Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(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 (ie 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. For example, from a sample of over 132,000 ICAs, Patel et al (2010) found 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 (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; there are few who might benefit from ICA if they have not first failed optimal medical therapy.(2)

Clinical Risk Prediction

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.

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. A commonly cited clinical prediction model based on age, sex and type of pain symptoms, originally developed by Diamond and Forrester (1979),(4) has been further studied and extended in a report by Genders et al (2011) (5) and compared to the Duke Clinical Score by Wasfy et al (2012).(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) An additional model has been published by Min et al (2015) (8) and an online calculator has been developed by a CAD consortium.(9,10)

Gatekeepers to 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). For example, using the National Inpatient Sample, Pothineni et al (2016) reported that 201,705 PCIs were performed in 2012, but just 21,365 FFR guided 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 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 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) 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 or less provides level 1a evidence for revascularization for “significant stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy.”(3) In addition, 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 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]), 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.

Noninvasive FFR Measurement

FFR can be modeled noninvasively using images obtained during CCTA (28)—so-called fractional flow reserve using coronary computed tomography angiography (FFR-CT; HeartFlow software termed FFR_{CT}; Siemens cFFR) using routinely collected CCTA imaging data. 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 1 to 3 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."

Medical Policy Statement

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

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Patients must meet both criteria:

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

Meet one of the following:

- Diagnosis of congestive heart failure/cardiomyopathy/left ventricular dysfunction when all the following are met:
  - Left ventricular ejection fraction < 55%
  - Low to moderate coronary heart disease risk[a]
  - Coronary artery disease has not been excluded as the etiology of the cardiomyopathy **OR**
- Symptomatic[b] or asymptomatic patients 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] patients 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
    - Patient 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] patient 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
- Patients with any cardiac symptom who have any 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%)

Exclusions:

- Assessment of coronary arteries for suspected congenital anomalies
- Patients 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)
- Patients who require emergent procedures
- Patients 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	0501T	0502T	0503T	0504T	0523T*

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

N/A

** Add on code - List separately in addition to code for cardiac catherization (93453, 93460)*

Rationale

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY WITH SELECTIVE NONINVASIVE FRACTIONAL FLOW RESERVE

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does noninvasive FFR-CT guide decisions to use or not use ICA in patients with stable chest pain or suspected SIHD?

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

Patients

The population of interest includes patients with stable chest pain at intermediate risk of CAD (ie, with suspected or presumed SIHD) who are being considered for ICA. Patients 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. 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 (eg, ≤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 setting is a general cardiology practice for patients undergoing nonemergent chest pain evaluation.

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

Technical Reliability

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Studies Included in FFR-CT Systematic Reviews: Per-Patient Diagnostic Accuracy

Twenty-six studies have contributed patient-level results to a 2015 meta-analysis that examined 5 non-FFR-CT imaging modalities (see Table 1).(30) Five studies contributed results to 2 meta-analyses, Wu et al (2016) (31) and Danad et al (2017),(32) evaluating the diagnostic accuracy of FFR-CT using 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 3 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 NXT Trial, the basis for device clearance by FDA, was conducted at 11 sites in 8 countries (Canada, EU, Asia).(27) Although not examined in the 2 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.

Danad et al

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 3 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 other studies. HeartFlow funded publication Open Access; 1 author was a consultant to, and another a cofounder of, HeartFlow.

On the patient level, MRI had the highest combined sensitivity (90%; 95% CI, 75% to 97%) and specificity (94%; 95% CI, 79% to 99%) for invasive FFR, but were estimated from only 2 studies (70 patients). FFR-CT had similar sensitivity (90%; 95% CI, 85% to 93%), but lower specificity (71%; 95% CI, 65% to 75%), and accordingly a lower positive likelihood ratio (3.34; 95% CI, 1.78 to 6.25) than MRI (10.31; 95% CI, 3.14 to 33.9). The negative likelihood ratios were low (lower is better) for both FFR-CT (0.16; 95% CI, 0.11 to 0.23) and MRI (0.12; 95% CI, 0.05 to 0.30); however, the confidence interval is narrower for FFR-CT due to larger sample for FFR-CT. CCTA had a slightly higher negative likelihood ratio (0.22; 95% CI, 0.10 to 0.50). Per-vessel area under the summary receiver operating characteristic curve results were similar except for CCTA where per-patient results were considerably worse (eg, C statistic of 0.57 vs. 0.85). Reviewers noted heterogeneity in many estimates (eg, CCTA sensitivity, I^2=80%). Finally, pooled results for some imaging tests included few studies.

Wu et al

Wu et al (2016) identified 7 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, 1 additional study using HeartFlow technique (44 patients; 48 vessels) and 3 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 5 studies were pooled and 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, 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 2 studies, FFR-CT results were uninterpretable in 12.0% (27) and 8.2% (39) of participants.

Takx et al

Takx et al (2015) identified studies reporting on the ability of perfusion computed tomography (CT), MRI, SECHO, PET, and SPECT to detect hemodynamically significant CAD as measured by ICA with invasive FFR.(30) Studies published through May 2014 were eligible for inclusion; PubMed, EMBASE, and Web of Science were searched. QUADAS-2 was used to assess study quality;(38) studies generally rated poorly on blinding of the index test result from the assessor and study population selection. Reviewers designated the negative likelihood ratio as the diagnostic characteristic of interest (ie, ability to exclude disease) noting that MPI (eg, MRI, SPECT, PET, or CT) has been proposed to be a gatekeeper to ICA. No funding was obtained for the review and the study was registered on PROSPERO (40) (the 2 other meta-analyses were not).

The pooled negative likelihood ratios for MRI, PET, and perfusion CT were similar in magnitude (0.12 to 0.14; see Table 1) although the confidence interval for PET was wide. Heterogeneity among studies included in the pooled patient-level results was considered high for PET (I^2=84%), moderate for CT (I^2=70%) and SPECT (I^2=55%), and low for MRI (I^2=0%) and SECHO (I^2=0%). Publication bias, when able to be assessed, was not suspected. With respect to ability to detect hemodynamically significant ischemia, reviewers concluded that "MPI with MRI, CT, or PET has the potential to serve as a gatekeeper for invasive assessment of hemodynamic significance by ICA and FFR." Studies of FFR-CT were not included in the analysis.

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)
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)

FFR-CT	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)
SECHO	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]							
FFR-CT	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)
Takx et al (2015)[30]							
MRI	10	798	89 (86 to 92)	87 (83 to 90)	0.94	6.3 (4.88 to 8.12)	0.14 (0.10 to 0.18)
PCT	5	316	88 (82 to 92)	80 (73 to 86)	0.93	3.8 (1.94 to 7.40)	0.12 (0.04 to 0.33)
SECHO	4	177	69 (56 to 79)	84 (75 to 90)	0.83	3.7 (1.89 to 7.15)	0.42 (0.30 to 0.59)
SPECT	8	533	74 (67 to 79)	79 (74 to 83)	0.82	3.1 (2.09 to 4.70)	0.39 (0.27 to 0.55)
PET	2	224	84 (75 to 91)	87 (80 to 92)	0.93	6.5 (2.83 to 15.1)	0.14 (0.02 to 0.87)

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.

Section Summary: Clinically Valid

Three studies including 609 patients have evaluated diagnostic accuracy of the FDA-cleared HeartFlow software. Software used in successive studies was also revised to improve performance characteristics, particularly specificity. For example, using an earlier software version, the DeFACTO Trial reported a specificity of 54%.(41) Accordingly, pooled results from the Danad systematic review must be interpreted carefully. In addition, there is some uncertainty in the generalizability of results obtained in these studies conducted under likely controlled conditions (eg, data from the NXT Trial [27] forming the basis for 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—ie, excluding a patient with vessels having a high FFR from ICA. While confidence intervals are relatively wide and overlapping, the negative likelihood ratio estimates of FFR-CT for excluding physiologically significant coronary stenoses tended to be lower (ie, better) than CCTA alone, SECHO, SPECT, and ICA. Only MRI yielded a similarly low or lower negative likelihood ratio than FFR-CT.

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.

We identified two prospective comparative studies including one prospective nonrandomized study that compared an FFR-CT strategy (CCTA plus noninvasive FFR measurement when requested or indicated) with ICA and one randomized controlled trial that examined CCTA as a gatekeeper to ICA (see Tables 2 and 3). Also, we identified one prospective cohort study and two retrospective cohort studies of patients referred for CCTA, which included FFR-CT evaluation.

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 (ie, 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 1-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 at 90 days was the primary end point in patients with planned invasive testing—“no stenosis ≥ 50% by core laboratory quantitative analysis or invasive FFR < 0.80.” Secondary end points included ICA without obstructive disease following planned noninvasive testing, and (1) MACE at 1 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 of 134 (87.3%) in the FFR-CT group. 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 1 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.

CAD-Man Trial

Dewey et al (2016) conducted the Coronary Artery Disease Management (CAD-Man) trial, a single-center, parallel-group assignment trial examining CCTA as a gatekeeper to ICA in patients with atypical angina or chest pain and suspected CAD who were indicated for ICA.(44) Patients were randomized to direct ICA or to ICA only if a prior CCTA was positive (a stenosis ≥70% stenosis in any vessel or ≥50% in the left main coronary artery). The trialists reported that when obstructive disease was suspect following CCTA, late enhancement MRI was performed to evaluate the extent of viable myocardium (completed in 17 patients) to guide revascularization; however, the study protocol clarified that MRI was not used for decisions to proceed to ICA. A major procedural complication (death, stroke, MI, or event requiring >24-hour hospitalization) within 24 hours was the primary outcome; secondary outcomes included ICA with obstructive CAD (diagnostic yield), revascularizations, and MACE during long-term follow-up. The trial was performed in Germany. Patients were excluded if they had evidence of ischemia or signs of MI and just over half (56.5%) were inpatients at the time of enrollment. Obstructive disease was defined as “at least one 50% diameter stenosis in the left main coronary artery or at least one 70% diameter stenosis in other coronary arteries.” Allocation concealment appeared adequate, but the trial was unblinded owing to the nature of the intervention. In addition, the mean pretest probability of CAD at baseline was higher in the ICA-only arm (37.3% vs. 31.3%; see Table 4). The research was supported by public funding.

ICAs were reduced by 85.6% in the CCTA arm and by 80.9% for ICA with no obstructive disease. A major procedural complication (the primary outcome) occurred in a single patient undergoing CCTA. PCIs were less frequent when CCTA was performed—9.6% versus 14.2% ($p<0.001$). Over a median follow-up of 3.3 years, MACE rates were similar in the trial arms (4.2% in the CCTA group vs 3.7% with ICA; adjusted hazard ratio [HR], 0.90; 95% CI, 0.30 to 2.69). In the CCTA arm, there was one death, two patients with unstable angina, and six revascularizations; in the ICA arm there was one MI, one stroke, and five revascularizations.

The trial demonstrated that CCTA as a gatekeeper to planned ICA can avoid a large number of procedures, a corresponding increase in the diagnostic yield, and fewer revascularizations. Of note, the prevalence of obstructive CAD found on ICA in this study population was 13% (43/334 eligible for primary outcome analysis), which is lower than the prevalence of obstructive CAD in the PLATFORM population (26.7%). Thus, the subset of individuals who went onto ICA following CCTA findings of obstructive CAD was 20 (12%) of 167 eligible for primary outcome analysis and only 3 (1.7%) were found to have no obstructive CAD on ICA.

MACE rates did not differ between arms. The trial was powered neither to detect a difference nor to assess noninferiority—implications of the absence of a difference are limited. Finally, although the patient population included those scheduled for elective ICA, it was heterogeneous, including those with recent onset and longer standing chest pain. The single-center nature of the trial is an additional limitation; a subsequent Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Disease trial is ongoing.

Table 2. Characteristics of Comparative Studies

Characteristics	Nonrandomized		Randomized	
	PLATFORM		CAD-Man	
	ICA	FFR-CT	ICA	CCTA
	(n=187)	(n=193)	(n=162)	(n=167)
Age (SD), y	63.4 (10.9)	60.7 (10.2)	60.4 (11.4)	60.4 (11.3)
Female, n (%)	79 (42.2)	74 (38.3)	88 (52.7)	78 (48.1)
Race/ethnic minority, n (%)	2 (1.1)	1 (0.5)		
Pretest probability obstructive CAD (SD), %	51.7 (16.7)	49.4 (17.2)	37.3 (24.8)	31.3 (21.1)
Angina, n (%)				
Typical	52 (27.8)	45 (23.3)		
Atypical	122 (65.2)	142 (73.6)	79 (48.8)	65 (38.9)
Noncardiac	12 (7.0)	5 (2.6)	80 (49.4)	97 (58.1)
Other chest discomfort			3 (1.8)	5 (3.0)
Prior noninvasive testing, n (%)	92 (49.2)	101 (52.3)	84 (50.3)	92 (56.8)
Diabetes, n (%)	36 (19.3)	30 (15.5)	30 (18.5)	15 (9.0)
Current smoker			34 (21.0)	41 (24.5)
Current or past smoker	103 (55.1)	101 (52.3)	85 (52.4)	88 (52.6)

Adapted from Douglas et al (2015, 2016)[42,]NA[43,] and Dewey et al (2016).[45,]
CAD: coronary artery disease; CCTA: coronary computed tomography angiography; FFR-CT: fractional flow reserve using coronary computed tomography angiography; ICA: invasive coronary angiography; SD: standard deviation.

Table 3. Results of Comparative Studies

Outcomes	Nonrandomized		Randomized	
	PLATFORM		CAD-Man	
	ICA	FFR-CT	ICA	CCTA
	(n=187)	(n=193)	(n=162)	(n=167)
Noninvasive FFR-CT, n (%)				
Requested		134 (69.4)		
Successfully performed		117 (60.1)		
ICA no obstructive disease, n (%)	137 (73.3)	24 (12.4)	137 (84.5)	6 (3.6)
Absolute difference (95% CI), %	60.8 (53.0 to 68.7)		80.9 (74.6 to 87.2)	
ICA, n (%)	187 (100)	76 (39.4)	162 (100)	24 (14.4)
Absolute difference (95% CI), %	60.6 (53.7 to 67.5)		85.6 (80.3 to 90.9)	
Revascularization, n (%)				
PCI	49 (26.2)	55 (28.5)		
CABG	18 (9.6)	10 (5.2)		
Any	67 (35.8)	65 (33.7)	23 (14.2)	16 (9.6)
1-year outcomes, n (%)				
MACE[a]	2 (1.1)	2 (1.0)		
MACE[b]			6 (3.7)	7 (4.2)

Adapted from Douglas et al (2015, 2016)[42,]NA[43,] and Dewey et al (2016).[45,]
CABG: coronary artery bypass grafting; CCTA: coronary computed tomography angiography; CI: confidence interval; FFR-CT: fractional flow reserve using coronary computed tomography angiography; ICA: invasive coronary angiography; MACE: major adverse cardiovascular events; PCI: percutaneous coronary intervention.

[a] Death, myocardial infarction, unplanned urgent revascularization.
[b] Cardiac death, myocardial infarction, stroke, unstable angina, any revascularization.

Jensen et al Prospective Cohort

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 2 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.

Nørgaard et al Retrospective Cohort

Nørgaard 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 apparently retrospectively conducted. Follow-up through 6 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 Retrospective Cohort

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 2 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 1 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 (ie, 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 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%.

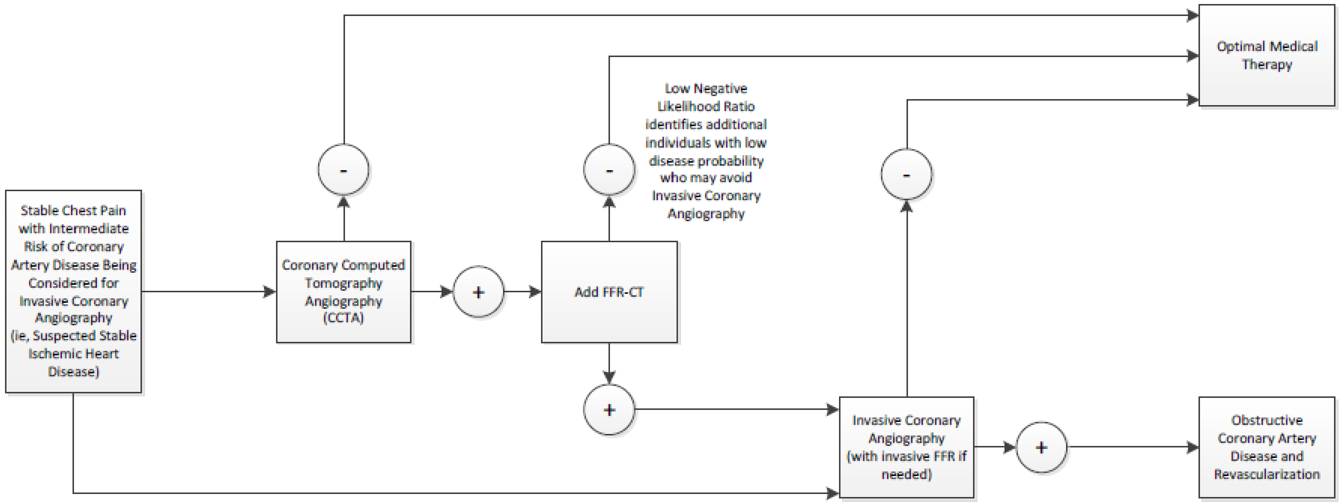
The authors suggested that when CCTA is used as the initial evaluation for patients with suspected SIHD, adding FFR-CT could have decreased the referral rate to ICA in PROMISE from 12.2% to 9.5%, or close to the 8.1% rate observed in the PROMISE functional testing arm. They also noted similarity of their 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 (eg, ≥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 most likely those patients would proceed in practice 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%).

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 4 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 (95% CI, 0.09 to 0.33); and following a negative SECHO, 0.25 (95% CI, 0.15 to 0.40) or SPECT, 0.29 (95% CI, 0.16 to 0.45). In contrast, beginning with a pretest probability of 0.50, a negative FFR-CT would yield a posttest probability of 0.14 (95% CI, 0.10 to 0.19) (Danad et al) and 0.12 (95% CI, 0.08 to 0.17) (Wu et al). Overall, the negative likelihood ratios and posttest probability estimates for FFR-CT are slightly better than CCTA as well as SECHO and SPECT.

Table 4. 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.

A literature search identified one study (Curzen et al [2016]) 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.(50) 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: "1) optimal medical therapy (OMT) alone; 2)

PCI + OMT; 3) coronary artery bypass graft + OMT; or 4) more information about ischemia required – they committed to option 1 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 5) 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 (ie, 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 5. 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	-
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)

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.

Section Summary: Clinical Useful

There is direct evidence, provided by two prospective and two 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 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 CAD (ie, suspected or presumed stable ischemic heart disease) being considered for ICA who receive noninvasive FFR measurement following positive CCTA, the evidence includes both direct and indirect evidence: two meta-analyses on diagnostic performance; one prospective, multicenter nonrandomized comparative study; one prospective cohort; two 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, 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 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 meaningful improvements in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

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.”(51)

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 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02173275	Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia	618	Mar 2018 (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 Randomized Controlled Trial of CT Versus ICA	3546	Sept 2019
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
NCT02499679[a]	Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE)	5000	Feb 2021
NCT02208388	Prospective Evaluation of Myocardial Perfusion Computed Tomography Trial	1000	Apr 2024

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored 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: 7/1/19

The following lists Category III services determined by WPS GHA to be reasonable and medically necessary. Coverage will only be allowed when the service is delivered in clinical situations meeting medical necessity.

Group 3 Codes:

CODE	DESCRIPTION
0501T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software

	analysis of functional data to assess the severity of coronary artery disease; data preparation and transmission, analysis of fluid dynamics and simulated maximal coronary hyperemia, generation of estimated FFR model, with anatomical data review in comparison with estimated FFR model to reconcile discordant data, interpretation and report
0502T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery disease; data preparation and transmission
0503T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery disease; analysis of fluid dynamics and simulated maximal coronary hyperemia, and generation of estimated FFR model
0504T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery disease; anatomical data review in comparison with estimated FFR model to reconcile discordant data, interpretation and report

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

Related Policies

- Computed Tomography to Detect Coronary Artery Calcification
- Contrast-Enhanced Computed Tomography Angiography of the Heart and/or Coronary Arteries (CTA, CCTA)
- Positron Emission Tomography (PET Scans) for 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 September 9, 2019, 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

Next Review Date: 4th Qtr, 2020

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.