Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Positron Emission Tomography (PET Scans) for Cardiac Applications

Description/Background

Coronary Artery Disease

Heart disease is the leading cause of death for men and women in the United States (U.S.).(1) Heart disease is also the leading cause of death for people of most racial and ethnic groups in the U.S., including African American, American Indian, Alaska Native, Hispanic, and white men. For women from the Pacific Islands and Asian American, American Indian, Alaska Native, and Hispanic women, heart disease is second only to cancer. Coronary artery disease (CAD) is the most common type of heart disease in the U.S., killing more than 375,000 people per year. Angina is the most common symptom of CAD. Risk factors for CAD include being overweight, physical inactivity, poor diet, and smoking. A family history of heart disease also increases the risk for CAD, especially in cases where there is a family history of early onset heart disease (i.e., age 50 years or younger).

Positron Emission Tomography

Positron emission tomography (PET) scans use positron-emitting radionuclide tracers, which simultaneously emit 2 high-energy photons in opposite directions. These photons can be simultaneously detected (referred to as coincidence detection) by a PET scanner, consisting of multiple stationary detectors that encircle the thorax. Compared to single photon emission computed tomography (SPECT) scans, coincidence detection offers greater spatial resolution.

Myocardial Perfusion Imaging

For myocardial perfusion studies, individual selection criteria for PET scans include individual assessment of the pretest probability of coronary artery disease (CAD), based both on individual symptoms and risk factors. Individuals at low risk for CAD may be adequately evaluated with exercise electrocardiography. Individuals 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 individuals at intermediate risk of CAD (variably defined as 25% to 75% or 10% to 90% disease probability).(2)[a] Risk can be estimated using the patient's age, sex, and chest pain quality. Table 1 summarizes patient populations at intermediate risk for CAD.(3)

[a]Intermediate-risk ranges used in different studies may differ from the range used here. These pretest probability risk groups are based on a TEC Assessment (1995) and take into account spectrum effect. The American College of Cardiology guidelines have defined low risk as less than 10%, intermediate risk as 10% to 90%, and high risk as greater than 90%.

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

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

Among individuals with CAD, myocardial perfusion imaging can be used to quantify myocardial blood flow and myocardial flow reserve (MFR).(4) Quantitative assessment of myocardial perfusion is sensitive for detection of ischemic tissue within the myocardium and can allow for accurate determination of risk for cardiovascular events. These quantitative measurements can also be predictive of adverse cardiovascular outcomes. For example, the presence of an abnormally low MFR can identify individuals at higher risk of cardiovascular death.

Myocardial perfusion studies with PET are also useful in the diagnosis of cardiac sarcoidosis.(5) Perfusion studies performed in individuals with sarcoidosis and suspected cardiac involvement can detect presence of inflammation, fibrosis of the myocardial tissue, and function and involvement of the left and right ventricles.

Myocardial Viability

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

Radionuclide Tracers

A variety of radionuclide tracers are used for PET scanning, including fluorine-18, rubidium-82, oxygen-15, nitrogen-13 and carbon-11. Most tracers have a short half-life and must be manufactured with an on-site cyclotron. Rubidium-82 is produced by a strontium-82/rubidium-82 generator. The half-life of fluorine-18 is long enough that it can be manufactured commercially at offsite locations and shipped to imaging centers. Radionuclides may be coupled to a variety of physiologically active molecules, such as oxygen, water and ammonia. Fluorine-18 is often

coupled with fluorodeoxyglucose (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.

Regulatory Status

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

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

In December 2009, the FDA issued guidance for Current Good Manufacturing Practice (CGMP) for PET drug manufacturers,(6) and in August 2011, FDA issued similar CGMP guidance for small businesses.(7) An additional final guidance document issued in December 2012 required all PET drug manufacturers and compounders to operate under an approved new drug application (NDA) or abbreviated NDA, or investigational new drug application, by December 2015.(8)

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

Table 2. Radiopharmaceuticals Approved for Use Prior to 2012 with PET for Cardiac Indications[a]

Radiopharmaceutical	Manufacturer	NDA	Approved	Cardiac-Related Indication With PET
Fluorine 18 fluorodeoxyglucose (F-18-FDG)	Various	20306	2000	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
Ammonia N 13	Zevacor Pharma	22119	2000	Imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing CAD
Rubidium 82 chloride	Bracco Diagnostics	19414	1989	Assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction

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

[a]This table only lists products that received an approved NDA prior to the final guidance for Current Good Manufacturing Practice for PET drug manufacturers issued by the Food and Drug Administration in December 2012.

Medical Policy Statement

The safety and effectiveness of cardiac PET scanning have been established. It may be considered a useful diagnostic option for individuals meeting specified selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Cardiac PET scanning is established for the following indications:

- Assessing myocardial perfusion for diagnosing coronary artery disease in individuals with indeterminate SPECT scan
- For individuals for whom SPECT could be reasonably expected to be suboptimal in quality on the basis of body habitus. (e.g., BMI > 40, large breasts, breast implants, mastectomy, chest wall deformity, pleural or pericardial effusion)
- For assessing the myocardial viability in individuals with severe left ventricular dysfunction as a technique to determine candidacy for a revascularization procedure
- For diagnosing cardiac sarcoidosis in individuals who are unable to undergo magnetic resonance imaging (MRI) scanning. Examples of individuals who are unable to undergo MRI include, but are not limited to, individuals with pacemakers, automatic implanted cardioverter-defibrillators (AICDs), or other metal implants.

Exclusions:

- Quantification of myocardial blood flow in individuals diagnosed with CAD.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

78429	78430	78431	78432	78433	78459
78491	78492	A9526	A9552	A9555	

Other codes (investigational, not medically necessary, etc.):

78434

Rationale

SUSPECTED CORONARY ARTERY DISEASE

Clinical Context and Test Purpose
The purpose of PET scanning in individuals who have suspected coronary artery disease (CAD) is to evaluate perfusion to the heart. Positron emission tomography can assess relative perfusion, coronary flow reserve, absolute myocardial blood flow (MBF) at stress and rest, left ventricular ejection fraction (LVEF), possible ischemic dilatation, and coronary artery calcium levels. These parameters can be used to diagnose CAD.

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

Populations
The population of interest includes individuals with suspected CAD who have indeterminate single-photon emission computed tomography (SPECT) scans.

Interventions
The intervention of interest is cardiac PET perfusion imaging.

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

Outcomes
For individuals with suspected CAD, the outcomes of interest are the avoidance of unnecessary invasive procedures, cardiac events, and mortality. Additional outcomes of interest, including PET sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and test accuracy are measured from time to diagnosis.

Study Selection Criteria
For the evaluation of the clinical validity of cardiac PET perfusion imaging, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

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

The sensitivity and specificity of PET may be slightly better than for SPECT. Performance characteristics for PET and SPECT based on the 2007 Canadian Joint Position Statement are shown in Table 3.(9)

Table 3. Performance Characteristics of PET and SPECT

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

Adapted from Beanlands et al (2007).
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.

Review of Evidence

Diagnostic Performance

Systematic Reviews

Xu et al (2021) conducted a meta-analysis that compared cardiac magnetic resonance imaging (MRI), SPECT, and PET for the diagnosis of CAD.(10) Diagnostic studies were eligible for inclusion if either coronary angiography or fractional flow reserve (FFR) was used as the reference standard. The literature search, conducted through July 2020, identified 203articles (N=23,942) that assessed the diagnostic performance of cardiac MRI (56 articles), SPECT (134 articles), and PET (25 articles). There were no statistically significant differences in sensitivities between cardiac MRI, SPECT, and PET(86% [95% CI, 84% to 88%], 83% [95% CI, 81% to 85%], 85% [95% CI, 80% to 89%], respectively; p=.109). For specificity, cardiac MRI (83% [95% CI, 81% to 86%]) and PET (86% [95% CI, 81% to 89%]) performed significantly better than SPECT (77% [95% CI, 74% to 80%]; p<.01 for both comparisons); there was no statistically significant difference between cardiac MRI and PET. Similarly, the area under the curve values of cardiac MRI (0.92 [95% CI, 0.89 to 0.94]),SPECT (0.87 [95% CI, 0.84 to 0.90]), and PET (0.92 [95% CI, 0.89 to 0.94) indicated that cardiac MRI and PET had better diagnostic performance for the detection of CAD as compared with SPECT (p<.01 for both comparisons).

Knuuti et al (2018) reported on the results of a meta-analysis of the performance of noninvasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina including publications through April 2017 that included at least 100 patients with stable CAD and either invasive coronary angiography (ICA) or ICA with fractional flow reserve (FFR) measurement as reference standard.(11) A total of 132 studies (n=28,664) using ICA as the reference standard and 23 studies (n=4131) using FFR as the reference standard were included. The pooled analysis for the outcome of anatomically significant CAD included 418 patients for PET and the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were as follows: 90% (95% confidence interval [CI], 78% to 96%); 85% (95% CI, 78% to 90%); 5.87 (95% CI, 3.40 to 10.15); and 0.12 (95% CI, 0.05 to 0.29), respectively. The pooled analysis for outcome of functionally significant CAD included 709 patients for PET and the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were as follows: 89% (95% CI, 82% to 93%); 85% (95% CI, 81% to 88%); 6.04 (95% CI, 4.29 to 8.51); and 0.13 (95% CI, 0.08 to 0.22), respectively.

Dai et al (2016) 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.(12) 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 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%]).

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.(13) Literature was searched to May 2014, and 37 studies met inclusion criteria (n=4698 vessels). Three PET studies of moderate-to-high quality were included (n=870 vessels); pretest probability of CAD was intermediate to intermediate-high in these studies. Negative likelihood ratio 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 negative likelihood ratios for PET, MRI, and CT were similar and were lower (better) than the pooled negative likelihood ratio for SPECT (PET pooled negative likelihood ratio 0.15 [95% CI, 0.05 to 0.44]; SPECT pooled negative likelihood ratio 0.47 [95% CI, 0.37 to 0.59]). Similarly, at the patient-level, pooled negative likelihood ratios for PET, MRI, and CT were better than the pooled negative likelihood ratios for SPECT and echocardiography (PET pooled negative likelihood ratio 0.14 [95% CI, 0.02 to 0.87]; SPECT pooled negative likelihood ratio 0.39 [95% CI, 0.27 to 0.55]). The area under the receiver operating characteristic analyses was similar at both the vessel level (PET, 0.95 vs SPECT, 0.83) and the patient-level (PET, 0.93 vs SPECT, 0.82).

Retrospective Studies

Another consideration is that there are fewer indeterminate results with PET than SPECT. Bateman et al (2006) retrospectively matched 112 SPECT and 112 PET studies by gender, body mass index (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).(14) 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>30kg/m^2), the accuracy of SPECT was 67% versus 85% for PET; accuracy in nonobese patients was 70% for SPECT and 87% for PET.

Prognostic Performance

Systematic Reviews

Chen et al (2017) published a meta-analysis assessing the prognostic value of PET myocardial perfusion imaging in patients with known or suspected CAD.(15) For inclusion, studies had to have at least 1 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 2 were fair. All 11 studies included cardiac death as the primary or secondary outcome, with a pooled negative predictive value (NPV) of 99% (95% CI, 98% to 99%). Seven studies included all-cause death as an outcome, with a pooled NPV of 95% (95% CI, 93% to 96%). Four studies included MACE as an outcome, with a pooled NPV of 90% (95% CI, 78% to 96%).

Smulders et al (2017) published a meta-analysis comparing the prognostic value of the following negative noninvasive cardiac tests: coronary computed tomography angiography, cardiovascular MRI, exercise electrocardiographic testing, PET, stress echocardiography, and SPECT.(16) 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, 4 of which involved PET. Study quality was assessed using the Newcastle-Ottawa Scale for observational studies. Pooled annual event rates for cardiac death and myocardial infarction for PET were low (0.41; 95% CI, 0.15 to 0.80), indicating that a patient with a negative PET test has a good prognosis.

Clinically Useful

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

Direct Evidence

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

No RCTs comparing outcomes for individuals undergoing PET perfusion imaging to individuals who did not undergo PET perfusion imaging were identified.

Chain of Evidence

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

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

Section Summary: Suspected Coronary Artery Disease

Evidence on the diagnostic accuracy of PET for CAD consists of several systematic reviews and meta-analyses. Meta-analyses comparing PET with reference standards such as coronary angiography and FFR have shown that PET is comparable in diagnostic accuracy. Additionally, some of these meta-analyses found PET to have significantly greater sensitivity or specificity compared to SPECT, which further validates its use among individuals with indeterminate SPECT results. Meta-analyses evaluating the clinical utility of PET have looked at outcomes such as mortality and adverse cardiac events. These meta-analyses have shown that PET is a useful prognostic tool.

SEVERE LEFT VENTRICULAR DYSFUNCTION CONSIDERING REVASCULARIZATION

Clinical Context and Test Purpose

The purpose of PET scanning in individuals with severe left ventricular (LV) dysfunction is to determine myocardial viability to assist with revascularization.

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

Populations

The population of interest are individuals with severe LV dysfunction who are potential candidates for revascularization.

Interventions

The intervention of interest is PET scanning.

Comparators

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

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

Study selection criteria
For the evaluation of the clinical validity of cardiac PET perfusion imaging, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate
- scores)
- Included a suitable reference standard (describe the reference standard)
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

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

Review of Evidence

Diagnostic Performance

PET has perhaps been most thoroughly researched as a technique to assess myocardial viability to determine candidacy for a coronary revascularization procedure. A fixed perfusion defect, as imaged on single photon emission computed tomography (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 fluorine18-labeled fluorodeoxyglucose (18F-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 individuals who experience improvement in left ventricular (LV) dysfunction after revascularization of hibernating myocardium, as identified by PET scanning.

SPECT scanning may also be used to assess myocardial viability. While initial myocardial uptake of thallium-201 reflects myocardial perfusion, 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); i.e., 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.

Studies identified in the literature have shown the equivalence of SPECT and PET in their ability to assess myocardium viability.

Using a thorax-cardiac phantom with different sized inserts that simulated infarcts, Knesaurek and Machac (2006) tested SPECT and PET images.(17) The investigators concluded that PET was better at detecting smaller defects than SPECT. In this study, a 1-cm insert was not detectable by SPECT, yet it was detectable 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.(18) Tracer uptake for PET and SPECT was compared by linear regression and correlation analysis, which showed there was an overall good agreement between SPECT and PET for the assessment of myocardial viability in patients with severe LV dysfunction.

Clinically Useful

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

Direct Evidence

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

Prognostic Performance

Randomized Controlled Trials

The Positron Emission Tomography and Recovery Following Revascularization evaluated the impact of FDG-PET viability imaging on individuals with severe LV dysfunction. Individuals 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). Physicians in the standard care management group could order a different test to determine viability; however, the study did not indicate what specific tests were ordered or in what frequency. 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.(19) 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 individuals 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 individual refusal. When subgroup analysis included only those individuals who received the treatment as recommended based on PET images, the HR for a composite event was significant (0.62; 95% CI, 0.42 to 0.93).

Mc Ardle et al (2016) published long-term follow-up results for the Positron Emission Tomography and Recovery Following Revascularization trial.(20) 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.(21) 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 two imaging techniques. The authors concluded that either technique could be used to manage patients considered for revascularization. However, the sample size for the study was determined based on the assumption that patients randomized to SPECT would have a 20% higher cardiac event rate. Therefore, the study may have been underpowered to detect a difference in cardiac outcomes between groups.

Nonrandomized Studies

Srivatsava et al (2016) published a study of 120 patients with LV dysfunction who underwent both SPECT-CT and FDG-PET/CT to determine myocardial viability.(22) If both tests showed defects (i.e., matched defects), the tissue was considered nonviable. If a defect was seen in the SPECT-CT test but uptake of 18F-FDG was seen with the FDG-PET test (i.e., mismatched defects), the tissue was considered hibernating 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). Among 786 segments of myocardium with evidence of reduced perfusion, 432 segments (55%) were matched defects, and 354 segments (45%) were mismatched defects. 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). All patients with observed viability of the myocardium on PET were managed surgically. A decline in LVEF was seen in 5 patients (6.4%) who received surgical management compared with 9 patients (21.4%) who were managed medically.

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: 1 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 one year and 5 years showed that when individuals received care as indicated by the PET images, they were at decreased risk for cardiac death, myocardial infarction, or recurrent hospital stay compared with individuals who did not. Although the study did not define what standard care consisted of, physicians were permitted to order non-PET viability tests for individuals in the standard care group. However, it is unclear how many individuals received other tests for viability, and what tests were administered. A small prospective study has suggested that the accuracy of PET and SPECT are roughly similar for this purpose; however, this study may have been underpowered

to detect a difference between groups. A small, nonrandomized study also showed that PET may be useful for detecting viable myocardium when SPECT shows nonviable tissue.

MYOCARDIAL BLOOD FLOW QUANTIFICATION

Clinical Context and Test Purpose
The purpose of PET scanning in individuals who have CAD is to quantify MBF for cardiac event risk stratification.

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

Populations
The population of interest is individuals with CAD in need of quantifying myocardial blood flow (MBF) for cardiac event risk stratification.

Interventions
The intervention of interest is quantitative cardiac PET perfusion imaging. Both MBF and myocardial flow reserve (MFR; defined as stress MBF/rest MBF) can be quantified. Generally, a MFR ≥ 2 is indicative of normal perfusion and is associated with a good prognosis.(23) Lower values of MFR may require further invasive testing to rule out epicardial CAD. As MFR decreases, the likelihood of multivessel obstructive CAD increases with a corresponding worsening prognosis

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

Outcomes
For individuals with CAD who require MBF quantification, the intermediate outcome is accurate quantification. The clinical outcome of interest is cardiac events. The relevant follow up would be time to cardiac events.

Study Selection Criteria
Study selection criteria are described above.

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

Review of Evidence

Diagnostic Performance

Cohort Studies
Several publications have described the use of PET imaging to quantify both MBF and myocardial flow reserve.(24,25) However, as noted in an accompanying editorial (26) and by subsequent reviewers,(27) larger prospective clinical trials are needed to understand the clinical utility of these approaches. Diagnostic accuracy of PET myocardial perfusion imaging, as compared to FFR as a reference standard, is limited to 15-oxygen (O)-water PET imaging,

which is not available in the US.(13) Most PET examinations are performed with 82-Rubidium (Rb) chloride instead, which has less favorable flow-extraction characteristics. Therefore, it is not possible to extrapolate the findings from 15O-water PET studies to clinical settings in which 82Rb-chloride is used.

Prognostic Performance

Systematic Reviews

Green et al (2021) conducted a meta-analysis on the prognostic value of MFR (called coronary flow reserve [CFR] in this analysis), as assessed by PET, for predicting adverse cardiovascular events in patients with suspected or known CAD.(28) The prognostic value of MFR was analyzed as a dichotomous variable (i.e., impaired vs. preserved MFR); cut-off values used were as reported by the individual study. Thirteen studies (N=12,334) were identified. Four of the studies included patients with suspected CAD only; the remainder of the studies included a mixed population (suspected or known CAD).Eleven studies reported MACE outcomes, and the pooled HR for patients with impaired versus preserved MFR was 1.93(95% CI, 1.65 to 2.27; $I2$=11%). Only 5 studies reported on hard events (i.e., cardiac death, myocardial infarction) and there was significant heterogeneity ($I2$=72.8%); the pooled HR was 3.11 (95% CI, 1.88 to 5.14). Six studies included data useful to calculate separately the incidence rate of MACE events. The pooled incidence rate ratio for patients with impaired versus preserved MFR was 2.26 (95% CI, 1.79 to 2.85: I^2=20.3%). Funnel plots for the MACE, but not hard events, indicated significant bias towards positive results. Publication bias may result in overstating the benefits of MFR prognostic value. Heterogeneity between studies and small sample sizes of some of the included studies further complicate interpretation. For instance, the cut-off value for designating an impaired MFR was not consistent across trials, stemming from differences in tracers, imaging protocols, and stress agents used in the studies. The authors note that due to the large heterogeneity in the study population, there is a need for further investigations to maximize the prognostic role of MFR.

Juarez-Orozco et al (2017) reported on the results of a systematic review of prognostic studies of quantitative myocardial perfusion evaluation with PET in patients with suspected or known CAD.(29) Eight studies (total n=6804 patients) were included. Risk of bias was assessed using the Quality in Prognostic Studies tool. The risk of bias was rated as low overall with the exception of one domain (prognostic factor measurement) with the uncertain risk of bias due to the differences in population characteristics and tracer used. The mean follow-up range was 12 to 117 months for the MACE outcome, 66 to 88 months for the cardiac death outcome, and 43 to 117 months for the all-cause mortality outcome. MFR was independently associated with MACE in all 8 studies with the range of adjusted HRs from 1.19 to 2.93. Pooled analyses for MACE included only 2 studies due to the differences in populations and cutoff values for MFR; the pooled HR was 1.92 (95% CI,1.29 to 2.84) for the 2 studies, which included patients with a previous myocardial infarction and a MFR cut-off of 2.0.There was not enough evidence to pool reported HRs to establish the prognostic value of MFR for cardiac death or all-cause mortality.

Cohort Studies

As available meta-analyses have identified the need for larger, and preferably prospective, cohort investigations to more precisely identify the prognostic value of MFR measurements, cohort studies not included in the previously summarized meta-analyses that included at least 1000 participants are included below. Meta-analyses by Green et al (2021) and Juarez-Orozco

et al (2017) incorporated 16 studies, which evaluated diverse populations that included both patients with suspected and confirmed CAD.(23,30-44)

Gould et al (2021) prospectively examined the relationship between regional, artery specific MFR (called CFR in this analysis) and coronary flow capacity (CFC) and mortality in patients with suspected or known CAD who received and did not receive revascularization.(45) Patients were recruited from a single center institution that routinely performs quantitative PET myocardial perfusion imaging in all patients with or at risk of CAD. CFC color maps are created using 5 color ranges for combined CFR and stress perfusion values of each pixel, which is mapped back to its location in the left ventricle. For the CFC maps, any with pixels that had both MFR ≤1.27 and stress perfusion ≤0.83 were defined as severely reduced CFC (CFC severe). A total of 5274 patients were included in the cohort, who were followed for 4.2 years on average. Thirty-eight percent of patients had established CAD and 73% were male. Within 90days of the PET scan, 245 patients (7.4%) received a coronary angiogram; of those patients, 76% underwent a revascularization procedure and 24% were deemed to not be appropriate candidates due to diffuse or complex CAD. Among the patients undergoing revascularization procedures (n=187), 152 (81%) were classified as CFC severe and 35 (19%) were classified as moderately reduced CFC (no CFC severe). Severely reduced regional MFR of 1.0 to 1.5 was associated with an increasing risk of all-cause death, myocardial infarction, stroke, or revascularization. Cox regression modeling showed that mortality risk was 54% lower (HR, 0.46; 95%CI, 0.26 to 0.79) after revascularization in patients classified as CFC severe. For global assessments, patients with a global MFR <2.0and global stress perfusion <1.8 had a significantly lower mortality risk with revascularization compared to no revascularization (p<.003). For other combinations with less severe global MFR or global stress perfusion, revascularization had no statistically significant impact on mortality risk. The authors note that generalizability may be a limitation as protocols, methodologies, and thresholds for intervention vary among institutions.

Patel et al (2020) retrospectively evaluated the association between MFR and mortality, and whether the association was modified by early revascularization in a cohort of 12,549 patients referred for rest/stress 82Rb PET myocardial perfusion imaging.(46) Patients with a history of CABG or LVEF <40% were excluded. The primary outcome was all-cause mortality; cardiac mortality was a secondary outcome. Early revascularization was defined as receipt of percutaneous coronary intervention or CABG within 90 days of the myocardial perfusion imaging test. All patients had at least 1 year of follow-up and the median duration was 3.2 years. The majority of patients (77.4%) did not have a documented history of CAD and 47.2% were male. Chest pain was the predominant presenting symptom in approximately 60% of all patients. Mean MFR values were classified as low (<1.8), intermediate (1.8 to 2), and normal (≥2); 38.5%, 15%, and 46.4%of the cohort fell into these categories, respectively. Early revascularization was performed in 897 patients; of those, 66.8%, 10.8%,and 22.4% had MFR values of low, intermediate, or normal, respectively. The all-cause mortality rate through the study follow-up period was 13.5% for the entire cohort. The mortality rate in the low, intermediate, and normal MFR was 21.9%, 12.4%, and 6.9%,respectively (p<.001). Adjusted HR estimates found that every 0.1-unit decrease in MFR was associated with 9% greater hazard of all-cause death [HR, 1.09; 95% CI, 1.08 to 1.10). In the fully adjusted Cox proportional hazards model, there was a significant interaction between MFR and early revascularization; such that patients with MFR ≤1.8 had a survival benefit with early revascularization (HR,0.76; 95% CI, 0.62 to 0.94), and those with MBFR >1.8 had similar or worse outcomes with early revascularization (HR, 1.39; 95% CI,1.01 to 1.94).

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

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

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

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

Specificity on how the test would fit into current management guidelines for making treatment decisions is needed to evaluate a chain of evidence.

Section Summary: Myocardial Blood Flow Quantification
Evidence is accumulating on the association between quantitative myocardial blood flow (MBF) and myocardial flow reserve (MFR) and cardiovascular outcomes, including if quantifying MFR can assist in identifying patients who may gain a survival benefit from early revascularization. Meta-analyses of cohort studies and individual cohorts have found that impaired MFR is significantly associated with an increase in all-cause mortality. Interpretation of the available literature is complicated due to differences in populations studied, procedures and radiotracers used, cut points used for classification, covariates used in models, lack of reclassification analyses, and potential for publication bias. Recent prospective and retrospective cohorts have reported that identification of MFR can assist in identifying individuals who may receive a survival benefit with early revascularization compared to medical therapy. The benefits observed in these single-center studies may be difficult to generalize due to differences in protocols, methodologies, and thresholds for intervention among institutions. These methods are considered to be in a developmental stage for clinical use. Large, prospective clinical trials are needed to better define the potential utility of MBF quantification.

CARDIAC SARCOIDOSIS

Clinical Context and Test Purpose
The purpose of PET scanning in individuals with suspected cardiac sarcoidosis is to diagnose sarcoidosis via detection of inflammatory lesions.

There are no universally accepted diagnostic criteria for cardiac sarcoidosis. The American Thoracic Society guideline (2020) notes that diagnosis is based on 3 major criteria: compatible clinical presentation, finding non-necrotizing granulomatous inflammation in ≥1 tissue samples, and the exclusion of alternative causes of granulomatous disease.(47) Imaging techniques are

commonly used for cardiac sarcoidosis detection, along with the collection of additional clinical data. Transthoracic echocardiogram, cardiac MRI, and FDG PET have all been evaluated for making a sarcoidosis diagnosis.

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

Populations
The population of interest includes individuals with suspected cardiac sarcoidosis who cannot undergo MRI.

Interventions
The intervention of interest is PET scanning.

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

Outcomes
For individuals with suspected cardiac sarcoidosis, the outcome of interest is a diagnosis confirmation.

Study Selection Criteria
Study selection criteria are described above.

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

Review of Evidence

Diagnostic Performance
Studies evaluating the diagnostic performance of PET for cardiac sarcoidosis are limited by the absence of a gold standard reference.(48) The Japanese Ministry of Health and Welfare (JMHW), the modified JMHW, or the Heart Rhythm Society diagnostic criteria are often used as the reference standard, but all have imperfect diagnostic accuracy.

Systematic Review
Aitken et al (2022) conducted a systematic review on the diagnostic performance of 18F-FDG PET or MRI for cardiac sarcoidosis.(49) Cardiac MRI was evaluated in 17 studies (n=1031) and 18F-FDG PET was evaluated in 26 studies (N=1363). Results demonstrated that cardiac MRI and 18F-FDG PET had similar specificity (85% vs. 82%; p=.85), but MRI demonstrated higher sensitivity (95% vs. 84%; p=.002).

Kim et al (2020) conducted a systematic review on the diagnostic performance of 18F-FDG PET or PET/CT for cardiac sarcoidosis.(50) A total of 17 studies (N=891) were identified for inclusion. Thirteen studies were retrospectively designed, with the other 4 studies enrolling patients prospectively. The reference standards used in the included studies was the JMHW guideline or the modified JMHW. Across all studies, the pooled sensitivity was 84% (95% CI, 71% to 91%: I^2=77.5) and the pooled specificity was 83% (95% CI, 74% to 89%: I^2=80.0). The

pooled sensitivity and specificity for the6 studies that evaluated 18F-FDG PET alone was 92% (95% CI, 79% to 97%) and 66% (95% CI, 47% to 81%), respectively. The pooled sensitivity and specificity for the 11 studies that evaluated combination 18F-FDG PET/CT was 72% (95% CI, 66%to 78%) and 89% (95% CI, 86% to 92%), respectively. The overall positive likelihood ratio was 4.9 (95% CI, 3.3 to 7.3) and the negative likelihood ratio was 0.2 (95% CI, 0.11 to 0.35). The pooled diagnostic odds ratio was 27 (95% CI, 14 to 55).Pooled accuracy was assessed using a summary receiver operator characteristic curve; the area under the curve was 0.90 (95% CI, 0.87 to 0.92). The authors concluded that further large multicenter studies are necessary to substantiate the diagnostic accuracy of 18F-FDG PET for cardiac sarcoidosis.

Nonrandomized Studies

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

Lapa et al (2016) published a study to determine whether PET/CT using radiolabeled somatostatin receptor (SSRT) ligands for visualization of inflammation would accurately diagnose cardiac sarcoidosis.(52) Fifteen patients with sarcoidosis and suspicion of cardiac involvement underwent both SSRT-PET/CT and cardiac MRI. Concordant results between PET/CT and MRI occurred in 12 of the 15 patients.

Clinically Useful

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

Direct Evidence

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

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

Chain of Evidence

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

Cardiac sarcoidosis can lead to arrhythmia, heart failure, pericarditis, and myocardial infarction. There is no criterion standard for diagnosing cardiac sarcoidosis, but clinical diagnosis is made through a combination of clinical evaluations and imaging. Results from

nonrandomized studies have shown that PET can be a useful tool in the clinical diagnostic process.

Section Summary: Cardiac Sarcoidosis
Left untreated, cardiac sarcoidosis can lead to serious developments such as arrhythmia, heart failure, pericarditis, and myocardial infarction. 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. Magnetic resonance imaging is generally recommended first-line for imaging of individuals with suspected cardiac sarcoidosis; however, PET may be utilized in individuals who are unable to undergo MRI. A meta-analysis found moderate sensitivity and specificity of 18F-FDG PET or PET/CT for diagnosis of cardiac sarcoidosis. A systematic review and 2 nonrandomized studies have been published comparing MRI and PET for diagnosis of cardiac sarcoidosis. Data demonstrates concordance between the 2 tests in their ability to detect cardiac sarcoidosis, thus supporting the use of PET scanning in patients with sarcoidosis unable to undergo MRI.

SUMMARY OF EVIDENCE
For individuals with suspected coronary artery disease and an indeterminate SPECT scan who receive PET, the evidence includes several systematic reviews and meta-analyses. The relevant outcomes are test accuracy, disease-specific survival, morbid events and resource utilization. Meta-analyses of studies in which PET results were compared with results from coronary angiography and fractional flow reserve have shown that PET is comparable in diagnostic accuracy to these referent standards. In meta-analyses of studies that included clinical outcomes such as mortality and adverse cardiac events, results have shown that PET is a useful prognostic tool. Meta-analyses have also found PET to have greater sensitivity or specificity compared to SPECT, which provides further evidence to support the use of PET when SPECT is indeterminate. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with left ventricular dysfunction who are potential candidates for revascularization who receive cardiac PET scanning to assess myocardial viability, the evidence includes a large randomized controlled trial with long-term follow-up and several small trials comparing SPECT with PET. Relevant outcomes are test accuracy, disease specific survival and morbid events. In the large randomized controlled trial, patients with left ventricular 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. Physicians who would make management decisions without PET images were permitted to administer other tests for myocardial viability, although details were not available as to which tests were performed, if any. 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. One trial comparing SPECT with PET showed that both modalities were useful in managing patients considering revascularization; however, this trial was small and may have been underpowered to detect a difference in outcomes. 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 an improvement in the net health outcome.

For individuals with coronary artery disease who require myocardial blood flow quantification for cardiac event risk stratification who receive quantitative cardiac PET perfusion imaging, the evidence includes observational studies and meta-analysis of those observational studies. Relevant outcomes are disease-specific survival and morbid events. Studies evaluating PET-derived quantitative myocardial blood flow and myocardial flow reserve have found that impaired MFR is significantly associated with an increase in all-cause mortality and can assist in identifying patients who may receive survival benefit with early revascularization compared to medical therapy. The benefits observed in these single-center studies maybe difficult to generalize due to differences in protocols, methodologies, and thresholds for intervention among institutions. These methods are considered to be in a developmental stage for clinical use. Large, prospective clinical trials are needed to better define the potential utility of MBF quantification. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with suspected cardiac sarcoidosis who cannot undergo MRI, the evidence includes nonrandomized studies and a meta-analyses of observational studies. Relevant outcomes are disease-specific survival, test accuracy, and morbid events. Currently, there is no criterion standard for diagnosing cardiac sarcoidosis. A combination of clinical evaluations and results from imaging techniques, usually magnetic resonance imaging (MRI), are used during the clinician's assessment. Meta-analyses have found moderate sensitivity and specificity of18F-FDG PET or PET/CT for diagnosis of cardiac sarcoidosis. Two small studies have evaluated variations in PET techniques such as using a radiolabeled somatostatin receptor ligand and adding a simultaneous cardiac MRI. Reported results were positive in these small studies, but larger samples are needed to confirm the usefulness of these changes. While MRI is the 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 an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

BCBSA received response to requests for input while this policy was under review in 2011. The input was in general agreement with the medical necessity of positron emission tomography (PET) for myocardial viability or for individuals with an indeterminate single-photon emission computed tomography (SPECT) scan. However, reviewers disagreed on using a strict body mass index cutoff to define individuals 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 individuals with indeterminate SPECT scan; or in individuals 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 individuals with suspected cardiac sarcoidosis. All 3 agreed that PET scanning was medically necessary in this patient group. Two of these reviewers offered that MRI scanning was the preferred test in the workup of cardiac sarcoidosis but PET scanning

was medically necessary in individuals 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 individuals who are unable to undergo MRI scanning. Examples of individuals who are unable to undergo MRI include, but are not limited to, patients with pacemakers, automatic implanted cardioverter-defibrillators (AICDs), or other metal implants.”

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Nuclear Cardiology/Society of Nuclear Medicine and Molecular Imaging

The American Society of Nuclear Cardiology (ASNC) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) (2016) updated their joint guideline on procedure standards for cardiac PET procedures.(53) PET myocardial perfusion imaging is used "to detect physiologically significant coronary artery narrowing to guide clinical management of patients with known or suspected CAD[coronary artery disease] and those without overt CAD but with cardiovascular risk factors in order to: evaluate the progression of atherosclerosis, determine cause of ischemic symptoms and recommend medical or revascularization therapy, estimate the potential for future adverse events, and improve patient survival." Perfusion defects can be reported through qualitative scoring, semiquantitative scoring systems, or absolute quantification of myocardial blood flow (MBF). The guideline is limited by not providing direct recommendations with associated levels of evidence and strength of recommendations. However, the authors note that" quantitative absolute MBF measurements with PET appear most helpful in:

- patients without known prior history of cardiac disease who present with symptoms suspicious for myocardial ischemia,
- patients with known CAD, in whom more specific physiological assessment is desired,
- identifying an increased suspicion for multivessel CAD,
- situations with a disparity between visual perfusion abnormalities and apparently normal coronary angiography, in order to assess possible microvascular dysfunction, and
- heart transplant when there is a question of vasculopathy.

In contrast, there are particular patients for whom reporting hyperemic blood flow or flow reserve may not add diagnostic value or can be ambiguous or misleading, including:

- patients’ post-CABG [coronary artery bypass graft] who can have diffuse reduction on MBF despite patent grafts,
- patients with large transmural infarcts where resting flow may be severely reduced such that small increases in flow lead to normal or near-normal flow reserve,
- patients with advanced severe chronic renal dysfunction who likewise often have diffuse coronary disease, and
- patients with severe LV [left ventricular] dysfunction."

A joint position paper from SNMMI/ASNC (2018) further discussed clinical quantification of myocardial flow (MBF).(54) Stress MBF and MFR are associated with improved diagnostic sensitivity, but specificity has varied in studies. Treatment guidance noted that "[a]t present there are no randomized data supporting the use of any stress imaging modality for selection of patients for revascularization or for guidance of medical therapy. Observational data have established a paradigm that patients with greater degrees of ischemia on relative MPI [myocardial perfusion imaging] are more likely to benefit from revascularization. This paradigm

has been conceptually extended to include MFR and stress MBF but has not yet been evaluated prospectively." The following key points were highlighted:

- "Use of stress MBF and MFR for diagnosis is complex, as diabetes, hypertension, age, smoking, and other risk factors may decrease stress MBF and MFR without focal epicardial stenosis.
- Patients with preserved stress MBF and MFR are unlikely to have high-risk epicardial CAD.
- Preserved stress MBF of more than 2 mL/min/g and MFR of more than 2 reliably exclude the presence of high-risk angiographic disease (negative predictive value > 95%) and are reasonable to report when used in clinical interpretation.
- A severely decreased global MFR (<1.5 mL/min/g) should be reported as a high-risk feature for adverse cardiac events but is not always due to multivessel obstructive disease. The likelihood of multivessel obstructive disease may be refined by examination of the electrocardiogram, regional perfusion, coronary calcification, and cardiac volumes and function.
- Regional decreases in stress MBF (<1.5 mL/min/g) and MFR (<1.5) in a vascular territory may indicate regional flow-limiting disease."

The position paper additionally calls for further data on quantifying MBF and MFR in suspected or established CAD: "[t]hese methods are at the cusp of translation to clinical practice. However, further efforts are necessary to standardize measures across laboratories, radiotracers, equipment, and software. Most critically, data are needed supporting improved clinical outcomes when treatment selection is based on these measures."

A joint expert consensus document from SNMMI/ASNC (2017) covered the role of Fluorine 18 fluorodeoxyglucose (18F-FDG) PET for cardiac sarcoidosis detection and therapy monitoring.(48) The document discusses the need to integrate multiple sources of data, including 18F-FDG PET in some cases, to diagnose cardiac sarcoidosis. The following outlines clinical scenarios where cardiac PET may be useful in patients with suspected or known disease. Associated levels of evidence and strength of recommendations were not provided with these scenarios.

- "Patients with histologic evidence of extra CS [extracardiac sarcoidosis], and abnormal screening for CS [cardiac sarcoidosis],defined as one or more of following:
  - Abnormal electrocardiographic findings of complete left or right bundle branch block or presence of unexplained pathologic Q waves in two or more leads
  - Echocardiographic findings of regional wall motion abnormality, wall aneurysm, basal septum thinning, or LVEF [left ventricular ejection fraction] ≤ 50%
  - Holter findings of sustained or non-sustained ventricular tachycardia
  - Cardiac MRI findings suggestive of CS
  - Unexplained palpitations or syncope
- Young patients (<60 y) with unexplained, new onset, significant conduction system disease (such as sustained second- or third-degree atrioventricular block)
- Patients with idiopathic sustained ventricular tachycardia, defined as not fulfilling any of the following criteria:
  - Typical outflow tract ventricular tachycardia
  - Fascicular ventricular tachycardia
  - Ventricular tachycardia secondary to other structural heart disease (coronary artery disease or any cardiomyopathy other than idiopathic)
- Patients with proven CS as adjunct to follow response to treatment"

In 2021, the ASNC/SNMMI published a guide for interpretation and reporting of MBF with cardiac PET MPI to encourage and assist clinicians in the implementation of this relatively new approach to evaluate patients with known or suspected CAD.(23) The guide notes that "MBF evaluation provides complementary information to MPI that adds considerably to the value of the testing procedure in the diagnosis and risk stratification of CAD and cardiac events."

Per this guide, the clinical value of MBF reserve for patients with known CAD is as follows:

- "Often abnormal after CABG, CAD history, myocardial infarction
- Cardiomyopathy less useful but if normal, helps exclude CAD
- Renal failure patients generally abnormal
- Post PCI may be abnormal, but most useful if pre-PCI data available
- Identify non-responder: all patients"

American College of Cardiology et al

The American College of Cardiology and American Heart Association (2009) collaborated with six other imaging societies to develop Appropriate Use Criteria for cardiac radionuclide imaging (RNI).(55) Their report stated:

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

In 2021, the ACC in collaboration with several other medical societies published a guideline on the evaluation and diagnosis of chest pain.(56) Per the guideline, after an acute coronary syndrome has been ruled out, PET or SPECT MPI allows for detection of perfusion abnormalities, measures of left ventricular function, and high-risk findings, such as transient ischemic dilation. The guideline goes on to state that: "For PET, calculation of myocardial blood flow reserve (MBFR, the ratio of peak hyperemia to resting myocardial blood flow) adds diagnostic and prognostic information over MPI data."

In 2023, the ACC and several other medical societies authored a guideline on management of chronic coronary disease.(57) The guideline recommends PET or SPECT MPI, cardiovascular magnetic resonance imaging, or stress echocardiography, in patients with chronic coronary disease and a change in symptoms or functional capacity despite guideline-directed medical therapy(strong recommendation, moderate quality evidence). This testing facilitates detection of myocardial ischemia, estimation of the risk of major cardiovascular events, and therapeutic decisions. Preference is given to PET (over SPECT) due to greater diagnostic accuracy.

American College of Radiology

The American College of Radiology (ACR) Appropriateness Criteria (2021) considers both SPECT and PET to be appropriate for the evaluation of patients with a high probability of CAD.(58) ACR indicated that PET perfusion imaging has advantages over SPECT, including higher spatial and temporal resolution. Routine performance of both PET and SPECT are unnecessary. The 2021 update stated:

> "Hybrid PET scanners use CT [computed tomography] for attenuation correction (PET/CT) following completion of the PET study. By coupling the PET perfusion examination findings to a CCTA [cardiac computed tomographic angiography], PET/CT permits the fusion of

anatomic coronary arterial and functional (perfusion) myocardial information and enhances diagnostic accuracy. The fused examinations can accurately measure the atherosclerotic burden and identify the hemodynamic functional significance of coronary stenosis. The results of the combined examinations can more accurately identify patients for revascularization."

The ACR Appropriateness Criteria (2018) also recommended PET for the evaluation of patients with chronic chest pain that is unlikely to be from a noncardiac etiology and low-to-intermediate probability of CAD.(59)

The ACR does not recommend PET for patients with acute nonspecific chest pain who have low probability of CAD (60) or for asymptomatic patients at risk for CAD.(61)

Society of Nuclear Medicine and Molecular Imaging, et al
In 2023, the SNMMI published an expert panel consensus document on PET myocardial perfusion imaging for coronary microvascular dysfunction.(62) The document recommends PET imaging to detect coronary microvascular dysfunction in patients with chest pain but no evidence of CAD. Several scenarios are described that can facilitate test interpretation and application to therapeutic decision-making.

A joint guidance from SNMMI/ACC/ASNC/AHA/Canadian Cardiovascular Society/Canadian Society of Cardiovascular Nuclear and CT Imaging/Society of Cardiovascular CT/American College of Physicians/European Association of Nuclear Medicine (2020) developed appropriate use criteria for PET myocardial perfusion imaging for the most common scenarios encountered.(63) The summary of recommendations for patients with suspected or known CAD with symptoms state that rest-stress PET myocardial perfusion imaging is appropriate for those with an intermediate-to-high pretest likelihood of disease regardless of whether the patient has a normal electrocardiogram result or can (or cannot) exercise. In ordering tests, both the diagnostic accuracy and prognostic value are considerations. In patients with a low pretest likelihood of disease, PET myocardial perfusion imaging is not appropriate. The document also stated: "[o]nly a few studies describe the effects of PET MPI [myocardial perfusion imaging] perfusion and flow quantification on the clinical decision-making process and clinical outcome, which thus warrants further evaluation in well-designed and large-scale clinical trials."

For the evaluation of patients with known or suspected cardiac sarcoidosis, "rest PET MPI [myocardial perfusion imaging] was rated by the experts as appropriate in patients undergoing assessment of myocardial inflammation with 18F-FDG PET at baseline and during reevaluation for response to therapy or recurrent inflammation.(63) In contrast, stress MPI was rated as may be appropriate in the evaluation of patients with suspected sarcoidosis who have not been previously evaluated for CAD, and as rarely appropriate inpatients with suspected sarcoidosis who have been previously evaluated for CAD."

American Thoracic Society
The American Thoracic Society (2020) published guideline recommendations on detection and diagnosis of sarcoidosis.(47) This guideline generally recommends cardiac MRI over PET or transthoracic echocardiography (TTE) for obtaining diagnostic or prognostic information in patients with sarcoidosis and potential cardiac involvement. In cases where cardiac MRI is unavailable or inconclusive, PET is recommended over TTE to obtain diagnostic or prognostic

information. Both of these recommendations are conditional and based on very low-quality evidence.

U.S. PREVENTIVE SERVICES TASK FORCE

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05634031	Development and Validation of a Non-invasive Algorithm for Diagnosis of Microvascular Angina Among Patients With Ischemia and Non-obstructive Coronary Artery Disease (IMAGING-CMD Study)	70	Dec 2024
NCT00756379	Randomized Trial of Comprehensive Lifestyle Modifications, Optimal Pharmacological Treatment and PET Imaging for Detection and Management of Stable Coronary Artery Disease	1085	Mar 2022
Unpublished			
NCT01288560	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)	1511	Jun 2022

NCT: national clinical trial.

Government Regulations
National:

Effective January 1, 2022, the Centers for Medicare & Medicaid Services removed the umbrella national coverage determination(NCD) for PET scans.(64) In the absence of an NCD, coverage determinations for all oncologic and non-oncologic uses of PET that are not included in another NCD under section 220.6 will be made by the Medicare Administrative Contractors under section1862(a)(1)(A) of the Social Security Act. All PET indications currently covered or non-covered under NCDs under section 220.6 remain unchanged and MACs shall not alter coverage for indications covered under NCDs.

PET for Perfusion of the Heart; Pub 100-3; v. 2; Manual Section Number. 220.6.1; Effective date: 4/3/09; Implemented: 10/30/09

Indications and Limitations of Coverage

Effective for services performed on or after March 14, 1995, PET scans performed at rest or with pharmacological stress used for noninvasive imaging of the perfusion of the heart for the diagnosis and management of patients with known or suspected coronary artery disease using the FDA-approved radiopharmaceutical Rubidium 82 (Rb 82) are covered, provided the requirements below are met:

- The PET scan, whether at rest alone, or rest with stress, is performed in place of, but not in addition to, a single photon emission computed tomography (SPECT); or

- The PET scan, whether at rest alone or rest with stress, is used following a SPECT that was found to be inconclusive. In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the patient. (For purposes of this requirement, an inconclusive test is a test(s) whose results are equivocal, technically uninterpretable, or discordant with a patient's other clinical data and must be documented in the beneficiary's file.)

FDG PET for Myocardial Viability; Pub 100-3; v. 1; Manual Section Number. 220.6.8; Effective date: 1/28/05; Implemented: 4/18/05

Indications and Limitations of Coverage

- FDG PET is covered for the determination of myocardial viability following an inconclusive single photon emission computed tomography (SPECT) test from July 1, 2001, through September 30, 2002. Only full ring PET scanners are covered from July 1, 2001, through December 31, 2001. However, as of January 1, 2002, full and partial ring scanners are covered.

- Beginning October 1, 2002, Medicare covers FDG PET for the determination of myocardial viability as a primary or initial diagnostic study prior to revascularization or following an inconclusive SPECT. Studies performed by full and partial ring scanners are covered.

Limitations: In the event a patient receives a SPECT test with inconclusive results, a PET scan may be covered. However, if a patient receives a FDG PET study with inconclusive results, a follow up SPECT test is not covered.

Documentation that these conditions are met should be maintained by the referring physician in the beneficiary's medical record, as is normal business practice.

(This NCD last reviewed September 2002.)

Local:

There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Computed Tomography to Detect Coronary Artery Calcification
- Contrast-Enhanced Computed Tomography Angiography of the Heart and/or Coronary Arteries (CTA, CCTA)
- Positron Emission Tomography (PET) Scans for Miscellaneous Applications
- Positron Emission Tomography (PET) Scans for Oncologic Applications

---

References

1. Centers for Disease Control and Prevention. Heart Disease Facts. Updated July 15, 2022. https://www.cdc.gov/heartdisease/facts.htm. Accessed August 29, 2022.
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.
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 1980; 65(5):1210-21.
4. Waller AH, Blankstein R, Kwong RY, et al. Myocardial blood flow quantification for evaluation of coronary artery disease by positron emission tomography, cardiac magnetic resonance imaging, and computed tomography. Curr Cardiol Rep. May 2014; 16(5): 483. PMID 24718671
5. Akaike G, Itani M, Shah H, et al. PET/CT in the Diagnosis and Workup of Sarcoidosis: Focus on Atypical Manifestations. Radiographics. Sep-Oct 2018; 38(5): 1536-1549. PMID 30118393
6. Food and Drug Administration (FDA). PET drugs - current good manufacturing practice (CGMP). 2009; https://www.fda.gov/downloads/drugs/guidances/ucm070306.pdf. Accessed August 4, 2022.
7. 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, 2022.
8. Food and Drug Administration (FDA). Guidance: Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs. 2012; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf. Accessed August 5, 2022.
9. 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 2007; 23(2):107-19.
10. Xu J, Cai F, Geng C, et al. Diagnostic Performance of CMR, SPECT, and PET Imaging for the Identification of Coronary Artery Disease: A Meta-Analysis. Front Cardiovasc Med. 2021; 8: 621389. PMID 34026862
11. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. Eur Heart J. May 29 2018. PMID 29850808
12. 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
13. 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
14. 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 2006; 13(1):24-33.
15. 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

16. 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
17. Knesaurek K, Machac J. Comparison of 18F SPECT with PET in myocardial imaging: a realistic thorax-cardiac phantom study. BMC Nucl Med 2006; 6:5.
18. 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 2005; 32(8):972-9.
19. 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
20. 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
21. 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 2001; 37(1):81-8.
22. Srivatsava MK, Indirani M, Sathyamurthy I, Sengottuvelu G, Jain AS, Shelley S. 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
23. Bateman TM, Heller GV, Beanlands R, et al. Practical guide for interpreting and reporting cardiac PET measurements of myocardial blood flow: an Information Statement from the American Society of Nuclear Cardiology, and the Society of Nuclear Medicine and Molecular Imaging. J Nucl Med. Mar 31 2021. PMID 33789935
24. 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.
25. 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 2010; 3(6):623-40.
26. Beanlands RS, Ziadi MC, Williams K. Quantification of myocardial flow reserve using positron emission imaging the journey to clinical use. J Am Coll Cardiol 2009; 54(2):157-9.
27. 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 2013; 62(18):1639-53.
28. Green R, Cantoni V, Acampa W, et al. Prognostic value of coronary flow reserve in patients with suspected or known coronary artery disease referred to PET myocardial perfusion imaging: A meta-analysis. J Nucl Cardiol. Jun2021; 28(3): 904-918. PMID 31875285
29. Juarez-Orozco LE, Tio RA, Alexanderson E, et al. Quantitative myocardial perfusion evaluation with positron emission tomography and the risk of cardiovascular events in patients with coronary artery disease: a systematic review of prognostic studies. Eur Heart J Cardiovasc Imaging. Dec 27 2017. PMID 29293983

30. Tio RA, Dabeshlim A, Siebelink HM, et al. Comparison between the prognostic value of left ventricular function and myocardial perfusion reserve in patients with ischemic heart disease. J Nucl Med. Feb 2009;50(2):214-219. PMID 19164219
31. 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 2011; 58(7):740-8.
32. Fukushima K, Javadi MS, Higuchi T, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. J Nucl Med. May 2011;52(5):726-732. PMID 21498538
33. Slart RH, Zeebregts CJ, Hillege HL, et al. Myocardial perfusion reserve after a PET-driven revascularization procedure: a strong prognostic factor. J Nucl Med. Jun 2011;52(6):873-879. PMID 21571798
34. Farhad H, Dunet V, Bachelard K, et al. Added prognostic value of myocardial blood flow quantitation in rubidium-82 positron emission tomography imaging. Eur Heart J Cardiovasc Imaging. Dec 2013;14(12):1203-1210. PMID 23660750
35. Maaniitty T, Stenstrom I, Bax JJ, et al. Prognostic value of coronary CT angiography with selective PET perfusion imaging in coronary artery disease. JACC Cardiovasc Imaging. Nov 2017;10(11):1361-1370. PMID 28528146
36. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. Circulation. Dec 12 2017;136(24):2325-2336. PMID 28864442
37. Murthy VL, Naya M, Foster CR et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation 2011; 124(20):2215-24. PMID 22007073
38. 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
39. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation. Jun 17 2014; 129(24): 2518-27. PMID 24787469
40. Majmudar MD, Murthy VL, Shah RV, et al. Quantification of coronary flow reserve in patients with ischaemic and non-ischaemic cardiomyopathy and its association with clinical outcomes. Eur Heart J Cardiovasc Imaging. Aug2015; 16(8): 900-9. PMID 25719181
41. Taqueti VR, Everett BM, Murthy VL, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation. Feb 10 2015;131(6): 528-35. PMID 25480813
42. Assante R, Acampa W, Zampella E, et al. Prognostic value of atherosclerotic burden and coronary vascular function in patients with suspected coronary artery disease. Eur J Nucl Med Mol Imaging. Dec 2017; 44(13): 2290-2298. PMID 28815291
43. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. Eur Heart J. Mar 07 2018; 39(10): 840-849. PMID 29293969
44. Gebhard C, Fiechter M, Herzog BA, et al. Sex differences in the long-term prognostic value of 13 N-ammonia myocardial perfusion positron emission tomography. Eur J Nucl Med Mol Imaging. Oct 2018; 45(11): 1964-1974.PMID 29779046

45. Gould KL, Kitkungvan D, Johnson NP, et al. Mortality Prediction by Quantitative PET Perfusion Expressed as Coronary Flow Capacity with and Without Revascularization. JACC Cardiovasc Imaging. May 2021; 14(5): 1020-1034. PMID 33221205
46. Patel KK, Spertus JA, Chan PS, et al. Myocardial blood flow reserve assessed by positron emission tomography myocardial perfusion imaging identifies patients with a survival benefit from early revascularization. Eur Heart J. Feb 01 2020; 41(6): 759-768. PMID 31228200
47. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. Apr 15 2020; 201(8): e26-e51. PMID 32293205
48. Chareonthaitawee P, Beanlands RS, Chen W, et al. Joint SNMMI-ASNC Expert Consensus Document on the Role of 18 F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring. J Nucl Med. Aug 2017; 58(8): 1341-1353. PMID 28765228
49. Aitken M, Chan MV, Urzua Fresno C, et al. Diagnostic Accuracy of Cardiac MRI versus FDG PET for Cardiac Sarcoidosis: A Systematic Review and Meta-Analysis. Radiology. Sep 2022; 304(3): 566-579. PMID 35579526
50. Kim SJ, Pak K, Kim K. Diagnostic performance of F-18 FDG PET for detection of cardiac sarcoidosis; A systematic review and meta-analysis. J Nucl Cardiol. Dec 2020; 27(6): 2103-2115. PMID 30603894
51. Wicks EC, Menezes LJ, Barnes A, et al. Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging. Jul 1 2018;19(7):757-767. PMID 29319785
52. 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
53. Dilsizian V, Bacharach SL, Beanlands RS, et al. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. J Nucl Cardiol. Oct 2016; 23(5): 1187-1226. PMID 27392702
54. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC. J Nucl Med. Feb 2018; 59(2): 273-293. PMID 29242396
55. 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
56. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. Nov 30 2021; 144(22): e368-e454. PMID 34709879
57. American College of Radiology (ACR). ACR Appropriateness Criteria: Chronic Chest Pain -- High Probability of Coronary Artery Disease. 2016; https://acsearch.acr.org/list. Accessed August 2, 2022.

58. American College of Radiology (ACR). ACR Appropriateness Criteria: Chronic Chest Pain - Noncardiac Etiology Unlikely: Low to Intermediate Probability of Coronary Artery Disease. 2018; https://acsearch.acr.org/list. Accessed August 3, 2022.
59. American College of Radiology (ACR). ACR Appropriateness Criteria: Acute Nonspecific Chest Pain--Low Probability of Coronary Artery Disease. 2020; https://acsearch.acr.org/list. Accessed August 5, 2022..
60. American College of Radiology (ACR). ACR Appropriateness Criteria: Asymptomatic Patient at Risk for Coronary Artery Disease. 2020; https://acsearch.acr.org/list. Accessed August 4, 2022.
61. Schindler TH, Bateman TM, Berman DS, et al. Appropriate Use Criteria for PET Myocardial Perfusion Imaging. J Nucl Med. Aug 2020; 61(8): 1221-1265. PMID 32747510
62. Centers for Medicare and Medicaid Services (CMS). Positron Emission Tomography (PET) Scans. 2022. Pub 100-3; Manual 220.6:v.6. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=211&ncdver=6&keyword=pet&keywordType=starts&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed September 20, 2023.
63. Centers for Medicare and Medicaid Services (CMS). PET for Perfusion of the Heart. 2009. Pub 100-3; Manual 220.6.1:v.1. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=292&ncdver=2&keyword=pet&keywordType=starts&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed September 20, 2023.
64. Centers for Medicare and Medicaid Services (CMS). FDG PET for Myocardial Viability. 2005. Pub 100-3; Man 220.6.8:v. 1. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=298&ncdver=1&keyword=pet&keywordType=starts&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed September 20, 2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/20/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/12	10/11/11	11/9/11	Joint policy established; PET scans for cardiac applications was separated out of the consolidated PET scan policy.
7/1/12	4/10/12	5/18/12	Clarified inclusionary criteria; changed criteria to read, “For patients for whom SPECT could be reasonably expected to be suboptimal in quality on the basis of body habitus. (e.g., BMI > 40), large breasts, breast implants, mastectomy, chest wall deformity, pleural or pericardial effusion)”.
3/1/14	12/10/13	1/6/14	Routine maintenance. No change in policy status.
9/1/15	6/19/15	7/16/15	Routine maintenance. References and rationale updated.
9/1/16	6/21/16	6/21/16	• Routine maintenance. • Added quantification of myocardial blood flow in patients with CAD to the exclusions.
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (slp) Vendor managed: Carelon
3/1/24	12/19/23		• Routine maintenance (slp) • Vendor managed: Carelon

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: PET SCANS FOR CARDIAC APPLICATIONS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.