Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/25**
(See policy history boxes for previous effective dates)

Title: Coronary Computed Tomography Angiography with Selective Noninvasive Fractional Flow Reserve (FFR_{CT})

Description/Background

Fractional Flow Reserve – Computed Tomography (FFR_{CT}) helps to assess and guide management of stable coronary artery disease with the ultimate goal of reducing the need for invasive intervention (i.e., percutaneous coronary catherizations). Using noninvasive computed tomography angiography (CTA), the technology known as fractional flow reserve (FFR) creates a complete geometric and physiologic model of the individuals unique coronary anatomy. Data from the non-invasive CTA is securely sent from the provider to the manufacturers software application. The manufacturer then builds a 3D model of the individuals unique coronary anatomy, calculates any blockages and simulates the effect on blood flow. The result is a color coded map of the coronary arteries showing the extent of any arterial narrowing and the extent of the disrupted blood flow. The reports aid qualified clinicians in their evaluation, assessment and treatment plan of coronary artery disease. Reports indicate FFR-CT has helped reduce the number of patients, with stable cardiac ischemia, who have been referred for unnecessary catheterization procedures.

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.

STABLE ISCHEMIC HEART DISEASE

Coronary artery disease (CAD) is a significant cause of morbidity and mortality and 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 in patients with a low clinical likelihood of significant CAD. However, invasive coronary angiographies (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).(1) ICA is clinically useful when patients with stable angina have failed optimal medical therapy and may benefit from revascularization. A noninvasive imaging test, performed prior to ICA as a gatekeeper, that can distinguish candidates who may benefit from early revascularization (e.g., 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; there are few who might benefit from ICA if they have not first failed optimal medical therapy.(2)

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 use of noninvasive testing in patients with suspected stable ischemic heart disease.(3) 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 interpretability of the electrocardiogram, capacity to exercise, and presence of comorbidity. In 2023, an updated collaborative medical association guideline for patients with chronic coronary disease was published to provide an update to and consolidate new evidence since the 2012 guideline for the diagnosis and management of patients with stable heart disease and the corresponding 2014 focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease.(68) A class 1 recommendation states that "in patients with chronic coronary disease, it is recommended that risk stratification incorporate all available information, including noninvasive, invasive, or both cardiovascular diagnostic testing results or use validated risk scores to classify patients as low (<1%), intermediate (1%-3%), or high (>3%) yearly risk for cardiovascular death or nonfatal myocardial infarction." The text further states that noninvasive test results alone are insufficient to adequately risk stratify patients with chronic coronary disease, and the additional information improves risk prediction.

Clinical prediction scores or models have been developed to help estimate the pre-test probability of coronary artery disease 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.(4) Genders et al (2011) further studied and extended the model.(5) Wasfy et al (2012) compared it to the Duke Clinical Score.(6) Versteylen et al (2011) published a comparison of clinical prediction results for the Diamond and Forrester model, the Framingham risk score, and the PROCAM risk score, and the SCORE risk estimation model.(7) Min et al (2015) published another model and in 2016 a COD consortium developed an online calculator.(9,10)

Gatekeepers to Invasive Coronary Angiography (ICA)

Imposing an effective noninvasive gatekeeper strategy with 1 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 posttest 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 prior to 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.(11-13) 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 a stenosis.

Invasive FFR is rarely used in the United States 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.(14) 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.(15) For example, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial randomized 1005 patients with multivessel disease and planned PCI.(13,16) At one 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 two years, although by five years events rates were similar between groups.(17)

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 in patients with angina symptoms or a positive stress test.”(18) A 2019 European guideline on chronic coronary syndromes recommends to "consider revascularization on top of medical therapy" in patients without evidence of ischaemia but with fractional flow reserve ≤0.80.(69) Other guidelines (2014) have also recommended using “FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available” (class 1a recommendation).(19) U.S. guidelines (2012) have stated that an FFR of 0.80 provides level 1a

evidence for revascularization for “significant stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy.”(3) A 2023 U.S guideline for patients with chronic coronary disease notes the following for patients with fractional flow reserve of 0.80 or less: "consideration of revascularization, antianginal therapy as per guidelines."(68) Also, the importance of FFR in decision making appears prominently in the 2017 appropriate use criteria for coronary revascularization in patients with SIHD.(20)

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,(21) and reproducibility is high.(22) 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 (23) (11% to 13% in recent studies [24-27]), e.g., in obese individuals (e.g., 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.

Noninvasive FFR Measurement
FFR can be modeled noninvasively using images obtained during CCTA (28) (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-CT can also be used for “virtual stenting” to simulate how stent placement would be predicted to improve vessel flow.(29)

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

Regulatory Status

In November 2014, FFR_{CT} simulation software (HeartFlow) was cleared for marketing by the U.S. Food and Drug Administration (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} postprocessing 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 FFR_{CT}, 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. FFR_{CT} 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 FFR_{CT} 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."

In April 2022, DeepVessel® FFR software (Keya Medical) received FDA approval through the 510(k) process.

DeepVessel FFR software is cleared:

> "for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography [CT] DICOM data for clinically stable symptomatic patients with coronary artery disease. It provides DVFFR (a CT-derived FFR measurement) computed from static coronary CTA images using deep learning neural networks that encode imaging, structural, and functional characteristics of coronary arteries through learning. DEEPVESSEL FFR analysis is intended to support the functional evaluation of coronary artery disease. The results of the analysis are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. DEEPVESSEL FFR results are intended to be used by qualified clinicians in conjunction with the with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment."

Medical Policy Statement

The use of noninvasive fractional flow reserve to guide decisions about the use of invasive coronary angiography in select individuals has been established. It is a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

Individuals must meet both criteria:

- Have stable chest pain
- Have intermediate risk of coronary artery disease (i.e., suspected or presumed stable ischemic heart disease) **AND**

Meet one of the following:

- Diagnosis of congestive heart failure/left ventricular dysfunction when all the following are met:
  - Left ventricular ejection fraction < 55%
  - Low to moderate coronary heart disease risk[a] **OR**

- Symptomatic[b] or asymptomatic individuals undergoing non-coronary surgery (including open and percutaneous valvular procedures or ascending aortic surgery)
    - All the pre-operative information can be obtained using cardiac CT **AND**
    - Moderate coronary heart disease risk[a] **OR**

- Symptomatic[b] individuals who are suspected of having coronary artery disease and meet **one** of the following:
    - During a planned outpatient exercise stress test (without imaging) **all** the following apply:
        - Performed within the past 60 days
        - Individual is symptomatic[b]
        - During the test **one** of the following occurred:
            - Exercise-induced chest pain
            - ST segment change
            - Abnormal blood pressure response
            - Complex ventricular arrhythmias **OR**
    - Have undergone either myocardial perfusion imaging or a stress echocardiogram within the past 60 days and imaging is **one** of the following:
        - Neither normal or abnormal
        - Abnormal **OR**
    - No coronary artery disease imaging has been performed within the preceding 60 days (i.e. Myocardial perfusion imaging, cardiac PET scan, stress echo or coronary angiogram)

- Symptomatic[b] individual with abnormal resting EKG
    - Exercise stress test (without imaging) would be uninterpretable related to one of the following:
        - Left bundle branch block
        - Paced ventricular rhythm
        - Left ventricular hypertrophy with repolarization abnormalities
        - Resting ST segment depression
            - ≥ 1 mm
        - Digoxin effects as evidence by one of the following:
            - ST depression in a concave shape
            - Flattened, inverted, or biphasic T waves
            - Shortened QT interval
        - Pre-excitation syndrome (i.e. Lown-Ganong-Levine Syndrome, Wolff-Parkinson-White Syndrome)
            - Short PR interval (< 0.12 sec)

*Fractional flow reserve using coronary tomography angiography requires at least 64-slice coronary computed tomography angiography and cannot be calculated when images lack sufficient quality

[a] Risk factor is determined using standard assessment methods (i.e., SCORE risk chart)
[b] Symptomatic is defined by one or more of the following:

- Chest pain with low probability of coronary artery disease, but high risk
- Moderate to high risk of coronary artery disease and one of the following:
    - Chest, jaw, neck, shoulder, arm, hand, epigastric or back pain
    - Diaphoresis
    - Syncope
    - Shortness of breath
- High risk of coronary artery disease and one of the following:
    - Palpitations
    - Lightheadedness
    - Near syncope
    - Nausea/vomiting
    - Anxiety
    - Weakness
    - Fatigue
- Individuals with any cardiac symptom who have <u>any</u> of the following diseases associated with coronary artery disease
    - Abdominal aortic aneurysm
    - Chronic renal insufficiency or renal failure
    - Diabetes mellitus
    - Established and symptomatic peripheral vascular disease
    - History of:
        - Cerebrovascular accident
        - Transient ischemic attack
        - Carotid endarterectomy
        - High grade carotid stenosis (>70%)

<u>Exclusions:</u>

- Assessment of coronary arteries for suspected congenital anomalies
- Individuals who have:
    - BMI > 35% kg/m^2
    - Presence of uncontrolled rapid heart rate or arrhythmia
    - Suspicion of acute coronary syndrome when acute myocardial infarction or unstable angina have not been ruled out
    - History of:
        - Myocardial infarction within the last 30 days)
        - Coronary artery bypass graft surgery
        - Presence of dense arterial calcification or intracoronary stent

- Evidence of clinical instability (i.e. unstable blood pressure – Systolic < 90 mmHg, severe congestive heart failure, acute pulmonary edema, cardiogenic shock)
- Individuals who require emergent procedures
- Individuals not meeting inclusionary guidelines

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

Established codes:

75574 75580

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

N/A

Rationale

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY WITH SELECTIVE NONINVASIVE FRACTIONAL FLOW RESERVE

Clinical Context and Test Purpose
The purpose of selective noninvasive fractional flow reserve (FFR) using coronary computed tomography angiography (CCTA; collectively FFR-CT) in individuals with stable chest pain who have suspected SIHD and who are being considered for ICA is to select individuals who may be managed safely with observation only, instead of undergoing ICA in the short term.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with stable chest pain at intermediate risk of CAD (i.e., with suspected or presumed SIHD) who are being considered for ICA. Individuals may have undergone prior noninvasive testing and been treated for presumed stable angina.

Interventions
The intervention of interest is CCTA with selective FFR-CT when CCTA shows evidence of coronary artery stenosis.

Comparators
The following tests are currently being used: CCTA and conventional noninvasive imaging tests. Patients may receive CCTA, which may be performed alone without FFR. They may proceed directly to ICA. Conventional noninvasive imaging tests providing functional information, including myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT), stress echocardiography (SECHO), and cardiac positron emission tomography (PET), may be used before ICA. Cardiovascular magnetic resonance imaging (MRI) is also an option.

Outcomes

The final outcomes of interest include ICA rates, ICA without obstructive CAD, major adverse cardiovascular events (MACE), and adverse events attributed to testing and treatment. Rates of ICA and treatment-related morbidity are typically short-term (e.g., ≤3 months). Also, rates of subsequent ICA, treatment-related morbidity, MACE, quality of life (QOL), and resource utilization ascertained over a period of one to three years are also of interest.

The intermediate outcome of interest is the ability of the test to distinguish clinically significant CAD for which revascularization may provide benefit.

Study Selection Criteria

For the evaluation of clinical validity of this test, studies that meet the following eligibility criteria were considered:

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

Clinically Valid

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

Review of Evidence

Meta-Analyses of Per-Patient Diagnostic Accuracy

Pontone et al (2020) conducted a meta-analysis of 77 studies that evaluated the accuracy of noninvasive cardiovascular imaging modalities.(54) Wu et al (2016) and Danad et al (2017) each had five studies contributing results to two meta-analyses that evaluated the diagnostic accuracy of fractional flow reserve measurement using CCTA with patients as the unit of analysis. Only the FDA-cleared HeartFlow software has been evaluated prospectively across multiple sites. Two small retrospective studies have reported per-patient performance characteristics for the prototype Siemens workstation-based software.(33-35) The three HeartFlow FFR_{CT} studies used successive software versions with reported improvement in specificity (from 54% to 79%) between versions 1.2 and 1.4.(24,27,36) The Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) Trial, the basis for device clearance by FDA, was conducted at 11 sites in eight countries (Canada, EU, Asia).(27) Although not examined in the two included meta-analyses, subgroup analyses suggested little variation in results by sex and age.(37) Effectively, the entirety of the data was obtained in patients of White or Asian decent; almost all patients were appropriate for testing according to FDA clearance.

Pontone et al (2020) performed a meta-analysis of 77 studies published through March 2017 that reported patient-level results of noninvasive imaging modalities in patients with stable CAD (either suspected or known), 7 of which were prospective studies that evaluated fractional flow reserve measurement using CCTA.(54) No heterogeneity was found among these 7 studies (I^2=0%). Per-patient and per-vessel meta-analyses were performed. Five of the 7

studies specific to fractional flow reserve measurement using CCTA reported per-patient results. The pooled per-patient results showed that fractional flow reserve measurement using CCTA had a high sensitivity and specificity (90% [*I*2=46.1%] and 69% [*I*2=88%],respectively). Among the other imaging modalities, both sensitivity and specificity were high for stress cardiac magnetic resonance (87% and 88%),PET (88% and 86%), and CCTA plus stress myocardial computed tomography perfusion (89% and 83%). Alone, CCTA had high sensitivity (93%) but poor specificity (42%). The other imaging modalities did not perform as well on a per-patient level (i.e., stress echocardiogram, stress SPECT, and stress myocardial computed tomography perfusion).

Danad et al (2017) included 23 studies published between January 2002 and February 2015 evaluating the diagnostic performance of CCTA, FFR-CT, SPECT, SECHO, MRI, or ICA compared with an invasive FFR reference standard.(32) The three included FFR-CT studies used the HeartFlow software and had performed FFR in at least 75% of patients. A cutoff of 0.75 defined significant stenosis in 8 (32%) studies and in the remainder 0.80 (the current standard used in all FFR-CT studies). Per-patient and per-vessel meta-analyses were performed. Study quality was assessed using QUADAS-2;(38) no significant biases were identified in FFR-CT studies but a high risk of biased patient selection was judged in 10 (43.4%) of the other studies. HeartFlow funded the Open Access publication; one author was a consultant to, and another a cofounder.

On the patient level, MRI had the highest combined sensitivity (90%) and specificity (94%) for invasive FFR, but these were estimated from only two studies (70 patients). FFR-CT had similar sensitivity, but lower specificity and, accordingly, a lower positive likelihood ratio than MRI. The negative likelihood ratios were low (lower is better) for both FFR-CT and MRI; however, the confidence interval is narrower for FFR-CT due to larger sample for FFR-CT. CCTA had a slightly higher negative likelihood ratio. Results for the per-vessel area under the summary receiver operating characteristic curve were similar except for CCTA, for which per-patient results were considerably worse (e.g., C statistic of 0.57 vs. 0.85). Reviewers noted heterogeneity in many estimates (e.g., CCTA sensitivity, I^2=80%). Finally, pooled results for some imaging tests included few studies (see Table 1 for detailed results).

Wu et al (2016) identified seven studies (833 patients, 1377 vessels) comparing FFR-CT with invasively measured FFR from searches of PubMed, Cochrane, EMBASE, Medion, and meeting abstracts through January 2016.(31) Studies included patients with established or suspected SIHD. In addition to the 3 FFR-CT studies pooled by Danad et al, one additional study using HeartFlow technique (44 patients; 48 vessels) and three additional studies (180 patients; 279 vessels) using Siemens cFFR software (not FDA approved or cleared) were identified. An invasive FFR cutoff of 0.80 was the reference standard in all studies. Per-patient results reported in five studies were pooled and are reported in Table 1. All studies were rated at low risk of bias and without applicability concerns using the QUADAS-2 tool.(38) Appropriate bivariate meta-analyses (accounting for correlated sensitivity and specificity) were used.

As expected given study overlap, FFR-CT performance characteristics were similar to those reported by Danad et al (2017), but with a slightly higher specificity (see Table 1). The pooled per-vessel C statistic was lower (0.86) than the per-patient result (0.90). No evidence of publication bias was detected, but the number of studies was too small to adequately assess. Reviewers noted that, in two studies, FFR-CT results were uninterpretable in 12.0% (27) and 8.2% (39) of participants.

An et al (2023) conducted a meta-analysis of machine learning-based methods of determining fractional flow reserve compared to invasive methods.(64) A total of 13 studies in patients with suspected or confirmed CAD were combined for the analysis. Characteristics of the studies were not provided, including the potential for bias, but the authors stated that none of the studies were "large sample size diagnostic performance studies". Machine learning fractional flow reserve had a lower sensitivity and higher specificity than invasive fractional flow determination (0.80 vs. 0.87; p<.01 and 0.86 vs. 0.35; p<.01, respectively). Heterogeneity for all assessments was high (I2, 57.12% to 94.52%) and the authors noted that machine learning methods differed among studies.

Table 1. Pooled Per-Patient Pooled Diagnostic Performance of Noninvasive Tests for Invasive FFR

Test	Studies	N	Sensitivity (95% CI), %	Specificity (95% CI), %	C	LR+ (95% CI)	LR- (95% CI)
Pontone et al (2020)[54],							
Stress echocardiography	7	361	64 (56 to 71)	84 (78 to 89)	NR	3.51 (2.53 to 4.87)	0.45 (0.35 to 0.57)
Stress SPECT	10	682	71 (66 to 76)	79 (74 to 83)	NR	2.94 (1.96 to 4.40)	0.42 (0.28 to 0.62)
PET	4	609	88 (83 to 92)	86 (82 to 89)	NR	6.35 (4.45 to 9.07)	0.13 (0.06 to 0.28)
Stress cardiac magnetic resonance	14	1085	87 (84 to 90)	88 (85 to 90)	NR	6.65 (5.30 to 8.34)	0.15 (0.12 to 0.19)
CCTA	14	1478	93 (91 to 95)	42 (39 to 46)	NR	1.72 (1.35 to 2.18)	0.17 (0.10 to 0.30)
Stress perfusion computed tomography	6	410	79 (73 to 84)	88 (82 to 92)	NR	5.15 (2.22 to 11.92)	026 (0.16 to 0.42)
Fractional flow reserve using CCTA	5	664	90 (86 to 94)	69 (64 to 74)	NR	2.68 (1.66 to 4.34)	0.16 (0.11 to 0.23)
CCTA + stress perfusion computed tomography	4	248	89 (84 to 94)	83 (74 to 90)	NR	4.72 (2.60 to 8.57)	0.13 (0.08 to 0.21)
Danad et al (2017)[32],							
MRI	2	70	90 (75 to 97)	94 (79 to 99)	0.94	10.3 (3.14 to 33.9)	0.12 (0.05 to 0.30)
Fractional flow reserve using CCTA	3	609	90 (85 to 93)	71 (65 to 75)	0.94	3.3 (1.78 to 6.25)	0.16 (0.11 to 0.23)
CCTA	4	694	90 (86 to 93)	39 (34 to 44)	0.57	1.5 (1.25 to 1.90)	0.22 (0.10 to 0.50)
Stress echocardiography	2	115	77 (61 to 88)	75 (63 to 85)	0.82	3.0 (1.94 to 4.65)	0.34 (0.17 to 0.66)
SPECT	3	110	70 (59 to 80)	78 (68 to 87)	0.79	3.4 (1.04 to 11.1)	0.40 (0.19 to 0.83)
ICA	2	954	69 (65 to 75)	67 (63 to 71)	0.75	2.5 (1.25 to 5.13)	0.46 (0.39 to 0.55)
Wu et al (2016)[31],							
Fractional flow reserve using CCTA	5	833	89 (85 to 93)	76 (64 to 84)	0.90	3.7 (2.41 to 5.61)	0.14 (0.09 to 0.21)
An et al (2023)[64],	13	NR			NR	5.8	0.22

Fractional flow reserve using machine learning			0.80 (0.76 to 0.83)	0.86 (0.79 to 0.91)			
Fractional flow reserve using invasive methods	12	NR	0.87 (0.84 to 0.90)	0.35 (0.28 to 0.43)	NR	1.3	0.36

CCTA: coronary computed tomography angiography; CI: confidence interval; FFR-CT: fractional flow reserve using coronary computed tomography angiography; ICA: invasive coronary angiography; LR: likelihood ratio; MRI: magnetic resonance imaging; PCT: perfusion computed tomography; PET: positron emission tomography; SECHO: stress echocardiography; SPECT: single-photon emission computed tomography.

Clinically Useful

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

Direct Evidence

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

Comparative Studies

PLATFORM Study

The Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource Impacts(PLATFORM) study compared diagnostic strategies with or without FFR-CT in patients with suspected stable angina but without known CAD.(42,43) The study was conducted at 11 EU sites (i.e., practices and ethnicities in the U.S. may differ from those in the EU). All testing was non-emergent. Patients were divided into 2 strata according whether the test planned prior to study enrollment was: (1) noninvasive or (2) ICA (the patient population of interest in this evidence review). Patients were enrolled in consecutive cohorts with the first cohort undergoing a usual care strategy followed by a second cohort provided CTA with FFR-CT performed when requested (recommended if stenoses ≥30% were identified). Follow-up was scheduled at 90 days and 6 and 12 months after entry (99.5% of patients had one-year follow-up data). Funding was provided by HeartFlow and multiple authors reported receiving fees, grants, and/or support from HeartFlow. Data analyses were performed by the Duke Clinical Research Institute.

ICA without obstructive disease (“no stenosis ≥ 50% by core laboratory quantitative analysis or invasive FFR < 0.80”) at 90 days was the primary end point in patients with planned invasive testing. Secondary end points included ICA without obstructive disease following planned noninvasive testing, and (1) MACE at one year defined as a composite of all-cause mortality, myocardial infarction (MI), and urgent revascularization and (2) MACE and vascular events within 14 days. Quality of life (QOL) was evaluated using the Seattle Angina Questionnaire, and EQ-5D (5-item and 100-point visual analog scale). CCTA studies were interpreted by site investigators; quantitative coronary angiography measurements were performed at a central laboratory, as was FFR-CT. Cumulative radiation was also assessed. A sample size of 380 patients in the invasive strata yielded a 90% power to detect a 50% decrease in the primary end point given a 30% event rate (ICA without obstructive disease) with a usual care strategy and a dropout rate up to 10%.

ICA was planned in 380 participants, of whom 193 (50.8%) had undergone prior noninvasive testing. The mean pretest probability in the planned ICA strata was approximately 50% (51.7% and 49.4% in the 2 groups). FFR-CT was requested in 134 patients and successfully obtained in 117 (87.3%) patients. At 90 days, 73.3% of those in the usual care group had no obstructive findings on ICA compared with 12.4% in the FFR-CT group based on core laboratory readings (56.7% and 9.3% based on site readings). The difference was similar in a propensity-matched analysis of a subset of participants (n=148 from each group, or 78% of the entire sample). Prior noninvasive testing did not appear associated with nonobstructive findings. MACE rates were low and did not differ between strategies. Mean level of radiation exposure though one year was also similar in the usual care group (10.4 mSv) and the planned ICA group (10.7 mSv). No differences in QOL were found between groups.(44)

Results of the PLATFORM study support the notion that, in patients with planned ICA, FFR-CT can decrease the rate of ICAs and unnecessary procedures (finding no significant obstructive disease) and that FFR-CT may provide clinically useful information to physicians and patients. Study limitations include a nonrandomized design; high rate of no obstructive disease with a usual care strategy (73.3%), which was higher than the 30% rate assumed in the sample size estimates; and a sample size that was small with respect to evaluating adverse cardiac events. Although finding a large effect in patients with planned invasive testing, the nonrandomized design limits causal inferences and certainty that the magnitude of effect. The propensity-matched analysis (in a matched subset) offers some reassurance, but the sample size was likely too small to provide robust results.

FORECAST Study

The Fractional FlOw Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST) study evaluated whether fractional flow reserve using CCTA improved economic and clinical outcomes as compared to standard care in 1400 patients with stable chest pain who presented to 11 rapid access chest pain clinics in the United Kingdom.(59)This open-label study randomly assigned patients to a usual care strategy based on clinical pathways (n=700) or an experimental strategy of CCTA with selective fractional flow reserve (n=700). In the usual care group, patients with a high pre-test likelihood of significant coronary disease could be referred for ICA, while those with an intermediate pre-test likelihood were referred for non-invasive evaluation, which could include stress testing and CCTA without fractional flow reserve. In the experimental group, all patients underwent CCTA as the initial test and were then selectively referred for fractional flow reserve if the CCTA demonstrated a stenosis of ≥40% in a coronary artery segment of diameter suitable for revascularization by either a coronary stent or coronary artery bypass graft surgery.

The primary endpoint of FORECAST was cardiovascular costs over 9 months of follow-up. (59) Secondary endpoints included assessments of quality of life, angina status, and major adverse cardiac and cerebrovascular events (MACCE). In the standard care group, 439 (63%) underwent CCTA as the initial test, 187 (27%) had an initial stress test, and 47 (7%) underwent ICA. In the experimental group, 674 (96%) underwent CCTA and 254(38%) were selected for a fractional flow reserve analysis per protocol with 5 additional patients referred for fractional flow reserve who did not meet protocol criteria. Of these 259 patients, 220 had fractional flow reserve performed; 39 patients had technical issues resulting in scans that could not be analyzed. Mean total cardiac costs at 9 months of follow-up were slightly higher in the

experimental versus standard care group; however, the difference in mean costs was not significant (p=.10). For the major secondary endpoints, no significant differences between the groups were noted: improvement in quality of life (p=.61), improvement in angina severity (p=.22), and MACCE occurrence (p=.80). The experimental strategy was associated with a significant reduction in ICA (19% vs. 25%; p=.01). Limitations of this study include its open-label design, costs were based on UK National Health Service cost tariffs and therefore may not be generalizable to other countries, and the precise rate of CCTA in the standard arm could not be anticipated as national guidelines were revised during the planning stage of the FORECAST study.

TARGET Study

The TARGET RCT (Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision Making for Patients With Stable Chest Pain) evaluated the clinical and economic effect of on-site CCTA fractional flow reserve using machine learning in patients with stable coronary artery disease and an intermediate stenosis on CCTA.(70) The study took place at 6 tertiary hospitals across China. Enrolled patients had an intermediate to high pretest probability of obstructive CAD and a CCTA demonstrating stenosis ranging from 30% to 90% in ≥1 major coronary artery. Patients were randomly assigned to the CCTA fractional flow reserve care group (n=608) (guideline-directed medical therapy or ICA guided by on-site CCTA fractional flow reserve) or the usual care group (n=608) (guideline-directed medical therapy or ICA guided by stress tests). The DEEPVESSEL device, which simulates fractional flow reserve values using a deep learning algorithm, was used for patients in the CCTA fractional flow reserve care group. If the CCTA fractional flow reserve was ≤0.80 in 1 or more major coronary arteries, the patient was referred directly for ICA; if the CCTA fractional flow reserve was >0.80, optimal medical therapy was recommended.

The primary outcome was the proportion of patients undergoing ICA without obstructive CAD or with obstructive CAD who did not undergo intervention (balloon dilatation, stent implantation, or coronary artery bypass surgery) within 90 days.(70) Obstructive CAD was defined as "1 or more stenoses ≥70% on quantitative coronary analysis in a core laboratory or an invasive fractional flow reserve ≤0.80, if available during the procedure." Secondary outcomes included MACE (hospitalization for unstable angina, revascularization after 90 days, nonfatal myocardial infarction, or cardiovascular death), quality of life, symptoms of angina, and overall medical expenditure during follow-up to 1 year.

Results demonstrated that 69.2% (421/608) of patients in the CCTA fractional flow reserve care group and 79.4% (483/608) of patients in the standard care group underwent ICA.(70) The use of CCTA fractional flow reserve significantly reduced the proportion of patients undergoing ICA without obstructive CAD or with obstructive CAD not undergoing intervention, when compared to usual care (28.3% [119/421] vs 46.2% [223/483]; p<.001). Results were driven by a reduction in the proportion of patients undergoing ICA without obstructive CAD in the CCTA fractional flow reserve care group (20.9% [88/421]) compared with the usual care group (38.0% [184/483]). There were no statistically significant differences between treatment groups for key secondary outcomes at 1 year follow up, including MACE, quality of life and angina scores measured using the Seattle Angina Questionnaire-7, and costs. However, overall revascularization rates were increased in the CCTA fractional flow reserve care group when compared to usual care (49.7% [302/608] vs 42.8% [260/608]; p=.02). Authors stated that on-site CCTA fractional flow reserve can improve the selection of patients for ICA by identifying those who are more likely to have obstructive CAD suitable for revascularization.

Prospective Cohort Studies

Jensen et al (2018) reported on a single-institution study of 774 consecutive individuals with suspicion of CAD referred for nonemergent ICA or CCTA.(46) Subjects were analyzed in two groups: a low-intermediate-risk group accounting for 76% of patients with mean pretest probability of CAD 31% and a high-risk group accounting for 24% of patients with mean pretest probability of CAD 67%. Among the 745 who received CCTA, FFR-CT was selectively ordered in 28% of patients overall (23% in the low-intermediate-risk group, 41% in the high-risk group). CCTA was considered inconclusive in 3% of subjects and among those with conclusive CCTA, FFR-CT yielded few inconclusive results, with less than 3% of cases. During a minimum 90-day follow-up, the combined testing strategy of selective FFR-CT following CCTA resulted in avoiding ICA in 91% of low-intermediate-risk and 75% of high-risk individuals. None of the patients who avoided ICA based on CCTA with selective FFR-CT were associated with serious clinical adverse events over an average of 157 days of follow-up.

Wang et al (2019) conducted a single-center prospective cohort study of the diagnostic accuracy of the DeepVessel FFR platform.(65) In 63 patients who underwent CCTA, the deep learning software was compared to wire-based (invasive) FFR. DeepVessel FFR had a higher diagnostic performance as assessed by area under the receiver-operation characteristics curve (0.928) compared to wire-based FFR (0.664). DeepVessel FFR had a sensitivity, specificity, positive predictive value, and negative predictive value of 97.14%, 75%, 82.93%, and 95.45%, respectively.

Nous et al (2020) conducted an observational study of patients with suspected CAD who were enrolled in the randomized Computed Tomography vFlins. Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) I and II trials.(66) The analysis included patients with evidence of ≥50% stenosis on CCTA (N=53) who lacked contraindications to the procedure and therefore underwent machine learning fractional flow reserve measurement using CCTA (n=42). Hemodynamically significant stenosis (≤0.8) was identified in 27 of 53 patients (51%) using fractional flow reserve measurement using CCTA. The proportion of patients who required additional testing (37/53 with CCTA alone) would have been significantly less with fractional flow reserve measurement using CCTA (7/53; p<.001) and ICA would have been avoided in 13% of patients within 6 to 12 months of follow-up (p=.016). Fractional flow reserve measurement using CCTA would have changed the initial management strategy in 57% of patients (p<.001). Specifically, 17 patients would have avoided additional testing, 6 patients would have avoided revascularization, and 7 patients would have received revascularization instead of additional testing.

Qiao et al (2022) conducted a prospective, single-center, nonrandomized cohort study in patients with suspected CAD.(67) Patients received either CCTA alone (n=567) or fractional flow reserve measurement using CCTA (n=566). The primary outcome of interest, ICA that showed nonobstructive disease at 90 days, occurred in 33.3% of the CCTA alone group and 19.8% of the fractional flow reserve group (risk difference, 13.5%; 95% CI, 8.4% to 18.6%; p=.03). ICA was utilized more frequently in the CCTA alone group than the fractional flow reserve group (27.5% vs. 20.3%; p=.003). At 1 year, MACE was more common in the CCTA alone group compared to the fractional flow reserve group (6.7% vs. 3.9%; hazard ratio [HR], 1.73; 95% CI, 1.01 to 2.95; p=.04).

Retrospective Cohort

Norgaard et al (2017) reported on results from symptomatic patients referred for CCTA at a single center in Denmark from May 2014 to April 2015.(47) All data were obtained from medical records and registries; the study was described as a “review” of diagnostic evaluations and was retrospectively conducted. Follow-up through six to 18 months was ascertained. From 1248 referred patients, 1173 underwent CCTA; 858 received medical therapy, 82 underwent ICA, 44 MPI, and 189 FFR-CT (185 [98%] obtained successfully). Of the 185 individuals who successfully obtained FFR-CT, FFR-CT demonstrated values of 0.80 or less in 1 or more vessels in 57 (31%) patients and 49 (86%) went on to ICA; whereas of the 128 with higher FFR-CT values, only 5 (4%) went on to ICA. Assuming ICA was planned for all patients undergoing FFR-CT, these results are consistent with FFR-CT being able to decrease the rate of ICA. However, implications are limited by the retrospective design, performance at a single center, and lack of a comparator arm including one for CCTA alone.

Lu et al (2017) retrospectively examined a subgroup referred to ICA (48) from the completed PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. PROMISE was a pragmatic trial comparing CCTA with functional testing for the initial evaluation of patients with suspected SIHD.(49) Of 550 participants referred to ICA within 90 days, 279 were not considered for the analyses due to CCTA performed without nitroglycerin (n=139), CCTA not meeting slice thickness guidelines (n=90), or nondiagnostic studies (n=50). Of the remaining 271 patients, 90 scans were inadequate to obtain FFR-CT, leaving 181 (33%) of those referred to ICA for analysis. Compared with those excluded, patients in the analytic sample were less often obese, hypertensive, diabetic, minority, or reported a CAD equivalent symptom. The two groups had similar pretest probabilities of disease, revascularization rates, and MACE, but the distribution of stenoses in the analytic sample tended to be milder (p=0.06). FFR-CT studies were performed in a blinded manner and not available during the conduct of PROMISE for decision making.

Severe stenoses (≥70%) or left main disease (≥50%) were present in 110 (66%) patients by CCTA result and in 54% by ICA. Over a 29-month median follow-up, MACE (death, nonfatal MI, hospitalization for unstable angina) or revascularization occurred in 51% of patients (9% MACE, 49% revascularization). A majority (72%) of the sample had at least one vessel with an FFR-CT ≤0.80, which was also associated with a higher risk of revascularization but with a wide confidence interval (HR = 5.1; 95% CI, 2.6 to 11.5). If reserved for patients with an FFR-CT of 0.80 or less, ICAs might have been avoided in 50 patients (i.e., reduced by 28%) and the rate of ICA without 50% or more stenosis from 27% (calculated 95% CI, 21% to 34%) to 15% (calculated 95% CI, 10% to 23%). If the 90 patients whose images were sent for FFR-CT but were unsatisfactory proceeded to ICA—as would have occurred in practice—the rate of ICA might have decreased by 18% and ICA without significant stenosis from 31% to 25%.
The authors suggested that when CCTA is used as the initial evaluation for patients with suspected SIHD, adding FFR-CT could have decreased the referral rate to ICA in PROMISE from 12.2% to 9.5%, or close to the 8.1% rate observed in the PROMISE functional testing arm. They also noted similarity of their findings to PLATFORM and concluded, “In this hypothesis-generating study of patients with stable chest pain referred to ICA after [C]CTA, we found that adding FFR_{CT} may improve the efficiency of referral to ICA, addressing a major concern of an anatomic [C]CTA strategy. FFR_{CT} has incremental value over anatomic [C]CTA in predicting revascularization or major adverse cardiovascular events.”

This retrospective observational subgroup analysis from PROMISE would suggest that when CCTA is the initial noninvasive test for the evaluation of suspected SIHD, FFR-CT before ICA has the potential to reduce unnecessary ICAs and increase the diagnostic yield. However,

study limitations and potential generalizability are important to consider. First, analyses included only a third of CCTA patients referred to ICA and some characteristics of the excluded group differed from the analytic sample. Second, conclusions assume that an FFR-CT greater than 0.80 will always dissuade a physician from recommending ICA and even in the presence of severe stenosis (e.g., ≥70% in any vessel or ≥50% in the left main), or almost half (46%) of patients with an FFR-CT greater than 0.80. Finally, estimates including patients with either nondiagnostic CCTA studies (n=50) or studies inadequate for calculating FFR-CT (n=90) are more appropriate because in practice those patients would most likely proceed to ICA. Accordingly, the estimates are appropriately considered upper bounds for what might be seen in practice. It is also important to note that in strata of the PLATFORM trial enrolling patients for initial noninvasive testing (not planned ICA), ICA was more common following CCTA and contingent FFR-CT than following usual care (18.3% vs. 12.0%) and ICA, with no obstructive disease more frequent in the FFR-CT arm (12.5% vs. 6.0%).

Qiao et al (2020) conducted a single-center retrospective study of 1121 patients who underwent CCTA followed by ICA within 90 days for evaluation of chest pain between January 2007 and December 2016. (60) Fractional flow reserve measurement using CCTA was calculated using a machine learning algorithm. Discordant fractional flow reserve findings between CCTA and ICA were found in 16.4% of patients. After the fractional flow reserve results were known, the management plan was changed in 167 patients (14.9%). Among patients who were treated with optimal medical therapy, 22.6% were reassigned to revascularization. Revascularization was avoided in 8.7% of patients. The overall rate of MACE was10.2%. During the median follow-up of 26 months (range, 4 to 48 months), the occurrence of MACE was associated with fractional flow reserve ≤0.8 (hazard ratio, 6.84; 95% CI, 3.57 to 13.11; p<.001). Availability of fractional flow reserve using CCTA information could have reduced the rate of ICA from 100% to 45.5% and decreased the number of PCIs by 4.4%.

Yang et al (2021) conducted a single-center retrospective study between January 2006 and December 2017 in patients with suspected or known CAD. (61) All patients had received at least 2 CCTAs separated by at least 1 year with no MACE events in the interim. Machine learning fractional flow reserve measurement using CCTA datasets were available for 284 patients. Within a median follow-up of 4 years after the final CCTA, MACE (defined as acute coronary syndrome, rehospitalization, PCI, or death from cardiovascular causes), occurred in 45 patients. Both lesion-specific(p=.02) and vessel-specific (p<.001) fractional flow reserve measurement using CCTA were lower in vessels in individuals who experienced MACE than individuals who did not experience MACE. A multivariable analysis found that vessel-specific functional flow reserve measurement using CCTA ≤0.8 (hazard ratio, 2.4; 95% CI, 1.3 to 4.4; p=.005) was a predictor for MACE, along with several other parameters (i.e., plaque progression, elevated coronary artery calcium, and the presence of a high risk plaque). Fractional flow reserve measurement using CCTA ≤0.8 significantly increased the rate of MACE in a time to event analysis (p<.001).

Liu et al (2021) retrospectively studied 296 patients with CAD and ≥50% stenosis on CCTA performed between January 2014 and December2016. (62) All patients underwent ICA; machine learning fractional flow reserve measurement using DeepVessel FFR software was done retrospectively. After 2 years of follow-up, 72% of ICA procedures could have been avoided. Rates of MACE were similar among patients who underwent revascularization regardless of imaging modality (2.9% and 3.3%; p=.838).

The ADVANCE Registry Case Series

Patel et al (2020) conducted a registry study on the one-year medical practice and clinical outcomes of FFRCT for patients in the international Assessing Diagnostic Value of Non-Invasive FFRCT in Coronary Care (ADVANCE) registry.(50) Patients suspected of having CAD and with atherosclerosis identified by CCTA (N=5083 from 38 international sites) were prospectively enrolled in the registry from July 15, 2015 to October 20, 2017. Investigators recorded demographics, symptoms, CCTA and FFRCT findings, treatment plans, and clinical outcomes through one year, and these were then adjudicated by a blinded central laboratory. At one year, investigators had follow-up data from 4737 (93.2%) patients with FFRCT. Outcomes, detailed in Table 4, were revascularization, major adverse cardiac events, and time to first event (all cause death or MI), and time to first event (cardiovascular death or MI). The one-year outcomes showed low event rates in all patients; lower major adverse cardiac events and significantly lower cardiovascular death or MI were found in patients with an FFRCT >0.80 (negative) compared with those with positive (abnormal) FFRCT.

Table 2. 1-Year Outcomes From the ADVANCE Registry (N=4,634)

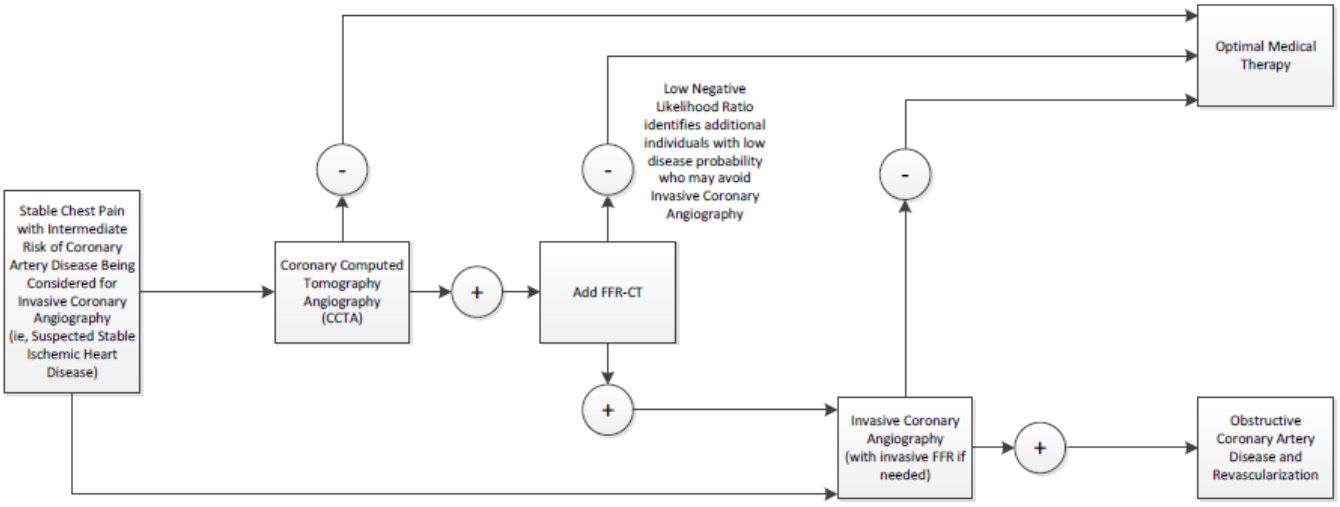
	Revascularization	**MACE**	**Time to First Event**	
			All-Cause death or MI	***Cardiovascular death or MI***
FFR_{CT} ≤ 0.80 n=3145, 66.39%	n=1208 (38.40%)	n=43 (1.37%)	n=38 (1.20%)	n=25 (0.80%)
FFRCT > 0.80 (n=1592, 33.6%)	n=89 (5.60%)	n=12 (0.75%)	n=10 (0.60%)	n=3 (0.20%)
RR	6.8	1.81	1.92	4.22
95% CI	5.59-8.45	0.96-3.43	0.96-3.85	1.28-13.95
p-value	< 0.001	0.06	0.06	0.01

Source: Patel et al (2020)(50),
CI: confidence interval; FFR_{CT}: fractional flow reserve derived from coronary computed tomography angiography; MACE: major adverse cardiac events; MI: myocardial infarction; RR: relative risk.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Diagnostic performance can offer indirect evidence of clinical utility, assuming providers act according to a test result. As previously noted, an effective gatekeeper strategy must be able to decrease the probability of disease (rule out) sufficiently that a planned ICA would not be performed. Ruling out the disease is a function of the negative likelihood ratio that defines the degree to which a negative test decreases the posttest odds (and probability) of disease. The steps in the logic are illustrated in Figure 1.

Figure 1. Pathway for Clinical Use of FFR-CT to Support Clinical Utility



FFR-CT: fractional flow reserve using coronary computed tomography angiography.

Table 3 illustrates how a negative test would lower the probability of a hemodynamically significant obstruction from pretest probabilities of 0.25, 0.50, or 0.75 for the various tests examined in the meta-analyses. For example, according to the results of Danad et al, if the pretest probability was 0.50, following a negative CCTA study the posttest probability would be 0.18. In contrast, beginning with a pretest probability of 0.50, a negative FFR-CT would yield a posttest probability of 0.14 (Danad et al [2017]) and 0.12 (Wu et al [2016]). Overall, the negative likelihood ratios and posttest probability estimates for FFR-CT are slightly better than CCTA as well as SECHO and SPECT.

Table 3. Change in Disease Probability Following a Negative Test

Study	Modality	Negative LR (95% CI)	Pretest Probability 0.25	Pretest Probability 0.50	Pretest Probability 0.75
Danad et al (2017)[32]					
	MRI	0.12 (0.05 to 0.30)	0.04 (0.02 to 0.09)	0.11 (0.05 to 0.23)	0.26 (0.13 to 0.47)
	FFR-CT	0.16 (0.11 to 0.23)	0.05 (0.04 to 0.07)	0.14 (0.10 to 0.19)	0.32 (0.25 to 0.41)
	CCTA	0.22 (0.10 to 0.50)	0.07 (0.03 to 0.14)	0.18 (0.09 to 0.33)	0.40 (0.23 to 0.60)
	SECHO	0.34 (0.17 to 0.66)	0.10 (0.05 to 0.18)	0.25 (0.15 to 0.40)	0.50 (0.34 to 0.66)
	SPECT	0.40 (0.19 to 0.83)	0.12 (0.06 to 0.22)	0.29 (0.16 to 0.45)	0.55 (0.36 to 0.71)
	ICA	0.46 (0.39 to 0.55)	0.13 (0.12 to 0.15)	0.32 (0.28 to 0.35)	0.58 (0.54 to 0.62)
Wu et al (2016)[31.]					
	FFR-CT	0.14 (0.09 to 0.21)	0.04 (0.03 to 0.07)	0.12 (0.08 to 0.17)	0.30 (0.21 to 0.39)
Takx et al (2015)[30.]					
	MRI	0.14 (0.10 to 0.18)	0.04 (0.03 to 0.06)	0.12 (0.09 to 0.15)	0.30 (0.23 to 0.35)
	Perfusion CT	0.12 (0.04 to 0.33)	0.04 (0.01 to 0.10)	0.11 (0.04 to 0.25)	0.26 (0.11 to 0.50)
	SECHO	0.42 (0.30 to 0.59)	0.12 (0.09 to 0.16)	0.30 (0.23 to 0.37)	0.56 (0.47 to 0.64)
	SPECT	0.39 (0.27 to 0.55)	0.12 (0.08 to 0.15)	0.28 (0.21 to 0.35)	0.54 (0.45 to 0.62)
	PET	0.14 (0.02 to 0.87)	0.04 (0.01 to 0.22)	0.12 (0.02 to 0.47)	0.30 (0.06 to 0.72)

CCTA: coronary computed tomography angiography; CI: confidence interval; CT: computed tomography; FFR-CT: fractional flow reserve using coronary computed tomography angiography; ICA: invasive coronary angiography; LR: likelihood ratio; MRI: magnetic resonance imaging; PET: positron emission tomography; SECHO: stress echocardiography; SPECT: single-photon emission computed tomography.

Curzen et al 2016 conducted a literature search that identified one study that examined 200 consecutive individuals selected from the NXT trial population “to reproduce the methodology

of the invasive RIPCORD study" with the elective management of stable chest pain.(51) All subjects received CCTA including FFR-CT "in at least one vessel with diameter ≥ 2 mm and diameter stenosis ≥ 30%" as well as ICA within 60 days of CCTA. Three experienced interventional cardiologists reviewed the CCTA results (initially without the FFR-CT results) and selected a management plan from the following four options: one) optimal medical therapy (OMT) alone; two) PCI + OMT; three) coronary artery bypass graft + OMT; or four) more information about ischemia required – they committed to option one by consensus. Following the initial decision, results from the FFR-CT were shared with the same group of interventional cardiologists who again decided by consensus based on the same 4 options. A cutoff of 0.80 or less was considered significant on FFR-CT. A stenosis was considered significant on CCTA or ICA with 50% or more diameter narrowing. Change in management between the first decision based on CCTA only and the second decision based on CCTA plus FFR-CT was the primary end point of this study. Secondary end points included analysis of the vessels considered to have significant stenosis based on CCTA alone vs CCTA plus FFR-CT as well as vessels identified as targets for revascularization based on CCTA alone vs CCTA plus FFR-CT. This study was conducted by investigators in the United Kingdom and Denmark. Funding was provided by HeartFlow, and multiple authors reported receiving fees, grants, and/or support from HeartFlow.

Results for the primary end point (see Table 4) yielded a change in management category for 72 (36%) of 200 individuals. For the 87 individuals initially assigned to PCI based on CCTA alone, the addition of the FFR-CT results shifted management for 26 (30%) of 87 to OMT (i.e., no ischemic lesion on FFR-CT) and an additional 16 (18%) individuals remained in the PCI category, but FFR-CT identified a different target vessel for PCI. These findings provide supportive information that the improved diagnostic accuracy of FFR-CT in particular related to its better negative likelihood ratio compared with CCTA alone would likely lead to changes in management that would be expected to improve health outcomes.

Table 4. Summary of Overall Management Changes for Patients Using CCTA vs CCTA Plus FFR-CT

Management Category Consensus Decision	CCTA Alone, n (%)	CCTA Plus FFR-CT, n (%)	Strategy Change[a] (95% CI), %
More data required	38 (19.0)	0	NR
Optimal medical therapy	67 (33.5)	113 (56.5)	23 (18 to 29)
Percutaneous coronary intervention	87 (43.5)	78 (39.0)	-5 (-2 to -8)
Coronary artery bypass graft surgery	8 (4.0)	9 (4.5)	0.5 (0.1 to 3)

Source: Curzen et al (2016) (51)
CCTA: coronary computed tomography angiography; CI: confidence interval; FFR-CT: fractional flow reserve using coronary computed tomography angiography.
[a] p<0.001 for between-group change, CCTA alone vs CCTA + FFR-CT.

Baggiano et al (2020) conducted a retrospective analysis of patients (N=291) enrolled in the PERfusion Versus Fractional Flow Reserve CT Derived In Suspected CoroNary (PERFECTION) study, a prospective cohort study in patients with suspected CAD.(55) The study protocol determined the clinical management plan based on the results of the following potential assessments: CCTA, fractional flow reserve measurement using CCTA, CCTA plus stress myocardial perfusion using computed tomography, and all 3 imaging modalities combined. Clinical management included optimal medical therapy, ICA, or need for further information. Functionally significant CAD was identified in 49% of patients. Compared to CCTA alone, adding fractional flow reserve measurement using CCTA increased the proportion of patients who received optimal medical therapy (26% vs. 35%) and ICA (45% vs. 48%), and decreased the proportion of patients who needed further information (29% vs. 17%). There was a significant difference in the rate of agreement with the final management decision

between CCTA and fractional flow reserve measurement using CCTA (p=.042), and with all 3 imaging modalities combined compared to CCTA alone (p=.001).

Section Summary: Coronary Computed Tomography Angiography with Selective Noninvasive Fractional Flow Reserve

Three studies including 609 patients have evaluated the diagnostic accuracy of the FDA-cleared HeartFlow FFRCT software. Software used in successive studies was also revised to improve performance characteristics, particularly specificity. For example, using an earlier software version, the noninvasive fractional flow reserve derived from the computed tomography angiography for coronary lesions of intermediate stenosis severity trial reported a specificity of 54%. (41) Accordingly, pooled results from the Danad et al (2017) systematic review must be interpreted carefully. Also, there is some uncertainty in the generalizability of results obtained in these studies conducted under likely controlled conditions (e.g., data from the NXT Trial (27) forming the basis for the FDA clearance).

Given the purpose to avoid ICA, the negative likelihood ratio, or how a negative result might dissuade a clinician from proceeding to ICA, is of primary interest (i.e., excluding a patient with vessels having a high fractional flow reserve from ICA). While CIs are relatively wide and overlapping, the negative likelihood ratio estimates of fractional flow reserve measurement using CCTA for excluding physiologically significant coronary stenoses tended to be lower (i.e., better) than CCTA alone, stress echocardiography, SPECT, and ICA. Only MRI yielded a similarly low or lower negative likelihood ratio than fractional flow reserve measurement using CCTA.

There is direct evidence, provided by two prospective and two retrospective studies, that compares health outcomes observed during 90-day to one-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 CAD. Also, the benefits are likely to outweigh potential harms given that rates of revascularization for functionally significant obstructive CAD appear to be similar and cardiac-related adverse events do not appear to be increased following a CCTA with selective FFR-CT strategy. Moreover, the evidence on the diagnostic performance characteristics, particularly showing higher specificity of FFR-CT and better negative likelihood ratio as compared with CCTA alone, may be combined with indirect evidence that CCTA with a selective FFR-CT strategy would likely lead to changes in management that would be expected to improve health outcomes, particularly by limiting unnecessary ICA testing. While individual studies are noted to have specific methodologic limitations and some variation is 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.

SUMMARY OF EVIDENCE

For individuals with stable chest pain at intermediate risk of coronary artery disease (CAD) (i.e., suspected or presumed stable ischemic heart disease) being considered

for invasive coronary angiography (ICA) who receive noninvasive FFR measurement following positive CCTA, the evidence includes both direct and indirect evidence: four meta-analyses on diagnostic performance; two prospective, multicenter nonrandomized comparative studies; four prospective cohort; five retrospective cohort studies; and a study reporting changes in management associated with CCTA-based strategies with selective addition of FFR-CT and a randomized controlled trial comparing of CCTA alone with ICA. The relevant outcomes are test accuracy and validity, morbid events, QOL, 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 that compares health outcomes observed during 90-day to one-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 CAD. Also, the benefits are likely to outweigh potential harms because rates of revascularization for functionally significant obstructive CAD 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 an improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Heart Association, et al

In 2021, the American Heart Association, American College of Cardiology, American Society of Echocardiography, American College of Chest Physicians, Society for Academic Emergency Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance released a clinical practice guideline for the evaluation and diagnosis of chest pain. (63) The guideline states that for "intermediate-risk patients with acute chest pain and no known coronary artery disease (CAD), with a coronary artery stenosis of 40% to 90% in a proximal or middle coronary artery on coronary computed tomography angiography (CCTA), fractional flow reserve with computed tomography can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (class of recommendation [COR]: 2a (moderate; benefit >> risk); level of evidence [LOE]: B-NR (moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies)." This recommendation also applies to those intermediate-risk patients with acute chest pain and known CAD (COR: 2a; LOE: B-NR).

The National Institute for Health and Care Excellence (2017) endorsed fractional flow reserve using coronary computed tomography angiography (FFR-CT), with the following conclusions: "The committee concluded that the evidence suggests that HeartFlow FFR_{CT} is safe, has high diagnostic accuracy, and that its use may avoid the need for invasive investigations."(52)

Recommendations included:

- "The case for adopting HeartFlow FFR-CT 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 FFR-CT 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 FFR-CT may avoid the need for invasive coronary angiography and revascularization. For correct use, HeartFlow FFR-CT requires access to 64-slice (or above) CCTA facilities."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 6. A manuscript reporting one-year results of the ADVANCE registry (NCT02499679) has been accepted, but not yet published. An early, unedited version of the manuscript is currently available.(52)

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05174247	Addition of FFRct in the Diagnostic Pathway of Patients With Stable Chest Pain to Reduce Unnecessary Invasive Coronary Angiography	528	Apr 2025
NCT04939207	Improving the Cost-effectiveness Of Coronary Artery Disease Diagnosis	825	Apr 2025
NCT02208388	Prospective Evaluation of MyocaRdial PerFUSion ComputEd Tomography Trial; Ischemia-guided Revascularization Using Perfusion Coronary CT vs. Fractional Flow Reserve	1000	Mar 2028
NCT03329469	The Value of Fractional Flow Reserve Derived From Coronary CT Angiography as Compared to CCTA or CCTA and Stress MPI in the Triage of Low to Intermediate Emergent Chest Pain Patients With Toshiba CT- FFR	1142	Mar 2024
Unknown Status			
NCT02973126	Assessment of Fractional Flow reservE Computed Tomography	270	Jul 2022

	Versus Single Photon Emission Computed Tomography in the Diagnosis of Hemodynamically Significant Coronary Artery Disease. (AFFECTS)		
NCT04142021	A Multicenter, Pilot Study to Evaluate Safety and Feasibility Evaluation of Planning and Execution of Surgical Revascularization Solely Based on Coronary CTA and FFRCT in Patients With Complex Coronary Artery Disease (FASTTRACK CABG)	114	Dec 2022

NCT: national clinical trial.

Government Regulations

National:

There is no national coverage determination on this topic.

Local:

Category III Codes (L35490): Original Effective Date: 10/1/15; Revision Effective Date: 3/28/24

CPT Codes 0501T-0504T: coverage in L35490 no longer applicable. Please refer to L38839 Non-Invasive Fractional Flow Reserve (FFR) for Stable Ischemic Heart Disease and A58473 Billing and Coding: Non-Invasive Fractional Flow Reserve (FFR) for Stable Ischemic Heart Disease for Coverage Indications, Limitations, and/or Medical Necessity. Effective 04/25/2021.

Billing and Coding: Non-Invasive Fractional Flow Reserve (FFR) for Stable Ischemic Heart Disease (A58473) Effective Date: 4/25/21; Revision Effective Date: 1/1/24

The billing and coding information in this article is dependent on the coverage indications, limitations and/or medical necessity described in the associated LCD L38839 for Non-Invasive Fractional Flow Reserves (FFR) for Stable Ischemic Heart Disease.

The patient's medical record must document all of the following:

1. The clinical findings that led to the initial performance of the CCTA, and the CCTA must be fully reviewed before the performance of FFRct. (as evidenced by the submission of the Coronary Computed Tomographic Angiography Report)
2. Description of symptoms consistent with stable ischemic heart disease
3. Body mass index
4. Fractional Flow Reserve analysis report

Group 1 Codes:

CODE	DESCRIPTION
75580	NONINVASIVE ESTIMATE OF CORONARY FRACTIONAL FLOW RESERVE (FFR) DERIVED FROM AUGMENTATIVE SOFTWARE ANALYSIS OF THE DATA SET FROM A CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY, WITH INTERPRETATION AND REPORT BY A PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are

updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

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

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/19	10/24/18	10/24/18	• Joint policy established • Incorporates AIM criteria in inclusion/exclusion area
1/1/20	10/15/19		• Routine maintenance • Code update - 0523T added • Updated LCD covers codes 0501T-0504T
1/1/21	10/20/20		• Routine maintenance
1/1/22	10/19/21		• Routine maintenance • Policy statements unchanged • 0523T removed from policy as the code does not belong on this policy.
1/1/23	10/18/22		• Routine maintenance • Term change from patients to individuals on policy statement (ky)
1/1/24	10/25/23		• Routine maintenance • References updated • Vendor: Carelon • Carelon policy Imaging of the Heart April 9, 2023 no longer list the diagnosis of cardiomyopathy for the test coronary CT with selective FFR. When coronary artery disease (CAD) is not known, cardiac MRI is the procedure of choice. The below statement under Inclusions is updated to reflect this: Meet one of the following: • Diagnosis of congestive heart failure/left ventricular dysfunction when all the following are met: ○ Left ventricular ejection fraction < 55% ○ Low to moderate coronary heart disease risk[a] **OR** (ky)

			Post JUMP • Per code update - new procedure code 75580 which is effective 1/1/24 added to EST replacing codes 0501T-0504T which are being deleted 12/31/23.
1/1/25	10/15/24		• Routine maintenance • References updated • Vendor: Carelon Imaging of the Heart 2024-04-14. (ky)

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY WITH SELECTIVE NONINVASIVE FRACTIONAL FLOW RESERVE (FFR_{CT})

I. Coverage Determination:

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

II. Administrative Guidelines:

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