



## FEP Medical Policy Manual

### FEP 6.01.20 Cardiac Applications of Positron Emission Tomography Scanning

**Effective Policy Date: January 1, 2023**

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**Related Policies:**

6.01.06 - Miscellaneous (Noncardiac, Nononcologic) Applications of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography

6.01.26 - Oncologic Applications of Positron Emission Tomography Scanning

6.01.51 - Interim Positron Emission Tomography Scanning in Oncology to Detect Early Response During Treatment

## Cardiac Applications of Positron Emission Tomography Scanning

### Description

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

#### OBJECTIVE

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

## POLICY STATEMENT

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

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

Cardiac PET scanning is **investigational** for quantification of myocardial blood flow for cardiac event risk stratification in individuals diagnosed with coronary artery disease.

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

## POLICY GUIDELINES

A positron emission tomography (PET) scan involves 3 separate activities: (1) manufacture of the radiopharmaceutical, which may be manufactured on site or at a regional center with delivery to the institution performing PET; (2) actual performance of the PET scan; and (3) interpretation of the results. The Current Procedural Terminology (CPT) codes and Healthcare Common Procedure Coding System (HCPCS) codes for PET scans are in the Codes table.

When the radiopharmaceutical is provided by an outside distribution center, there may be separate charge, or this charge may be passed through and included in the hospital bill. Also, there will likely be an additional transportation charge for radiopharmaceuticals not manufactured on site.

## BENEFIT APPLICATION

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

PET scans are considered most appropriate in patients with an intermediate-risk of CAD, typically defined as a 25% to 75% probability of having CAD. Clinically, this group of patients typically includes those with chest pain but without a history of myocardial infarction or stroke. Patients at either low- or high-risk of CAD may not require a myocardial perfusion study at all.

In most situations, PET and single-photon emission computed tomography scans provide equivalent diagnostic information. Therefore, Plans may want to consider if their benefits or contractual language supports a management strategy of having patients obtain single-photon emission computed tomography scans as an alternative to PET scans.

## FDA REGULATORY STATUS

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

PET radiopharmaceuticals have been evaluated and approved by 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 for PET drug manufacturers,<sup>6</sup> and in August 2011, the FDA issued similar Current Good Manufacturing Practice guidance for small businesses<sup>7</sup>. 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.<sup>8</sup>

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 1.

**Table 1. Radiopharmaceuticals Approved for Use Prior to 2012 With Positron Emission Tomography for Cardiac Indication<sup>a</sup>**

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.

<sup>a</sup>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.

## RATIONALE

### Summary of Evidence

For individuals with suspected coronary artery disease (CAD) and an indeterminate single photon emission computed tomography (SPECT) scan who receive cardiac positron emission tomography (PET) perfusion imaging, the evidence includes several systematic reviews and meta-analyses. Relevant outcomes are test accuracy, disease-specific survival, morbid events, and resource utilization. Meta-analyses of studies in which PET results were compared with results from coronary angiography and fractional flow reserve (FFR) have shown that PET is comparable in diagnostic accuracy to these referent standards. In meta-analyses of studies that included clinical outcomes such as mortality and adverse cardiac events, results have shown that PET is a useful prognostic tool. 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 (LV) dysfunction who are potential candidates for revascularization who receive cardiac PET scanning to assess myocardial viability, the evidence includes a large randomized controlled trial with long-term follow-up and several small trials comparing SPECT with PET. Relevant outcomes are test accuracy, disease-specific survival, and morbid events. In the large controlled trial, patients with LV dysfunction were randomized to care from physicians who would make management decisions based on PET images or to care from physicians who would make management decisions without PET images. 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 a 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 CAD who require myocardial blood flow (MBF) quantification for cardiac event risk stratification who receive quantitative cardiac PET perfusion imaging, the evidence includes observational studies and meta-analyses of those observational studies. Relevant outcomes are disease-specific survival and morbid events. Studies evaluating PET-derived quantitative MBF and myocardial flow reserve (MFR) have found that impaired MFR is significantly associated with an increase in all-cause mortality and can assist in identifying patients 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. 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 magnetic resonance imaging (MRI), the evidence includes nonrandomized studies and 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 MRI, are used during the clinician's assessment. Meta-analyses have found moderate sensitivity and specificity of fluorine 18-labeled fluorodeoxyglucose PET or PET/computed tomography 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, showing concordance between MRI and PET, but larger samples are needed to confirm the usefulness of these changes. While MRI is the technique most often used to evaluate cardiac sarcoidosis, for patients who are unable to undergo MRI (eg, patients with a metal implant), evidence supports PET scanning as the preferred test. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### 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.<sup>53</sup> 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 MBF.<sup>54</sup> Stress MBF and myocardial flow reserve (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 ASNC/SNMMI (2017) covered the role of Fluorine 18 fluorodeoxyglucose (F-18 FDG) PET for cardiac sarcoidosis detection and therapy monitoring.<sup>48</sup> The document discusses the need to integrate multiple sources of data, including F-18 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 extraCS [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 nonsustained 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.<sup>23</sup> 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 know 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 (ACC) Foundation and American Heart Association (AHA) (2009) collaborated with 6 other imaging societies to develop Appropriate Use Criteria for cardiac radionuclide imaging.<sup>55</sup> 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 medial societies published a guideline on the evaluation and diagnosis of chest pain.<sup>56</sup> 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."

## American College of Radiology

The American College of Radiology (ACR) Appropriateness Criteria ( 2021) considered both SPECT and PET to be appropriate for the evaluation of patients with a high probability of CAD.<sup>57</sup> The 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.<sup>58</sup>

The ACR does not recommend PET for patients with acute nonspecific chest pain who have a low probability of CAD<sup>59</sup>, or for asymptomatic patients at risk for CAD.<sup>60</sup>

## Society of Nuclear Medicine and Molecular Imaging, et al

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.<sup>61</sup> 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 <sup>18</sup>F-FDG PET at baseline and during reevaluation for response to therapy or recurrent inflammation.<sup>61</sup> 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 in patients 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.<sup>47</sup> 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 Recommendations

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

## Medicare National Coverage

Effective January 1, 2022, the Centers for Medicare & Medicaid Services removed the umbrella national coverage determination (NCD) for PET Scans.<sup>62</sup> 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 section 1862(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.

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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<b>Date</b>	<b>Action</b>	<b>Description</b>
December 2011	New policy	
December 2012	Replace policy	Policy updated with literature review, References updated. No change in policy statements.
September 2013	Replace policy	Policy updated with literature review, References 4, 11, 12, and 17 added and some reordered, No change in policy statements.
September 2014	Replace policy	Policy updated with literature review, adding references 1, 2, 4, 19, 24, and 25. No change to the policy statement
September 2015	Replace policy	Policy updated with literature review through June 24, 2015; references 8, 18-19, 23-24, and 27 added. Investigational policy statement added for quantification of myocardial blood flow in patients diagnosed with CAD. Policy statements otherwise unchanged.
December 2018	Replace policy	Policy updated with literature review through July 9, 2018; references 8, 28-29, 31-35, and 43 added. Policy statements unchanged except Cardiac PET scanning for quantification of myocardial blood flow policy statement corrected from "not medically necessary" to "investigational" due to FDA 510 clearance
December 2019	Replace policy	Policy updated with literature review through July 8, 2019; no references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through July 31, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through July 20, 2021; references added. Policy statements unchanged.
December 2022	Replace policy	Policy updated with literature review through August 5, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.

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