BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 6.01.20 Cardiac Applications of Positron Emission Tomography Scanning

### Annual Effective Policy Date: January 1, 2024

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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 (Genitourinary)
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 individuals 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 individuals who are unable to undergo magnetic resonance imaging include, but are not limited to, individuals 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,[6,] and in August 2011, the FDA issued similar Current Good Manufacturing Practice 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 1.

**Table 1. Radiopharmaceuticals Approved for Use Prior to 2012 With Positron Emission Tomography for Cardiac Indication[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.

# RATIONALE

## Summary of Evidence

For individuals with suspected coronary artery disease 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 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 controlled trial, patients with left ventricular dysfunction were randomized to care from physicians who would make management decisions based on PET images or to care from physicians who would make management decisions without PET images. 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 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-analyses 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 myocardial flow reserve 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 myocardial blood flow 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.[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 MBF.[54,] 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 ( 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 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.[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 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.[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 medial 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) considered both SPECT and PET to be appropriate for the evaluation of patients with a high probability of CAD.[58,] 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.[59,]

The ACR does not recommend PET for patients with acute nonspecific chest pain who have a 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 $^{18}$F-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 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.[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 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.[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 (MACs) 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.

# REFERENCES


1. Centers for Disease Control and Prevention. Heart Disease Facts. Updated May 15, 2023. Accessed August 7, 2023. https://www.cdc.gov/heartdisease/facts.htm
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. May 1980; 65(5): 1210-21. PMID 6767741
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. 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 5, 2023.
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 6, 2023.
8. Food and Drug Administration (FDA). Guidance: Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs. 2012; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf. Accessed August 7, 2023.
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. Feb 2007; 23(2): 107-19. PMID 17311116

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. Sep 14 2018; 39(35): 3322-3330. 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: 665-73. 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. PMID 16464714
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. Sep 01 2017; 18(9): 980-987. PMID 28329376
17. Kne<9a>aurek K, Machac J. Comparison of 18F SPECT with PET in myocardial imaging: a realistic thorax-cardiac phantom study. BMC Nucl Med. Oct 31 2006; 6: 5. PMID 17076890
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. Aug 2005; 32(8): 972-9. PMID 15824927
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): 2002-12. 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. Jan 2001; 37(1): 81-8. PMID 11153777
22. Srivatsava MK, Indirani M, Sathyamurthy I, et al. Role of PET-CT in the assessment of myocardial viability in patients with left ventricular dysfunction. Indian Heart J. 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. Nov 2021; 62(11): 1599-1615. 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 07 2009; 54(2): 150-6. PMID 19573732
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. Jun 2010; 3(6): 623-40. PMID 20541718
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. Jul 07 2009; 54(2): 157-9. PMID 19573733
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. Oct 29 2013; 62(18): 1639-1653. PMID 23954338
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. Jun 2021; 28(3): 904-918. PMID 31875285
29. Jurez-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. Oct 01 2018; 19(10): 1179-1187. 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): 214-9. 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. Aug 09 2011; 58(7): 740-8. PMID 21816311
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): 726-32. 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): 873-9. 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): 1203-10. PMID 23660750
35. Maaniitty T, Stenstrm 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. Nov 15 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 06 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. Aug 2015; 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 01 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): 2201-29. 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. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. Aug 29 2023; 82(9): 833-955. PMID 37480922
58. American College of Radiology (ACR). ACR Appropriateness Criteria: Chronic Chest Pain -- High Probability of Coronary Artery Disease. 2021; https://acsearch.acr.org/list. Accessed August 4, 2023.
59. 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 5, 2023.
60. 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 7, 2023.
61. American College of Radiology (ACR). ACR Appropriateness Criteria: Asymptomatic Patient at Risk for Coronary Artery Disease. 2020; https://acsearch.acr.org/list. Accessed August 6, 2023.
62. Schindler TH, Fearon WF, Pelletier-Galarneau M, et al. Myocardial Perfusion PET for the Detection and Reporting of Coronary Microvascular Dysfunction: A JACC: Cardiovascular Imaging Expert Panel Statement. JACC Cardiovasc Imaging. Apr 2023; 16(4): 536-548. PMID 36881418
63. 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
64. Centers for Medicare & Medicaid Services (CMS). Coverage and Related Claims Processing Requirements for Positron Emission Tomography (PET) Scans for Breast Cancer and Revised Coverage Conditions for Myocardial Viability. Transmittal AB-02-065. 2002;

https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=211&ncdver=5&bc=AAAAEAAAAQAA&. Accessed August 7, 2023.

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

| Date | Action | Description |
|---|---|---|
| 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. |
| December 2023 | Replace policy | Policy updated with literature review through July 28, 2023; references added. Minor editorial refinements to policy statements; intent unchanged. |