Coronary Computed Tomography Angiography With Selective Noninvasive Fractional Flow Reserve

Policy # 00537
Original Effective Date: 02/15/2017
Current Effective Date: 09/26/2020

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

Note: Positron Emission Tomography (PET) Cardiac Applications is addressed in medical policy 00103.

Note: Contrast-Enhanced Coronary Computed Tomography Angiography (CCTA) for Coronary Artery Evaluation is addressed in medical policy 00153.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of noninvasive fractional flow reserve (FFR) following a positive coronary computed tomography angiography (CCTA) to guide decisions about the use of invasive coronary angiography (ICA) in patients who meet coverage criteria for CCTA (as noted in medical policy 00153) to be **eligible for coverage.**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of noninvasive fractional flow reserve (FFR) not meeting the criteria outlined above is considered to be **investigational.***

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Policy Guidelines

Fractional flow reserve using coronary computed tomography angiography requires at least 64-slice coronary computed tomography angiography and cannot be calculated when images lack sufficient quality (HeartFlow, 2013)(11% to 13% in recent studies; Koo et al, 2011; Min et al, 2012; Nakazato et al, 2013; Nørgaard et al, 2014), eg, in obese individuals (eg, body mass index, >35 kg/m^2).The presence of dense arterial calcification or an intracoronary stent can produce significant beam-hardening artifacts and may preclude satisfactory imaging. The presence of an uncontrolled rapid heart rate or arrhythmia hinders the ability to obtain diagnostically satisfactory images. Evaluation of the distal coronary arteries is generally more difficult than visualization of the proximal and mid-segment coronary arteries due to greater cardiac motion and the smaller caliber of coronary vessels in distal locations.

Background/Overview

Stable Ischemic Heart Disease

Coronary artery disease (CAD) is a significant cause of morbidity and mortality. Various epidemiologic risk factors have been well studied. Evaluation of obstructive CAD involves quantifying arterial stenoses to determine whether significant narrowing is present. Lesions with stenosis more than 50% to 70% in diameter accompanied by symptoms are generally considered significant. It has been suggested that coronary computed tomography angiography (CCTA) or other noninvasive functional cardiac testing may help rule out CAD and avoid invasive coronary angiography (ICA) in patients with a low clinical likelihood of significant CAD. However, ICAs are frequently unnecessary in patients with suspected stable ischemic heart disease (SIHD), as evidenced by low diagnostic yields for significant obstructive CAD. Patel et al (2010) found that from a sample of over 132 000 ICAs, 48.8% of elective ICAs performed in patients with stable angina did not detect obstructive CAD (left main stenosis ≥50% or ≥70% in a major epicardial or branch >2.0 mm in diameter). ICA is clinically useful when patients with stable angina have failed optimal medical therapy and may benefit from revascularization. A noninvasive imaging test performed before ICA as a gatekeeper, which can distinguish candidates who may benefit from early revascularization (eg, patients with unprotected left main stenosis ≥50% or hemodynamically significant disease) from those unlikely to benefit, could avoid unnecessary invasive procedures and their potential adverse consequences. Moreover, for the large majority of patients with SIHD, revascularization offers no

survival advantage over medical therapy; few might benefit from ICA if they have not first failed optimal medical therapy.

Clinical Risk Prediction for Stable Ischemic Heart Disease
The 2012 collaborative medical association guidelines for the diagnosis and management of patients with stable heart disease list several class I recommendations on the use of noninvasive testing in patients with suspected SIHD. A class I recommendation indicates that a test should be performed. In general, patients with at least intermediate risk (10%-90% risk by standard risk prediction instruments) are recommended to have some type of test, the choice depending on the interpretability of the electrocardiogram, the capacity to exercise, and presence of comorbidity.

Clinical prediction scores or models have been developed to help estimate the pretest probability of CAD in individuals with stable chest pain. Diamond and Forrester (1979) developed the original version of a commonly cited clinical prediction model based on age, sex, and type of pain symptoms., Genders et al (2011) further studied and extended the model. Wasfy et al (2012) compared it to the Duke Clinical Score. Versteylen et al (2011) published a comparison of clinical prediction results for the Diamond and Forrester (1979) model, the Framingham risk score, the PROCAM risk score, and the SCORE risk estimation model. Min et al (2015) published another model, and in 2016 a COD consortium developed an online calculator.

Gatekeepers to Invasive Coronary Angiography
Imposing an effective noninvasive gatekeeper strategy with one or more tests before planned ICA to avoid unnecessary procedures is compelling. The most important characteristic of a gatekeeper test is its ability to accurately identify and exclude clinically insignificant disease where revascularization would offer no potential benefit. From a diagnostic perspective, an optimal strategy would result in few false-negative tests while avoiding an excessive false-positive rate—it would provide a low post-test probability of significant disease. Such a test would then have a small and precise negative likelihood ratio and high negative predictive value. An effective gatekeeper would decrease the rate of ICA while increasing the diagnostic yield (defined by the presence of obstructive CAD on ICA). At the same time, there should be no increase in major adverse cardiac events. A clinically useful strategy would satisfy these diagnostic performance characteristics and impact the outcomes of interest. Various tests have been proposed as potentially appropriate for a gatekeeper function before planned ICA, including CCTA, magnetic resonance imaging, single-photon

emission computed tomography, positron emission tomography, and stress echocardiography. More recently, adding noninvasive measurement of fractional flow reserve (FFR) using CCTA has been suggested, combining functional and anatomic information.

Fractional Flow Reserve
Invasively measured FFR evaluates the severity of ischemia caused by coronary artery obstructions and can predict when revascularization may be beneficial. FFR has not been used as a diagnostic test for ischemic heart disease, but as a test to evaluate the degree of ischemia caused by stenosis.

Invasive FFR is rarely used in the U. S. to guide percutaneous coronary intervention (PCI). Pothineni et al (2016), using the National Inpatient Sample, reported that 201 705 PCIs were performed in 2012, but just 21 365 FFR procedures. Assuming the intention of FFR is to guide PCI, it would represent just 4.3% of PCI procedures. Whether noninvasively obtained FFR will influence decisions concerning ICA, over and above anatomic considerations, is therefore important to establish empirically.

Randomized controlled trials and observational studies have demonstrated that FFR-guided revascularization can improve cardiovascular outcomes, reduce revascularizations, and decrease costs. For example, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation trial randomized 1005 patients with multivessel disease and planned PCI. At 1 year, compared with PCI guided by angiography alone, FFR-guided PCI reduced the number of stents placed by approximately 30%, followed by lower rates (13.2% vs. 18.3%) of major cardiovascular adverse events (myocardial infarction, death, repeat revascularization) and at a lower cost. The clinical benefit persisted through 2 years, although by 5 years, event rates were similar between groups.

European guidelines (2013) for stable CAD have recommended that FFR be used "to identify hemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available" (class Ia), and "[r]evascularization of stenoses with FFR <0.80 is recommended for patients with angina symptoms or a positive stress test." Other guidelines (2014) have recommended using "FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available" (class Ia recommendation). The U.S. guidelines (2012) have stated that an FFR of 0.80 or less provides level Ia evidence for revascularization for "significant stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy."

Also, the importance of FFR in decision making appears prominently in the 2017 appropriate use criteria for coronary revascularization in patients with SIHD.

Measuring FFR during ICA can be accomplished by passing a pressure-sensing guidewire across a stenosis. Coronary hyperemia (increased blood flow) is then induced and pressure distal and proximal to the stenosis is used to calculate flow across it. FFR is the ratio of flow in the presence of a stenosis to flow in its absence. FFR levels less than 0.75 to 0.80 are considered to represent significant ischemia while those 0.94 to 1.0 are considered normal. Measurement is valid in the presence of serial stenoses, is unaffected by collateral blood flow, and reproducibility is high. Potential complications include adverse events related to catheter use such as vessel wall damage (dissection); the time required to obtain FFR during a typical ICA is less than 10 minutes.

FFR using CCTA requires at least 64-slice CCTA and cannot be calculated when images lack sufficient quality (11% to 13% in recent studies), eg, in obese individuals (body mass index, >35 kg/m^2). The presence of dense arterial calcification or an intracoronary stent can produce significant beam-hardening artifacts and may preclude satisfactory imaging. The presence of an uncontrolled rapid heart rate or arrhythmia hinders the ability to obtain diagnostically satisfactory images. Evaluation of the distal coronary arteries is generally more difficult than the visualization of the proximal and mid-segment coronary arteries due to greater cardiac motion and the smaller caliber of coronary vessels in distal locations.

Noninvasive Fractional Flow Reserve Measurement
FFR can be modeled noninvasively using images obtained during CCTA. CCTA (HeartFlow software termed FFR_{CT}; Siemens cFFR). The process involves constructing a digital model of coronary anatomy and calculating FFR across the entire vascular tree using computational fluid dynamics. FFR using CCTA can also be used for "virtual stenting" to simulate how stent placement would be predicted to improve vessel flow.

Only HeartFlow FFR_{CT} software has been cleared by the U.S. Food and Drug Administration (FDA). Imaging analyses require transmitting data to a central location for analysis, taking 1 to 3 days to complete. Other prototype software is workstation-based with onsite analyses.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In November 2014, FFR_{CT} simulation software (HeartFlow) was cleared for marketing by the FDA through the de novo 510(k) process (class II, special controls; FDA product code: PJA). In January 2016, the FFR_{CT} v2.0 device was cleared through a subsequent 510(k) process.

HeartFlow FFR_{CT} post-processing software is cleared:

> "for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography [CT] DICOM [Digital Imaging and Communications in Medicine] data for clinically stable symptomatic patients with coronary artery disease. It provides FFRCT [fractional flow reserve using coronary computed tomography angiography], a mathematically derived quantity, computed from simulated pressure, velocity and blood flow information obtained from a 3D computer model generated from static coronary CT images. FFRCT analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis [FFR_{CT}] are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. The results of HeartFlow FFRCT are intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment."

Rationale/Source

Invasive coronary angiography (ICA) is clinically useful in stable ischemic heart disease when there is coronary artery obstruction that may benefit from revascularization. However, many individuals currently undergoing ICA will not benefit from revascularization. Therefore, if there are noninvasive alternatives to guide decisions about the use of ICA to spare individuals from unnecessary ICA, there is potential to improve health outcomes. Using noninvasive measurement of fractional flow reserve (FFR) as part of a noninvasive imaging strategy may be beneficial to avoid the need for ICA.

For individuals with stable chest pain at intermediate risk of coronary artery disease (ie, suspected or presumed stable ischemic heart disease) being considered for ICA who receive noninvasive FFR measurement following positive coronary computed tomography angiography (CCTA), the evidence includes both direct and indirect evidence: 2 meta-analyses on diagnostic performance; 1

prospective, multi-center nonrandomized comparative study; 1 prospective cohort; 2 retrospective cohort studies; and 1 study reporting changes in management associated with CCTA-based strategies with selective addition of FFR using CCTA (FFR-CT), and 1 randomized controlled trial comparing of CCTA alone with ICA. Relevant outcomes are test accuracy and validity, morbid events, quality of life, resource utilization, and treatment-related morbidity. The meta-analyses indicated that CCTA has high sensitivity but moderately low specificity for hemodynamically significant obstructive disease. There is direct evidence, provided by 2 prospective and 2 retrospective studies, that compares health outcomes observed during 90-day to 1-year follow-up for strategies using CCTA particularly in combination with selective FFR-CT with strategies using ICA or other noninvasive imaging tests. The available evidence provides support that use of CCTA with selective FFR-CT is likely to reduce the use of ICA in individuals with stable chest pain who are unlikely to benefit from revascularization by demonstrating the absence of functionally significant obstructive coronary artery disease. Also, the benefits are likely to outweigh potential harms because rates of revascularization for functionally significant obstructive coronary artery disease appear to be similar and treatment-related adverse events do not appear to increase following CCTA with a selective FFR-CT strategy. Moreover, given the available evidence that CCTA alone has been used to select patients to avoid ICA, the studies showing higher specificity of FFR-CT and lower negative likelihood ratio of FFR-CT compared with CCTA alone may be used to build a chain of evidence that CCTA with a selective FFR-CT strategy would likely lead to changes in management that would be expected to improve health outcomes by further limiting unnecessary ICA testing. While individual studies are noted to have specific methodologic limitations and some variation has been noted in the magnitude of benefit across studies, in aggregate the evidence provides reasonable support that the selective addition of FFR-CT following CCTA results in a meaningful improvement in the net health outcome. The evidence is sufficient to determine that the technology results in meaningful improvements in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

In 2017, the National Institute for Health and Care Excellence (NICE) endorsed fractional flow reserve using coronary computed tomography angiography (FFR-CT), with the following

conclusions: "The committee concluded that the evidence suggests that HeartFlow FFRCT is safe, has high diagnostic accuracy, and that its use may avoid the need for invasive investigations." Recommendations included:

- "The case for adopting HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy."
- "HeartFlow FFRCT should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA as part of the NICE pathway on chest pain. Using HeartFlow FFRCT may avoid the need for invasive coronary angiography and revascularization. For correct use, HeartFlow FFRCT requires access to 64-slice (or above) CCTA facilities."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
In January 2018, the Centers for Medicare & Medicaid Services assigned a new technology ambulatory payment classification to HeartFlow, making Medicare-enrolled hospitals eligible for reimbursement for the technology.

Ongoing Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 7

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02400229	Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease: Comparative Effectiveness Research of Existing Technologies) - A Pragmatic Randomised Controlled Trial of CT Versus ICA	3546	Apr 2021

NCT02973126	Assessment of Fractional Flow reservE Computed Tomography Versus Single Photon Emission Computed Tomography in the Diagnosis of Hemodynamically Significant Coronary Artery Disease. (AFFECTS)	270	Oct 2020
NCT02208388	Prospective Evaluation of MyocaRdial PerFUSion ComputEd Tomography Trial	1000	Apr 2024
Unpublished			
NCT02173275	Computed TomogRaphic Evaluation of Atherosclerotic DEtermiNants of Myocardial IsChEmia (The CREDENCE TRIAL)	618	Jan 2018 (updated 11/13/2019)

NCT: national clinical trial.

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10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Policy title changed from "Noninvasive fractional Flow reserve Using Computed Tomography Angiography" to "Coronary Computed Tomography Angiography With Selective Noninvasive Fractional Flow Reserve". Changed coverage from investigational to eligible for coverage for individuals with stable chest pain at intermediate risk of coronary artery disease being considered for invasive coronary angiography. "Positive" added before CCTA to more explicitly state that FFR-CT is intended for selective use following CCTA with positive results.
01/01/2018	Coding update
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2019	Coding update
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. Replaced "patients with stable chest pain at intermediate risk of coronary artery disease (CAD i.e., suspected or presumed stable ischemic heart disease [SIHD])" with "patients who meet coverage criteria for CCTA (as noted in medical policy 00153)" in the eligible for coverage statement.
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0501T, 0502T, 0503T, 0504T, 0523T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety,

effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

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

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.