

6.01.59	Coronary Computed Tomography Angiography With Selective Noninvasive Fractional Flow Reserve		
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Section:	6.0 Radiology	Page:	Page 1 of 21

Policy Statement

The use of noninvasive fractional flow reserve following a positive coronary computed tomography angiography may be considered **medically necessary** to guide decisions about the use of invasive coronary angiography in patients with stable chest pain at intermediate risk of coronary artery disease (i.e., suspected or presumed stable ischemic heart disease).

The use of noninvasive fractional flow reserve not meeting the criteria outlined above is considered **investigational**.

Policy Guidelines

Fractional flow reserve using coronary computed tomography angiography requires at least 64-slice coronary computed tomography angiography and cannot be calculated when images lack sufficient quality (HeartFlow, 2013) (11% to 13% in recent studies; Koo et al, 2011; Min et al, 2012; Nakazato et al, 2013; Nørgaard et al, 2014), e.g., in obese individuals (e.g., body mass index, greater than 35 kg/m²). 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.

Coding

There is a category I CPT code for coronary computed tomographic angiography:

- **75574:** Computed tomographic angiography, heart, coronary arteries and bypass grafts (when present), with contrast material, including 3D image postprocessing (including evaluation of cardiac structure and morphology, assessment of cardiac function, and evaluation of venous structures, if performed)

Effective January 1, 2018, the following CPT codes are specific to this procedure:

- **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

Description

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.

Related Policies

- Cardiac Applications of Positron Emission Tomography Scanning
- Contrast-Enhanced Coronary Computed Tomography Angiography for Coronary Artery Evaluation

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In November 2014, FFR_{CT} simulation software (HeartFlow) was cleared for marketing by the Food and Drug Administration through the de novo 510(k) process (class II, special controls; Food and Drug Administration 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 FFRCT [fractional flow reserve using coronary computed tomography angiography], a mathematically derived quantity, computed from simulated pressure, velocity and blood flow information obtained from a 3D computer model generated from static coronary CT images. FFRCT analysis is intended to support the functional evaluation of coronary artery disease. The results of this analysis [FFR_{CT}] are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. The results of HeartFlow FFRCT are intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment."

Rationale

Background

Stable Ischemic Heart Disease

Coronary artery disease (CAD) is a significant cause of morbidity and mortality. Various epidemiologic risk factors have been well studied. Evaluation of obstructive CAD involves quantifying arterial stenoses to determine whether significant narrowing is present. Lesions with stenosis more than 50% to 70% in diameter accompanied by symptoms are generally considered significant. It has been suggested that coronary computed tomography angiography (CCTA) or other noninvasive functional cardiac testing may help rule out CAD and avoid invasive coronary angiography (ICA) in patients with a low clinical likelihood of significant CAD. However, ICAs are frequently unnecessary in patients with suspected stable ischemic heart disease (SIHD), as evidenced by low diagnostic yields for significant obstructive CAD. For example, from a sample of over 132000 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 $\geq 50\%$ or $\geq 70\%$ 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 before ICA as a gatekeeper, which can distinguish candidates who may benefit from early revascularization (e.g., patients with unprotected left main stenosis $\geq 50\%$ or hemodynamically significant disease) from those unlikely to benefit, could avoid unnecessary invasive procedures and their potential adverse consequences. Moreover, for the large majority of patients with SIHD, revascularization offers no survival advantage over medical therapy; few might benefit from ICA if they have not first failed optimal medical therapy.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 the use of noninvasive testing in patients with suspected SIHD.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 the interpretability of the electrocardiogram, the capacity to exercise, and presence of comorbidity.

Clinical prediction scores or models have been developed to help estimate the pretest probability of CAD in individuals with stable chest pain. 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 Versteysen et al (2011) published a comparison of clinical prediction results for the Diamond and Forrester (1979) model, the Framingham risk score, the PROCAM risk score, and the SCORE risk estimation model.⁷ Another model has been published by Min et al (2015)⁸ and an online calculator developed by a CAD consortium.^{9,10}

Gatekeepers to ICA

Imposing an effective noninvasive gatekeeper strategy with one or more tests before planned ICA to avoid unnecessary procedures is compelling. The most important characteristic of a gatekeeper test is its ability to accurately identify and exclude clinically insignificant disease where revascularization would offer no potential benefit. From a diagnostic perspective, an optimal strategy would result in few false-negative tests while avoiding an excessive false-positive rate—it would provide a low 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 before planned ICA, including CCTA, magnetic resonance imaging, single-photon emission computed tomography, positron emission tomography, and stress echocardiography. More recently, adding noninvasive measurement of fractional flow reserve (FFR) using CCTA has been suggested, combining functional and anatomic information.

Fractional Flow Reserve

Invasively measured FFR evaluates the severity of ischemia caused by coronary artery obstructions and can predict when revascularization may be beneficial.^{11,12,13} 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 stenosis.

Invasive FFR is rarely used in the U. S. to guide percutaneous coronary intervention (PCI). For example, using the National Inpatient Sample, Pothineni et al (2016) reported that 201705 PCIs were performed in 2012, but just 21365 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 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 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 for patients with angina symptoms or a positive stress test."¹⁸ Other guidelines (2014) have recommended using "FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available" (class Ia recommendation).¹⁹ The U.S. guidelines (2012) have stated that an FFR of 0.80 or less provides level Ia evidence for revascularization for "significant stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy."³ 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 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 minutes.

FFR using CCTA requires at least 64-slice CCTA and cannot be calculated when images lack sufficient quality²³ (11% to 13% in recent studies^{24,25,26,27}), e.g., in obese individuals (e.g., body mass index, >35 kg/m²). The presence of dense arterial calcification or an intracoronary stent can produce significant beam-hardening artifacts and may preclude satisfactory imaging. The presence of an uncontrolled rapid heart rate or arrhythmia hinders the ability to obtain diagnostically satisfactory images. Evaluation of the distal coronary arteries is generally more

difficult than the visualization of the proximal and mid-segment coronary arteries due to greater cardiac motion and the smaller caliber of coronary vessels in distal locations.

Noninvasive FFR Measurement

FFR can be modeled noninvasively using images obtained during CCTA²⁸—so-called FFR using CCTA (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 using CCTA can also be used for "virtual stenting" to simulate how stent placement would be predicted to improve vessel flow.²⁹

Only 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.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Coronary Computed Tomography Angiography with Selective Noninvasive Fractional Flow Reserve Clinical Context and Test Purpose

The purpose of selective noninvasive FFR using CCTA (collectively FFR-CT) in patients with stable chest pain who have suspected stable ischemic heart disease (SIHD) and who are being considered for invasive coronary angiography (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 PICO³⁰s were used to select literature to inform this review.

Patients

The population of interest includes patients with stable chest pain at intermediate risk of coronary artery disease (CAD; i.e., 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 test being considered 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 (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 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.

Technically Reliable

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 meta-analysis by Takx et al (2015) 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 U.S. Food and Drug Administration (FDA)-cleared HeartFlow software has been evaluated prospectively across multiple sites. Three small retrospective studies have reported per-patient performance characteristics for the prototype Siemens workstation-based software.^{33,34,35} 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 Analysis of Coronary Blood Flow Using CT Angiography: Next Steps(NXT) Trial, the basis for device clearance by the FDA, was conducted at 11 sites in 8 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 descent; almost all patients were appropriate for testing according to the 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 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-2³⁸; 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 Open Access publication; one 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 CI 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). Results for the per-vessel area under the summary receiver operating

characteristic curve were similar except for CCTA where 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.

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 (2017), an 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 five 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 (2017), but with 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 assess adequately. 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 quality³⁸; 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 (i.e., ability to exclude disease) noting that MPI (e.g., 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 the International prospective register of systematic reviews⁴⁰ (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 CI 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. Concerning the 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							

Test	Studies	N	Sensitivity (95% CI), %	Specificity (95% CI), %	C	LR+ (95% CI)	LR- (95% CI)
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 the 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 noninvasive fractional flow reserve derived from 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 Trial²⁷, 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—ie, excluding a patient with vessels having a high FFR from ICA. While CIs are relatively wide and overlapping, the negative likelihood ratio estimates of FFR-CT for excluding physiologically significant coronary stenoses tended to be lower (i.e., 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. All testing was nonemergent. Patients were divided into two strata, according to whether the test planned before study enrollment was: (1) noninvasive or (2) ICA (the patient population of interest in this evidence review). Patients were enrolled in consecutive cohorts (see Table 2), with the first cohort undergoing a usual care strategy followed by a second cohort provided CCTA

with FFR-CT performed when requested (recommended if stenoses $\geq 30\%$ were identified). Follow-up was scheduled for 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 endpoint in patients with planned invasive testing—"no stenosis $\geq 50\%$ by core laboratory quantitative analysis or invasive FFR < 0.80 ." Secondary endpoints 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. QOL was evaluated using the Seattle Angina Questionnaire, and EuroQol-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 radiotherapy 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 endpoint 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%) of 134 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) (see Table 3). 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 through 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 supported 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 (see Table 3). 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 in the magnitude of the 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 $\geq 70\%$ stenosis in any vessel or $\geq 50\%$ in the left main coronary artery) (see Table 2). 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. Also, the mean pretest probability of CAD at baseline was higher in the ICA-only arm (37.3% vs 31.3%; see Table 2). 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. Percutaneous coronary interventions (PCIs) were less frequent when CCTA was performed (9.6% vs 14.2%; $p < 0.001$) (see Table 3). 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, 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 could avoid a large number of procedures, a corresponding increase in the diagnostic yield, and fewer revascularizations (see Table 3). 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 (n=187)	FFR-CT (n=193)	ICA (n=162)	CCTA (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,NA43}, 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 (n=187)	FFR-CT (n=193)	ICA (n=162)	CCTA (n=167)
Noninvasive FFR-CT, n (%)				

Outcomes	Nonrandomized		Randomized	
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, NA⁴³, 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 a 31% mean pretest probability of CAD and a high-risk group accounting for 24% of patients with a 67% mean pretest probability of CAD. 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 ICA⁴⁸ 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 ($\geq 70\%$) or left main disease ($\geq 50\%$) 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 of 0.80 or less, which was also associated with a higher risk of revascularization but with a wide CI (hazard ratio=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 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%.

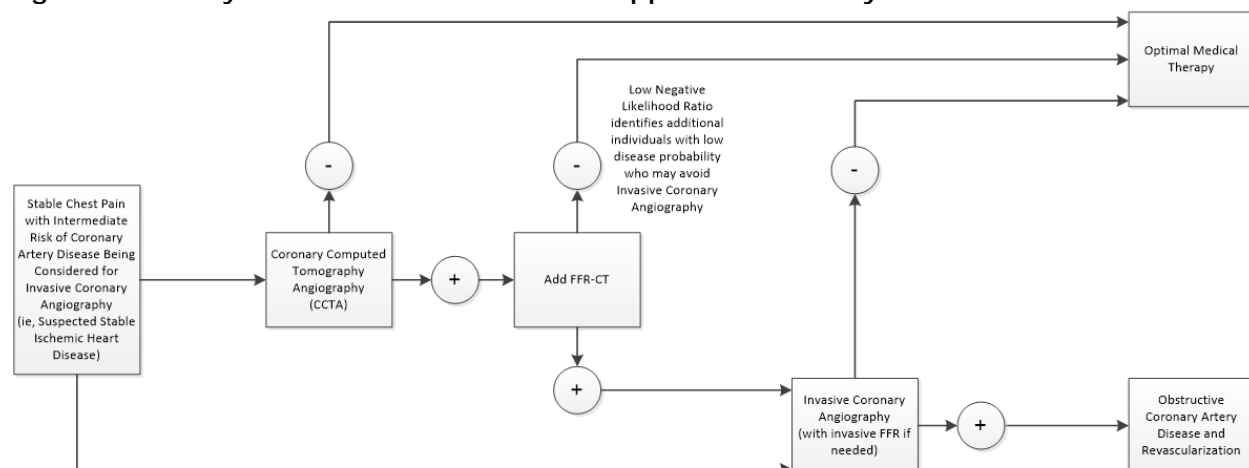
The authors suggested that when CCTA is used as the initial evaluation for patients with suspected SIHD, adding FFR-CT could have decreased the referral rate to ICA in PROMISE from 12.2% to 9.5%, or close to the 8.1% rate observed in the PROMISE functional testing arm. They also noted the similarity 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 FFRCT may improve the efficiency of referral to ICA, addressing a major concern of an anatomic [C]CTA strategy. FFRCT 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., $\geq 70\%$ in any vessel or $\geq 50\%$ 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 (2017), 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 [2017]) and 0.12 (95% CI, 0.08 to 0.17) (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 4. Change in Disease Probability Following a Negative Test

Study	Modality	Negative LR (95% CI)	Posttest Probability (95% CI) After Negative Test		
			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 1 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 1 vessel with diameter ≥ 2 mm and diameter stenosis $\geq 30\%$ " 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 four 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 endpoint of this study. Secondary endpoints 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 endpoint (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 (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 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: Clinically Useful

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 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 (i.e., 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

National Institute for Health and Care Excellence

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 FFRCT 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.

Medicare National Coverage

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

Ongoing Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 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 Randomised 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.

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - Current symptoms and clinical findings
 - Comorbidities
 - Activity and functional limitations
 - Reason for procedure
 - Prior conservative treatments, duration, and response

- Coronary computed tomography angiography results
- Radiology report(s) and interpretation (i.e., MRI, MPI, PET)

Post Service

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	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
	75574	Computed tomographic angiography, heart, coronary arteries and bypass grafts (when present), with contrast material, including 3D image postprocessing (including evaluation of cardiac structure and morphology, assessment of cardiac function, and evaluation of venous structures, if performed)
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
03/01/2017	BCBSA Medical Policy adoption	Medical Policy Committee
08/01/2017	Policy title change from Noninvasive Fractional Flow Reserve Using Computed Tomography Angiography Policy revision with position change	Medical Policy Committee
02/01/2018	Coding update	Administrative Review
07/01/2018	Policy revision without position change	Medical Policy Committee
07/01/2018	Policy revision without position change	Medical Policy Committee
08/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.