Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

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 PET scanning assessment of myocardial perfusion and diagnosis of 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/m^2); 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 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 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 MRI include, but are not limited to, patients with pacemakers, automatic implanted cardioverter-defibrillators (AICDs), or other metal implants.

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

When Services Are Considered Not Medically Necessary
Based on review on available data, the Company considers the use of 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 PET scanning for quantification of myocardial blood flow (MBF) in patients diagnosed with CAD to be **investigational.***

Background/Overview

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 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 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 (25%-75% disease prevalence). Risk can be estimated using the patient's age, sex, and chest pain quality. Table 1 summarizes patient populations at intermediate risk for CAD.

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

Populations	Typical Angina[a]	Atypical Angina[b]	Nonanginal Chest Pain[c]
Men	30-39	30-70	≥50
Women	30-60	≥50	≥60

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 cause attenuation of 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 LV dysfunction who are being considered for revascularization. A PET scan may determine whether the LV 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
For both of the above indications, 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.

Table 2. Advantages and Disadvantages of Cardiac PET and SPECT

Imaging Technique	Advantages	Disadvantages
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 (Rb-82), oxygen 15, nitrogen 13, and carbon 11. Most tracers have a short half-life and must be manufactured with an on-site cyclotron. Rb-82 is produced by a strontium 82/rb-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 also are being developed.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

PET radiopharmaceuticals have been evaluated and approved by FDA for use as diagnostic imaging agents. These radiopharmaceuticals are approved for specific conditions.

In December 2009, FDA issued guidance for Current Good Manufacturing Practice for PET drug manufacturers, and in August 2011, FDA issued similar Current Good Manufacturing Practice guidance for small businesses. An additional final guidance document issued in December 2012 required all PET drug manufacturers and compounders to operate under an approved new drug application (NDA) or abbreviated NDA, or investigational NDA, by December 2015.

To avoid interruption of the use of PET radiotracers already in use in clinical practice, before the issuance of specific guidance documents, FDA made determinations of safety and effectiveness for certain uses of PET radiotracers.

The following radiopharmaceuticals used with PET for cardiac-related indications were reviewed in this manner and subsequently had approved NDAs as summarized in Table 3.

Table 3. Radiopharmaceuticals Approved for Use With PET for Cardiac Indications

Date Approved	Radiopharmaceutical	Manufacturer	NDA	Cardiac-Related Indication With PET
2000	Fluorine 18 fluorodeoxyglucose (F-18-FDG)	Various	20306	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
2000	Ammonia N 13	Zevacor Pharma	22119	Imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with

				suspected or existing CAD
1989	Rubidium 82 chloride	Bracco Diagnostics	19414	Assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction

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

Centers for Medicare and Medicaid Services (CMS)
Beginning 2002, Medicare began to cover fluorodeoxyglucose-positron emission tomography (FDG-PET) for the determination of myocardial viability as a primary or initial diagnostic study before revascularization and continued to cover FDG-PET when used as a follow-up to an inconclusive SPECT. However, if a patient only receives FDG-PET with inconclusive results, a follow-up SPECT is not covered. U.S. FDA–approved or FDA-cleared full and partial ring PET scanners are covered.

> "Limitations: In the event that a patient receives a SPECT with inconclusive results, a PET scan may be performed and covered by Medicare. However, SPECT is not covered following a FDG PET with inconclusive results….
> Frequency: In the absence of national frequency limitations, contractors can, if necessary, develop reasonable frequency limitations for myocardial viability."

Rationale/Source

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value [NPV]) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes). The following is a summary of the key literature to date.

POSITRON EMISSION TOMOGRAPHY

Clinical Context and Test Purpose
The purposes of PET scanning in patients with suspected CAD, LV dysfunction who are potential candidates for revascularization, CAD who require MBF quantification, and cardiac sarcoidosis are to confirm a diagnosis or to inform a clinician in disease management decisions.

The question addressed in this evidence review is: Does the use of PET improve the net health outcome in individuals with suspected CAD, LV dysfunction considering revascularization, CAD in need of MBF quantification, and cardiac sarcoidosis?

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

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

Patients
The population of interest includes patients with suspected CAD who have indeterminate SPECT scans, severe LV dysfunction who are potential candidates for revascularization, CAD in need of quantifying MBF, and cardiac sarcoidosis who cannot undergo MRI.

Interventions
The intervention of interest is PET scanning.

Comparators
The comparators of interest for each indication include:

- For suspected CAD, coronary angiography or other noninvasive tests for CAD (e.g., stress echocardiography, exercise electrocardiography)
- For severe LV dysfunction, cardiac MRI or cardiac SPECT scanning
- For quantifying MBF in patients with CAD, coronary angiography with fractional flow reserve (FFR) or clinical risk models
- For cardiac sarcoidosis, clinical evaluation or myocardial biopsy

Outcomes
For patients with suspected CAD, the outcome of interest is confirmed diagnosis. With a confirmed diagnosis, appropriate treatment options can be pursued.

For patients with severe LV dysfunction who are potential candidates for revascularization, the outcome of interest is a viability assessment. If there is sufficient viable myocardium detected, the patient would be a candidate for revascularization.
For patients with CAD who require MBF quantification, the outcome of interest is accurate quantification to inform clinical management of the disease.

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 CAD, MBF quantification, and suspected cardiac sarcoidosis, the timing of the test would be during the disease confirmation process. For severe LV dysfunction, the timing would be prior to surgical (revascularization) and clinical decision making.

Setting
The setting is an imaging center equipped with a PET scanner.

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

Suspected Coronary Artery Disease

Technical Reliability

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

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

Table 4. Performance Characteristics of PET and SPECT Based on the 2007 Position Statement

Outcome Measures	PET	SPECT
Sensitivity	91%	88%
Specificity	89%	77%
Estimated positive likelihood ratio[a]	8.27	3.83
Estimated negative likelihood ratio[b]	0.10	0.16

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.

However, 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 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

Pretest Probability	Posttest Probability, %			
	Positive Test		Negative Test	
	PET	SPECT	PET	SPECT
30%	78	62	4	6
50%	89	79	9	13
70%	95	90	19	27

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

Clinical Validity

Systematic Reviews

In 2016, Dai et al conducted a meta-analysis comparing the abilities of the following cardiac imaging modalities in diagnosing CAD: SPECT, PET, dobutamine stress echocardiography, cardiac MRI, and

computed tomography (CT) perfusion imaging. 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% confidence interval [CI], 80% to 95%) and 84% (95% CI, 81% to 90%). These rates were similar to FFR, the reference standard (sensitivity, 90% [95% CI, 85% to 93%]; specificity, 75% [95% CI, 62% to 85%]).

In 2012, Jaarsma et al 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.

A second 2012 meta-analysis, by Parker et al, compared SPECT with 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 (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. 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]). The area under the receiver operating characteristic (AUROC) 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. Bateman et al (2006) retrospectively matched 112 SPECT and 112 PET studies by sex, BMI, and presence and extent of CAD, and compared diagnostic accuracy and degree of interpretative certainty (age, 65 years; 52% male; mean BMI, 32 kg/m^2; 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 (BMI, >30 kg/m^2), 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 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.

Clinical Utility

Systematic Reviews
In 2017, Chen et al 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 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%).

In 2017, Smulders et al published a meta-analysis comparing the prognostic value of the following negative noninvasive cardiac tests: coronary CT 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.

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 coronary angiography and FFR have shown that PET is comparable in diagnostic accuracy. Meta-analyses that have evaluated 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
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 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; i.e., 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.

Clinical Validity
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 that there was overall good agreement between SPECT and PET for the assessment of myocardial viability in patients with severe LV dysfunction.

Clinical Utility

Randomized Controlled Trials
A large randomized controlled trial, 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).

In 2016, Mc Ardle et al 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 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 Study
In 2016, Srivatsava et al 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 randomized 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
Several publications have described the use of PET imaging to quantify both MBF and myocardial flow reserve (MFR; defined as stress MBF/rest MBF). 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.

Clinical Validity
In 2017, Hsu et al published a study comparing SPECT with N 13 ammonia PET in blood flow quantitation. 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–labelled 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 (AUC) 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).

Clinical Utility
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 LVEF less than

40%, were excluded. Patients underwent 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, LV 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).

In 2011, Ziadi et al 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 (e.g., 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.

Section Summary: Myocardial Blood Flow Quantification
Evidence is growing for the association of quantitative MBF and MFR with 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 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 evidence review. There is no standard diagnostic criterion for cardiac sarcoidosis. The latest consensus statement (2014) issued by the Heart Rhythm Society (HRS) stated that if a histologic diagnosis along with at least 1 clinical symptom (e.g., reduced LVEF, heart block, patchy uptake of FDG-PET, late gadolinium enhancement on cardiac MRI, or cardiomyopathy) were present, the patient had 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 Validity
Systematic Reviews
In 2016, Tang et al 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). 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 2012 meta-analysis by Youssef et al identified 7 studies (total N=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. The pooled sensitivity of PET by random-effects meta-analysis was 89%, and pooled specificity was 78%. The summary AUROC was 93%, suggesting a good level of diagnostic discrimination.

A 2009 review by Sharma reported that cardiac MRI was the more established imaging modality in diagnosing sarcoidosis, with an estimated sensitivity of 100% and specificity of 80%. 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 and called for additional research on the role of MRI and/or PET for this use.

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

In 2017, Dweck et al published a study evaluating the usefulness of a hybrid of cardiac MRI and FDG-PET to diagnose cardiac sarcoidosis. 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.

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 AUC of 0.96 for identifying patients with cardiac sarcoidosis using optimized cut points for the maximum standardized uptake value on FDG-PET/CT.

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

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 SSRT ligand and adding a simultaneous cardiac MRI. These studies have shown positive results.

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

SUMMARY OF EVIDENCE

For individuals with suspected CAD and an indeterminate SPECT scan who receive PET, the evidence includes several systematic reviews and meta-analyses. Relevant outcomes are test accuracy and disease-specific survival. Meta-analyses of studies in which PET results were compared with results from coronary angiography and FFR 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 (e.g., 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 LV dysfunction who are potential candidates for revascularization who undergo 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 and morbid events. In the large randomized controlled trial, patients with LV dysfunction were randomized to care from physicians who would make management decisions based on PET images 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 determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with CAD who require MBF quantification who receive quantitative cardiac PET, the evidence includes observational studies. The relevant outcome is morbid events. Studies adding PET-derived quantitative MBF and MFR 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, the evidence includes systematic reviews and meta-analyses. The relevant outcome is test accuracy. 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 AUC estimates. Several small studies have evaluated variations in PET techniques such as using a radiolabeled SSTR 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 imaging technique most often used to evaluate cardiac sarcoidosis, for patients who are unable to undergo MRI (e.g., patients with a metal implant), evidence supports PET scanning as the preferred test. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Cardiac Applications of Positron Emission Tomography Scanning", 6.01.20, 9:2017.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). PET myocardial profusion imaging for the detection of coronary artery disease – clinical assessment. *TEC Assessments.* 1995;Volume 10:Tab 21. PMID
3. Diamond GA, Forrester JS, Hirsch M, et al. Application of conditional probability analysis to the clinical diagnosis of coronary artery disease. *J Clin Invest.* May 1980;65(5):1210-1221. PMID 6767741
4. Angelidis G, Giamouzis G, Karagiannis G, et al. SPECT and PET in ischemic heart failure. *Heart Fail Rev.* Mar 2017;22(2):243-261. PMID 28150111
5. Food and Drug Administration (FDA). PET drugs - current good manufacturing practice (CGMP). 2009; https://www.fda.gov/downloads/drugs/guidances/ucm070306.pdf. Accessed August 3, 2017.
6. Food and Drug Administration (FDA). PET drugs - current good manufacturing practice (CGMP) (small entity compliance guide). 2011; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm266640.pdf. Accessed August 3, 2017.
7. Food and Drug Administration (FDA). Guidance: Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs. 2012; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf. Accessed 3 Aug, 2017.
8. Beanlands RS, Chow BJ, Dick A, et al. CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease--executive summary. *Can J Cardiol.* Feb 2007;23(2):107-119. PMID 17311116
9. Dai N, Zhang X, Zhang Y, et al. Enhanced diagnostic utility achieved by myocardial blood analysis: A meta-analysis of noninvasive cardiac imaging in the detection of functional coronary artery disease. *Int J Cardiol.* Oct 15 2016;221:665-673. PMID 27423088
10. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol.* May 8 2012;59(19):1719-1728. PMID 22554604
11. Parker MW, Iskandar A, Limone B, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. *Circ Cardiovasc Imaging.* Nov 2012;5(6):700-707. PMID 23051888
12. Takx RA, Blomberg BA, El Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ Cardiovasc Imaging.* Jan 2015;8(1). PMID 25596143
13. Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol.* Jan-Feb 2006;13(1):24-33. PMID 16464714
14. Chen A, Wang H, Fan B, et al. Prognostic value of normal positron emission tomography myocardial perfusion imaging in patients with known or suspected coronary artery disease: a meta-analysis. *Br J Radiol.* Jun 2017;90(1074):20160702. PMID 28306335
15. Smulders MW, Jaarsma C, Nelemans PJ, et al. Comparison of the prognostic value of negative non-invasive cardiac investigations in patients with suspected or known coronary artery disease-a meta-analysis. *Eur Heart J Cardiovasc Imaging.* Feb 27 2017. PMID 28329376
16. Knesaurek K, Machac J. Comparison of 18F SPECT with PET in myocardial imaging: a realistic thorax-cardiac phantom study. *BMC Nucl Med.* Oct 31 2006;6:5. PMID 17076890
17. Slart RH, Bax JJ, de Boer J, et al. Comparison of 99mTc-sestamibi/18FDG DISA SPECT with PET for the detection of viability in patients with coronary artery disease and left ventricular dysfunction. *Eur J Nucl Med Mol Imaging.* Aug 2005;32(8):972-979. PMID 15824927
18. Beanlands RS, Nichol G, Huszti E, et al. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol.* Nov 13 2007;50(20):2002-2012. PMID 17996568
19. Mc Ardle B, Shukla T, Nichol G, et al. Long-term follow-up of outcomes with F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction secondary to coronary disease. *Circ Cardiovasc Imaging.* Sep 2016;9(9). PMID 27609816

20. Siebelink HM, Blanksma PK, Crijns HJ, et al. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomography-guided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardium. *J Am Coll Cardiol.* Jan 2001;37(1):81-88. PMID 11153777
21. Srivatsava MK, Indirani M, Sathyamurthy I, et al. Role of PET-CT in the assessment of myocardial viability in patients with left ventricular dysfunction. *Indian Heart J.* Sep - Oct 2016;68(5):693-699. PMID 27773409
22. Herzog BA, Husmann L, Valenta I, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J Am Coll Cardiol.* Jul 7 2009;54(2):150-156. PMID 19573732
23. Schindler TH, Schelbert HR, Quercioli A, et al. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. *JACC Cardiovasc Imaging.* Jun 2010;3(6):623-640. PMID 20541718
24. Beanlands RS, Ziadi MC, Williams K. Quantification of myocardial flow reserve using positron emission imaging the journey to clinical use [editorial]. *J Am Coll Cardiol.* Jul 7 2009;54(2):157-159. PMID 19573733
25. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol.* Oct 29 2013;62(18):1639-1653. PMID 23954338
26. Hsu B, Hu LH, Yang BH, et al. SPECT myocardial blood flow quantitation toward clinical use: a comparative study with 13N-Ammonia PET myocardial blood flow quantitation. *Eur J Nucl Med Mol Imaging.* Jan 2017;44(1):117-128. PMID 27585576
27. Stuijfzand WJ, Uusitalo V, Kero T, et al. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. *Circ Cardiovasc Imaging.* Jan 2015;8(1). PMID 25596142
28. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation.* Jan 6 2015;131(1):19-27. PMID 25400060
29. Ziadi MC, Dekemp RA, Williams KA, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. *J Am Coll Cardiol.* Aug 9 2011;58(7):740-748. PMID 21816311
30. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* Nov 15 2011;124(20):2215-2224. PMID 22007073
31. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation.* Oct 9 2012;126(15):1858-1868. PMID 22919001
32. Gould KL, Johnson NP. Physiologic stenosis severity, binary thinking, revascularization, and "hidden reality" [editorial]. *Circ Cardiovasc Imaging.* Jan 2015;8(1). PMID 25596144
33. Gould KL, Johnson NP. Physiologic severity of diffuse coronary artery disease: hidden high risk [editorial]. *Circulation.* Jan 6 2015;131(1):4-6. PMID 25400061
34. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm.* Jul 2014;11(7):1305-1323. PMID 24819193
35. Tang R, Wang JT, Wang L, et al. Impact of patient preparation on the diagnostic performance of 18f-FDG PET in cardiac sarcoidosis: a systematic review and meta-analysis. *Clin Nucl Med.* Jul 2016;41(7):e327-339. PMID 26646995
36. Youssef G, Leung E, Mylonas I, et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med.* Feb 2012;53(2):241-248. PMID 22228794
37. Sharma S. Cardiac imaging in myocardial sarcoidosis and other cardiomyopathies. *Curr Opin Pulm Med.* Sep 2009;15(5):507-512. PMID 19542892
38. Lapa C, Reiter T, Kircher M, et al. Somatostatin receptor based PET/CT in patients with the suspicion of cardiac sarcoidosis: an initial comparison to cardiac MRI. *Oncotarget.* Nov 22 2016;7(47):77807-77814. PMID 27780922
39. Dweck MR, Abgral R, Trivieri MG, et al. Hybrid magnetic resonance imaging and positron emission tomography with fluorodeoxyglucose to diagnose active cardiac sarcoidosis. *JACC Cardiovasc Imaging.* Jun 09 2017. PMID 28624396
40. Yokoyama R, Miyagawa M, Okayama H, et al. Quantitative analysis of myocardial (18)F-fluorodeoxyglucose uptake by PET/CT for detection of cardiac sarcoidosis. *Int J Cardiol.* Sep 15 2015;195:180-187. PMID 26043154
41. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol.* Oct 1 2003;42(7):1318-1333. PMID 14522503

42. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *J Am Coll Cardiol.* Jun 09 2009;53(23):2201-2229. PMID 19497454
43. Earls JP, White RD, Woodard PK, et al. ACR Appropriateness Criteria(R) chronic chest pain--high probability of coronary artery disease. *J Am Coll Radiol.* Oct 2011;8(10):679-686. PMID 21962781
44. Expert Panel on Cardiac Imaging, Akers SR, Panchal V, et al. ACR Appropriateness Criteria(R) Chronic Chest Pain-High Probability of Coronary Artery Disease. *J Am Coll Radiol.* May 2017;14(5S):S71-S80. PMID 28473096
45. American College of Radiology (ACR). ACR Appropriateness Criteria: Chronic Chest Pain - Low to Intermediate Probability of Coronary Artery Disease. 2012; https://acsearch.acr.org/list. Accessed August 3, 2017.
46. American College of Radiology (ACR). ACR Appropriateness Criteria: Acute Nonspecific Chest Pain--Low Probability of Coronary Artery Disease. 2015; https://acsearch.acr.org/list. Accessed August 3, 2017.
47. American College of Radiology (ACR). ACR Appropriateness Criteria: Asymptomatic Patient at Risk for Coronary Artery Disease. 2013; https://acsearch.acr.org/list. Accessed August 3, 2017.
48. McMurray JJ, Adamopoulos S, Anker SD, 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. *Eur Heart J.* Jul 2012;33(14):1787-1847. PMID 22611136
49. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* Aug 2016;18(8):891-975. PMID 27207191
50. Ishida Y, Yoshinaga K, Miyagawa M, et al. Recommendations for (18)F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology Recommendations. *Ann Nucl Med.* May 2014;28(4):393-403. PMID 24464391
51. Centers for Medicare and Medicaid Services (CMS). Coverage and Related Claims Processing Requirements for Positron Emission Tomography (PET) Scans – for Breast Cancer and Revised Coverage Conditions for Myocardial Viability, Transmittal AB-02-065. 2002; http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/ab02065.pdf. Accessed August 3, 2017.

Policy History

Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

10/18/2001	Medical Policy Committee review
11/12/2001	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
10/05/2004	Medical Director review
10/19/2004	Medical Policy Committee review
11/29/2004	Managed Care Advisory Council approval
10/05/2005	Medical Director review
10/18/2005	Medical Policy Committee review. Format revision. FDA approval information added. Coverage eligibility unchanged.
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

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

02/20/2008	Medical Policy Committee approval. Revised patient selection criteria changing obesity to severe obesity (BMI $\geq$ 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.
01/01/2018	Coding update
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

Positron Emission Tomography (PET) Cardiac Applications

Policy # 00103
Original Effective Date: 11/12/2001
Current Effective Date: 05/14/2018

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	78459, 78491, 78492 Code added eff 1/1/2018: 0482T
HCPCS	A9526, A9552, A9555, G0235, S8085
ICD-10 Diagnosis	All related diagnoses

*****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 U.S. Food and Drug Administration (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 technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.