Noninvasive Fractional Flow Reserve Using Computed Tomography Angiography

Policy # 00537
Original Effective Date: 02/15/2017
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When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers use of fractional flow reserve (FFR) using coronary computed tomography angiography (CTA) preceding invasive coronary angiography in patients with suspected stable ischemic heart disease (SIHD) to be investigational.*

Background/Overview
Invasively measured FFR evaluates the severity of ischemia caused by coronary artery obstructions and can predict when revascularization is beneficial. FFR is not a diagnostic test for ischemic heart disease, but evaluates ischemia resulting from a stenosis. It is now possible to obtain FFR noninvasively using CTA—so-called FFR-CT (HeartFlow software termed FFR\textsubscript{CT}; Siemens cFFR) using routinely collected CTA 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.

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

European guidelines for stable coronary artery disease recommend 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”. Guidelines also recommend using “FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available” (class Ia recommendation). U.S. guidelines state 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.”

Measuring FFR during invasive coronary angiography (ICA) requires first 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, and reproducibility high. Potential complications include adverse events related to catheter use such as vessel wall damage (dissection); the time required to obtain FFR during a typical ICA is less than 10 minutes.

ICAs are frequently unnecessary in patients with stable ischemic heart disease as evidenced by low diagnostic yields. 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 coronary artery disease (left main stenosis ≥50% or ≥70% in a major epicardial or branch >2.0mm in diameter). ICA is clinically useful when patients with stable angina have failed optimal medical therapy and may benefit from revascularization. A test such as FFR-CT that could identify candidates for revascularization—those with significant physiologic obstructions—prior to planned ICA could allow avoiding unnecessary procedures and any adverse consequences.

Only the HeartFlow FFRCT software has been cleared by the U.S. Food and Drug Administration (FDA). Imaging analyses require transmitting data to a central location, taking 1 to 3 days to complete. Other prototype software is workstation-based with onsite analyses. FFR-CT cannot be calculated when images lack sufficient quality (11% to 13% in recent studies), eg, in obese individuals (eg, body mass index, >35 kg/m2).

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration**

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

HeartFlow FFRCT 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, 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 [FFRCT] 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.”

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Rationale/Source
Evidence for this policy was organized by phase of diagnostic test development (technical performance, diagnostic accuracy, effect on patient outcomes). Technical performance (phase I) data reported in 2 studies and the FDA de novo 510(k) summary were included. Five diagnostic accuracy studies (phase II) were synthesized in 2 2016 meta-analyses. One nonrandomized study and a retrospective cohort study (phase III) have reported effect on patient outcomes. No postadoption use/safety studies (phase IV) were identified.

TECHNICAL PERFORMANCE (PHASE I)
Data supporting technical performance derive from the test-retest reliability of FFR-CT and invasively measured FFR (reference standard). Other technical performance considerations were summarized in the FDA documentation.

Johnson et al (2015) reported on the repeatability of invasive FFR. Data from 190 paired assessments were analyzed (patients measured twice over 2 minutes). The test-retest coefficient of variation of 2.5% (r²=98.2%) was reported using a “smart minimum” in the analyses ("the lowest average of 5 consecutive cardiac cycles of sufficient quality within a run of 9 consecutive quality beats"). Hulten and Di Carli noted that based on the Johnson results, an FFR of 0.8 would have a 95% confidence interval (CI) of 0.76 to 0.84.

Gaur et al (2014) analyzed data from 28 patients (58 vessels) with repeated FFR-CT and invasive FFR measurements. They reported coefficients of variation of 3.4% (95% CI, 1.5% to 4.6%) for FFR-CT and 2.7% (95% CI, 1.8% to 3.3%) for invasive FFR. Although reproducibility was acceptable, whether test-retest reliability over time might be similar is unclear.

The ability to obtain FFR-CT measurements is directly related to the quality of imaging data and values are not calculated for small vessels (<1.8 mm). Nitrate administration is recommended (generally standard practice unless contraindicated) for vasodilatation, and a lack of nitrates can affect FFR-CT results. In addition, the FDA de novo summary lists factors that can adversely impact FFR-CT results including: imaging data quality, incorrect brachial pressure, myocardial dysfunction and hypertrophy, and abnormal physiology (eg, congenital heart disease). Coronary calcium may also have some impact on measurements.

Section Summary: Technical Performance
The results have indicated that test-retest reliability is acceptable and other known factors can impact variability of FFR-CT results.

DIAGNOSTIC ACCURACY (PHASE II)
Studies Included in Meta-Analyses: Per-Patient Diagnostic Accuracy
Five studies contributed results to two 2016 meta-analyses 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. The 3 HeartFlow FFRCT studies used successive software versions with reported improvement in specificity (from 54% to 79%) between versions 1.2 and 1.4. The NXT Trial formed the basis for FDA clearance, and was conducted at 11 sites in 8
countries (Canada, EU, Asia). Although not examined in the 2 included meta-analyses, subgroup analyses suggested little variation in results by sex and age. 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 (2016)
Danad et al (2016) included 23 studies published between January 2002 and February 2015 evaluating diagnostic performance of CTA, FFR-CT, single-photon emission computed tomography (SPECT), stress echocardiography (SECHO), magnetic resonance imaging (MRI), or ICA compared with an invasive FFR reference standard. 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 (current standard used in all FFR-CT studies). Per-patient and per-vessel meta-analyses were performed. Study quality was assessed using QUADAS-2; no significant biases were identified in FFR-CT studies but a high risk of biased patient selection was judged in 10 (43.4%) 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). Per-vessel results were similar except for CTA where per-patient results were considerably better (eg, C statistic of 0.85 vs 0.57). The authors noted heterogeneity in many estimates (eg, CTA sensitivity I² of 80%), as would be anticipated in diagnostic accuracy studies. Finally, pooled results for specific tests included few studies precluding applying diagnostic meta-analytic approaches30 that account for correlation sensitivities and specificities.

Wu et al (2016)
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. Studies included patients with established or suspected SIHD. In addition to the 3 FFR-CT studies pooled by Danad et al, 4 additional studies (224 patients) 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 (reported in 5 studies) and per-vessel results were pooled. All studies were rated at low risk of bias and without applicability concerns using the QUADAS-2 tool. 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% and 8.2% of participants.
Table 1. Pooled Per-Patient Pooled Diagnostic Performance of Noninvasive Tests for Invasive Fractional Flow Reserve

<table>
<thead>
<tr>
<th>Test</th>
<th>Studies</th>
<th>N</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>C</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danad et al (2016)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>2</td>
<td>70</td>
<td>90% (75 to 97)</td>
<td>94% (79 to 99)</td>
<td>0.94</td>
<td>10.3 (3.14 to 33.9)</td>
<td>0.12 (0.05 to 0.30)</td>
</tr>
<tr>
<td>FFR-CT</td>
<td>3</td>
<td>609</td>
<td>90% (85 to 93)</td>
<td>71% (65 to 75)</td>
<td>0.94</td>
<td>3.3 (1.78 to 6.25)</td>
<td>0.16 (0.11 to 0.23)</td>
</tr>
<tr>
<td>CTA</td>
<td>4</td>
<td>694</td>
<td>90% (86 to 93)</td>
<td>39% (34 to 44)</td>
<td>0.57</td>
<td>1.5 (1.25 to 1.90)</td>
<td>0.22 (0.10 to 0.50)</td>
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<tr>
<td>SECHO</td>
<td>2</td>
<td>115</td>
<td>77% (61 to 88)</td>
<td>75% (63 to 85)</td>
<td>0.82</td>
<td>3.0 (1.94 to 4.65)</td>
<td>0.34 (0.17 to 0.66)</td>
</tr>
<tr>
<td>SPECT</td>
<td>3</td>
<td>110</td>
<td>70% (59 to 80)</td>
<td>78% (68 to 87)</td>
<td>0.79</td>
<td>3.4 (1.04 to 11.1)</td>
<td>0.40 (0.19 to 0.83)</td>
</tr>
<tr>
<td>ICA</td>
<td>2</td>
<td>954</td>
<td>69% (65 to 75)</td>
<td>67% (63 to 71)</td>
<td>0.75</td>
<td>2.5 (1.25 to 5.13)</td>
<td>0.46 (0.39 to 0.55)</td>
</tr>
<tr>
<td>Wu et al (2016)</td>
<td></td>
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</tr>
<tr>
<td>FFR-CT</td>
<td>5</td>
<td>683</td>
<td>89% (85 to 93)</td>
<td>76% (64 to 84)</td>
<td>0.90</td>
<td>3.7 (2.41 to 5.61)</td>
<td>0.14 (0.09 to 0.21)</td>
</tr>
</tbody>
</table>

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

Section Summary: Diagnostic Accuracy
The number of studies (n=3) and patients (n=609) evaluated using FDA-cleared HeartFlow software is not large. Software used in successive studies was also revised to improve performance characteristics, particularly specificity. For example, using an earlier software version in the DeFACTO Trial reported a specificity of 54%. Accordingly, pooled results from Danad et al must be interpreted carefully.

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 interest. The pooled negative likelihood ratio suggests the test could be of limited value in patients where a physician has even a modestly high pretest probability of disease and belief that ICA is necessary. For example, using the point estimate and upper bound of the pooled negative likelihood ratio from Danad et al, for a pretest probability of 0.6, a negative test would yield a posttest probability of 0.19 and 0.26, or possibly not sufficiently low to convince a clinician to avoid ICA.

The pooled sensitivity of FFR-CT for detecting physiologically significant coronary stenoses appeared to compare favorably with other noninvasive imaging modalities with lower specificity than MRI, SECHO, and SPECT. There is some uncertainty in the generalizability of results obtained in these studies conducted under likely controlled conditions (eg, data from the NXT Trial forming the basis for FDA clearance).

EFFECT ON PATIENT OUTCOMES (PHASE III)
We identified 1 observational study and 1 retrospective cohort study that reported outcomes and compared an FFR-CT strategy with usual care (eg, physician choice). We found no studies that compared an FFR-CT strategy with protocol-defined alternative strategies such as one including MRI or perfusion imaging that might be considered currently recommended. No studies were identified using FFR-CT prior to ICA in patients with established coronary artery disease (CAD).

PLATFORM Study
The PLATFORM (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts) study compared diagnostic strategies with or without FFR-CT in patients with suspected stable angina but without known CAD. The study was conducted at 11 EU sites. All testing was nonemergent. Patients were divided into...
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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—“(i) invasive FFR ≤0.80 in any segment, regardless of degree of stenosis, or (ii) QCA [quantitative coronary angiography] stenosis ≥50% in a vessel ≥2.0 mm diameter without an invasively measured FFR ≤0.80 in the same distribution.” Secondary end points included ICA without obstructive disease following planned noninvasive testing, and (1) major adverse cardiovascular events (MACE) at 1 year defined as a composite of all-cause mortality, myocardial infarction, 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). CTA 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 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%.

Across the 4 study groups (2 in each stratum), mean pretest probabilities of CAD ranged from 44.5% to 51.7%; between 65.2% and 91.0% angina was judged atypical with some imbalances between groups (see Table 2). Planned noninvasive testing was performed in 204 participants, and an invasive approach in 380 participants, of whom 193 (50.8%) had undergone prior noninvasive testing.

In the planned invasive stratum, FFR-CT was requested in 134 patients and successfully obtained 117 (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 the rate of nonobstructive findings. MACE rates were low in the planned invasive stratum and did not differ between strategies. Mean level of radiation exposure though 1 year was also similar in both groups with a planned invasive strategy (10.4 and 10.7 mSv with usual care and FFR-CT, respectively). No differences in QOL were found between planned invasive strategy groups.

In the noninvasive stratum, FFR-CT was requested in 67 patients and obtained in 60 (89.6%) in the FFR-CT group. ICA rates in the usual care and FFR-CT groups were 12.0% and 18.2% respectively. Rates of ICA with no obstructive disease did not differ significantly—usual care group was 6.0% and FFR-CT was 12.5% (difference, -6.5%; 95% CI, -14.4 to 1.4).

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 an observational design, high rate of no obstructive disease with a usual care strategy (73.3%), and somewhat small sample size. Although finding a large effect in patients with planned invasive testing, the observational design limits causal inferences and certainty in 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. Additionally, approximately half of the patients with planned invasive testing had not undergone noninvasive evaluation. Elective ICA as the initial evaluation of patients with suspected SIHD is infrequently indicated. Finally, the 73.3% rate of ICA without significant obstructive disease in the usual care arm was markedly higher than the 30% rate assumed in the sample size estimates.

### Table 2. PLATFORM Study Patient Characteristics and Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Noninvasive</th>
<th>Planned Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual Care</td>
<td>FFR-CT</td>
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<tr>
<td>Characteristics</td>
<td>(n=100)</td>
<td>(n=104)</td>
</tr>
<tr>
<td>Age (SD), y</td>
<td>57.9 (10.7)</td>
<td>59.5 (9.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>34 (34.0)</td>
<td>44 (42.3)</td>
</tr>
<tr>
<td>Race/ethnic minority, n (%)</td>
<td>5 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pretest probability CAD (SD), %</td>
<td>44.5 (15.3)</td>
<td>45.3 (16.8)</td>
</tr>
<tr>
<td>Typical, n (%)</td>
<td>8 (8.0)</td>
<td>18 (17.3)</td>
</tr>
<tr>
<td>Atypical, n (%)</td>
<td>91 (91.0)</td>
<td>80 (76.9)</td>
</tr>
<tr>
<td>Noncardiac, n (%)</td>
<td>1 (1.0)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Prior noninvasive testing, n (%)</td>
<td>92 (49.2)</td>
<td>101 (52.3)</td>
</tr>
<tr>
<td>FFR-CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requested, n (%)</td>
<td>67 (64.4)</td>
<td>134 (69.4)</td>
</tr>
<tr>
<td>Successfully performed, n (%)</td>
<td>60 (57.7)</td>
<td>117 (60.1)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
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<tr>
<td>ICA no obstructive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core lab, n (%)</td>
<td>6 (6.0)</td>
<td>13 (12.5)</td>
</tr>
<tr>
<td>Absolute difference, % (95% CI)</td>
<td>-6.5 (-14.4 to 1.4)</td>
<td>60.8 (53.0 to 68.7)</td>
</tr>
<tr>
<td>Site read, n (%)</td>
<td>5 (5.0)</td>
<td>8 (7.7)</td>
</tr>
<tr>
<td>Absolute difference, % (95% CI)</td>
<td>-2.7 (-9.4 to 4.0)</td>
<td>47.4 (39.2 to 55.6)</td>
</tr>
<tr>
<td>By prior noninvasive testing*a</td>
<td></td>
<td></td>
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<tr>
<td>Performed, n/N (%)</td>
<td>76/97 (78.3)</td>
<td>11/106 (10.4)</td>
</tr>
<tr>
<td>Not performed, n/N (%)</td>
<td>63/90 (70.0)</td>
<td>13/87 (14.9)</td>
</tr>
<tr>
<td>ICA, n (%)</td>
<td>12 (12.0)</td>
<td>19 (18.3)</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>3 (3.0)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Invasive FFR, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>1-year outcomes, n (%)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

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Nørgaard et al (2016) Retrospective Cohort

Nørgaard et al (2016) reported results from symptomatic patients referred for coronary CTA at a single center in Denmark from May 2014 to April 2015. 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 coronary CTA; 858 received medical therapy, 82 underwent ICA, 44 perfusion imaging, and 189 FFR-CT (185 [98%] obtained successfully). Of the 57 (31%) patients, 1 or more vessels had FFR-CT values of 0.80 or less and 49 (86%) went on to ICA; of the 128 with higher FFR-CT values, only 5 (4%) went on to ICA. The correlation between FFR-CT and invasive FFR was 0.77 from the 51 vessels where both results were obtained; the limit of agreement (95% CI) in FFR values was -0.06 to 0.14.

The authors noted: “This report demonstrates for the first time the real-world feasibility of FFRCT testing in consecutive patients with intermediate-range coronary stenosis.” The implications and generalizability of these single center results are somewhat limited. It is unclear whether ICA was planned in patients undergoing FFR-CT and information on provision and efficacy of medical therapy was unavailable. Agreement between FFR-CT and invasive FFR appeared similar to the diagnostic studies, but the estimate is subject to verification bias.

Section Summary: Effect on Patient Outcomes

The clinical usefulness of FFR-CT for avoiding ICA has been examined in 1 prospective observational study (PLATFORM) and 1 retrospective cohort study, both conducted outside the United States. Study results support the notion that, for patients with planned ICA, FFR-CT can decrease the rate of ICA and ICA finding no significant obstructive disease, ie, that FFR-CT may provide clinically useful information to clinicians and patients. However, the implications of PLATFORM results must consider its observational design, high rate of no obstructive disease with a usual care strategy (73.3%), limited sample size, EU setting, and generalizability. A single-center Danish retrospective cohort study including 189 patients undergoing FFR-CT was conducted outside investigational settings.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>NCT02805621</td>
<td>Machine leArning Based CT angiograpHy derIved FFR: a Multi- ceNteR, Registry</td>
<td>352</td>
<td>Jul 2017</td>
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<tr>
<td>NCT02173275</td>
<td>Computed TomogRaphic Evaluation of Atherosclerotic DEterminants of Myocardial IsChEmia</td>
<td>618</td>
<td>Jul 2017</td>
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</table>
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NCT02208388 Prospective Evaluation of Myocardial Perfusion Computed Tomography Trial 1000 Apr 2024
NCT02499679 Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) 5000 Feb 2021

NCT: national clinical trial.

SUMMARY OF EVIDENCE
For individuals who have suspected stable ischemic heart disease and planned ICA who receive FFR-CT, the evidence includes studies on test technical performance, 2 meta-analyses of diagnostic accuracy, and 2 studies of patient outcomes. Relevant outcomes are test accuracy and validity, morbid events, quality of life, resource utilization, and treatment-related mortality and morbidity. FFR-CT may offer an effective means to reduce unnecessary ICA with a rationale for a potential role in decision making. Test performance characteristics are consistent with a negative test reducing the probability of significant obstructive disease (eg, vessels with FFR <0.80) and potentially altering a decision to perform ICA. However, outcome data are limited and obtained entirely from nonrandomized studies with comparisons only to usual care. Limitations and uncertainties in body of evidence examining FFR-CT prevent conclusions concerning the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
2. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol. Jun 4 2013;61(22):2233-2241. PMID 23562923

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Noninvasive Fractional Flow Reserve Using Computed Tomography Angiography

Policy # 00537
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Current Effective Date: 02/15/2017


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Policy History
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02/02/2017 Medical Policy Committee review
02/15/2017 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 02/2018

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<th>Code Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>CPT</td>
<td>93799</td>
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<tr>
<td>HCPCS</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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</table>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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