 patients referred for rest/stress PET myocardial perfusion imaging. Coronary flow reserve was calculated as the ratio of stress to rest myocardial blood flow using semi quantitative PET interpretation. 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 CFR to a multivariate model significantly improved model fit and improved the c index, a measure of discrimination performance, from 0.82 to 0.84 (p=0.02). Coronary Flow Reserve 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 CFR was observed in both diabetic and nondiabetic patients.
Section Summary
Evidence for the association of quantitative myocardial blood flow and myocardial flow reserve with cardiovascular outcomes is growing. 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 some studies used data-driven cut points and did not include healthy volunteers to verify discriminative ability (spectrum bias), 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 policy. Published evidence on utility of PET scanning for cardiac sarcoidosis is limited due to the relatively small number of patients with this condition. A 2009 review by Sharma et al concluded that imaging studies had incremental value when combined with clinical evaluation and/or myocardial biopsy in the diagnosis of cardiac sarcoidosis. The authors reported that cardiac MRI was the more established imaging modality in diagnosing sarcoidosis, with an estimated sensitivity of 100% and specificity of 80%. A 2012 meta-analysis by Youssef et al identified seven studies with 164 patients. 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. Pooled sensitivity of PET by random effects meta-analysis was 89%, and pooled specificity was 78%. Area under the summary receiver operating characteristic curve was 93%, suggesting a good level of diagnostic discrimination. Yokoyama et al (2015) reported an AUC of 0.96 for identifying patients with cardiac sarcoidosis using optimized cut points for the maximum standardized uptake value on FDG PET/CT.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed below.

Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01934985</td>
<td>Dynamic Cardiac SPECT Imaging</td>
<td>160</td>
<td>Sep 2015</td>
</tr>
<tr>
<td>NCT01943903</td>
<td>Prospective Longitudinal Trial of FFRct: Outcome and Resource IMpacts</td>
<td>580</td>
<td>Dec 2015</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 2017</td>
</tr>
<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>1300</td>
<td>Jan 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Summary of Evidence
For assessing myocardial perfusion in patients with suspected coronary artery disease, PET scanning is less likely than SPECT scanning to provide indeterminate results. Therefore, PET scanning also is useful in...
patients with an indeterminate SPECT scan. It also is useful in patients whose body habitus is likely to result in indeterminate SPECT scans, eg, patients with moderate to severe obesity.

Evidence from the medical literature supports the use of PET scanning to assess myocardial viability in patients with severe left ventricular dysfunction who are being considered for revascularization. Results of primary studies and evidence-based recommendations from specialty societies conclude that PET scanning is at least as good as, and likely superior, to SPECT scanning for this purpose.

Studies of quantitative myocardial blood flow and myocardial flow reserve in patients with CAD indicates that these methods are in a developmental stage for clinical use. Current evidence is insufficient to permit conclusions about the impact on net health outcome in these patients.

For patients who are undergoing a workup for cardiac sarcoidosis, MRI is the preferred initial test. However, for patients who are unable to undergo MRI, such as patients with a metal implant, evidence supports PET scanning as the preferred test.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with 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.

Clinical input received in June 2011 was in general agreement with the medical necessity of PET for myocardial viability or for patients with an indeterminate SPECT scan. However, reviewers disagreed on using a strict BMI 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 of whether PET scanning was medically necessary in the workup of patients with suspected cardiac sarcoidosis. All three were in agreement that PET scanning was medically necessary in this patient group. Two of the three reviewers offered that MRI scanning was the preferred test in the workup of cardiac sarcoidosis but that PET scanning was medically necessary in patients who were unable to undergo MRI. As a result of this input, 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 cardioverter-defibrillators (AICD’S), or other metal implants.

Practice Guidelines and Position Statements
In 2003, the American College of Cardiology and American Heart Association published updated guidelines for cardiac radionuclide imaging, including cardiac applications of PET. The following table summarizes the
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guidelines for PET and SPECT imaging in patients with an intermediate risk of CAD. 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.

Table 5. American College of Cardiology/American Heart Association 2003 Guidelines for PET and SPECT Imaging in Patients with Intermediate Coronary Artery Disease Risk

<table>
<thead>
<tr>
<th>Indication</th>
<th>SPECT Class</th>
<th>PET Class</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>IIa</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>
<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>IIa</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>NA</td>
<td>I</td>
</tr>
</tbody>
</table>

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

These guidelines also conclude that PET imaging “appears to have slightly better overall accuracy for predicting recovery of regional function after revascularization in patients with LV dysfunction than single photon techniques (i.e., SPECT scans).” However, the guidelines indicate that either PET or SPECT scans are Class I indications for predicting improvement in regional and global LV function and natural history after revascularization and thus do not indicate a clear preference for either PET or SPECT scans in this situation.

In 2007, Canadian Cardiovascular Society, Canadian Association of Radiologists, Canadian Association of Nuclear Medicine, Canadian Nuclear Cardiology Society, and Canadian Society of Cardiac Magnetic Resonance recommended PET scanning for patients with intermediate pretest probability of CAD who have nondiagnostic noninvasive imaging tests, or where such a test does not agree with clinical diagnosis or may be prone to artifact that could lead to an equivocal other test, eg, obesity (class I recommendation, level B evidence).

2011 Appropriateness Criteria from the American College of Radiology (ACR) considers both SPECT and PET to be appropriate for the evaluation of patients with a high probability of CAD. American College of Radiology states that PET perfusion imaging has advantages over SPECT, including higher spatial and temporal resolution. Routine performance of both PET and SPECT are not necessary.

European Society of Cardiology published evidence-based consensus guidelines for the diagnosis and treatment of acute and chronic heart failure in 2012. Guideline authors concluded that myocardial perfusion/ischemia imaging should be considered in patients thought to have CAD, who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischemia and
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Viable myocardium. Recommended imaging modalities are echocardiography, cardiac MRI, SPECT, and PET. (Class 2a recommendation [weight of evidence/opinion is in favor of usefulness/efficacy]; level C evidence [based on consensus expert opinion and/or small or retrospective studies or registries].)

In 2014, the Japanese Society of Nuclear Cardiology published recommendations for PET imaging for cardiac sarcoidosis. In Japan, F-18-FDG PET is approved only for detecting sites of inflammation in cardiac sarcoidosis. In patients with cardiac sarcoidosis diagnosed by established guidelines (eg, 2006 update of JMHW guidelines), FDG PET may be used to assess lesion distribution. However, use of FDG PET to diagnose patients with suspected cardiac sarcoidosis is not covered by the health ministry’s insurance reimbursement.

References


31. Members ATF, McMurray JJV, Adamopoulos S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal. July 1, 2012 2012;33(14):1787-1847. PMID 22692307


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10/05/2005 Medical Director review
10/27/2005 Quality Care Advisory Council approval
10/04/2006 Medical Director review
10/18/2006 Medical Policy Committee approval. FDA information updated. Coverage eligibility unchanged. Updated with additional references.
02/13/2008 Medical Director review
02/20/2008 Medical Policy Committee approval. Revised patient selection criteria changing obesity to severe obesity (BMI > 40)
05/07/2009 Medical Director review
05/20/2009 Medical Policy Committee approval. No change to coverage eligibility.
01/01/2010 Coding revision
06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. No change to coverage eligibility.
02/03/2011 Medical Policy Committee review
05/02/2011 Medical Policy Implementation Committee approval. Patient selection criteria revised. Denial reason when patient selection criteria not met was changed from investigational to not medically necessary.
02/02/2012 Medical Policy Committee review
02/15/2012 Medical Policy Implementation Committee approval. An additional indication for PET scanning was added “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 (AICDs) or other metal implants.” Policy effective date 3/5/2012 to allow for AIM implementation of policy revisions.
10/02/2012 Revised to correct original effective date and notation added to history as of 3/5/2012 effective date.
02/07/2013 Medical Policy Committee review
02/20/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2014 Medical Policy Committee review
02/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/05/2015 Medical Policy Committee review
02/18/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016 Medical Policy Committee review
02/17/2016 Medical Policy Implementation Committee approval. Investigational statement for (PET) scanning for quantification of myocardial blood flow in patients with CAD added. Clarified existing NMN statement.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017 Medical Policy Committee review
02/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2018

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>CPT</td>
<td>78459, 78491, 78492</td>
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<tr>
<td>HCPCS</td>
<td>A9526, A9552, A9555, G0235, S8085</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
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3. reference to federal regulations.

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A. in accordance with nationally accepted standards of medical practice;

B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.
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