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Contrast-Enhanced Coronary Computed Tomography Angiography (CCTA) for Coronary Artery Evaluation

Policy # 00153
Original Effective Date: 07/15/2005
Current Effective Date: 07/02/2018

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

Note: Noninvasive Fractional Flow Reserve Using Computed Tomography Angiography is addressed in medical policy 00537.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

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

Based on review of available data, the Company may consider the use of contrast-enhanced coronary computed tomography angiography (CCTA) for coronary artery evaluation to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility will be considered when using at least a 64-slice multidetector row helical computed tomographic scanner for ANY of the following conditions:

- Evaluation of anomalous (native) coronary arteries in symptomatic patients when the results will impact treatment; OR
- Assessment of suspected or established complex congenital heart disease including anomalies of coronary circulation, great vessels and cardiac chambers and valves; OR
- Evaluation of pulmonary vein anatomy prior to invasive radiofrequency ablation for atrial fibrillation or flutter; OR
- Evaluation of patients with acute chest pain who do not have known coronary artery disease (CAD) in the emergency room/emergency department (ED) setting; OR
- For exclusion of CAD in patients with left ventricular ejection fraction < 55% and low or intermediate coronary heart disease risk (using standard methods of risk assessment such as Framingham or the American College of Cardiology [ACC] criteria) in patients whom CAD has not been excluded as the etiology of the cardiomyopathy; OR
- Patients at intermediate coronary heart disease risk (using standard methods of risk assessment such as Framingham or ACC criteria) being evaluated for non-coronary artery cardiac surgery (including valvular and ascending aortic surgery) to avoid an invasive angiogram, where all of the necessary preoperative information can be obtained using cardiac computed tomography (CT); OR
- To evaluate patients with suspected CAD who have low or intermediate coronary heart disease risk (using standard methods of risk assessment such as Framingham or ACC criteria) and have had an equivocal myocardial perfusion imaging (MPI) or stress echo within the preceding

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60 days; OR

- To evaluate patients with suspected CAD who have a low coronary heart disease risk (using standard methods of risk assessment) who have had an abnormal MPI or stress echo within the preceding 60 days suspected to be a false positive; OR
- To evaluate patients with suspected stable ischemic heart disease with at least intermediate risk (using standard methods of risk assessment such as Framingham or ACC criteria) when no CAD imaging evaluation (e.g., MPI, cardiac positron emission tomography (PET), stress echocardiogragphy (SE), CCTA, or coronary angiography) has been performed within the preceding sixty (60) days.

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 contrast-enhanced CCTA for coronary artery evaluation to be **investigational*** for all other indications.

Policy Guidelines

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

Background/Overview

CORONARY ARTERY DISEASE
Various noninvasive tests are used to diagnose CAD. They can be broadly classified as those that detect functional or hemodynamic consequences of obstruction and ischemia (exercise treadmill testing, MPI, stress echocardiography with or without contrast), and others that identify the anatomic obstruction itself (CCTA, coronary magnetic resonance imaging). Functional testing involves inducing ischemia by exercise or pharmacologic stress and detecting its consequences. However, not all patients are candidates. For example, obesity or obstructive lung disease can make obtaining echocardiographic images of sufficient quality difficult. Conversely, the presence of coronary calcifications can impede detecting coronary anatomy with CCTA.

Diagnostic Testing
Some tests will be unsuitable for particular patients. The presence of dense arterial calcification or an intracoronary stent can produce significant beam-hardening artifacts and may preclude a 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 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.

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 considered significant.

Contrast-enhanced CCTA is a noninvasive imaging test that requires the use of intravenously administered contrast material and high-resolution, high-speed CT machinery to obtain detailed volumetric images of blood vessels. It has been suggested that CCTA may help rule out CAD and avoid invasive coronary angiography (ICA) in patients with a low clinical likelihood of significant CAD. Also of interest is the potentially important role of nonobstructive plaques (i.e., those associated with <50% stenosis) because their presence is associated with increased cardiac event rates. CCTA also can visualize the presence and composition of these plaques and quantify plaque burden better than conventional angiography, which only visualizes the vascular lumen. Plaque presence has been shown to have prognostic importance.

CORONARY ARTERIAL ANOMALIES
Congenital coronary arterial anomalies (i.e., abnormal origin or course of a coronary artery) that lead to clinically significant problems are relatively rare. Symptomatic manifestations may include ischemia or syncope. Clinical presentation of anomalous coronary arteries is difficult to distinguish from other more common causes of cardiac disease; however, an anomalous coronary artery is an important diagnosis to exclude, particularly in young patients who present with unexplained symptoms (e.g., syncope). There is no specific clinical presentation to suggest a coronary artery anomaly.

RADIATION EXPOSURE
Levels of radiation delivered with current generation scanners using reduction techniques (prospective gating and spiral acquisition) have declined substantially—typically to under 10 mSv. For example, an international registry developed to monitor CCTA radiation exposure recently reported a median of 2.4 mSv (interquartile range, 1.3-5.5). By comparison, radiation exposure accompanying rest-stress perfusion imaging varies by isotope used—approximately 5 mSv for rubidium 82 (PET), 14 mSv for fluorine 18 fluorodeoxyglucose, 9 mSv for sestamibi (single-photon emission CT), and 41 mSv for thallium; during diagnostic ICA, approximately 7 mSv is delivered. Electron-beam CT using electrocardiogram triggering delivers the lowest dose (0.7-1.1 mSv with 3-mm sections). Any cancer risk due to radiation exposure from a single cardiac imaging test depends on age (higher with younger age at exposure) and sex (greater for women). Empirical data have suggested that every 10 mSv of exposure is associated with a 3% increase in cancer incidence over 5 years.

The use of electron-beam CT or spiral CT to detect coronary artery calcification is addressed separately in medical policy 00031.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
CCTA is performed using multidetector-row CT, and multiple devices have been cleared for marketing by the U.S. FDA through the 510(k) process. Current machines are equipped with at least 64 detector rows. Intravenous iodinated contrast agents used for CCTA also have received FDA approval.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

This review has been informed by a 2005, 2006, and 2011 Technology Evaluation Center (TEC) Assessment.

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) its technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (demonstration that the diagnostic information can be used to improve patient outcomes).

PATIENTS WITH ACUTE CHEST PAIN PRESENTING IN THE EMERGENCY SETTING

Clinical Context and Test Purpose
The purpose of CCTA imaging in patients with acute chest pain is to diagnose coronary artery obstruction and guide treatment decisions.

The question addressed in this evidence review is: Does CCTA improve the net health outcome of patients with acute chest pain?

The specific clinical context of each test is described briefly in the following sections. The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with acute chest pain and suspected CAD who are at intermediate to low risk.

Interventions
The intervention of interest is CCTA.

Comparators
The comparator of interest is standard ED care and alternative noninvasive testing including stress tests.

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Outcomes
The outcomes of interest are mortality, diagnostic accuracy, and utilization of invasive coronary artery angiography.

Timing
The time of interest is in the first few days after admission to an ED and after several years or more after CCTA to evaluate event rates.

Setting
The setting is hospital EDs.

Clinical Validity
The diagnostic characteristics of CCTA have not been directly assessed in patients in the ED setting. Because patients who test negative on CCTA are discharged from care and their disease status is unknown, there is verification bias, and diagnostic characteristics of CCTA cannot be determined. The diagnostic characteristics of CCTA, previously established in other studies, were assumed to apply to patients in the ED setting and were tested in randomized trials to establish clinical utility.

Clinical Utility
In 2016, the Agency for Healthcare Research and Quality published a comparative effectiveness review on noninvasive testing for CAD. The review found that:

- After CCTA, clinical outcomes for patients with an intermediate pretest risk
  - were similar when compared with usual care or functional testing (low-to-moderate strength of evidence).
  - were similar when compared with single-photon emission computed tomography (SPECT) (low strength of evidence).
- After CCTA, referral for ICA and revascularization
  - was more common than after functional testing (high strength of evidence).
  - was similar compared with SPECT and usual care (low strength of evidence).
- After CCTA, additional testing in the ED setting
  - was less common compared with usual care (moderate strength of evidence).
  - was more common than after SPECT (high strength of evidence).
- After CCTA, hospitalization
  - was less common compared with usual care in the ED setting (moderate to low strength of evidence).
  - was similar to functional testing in the outpatient setting (moderate strength of evidence).

Overall, the Agency for Healthcare Research and Quality review found no clear differences between strategies for clinical or management outcomes, although CCTA may lead to a higher frequency of referral for ICA and revascularization.

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A 2011 TEC Assessment examined evidence for patients with acute chest pain and without known CAD. Randomized controlled trials (RCTs) and prospective observational studies were identified. RCTs of CCTA procedures conducted in ED settings are described in Table 1.

A 2007 RCT by Goldstein et al randomized 197 patients from a single center without evidence of acute coronary syndromes to CCTA (n=99) or usual care (n=98). Over a 6-month follow-up, no cardiac events occurred in either arm. ICA rates were somewhat higher in the CCTA arm. Diagnosis was achieved more quickly after CCTA.

The CT-STAT RCT evaluated a similar sample of 699 patients from 16 centers. Over a 6-month follow-up, there were no deaths in either arm; there were 2 cardiac events in the CCTA arm and one in the perfusion imaging arm. ICA rates were similar in both arms. A second noninvasive test was obtained more often after CCTA (10.2% vs 2.1%), but cumulative radiation exposure in the CCTA arm (using retrospective gating) was significantly lower (mean, 11.5 mSv vs 12.8 mSv). Time to diagnosis was shorter and estimated ED costs lower with CCTA.

A 2012 RCT (AC RIN-PA) by Litt et al also evaluated the safety of CCTA in patients in the ED. Although the trial was a randomized comparison with traditional care, the principal outcome was safety after negative CCTA examinations. No patients who had negative CCTA examinations (n=460) died or had a myocardial infarction (MI) within 30 days. Compared with traditional care, patients in the CCTA group had higher rates of discharge from the ED (49.6% vs 22.7%), shorter lengths of stay, and higher rates of detection of coronary disease.

A 2012 RCT (ROMICAT II) by Hoffmann et al compared length of stay with outcomes in patients evaluated using CCTA or usual care. For patients in the CCTA arm, mean hospital length of stay was reduced by 7.6 hours, and more patients were discharged directly from the ED (47% vs 12%). There were no undetected coronary syndromes or differences in adverse events at 28 days. However, in the CCTA arm, there was more subsequent diagnostic testing and higher cumulative radiation exposure. Cumulative costs of care were similar between groups.

A 2014 RCT (CT-COMPARE) by Hamilton-Craig et al assessed length of stay and patient costs in 562 patients presenting to the ED with low-to-intermediate risk chest pain who received CCTA or exercise stress testing. Costs within 30 days of presentation were significantly lower in the CCTA group (mean, $2193) than in the exercise testing group (mean, $2704; $p<0.001$). Length of stay was significantly reduced in the CCTA patients compared with the exercise testing patients. Clinical outcomes at 30 days and at 12 months did not differ.

In 2015, Linde et al reported long-term follow-up from the CATCH trial. This trial randomized 600 patients to a CCTA-guided strategy or to standard of care (SOC). For the CCTA-guided strategy, referral for ICA required coronary stenosis greater than 70%. This trial differed in design from the other trials, because

patients had been discharged from the ED, and if there was intermediate stenosis (50%-70%) on CCTA, a stress test was used. The referral rate for ICA was 17% for the CCTA strategy vs 12% with SOC (p=0.1). At a median 18.7-month follow-up, a major cardiac event was observed in 5 patients in the CCTA-strategy arm compared with 14 in the SOC group (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.16 to 0.95; p=0.04). Three other follow-up studies reported no cardiac events after a negative CCTA in the ED after 12 (N=481), 24 (N=368), or 47 months (N=506).

Table 1. RCTs Comparing CCTA With SOC in the Evaluation of Acute Chest Pain

Study (Year)	N	Study Design	FU, mo	MI in Neg CCTA Arm	LOS, h (p)	ICA (CCTA vs Control), %
Goldstein et al (2007)	197	CCTA vs SPECT	6	0	3.4 vs 15	12.1 vs 7.1
Goldstein et al (2011)	699	CCTA vs SPECT	6	0	2.9 vs 6.3	7.2 vs 6.5
Litt et al (2012)	1370	CCTA vs SOC	1	0	18 vs 24	9.0 vs 3.5
Hoffmann et al (2012)	1000	CCTA vs SOC	1	0	23.2 vs 30.8	11 vs 7
Hamilton-Craig et al (2014)	562	CCTA vs SOC	12	0	13.5 vs 20.7	8.0 vs 3.8

Adapted from Marcus et al (2016).
CCTA: coronary computed tomography angiography; FU: follow-up; ICA: invasive coronary angiography; LOS: length of stay; MI: myocardial infarction; Neg: negative; RCT: randomized controlled trial; SOC: standard of care; SPECT: single-photon emission computed tomography.

Section Summary: Acute Chest Pain Presenting in the Emergency Setting
The high negative predictive value of CCTA in patients presenting to the ED with chest pain permits ruling out coronary disease with high accuracy. The efficiency of the workup is improved, because patients are safely and quickly discharged from the ED with no adverse outcomes among patients with negative CCTA examinations.

Other important outcomes that require consideration when comparing technologies include ICA rates, use of a second noninvasive test, radiation exposure, and follow-up of any incidental findings. Some studies have shown that subsequent invasive testing is more frequent in patients who received CCTA. Studies have differed over which treatment strategies result in higher overall radiation exposure. Incidental findings after CCTA are common and lead to further testing, but the impact of these findings on subsequent health outcomes is uncertain.

PATIENTS WITH STABLE CHEST PAIN AND SUSPECTED CAD

Clinical Context and Test Purpose
The purpose of CCTA in patients with stable chest pain and suspected CAD is to diagnose coronary artery obstruction and guide treatment decisions.

Before use of CCTA, the initial noninvasive test in a diagnostic strategy was always a functional test. Current practice guidelines recommend a noninvasive test be performed in patients with intermediate risk of

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CAD. The choice of functional test is based on clinical factors such the predicted risk of disease, electrocardiogram interpretability, and ability to exercise. When disease is detected, treatment alternatives include medical therapy or revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). If revascularization is indicated, patients undergo ICA to confirm the presence of stenosis. Which approach to adopt is based on the extent of anatomic disease, symptom severity, evidence of ischemia from functional testing, and, more recently, fractional flow reserve obtained during invasive angiography. Many studies have shown that only a subset of anatomically defined coronary lesions are clinically significant and benefit from revascularization. Other studies have shown only limited benefits of treating coronary stenoses in stable patients. Thus an assessment of the diagnostic characteristics of CCTA alone is insufficient to establish clinical utility. A difficulty in evaluating a noninvasive diagnostic test for CAD is that patient outcomes depend not only on the test results, but also on the management and treatment strategy. The most convincing evidence of clinical utility compares outcomes after anatomic-first (CCTA) and functional-first (e.g., perfusion imaging, stress echocardiography) strategies.

Relevant studies reviewed here include those comparing the diagnostic performance of CCTA with angiography, studies of outcomes of patients undergoing CCTA vs alternative tests, and studies of incidental findings and radiation exposure.

The question addressed in this evidence review is: Does CCTA improve the net health outcome of patients with stable chest pain?

The specific clinical context of each test is described briefly in the following sections. The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with stable chest pain and suspected CAD who are at intermediate to low risk.

Interventions
The intervention of interest is CCTA.

Comparators
The comparator of interest is noninvasive testing including exercise electrocardiography, MPI, and stress echocardiography.

Outcomes
The outcomes of interest are mortality, sensitivity and specificity, MI, hospitalization, and utilization of ICA.

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Timing
The time of interest is in the short-term to evaluate follow-up procedures after imaging and for several years or more after CCTA to determine event rates.

Setting
The setting is cardiology clinics equipped with standard noninvasive testing for CAD and CCTA.

Diagnostic Accuracy
There is a fairly large body of evidence evaluating the diagnostic characteristics of CCTA for identifying coronary lesions. The best estimate of the diagnostic characteristics of CCTA can be obtained from recent meta-analyses and systematic reviews. Table 2 shows ranges of sensitivity and specificity for functional noninvasive tests from studies of the diagnosis and management of stable angina reviewed by Fihn et al (2012). Sensitivities tended to range between 70% and 90%, depending on the test and study, and specificities ranged between 70% and 90%.

For CCTA, estimates of sensitivity from various systematic reviews are considerably higher (see Table 3). The guideline statement from Fihn cited studies reporting sensitivities between 93% and 97%. A 2011 systematic review by Ollendorf et al of 42 studies showed a summary sensitivity estimate of 98% and a specificity of 85%. A 2010 meta-analysis of 8 studies conducted by the Health Quality Ontario showed a summary sensitivity estimate of 97.7% and a specificity of 79%. In the meta-analysis by Nielsen et al (2014), sensitivity rates for CCTA varied between 98% and 99% (depending on the analysis group).

Table 2. Sensitivity and Specificity Estimates for Functional Noninvasive Tests From Guidelines

Noninvasive Test	Sensitivity (Range or Single Estimates), %	Specificity (Range or Single Estimates), %
Exercise electrocardiography	61	70-77
Pharmacologic stress echocardiography	85-90	79-90
Exercise stress echocardiography	70-85	77-89
Exercise myocardial perfusion imaging	82-88	70-88
Pharmacologic stress myocardial perfusion imaging	88-91	75-90

Table 3. Sensitivity and Specificity Estimates for CCTA From Guidelines and Meta-Analyses

Study (Year)	Study Type	Sensitivity (Range or Single Estimates), %	Specificity (Range or Single Estimates), %
Fihn et al (2012)	Guideline	93-97	80-90
Ollendorf et al (2011)	Meta-analysis	98	85
Health Quality Ontario (2010)	Meta-analysis	97.7	79
Nielsen et al (2014)	Meta-analysis	98-99	82-88

CCTA: coronary computed tomography angiography.

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Clinical Utility

Randomized Controlled Trials
For patients at intermediate risk of CAD, 3 major RCTs were identified comparing the net health outcome following a CCTA strategy with outcomes from other noninvasive testing strategies.

The PROMISE trial randomized 10,003 patients to CCTA or exercise electrocardiography, nuclear stress testing, or stress echocardiography (as determined by physician preference) as the initial diagnostic evaluation. For the composite end point of death, MI, hospitalization for unstable angina, or major procedural complication, the outcome rates between the 2 groups showed no statistically significant difference (HR=1.04; 95% CI, 0.83 to 1.29). CCTA also did not meet prespecified noninferiority criteria compared with alternative testing. Some clinical outcomes assessed at 12 months favored CCTA, but the differences were nonsignificant. Coronary catheterization rates and revascularization rates were higher in the CCTA group. In further prespecified analysis of PROMISE trial data, Hoffmann et al (2017) found that there was no difference in event rates (death, MI, or angina) between the groups at a median of 26 months follow-up. However, CCTA had better discriminatory ability than functional testing to predict events (e.g., in categories of normal, mildly abnormal, moderately abnormal, and severely abnormal) in patients who had nonobstructive CAD (p=0.04). When the Framingham Risk Score was added to functional testing results, there was no significant difference in prognostic capability between the approaches (p=0.29).

In the SCOT-HEART trial, 4146 patients were randomized to CCTA plus SOC or SOC alone. The primary end point was the change in the proportion of patients with a more certain diagnosis (presence or absence) of angina pectoris. Secondary outcomes included death, MI, revascularization procedures, and hospitalizations for chest pain. Analysis of the primary outcome showed that patients who underwent CCTA had an increase in the certainty of their diagnosis relative to those in usual care (relative risk, 1.79; 95% CI, 1.62 to 1.96). Regarding health outcomes, the rates of heart disease death and MI were lower with CCTA (1.3% vs 2.0%; HR=0.62; p=0.053), but results were of marginal statistical significance. In 2017, Williams et al reported on symptoms and quality of life for participants in the SCOT-HEART trial. Symptoms improved in both groups; however, improvements in symptoms and quality of life at 6 months were lower in patients in the CCTA arm than the functional testing arm. This outcome was due primarily to patients who were diagnosed with moderate CAD or had a new prescription of preventative therapy compared with patients diagnosed with normal coronary arteries or who had their preventative therapy discontinued.

The CAPP trial (2015) randomized 500 patients with stable chest pain to CCTA or exercise stress testing. The primary outcome was the change difference in scores of Seattle Angina Questionnaire domains at 3 months. Patients were also followed for further diagnostic tests and management. In the CCTA arm, 15.2% of subjects underwent revascularization. In the exercise stress testing arm, 7.7% underwent revascularization. For the primary outcome, angina stability and quality of life showed significantly greater improvement in the CCTA arm than in the exercise stress testing arm.

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Nonrandomized Studies
Nonrandomized studies comparing outcomes of patients following a CCTA strategy with outcomes following other noninvasive testing strategies were also identified. Some studies have emphasized downstream utilization of diagnostic testing and procedures rather than patient outcomes.

Nielsen et al (2013) conducted an observational trial comparing patients who underwent CCTA with those having exercise stress testing. Patients had a low-to-intermediate pretest probability of CAD and presented with suspected angina. Patients were followed for 12 months after the initial test, and assessed for occurrence of major adverse events (e.g., cardiac death, nonfatal MI). Subsequent utilization of cardiovascular tests and therapy were also compared between groups. Clinical outcomes were not formally compared because there were few clinical events. No deaths were reported during the follow-up period. Three patients in the exercise testing group had MIs within 12 months. For downstream test utilization, the exercise test group had greater subsequent use of perfusion imaging (9% vs 4%, p=0.03) and greater mean total 1-year costs (€1777 vs €1510, p=0.03). Rates of ICA and revascularization did not differ significantly.

Shreibati et al (2011) used Medicare claims data to compare all-cause mortality, subsequent utilization of several cardiac tests, treatment, and total costs in patients who underwent initial noninvasive testing with CCTA, stress echocardiography, MPI, or exercise electrocardiography. In this study, patients undergoing CCTA had higher rates of several types of utilization subsequent to their tests than patients undergoing MPI. The study also presented outcomes for both stress echocardiography and exercise electrocardiography, but results tended not to differ from outcomes for MPI. There were increased rates of ICA (22.9% vs 12.1%) and revascularization (11.4% vs 4.6%). Total spending and CAD-related spending were also higher for CCTA than for MPI. There was no significant difference in all-cause mortality between CCTA and MPI. Although the mortality rate for CCTA (1.05%) was slightly lower than the mortality rate for MPI (1.28%), the adjusted odds ratio showed a higher risk of mortality, which may be due to unusual confounding. However, there was a slightly lower likelihood of hospitalization for MI (adjusted OR=0.60; p=0.04).

In Min et al (2008), costs and clinical outcomes for patients undergoing initial CCTA were compared with patients undergoing initial MPI. The data source for this study was a proprietary claims database from 2 regional health plans. Utilization of medical care was lower after CCTA. Additionally, overall costs were lower, the proportion receiving ICA was lower, and the proportion receiving revascularization was lower after CCTA. Regarding clinical outcomes, the proportion with a hospitalization for angina was lower in the CCTA group. The CCTA group also had a lower rate of a combined outcome of angina or MI hospitalization (HR=0.70; 95% CI, 0.55 to 0.90).

In 2825 patients evaluated for stable angina and suspected CAD in Japan, Yamauchi et al (2012) examined outcomes after initial CCTA (n=625), MPI (n=1205), and angiography (n=950). Average follow-up was 1.4 years. In a Cox proportional hazards model adjusted for potential confounders, the relative hazard rates of major cardiac events after MPI or CCTA were lower than after angiography; annual rates were 2.6%, 2.1%,

and 7.0%, respectively. Revascularization rates were higher after CCTA than MPI (OR=1.6; 95% CI, 1.2 to 2.2).

Section Summary: Stable Angina and Suspected CAD
A number of studies have evaluated the diagnostic accuracy of CCTA for diagnosing CAD in an outpatient population. In general, these studies have reported high sensitivity and specificity, although there is some variability in these parameters across studies. Meta-analyses of these studies have shown that, for detection of anatomic disease, CCTA has a sensitivity greater than 95%, which is superior to all other functional noninvasive tests. Specificity is at least as good as other noninvasive tests. However, the link between improved diagnosis and health outcomes is not as clear, and thus outcome studies are necessary to demonstrate the clinical utility of CCTA.

Direct clinical trial evidence comparing CCTA and other strategies in the diagnostic management of stable patients with suspected CAD has not demonstrated the superiority of CCTA in any of the single clinical trials. Clinical trials have demonstrated greater utilization of ICA and subsequent revascularization procedures after CCTA. An important problem when interpreting the clinical trials is that the comparator strategies differ: in the PROMISE and the CAPP trials, CCTA was compared with an alternative non-invasive test; in other studies, CCTA supplemented usual care (which may or may not have included a noninvasive test). These trial design differences are likely to reflect how CCTA is used in clinical practice—either as a substitute for another noninvasive test or as an adjunct to other noninvasive tests. The PROMISE trial explicitly compared CCTA with an alternative functional test as the initial diagnostic test. Although the trial did not show the superiority of CCTA and did not meet prespecified criteria for noninferiority, examination of some secondary clinical outcomes supports a conclusion of “at least” noninferiority. The results of the other randomized trials are consistent with the noninferiority of CCTA compared with other established noninvasive tests. Thus, the randomized studies indicate that outcomes of patients are likely to be similar with CCTA vs other noninvasive tests.

The nonrandomized studies of CCTA have several methodologic shortcomings, including reliance on administrative data and inability to assess and adjust fully for potential confounding. The findings have shown little difference in patient outcomes between diagnostic strategies. Downstream utilization of medical care showed variable findings.

SUSPECTED ANOMALOUS CORONARY ARTERIES
Anomalous coronary arteries are an uncommon finding during angiography, occurring in approximately 1% of coronary angiograms completed for evaluation of chest pain. However, these congenital anomalies can be clinically important depending on the course of the anomalous arteries. A number of case series have consistently reported that CCTA can delineate the course of these anomalous arteries, even when conventional angiography cannot. However, none of the studies reported results when the initial reason for the study was to identify these anomalies, nor did any of the studies discuss the impact on therapeutic

decisions. Given the uncommon occurrence of these symptomatic anomalies, it is unlikely that a prospective trial of CCTA could be completed.

INCIDENTAL FINDINGS AND RADIATION EXPOSURE

A number of studies using scanners with 64 or more detector rows were identified. Incidental findings were frequent (26.6%-68.7%) with pulmonary nodules typically the most common and cancers typically more rare (≈5/1000 or less). Aglan et al (2010) compared the prevalence of incidental findings when the field of view was narrowly confined to the cardiac structures with that when the entire thorax was imaged. As expected, incidental findings were less frequent in the restricted field (clinically significant findings in 14% vs 24% when the entire field was imaged).

Exposure to ionizing radiation increases lifetime cancer risk. Three studies have estimated excess cancer risks due to radiation exposure from CCTA. Assuming a 16-mSv dose, Berrington de Gonzalez et al (2009) estimated that the 2.6 million CCTAs performed in 2007 would result in 2700 cancers or approximately 1 per 1000. Smith-Bindman et al (2009) estimated that cancer would develop in 1 of 270 women and 1 of 600 men age 40 undergoing CCTA with a 22-mSv dose. Einstein et al (2007) employed a standardized phantom to estimate organ dose from 64-slice CCTA. With modulation and exposures of 15 mSv in men and 19 mSv in women, calculated lifetime cancer risk at age 40 was 7 per 1000 men (1/143) and 23 per 1000 women (1/43). However, estimated radiation exposure used in these studies was considerably higher than received with current scanners—now typically under 10 mSv and often less than 5 mSv with contemporary machines and radiation reduction techniques. For example, in the 47-center PROTECTION I study enrolling 685 patients, the mean radiation dose was 3.6 mSv, using a sequential scanning technique. In a 2012 study of patients undergoing an axial scanning protocol, mean radiation dose was 3.5 mSv, and produced equivalent ratings of image quality compared with helical scan protocols, which had much higher mean radiation doses of 11.2 mSv.

Section Summary: Incidental Findings and Radiation Exposure

Although studies of incidental findings and radiation exposure raise issues regarding the potential for adverse effects of CCTA, there is insufficient evidence that the magnitude of these effects is important for ascertaining the net benefit or risk of CCTA in this setting.

OTHER DIAGNOSTIC USES OF CCTA

Given its ability to define coronary artery anatomy, there are many potential diagnostic uses of CCTA, including patency of coronary artery bypass grafts, in-stent restenosis, screening, and preoperative evaluation.

Patency

Evaluating patency of vein grafts is less technically challenging due to vein size and lesser motion during imaging. In contrast, internal mammary grafts may be more difficult to image due to their small size and presence of surgical clips. Finally, assessing native vessels distal to grafts presents difficulties, especially when calcifications are present, due to their small size. For example, a 2008 systematic review, including

results from 64-slice scanners, reported high sensitivity (98%; 95% CI, 95% to 99%; 740 segments) and specificity (97%; 95% CI, 94% to 97%). Other small studies have reported high sensitivity and specificity. Lacking are multicenter studies demonstrating likely clinical benefit, particularly given the reasonably high disease prevalence in patients evaluated.

In-Stent Restenosis
Use of CCTA for evaluating in-stent restenosis presents other technical challenges—motion, beam hardening, and partial volume averaging. Whether these challenges can be overcome to obtain sufficient accuracy and impact outcomes has not been demonstrated.

Screening
Use for screening a low-risk population was recently evaluated in 1000 patients undergoing CCTA or control intervention of 1000 similar patients. Findings reported in this 2011 study were abnormal in 215 screened patients. Over 18 months of follow-up, screening was associated with more invasive testing, statin use, but no difference in cardiac event rates.

Preoperative Evaluation
Use for screening in a high-risk population was evaluated in the FACTOR-64 trial, which randomized 900 subjects with diabetes to screening with CCTA or SOC. Patients in this trial were asymptomatic, but considered to be at high risk for CAD due to long-standing diabetes. The primary outcome was a composite of mortality, nonfatal MI, or unstable angina requiring hospitalization. At a median follow-up of 4 years, there was no significant difference between the groups for the primary outcome (CCTA, 6.2% vs control, 7.6%; HR=0.80; p=0.38).

CCTA for preoperative evaluation before noncardiac surgery has been suggested, but evaluated only in small studies and lacking demonstrable clinical benefit.

SUMMARY OF EVIDENCE
For individuals who have acute chest pain and suspected CAD in the emergency setting, at intermediate to low risk, who receive CCTA, the evidence includes several RCTs. Relevant outcomes are overall survival, morbid events, and resource utilization. Trials have shown similar patient outcomes, with faster patient discharges from the ED, and lower short-term costs. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have stable chest pain, intermediate risk of CAD, meeting guideline criteria for noninvasive testing (i.e., intermediate risk) who receive CCTA, the evidence includes studies of diagnostic accuracy of CCTA, randomized trials comparing CCTA with alternative diagnostic strategies, and observational studies comparing CCTA with alternative diagnostic strategies. Relevant outcomes are overall survival, test accuracy, morbid events, and resource utilization. Studies of diagnostic accuracy have shown that CCTA has higher sensitivity and similar specificity to alternative noninvasive tests. Although

randomized trials have not shown the superiority of CCTA over other diagnostic strategies, results are consistent with noninferiority (i.e., similar health outcomes) to other diagnostic strategies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected anomalous coronary arteries who receive CCTA, the evidence includes case series. Relevant outcomes are overall survival, test accuracy, morbid events, and resource utilization. Series have shown that CCTA can detect anomalous coronary arteries missed by other diagnostic modalities. Anomalous coronary arteries are rare, and formal studies to assess clinical utility are unlikely to be performed. In most situations, these case series alone would be insufficient to determine whether the test improves health outcomes. However, in situations where patient management will be affected by CCTA results (e.g., with changes in surgical planning), a chain of evidence indicates that health outcomes are improved. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Policy History

Original Effective Date: 07/15/2005
Current Effective Date: 07/02/2018

06/07/2005	Medical Director review
06/21/2005	Medical Policy Committee review
07/15/2005	Managed Care Advisory Council approval
07/07/2006	Format revision including addition of FDA and or other governmental regulatory approval and Rationale/source. Coverage eligibility unchanged.
09/06/2006	Medical Director review
12/06/2006	Medical Director review
12/20/2006	Medical Policy Committee approval. Coverage eligibility unchanged
01/09/2008	Medical Director review
01/23/2008	Medical Policy Committee approval. Eligible for coverage statement added for CTA evaluation of anomalous (native) coronary arteries in symptomatic patients when conventional angiography is unsuccessful or equivocal and when the results will impact treatment.
05/07/2009	Medical Director review
05/20/2009	Medical Policy Committee approval. No change to coverage eligibility.
01/01/2010	Coding revision
06/03/2010	Medical Policy Committee approval
06/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2011	Medical Policy Committee review
05/18/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. Added coverage for evaluation of patients in the emergency room without known coronary artery disease and acute chest pain.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. Replaced the 1st eligible for coverage criteria bullet to match the one from the 2008 policy. Added four new criteria bullets to be eligible for

	coverage. Included examples of standard methods of risk assessment such as Framingham or ACC criteria in the Patient Selection Criteria of this policy. Added a table to the Background/Overview section on the determination of pretest probability for coronary artery disease.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Added bullet point with AIM guidelines to patient selection criteria.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated background, rationale and references added "coronary" to title and policy statement.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Removed "when conventional angiography is unsuccessful or equivocal" from the first eligible for coverage criteria bullet. Added "acute" to describe chest pain in the second eligible for coverage criteria bullet. Removed the last eligible for coverage criteria bullet and replaced it with: • "To evaluate patients with suspected stable ischemic heart disease with at least intermediate risk (using standard methods of risk assessment such as Framingham or American College of Cardiology [ACC] criteria) when no coronary artery disease (CAD) imaging evaluation (e.g., myocardial perfusion imaging (MPI), cardiac positron emission tomography (PET), stress echocardiogragphy (SE), coronary computed tomography angiography (CCTA), or coronary angiography) has been performed within the preceding sixty (60) days." Added a Policy Guidelines section to the policy.

Next Scheduled Review Date: 03/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Contrast-Enhanced Coronary Computed Tomography Angiography (CCTA) for Coronary Artery Evaluation

Policy # 00153
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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code			
CPT	71275, 75572, 75573, 75574			
HCPCS	No codes			
ICD-10 Diagnosis	I20.8-I20.9	I25.10	I25.110-I25.119	I25.3
	I25.41-I25.42	I25.5-I25.6	I25.700-I25.799	I25.810-I25.89
	I25.9	I70.0-I70.1	I70.201-I70.249	I70.25
	I70.261-I70.269	I70.291-I70.99	I70.301-I70.349	I70.35
	I70.361-I70.369	I70.391-I70.399	I70.401-I70.449	I70.45
	I70.461-I70.469	I70.491-I70.499	I70.501-I70.549	I70.55
	I70.561-I70.569	I70.591-I70.599	I70.601-I70.649	I70.65
	I70.661-I70.669	I70.691-I70.699	I70.701-I70.749	I70.75
	I70.761-I70.769	I70.791-I70.799	I70.8	I70.90-I70.92

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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

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

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

Contrast-Enhanced Coronary Computed Tomography Angiography (CCTA) for Coronary Artery Evaluation

Policy # 00153
Original Effective Date: 07/15/2005
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