Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers cardiac computed tomography (CT) angiography of the coronary arteries using 64-slice or greater medically necessary for the following indications:

A. Rule out significant coronary stenosis in persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix), with any of the following indications:

1. Evaluation of persons with chest pain who can not perform or have contraindications to exercise and pharmacological stress testing (see Appendix); or
2. Evaluation of persons with chest pain presenting to the emergency department in persons without acute ECG changes or positive coronary markers when an imaging stress test or coronary angiography are being deferred as the initial imaging study.
B. Rule out significant coronary stenosis in persons with a low pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix) with a positive (i.e., greater than or equal to 1 mm ST segment depression) stress test.

C. Evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease or atherosclerotic cardiovascular disease by Framingham risk scoring or Pooled Cohort Equations (see Appendix) who have an equivocal or uninterpretable exercise or pharmacological stress test. **Note:** Current guidelines from the American Heart Association recommend against routine stress testing for screening asymptomatic adults.

D. Pre-operative assessment of persons scheduled to undergo 'high-risk" non-cardiac surgery, where an imaging stress test or invasive coronary angiography is being deferred unless absolutely necessary. The ACC defines high-risk surgery as emergent operations, especially in the elderly, aortic and other major vascular surgeries, peripheral vascular surgeries, and anticipated prolonged surgical procedures with large fluid shifts and/or blood loss involving the abdomen and thorax.

E. Pre-operative assessment for planned non-coronary cardiac surgeries including valvular heart disease, congenital heart disease, and pericardial disease, in lieu of cardiac catheterization as the initial imaging study.

F. Detection and delineation of suspected coronary anomalies in young persons (less than 30 years of age) with suggestive symptoms (e.g., angina, syncope, arrhythmia, and exertional dyspnea without other known etiology of these symptoms in children and adults; dyspnea, tachypnea, wheezing, periods of pallor, irritability (episodic crying), diaphoresis, poor feeding and failure to thrive in infants).

G. Calculation of fractional flow reserve (HeartFlow FFR_{CT}) for persons who have a coronary CTA that has shown coronary artery disease of uncertain functional significance, or is
II. Aetna considers CT angiography of cardiac morphology for pulmonary vein mapping medically necessary for the following indications:

A. Evaluation of persons needing biventricular pacemakers to accurately identify the coronary veins for lead placement.
B. Evaluation of the pulmonary veins in persons undergoing pulmonary vein isolation procedures for atrial fibrillation (pre- and post-ablation procedure).

III. Aetna considers CT angiography medically necessary for preoperative assessment of the aortic valve annulus prior to anticipated transcatheter aortic valve replacement (TAVR).

IV. Aetna considers cardiac CT for evaluating cardiac structure and morphology medically necessary for the following indications:

A. Anomalous pulmonary venous drainage;
B. Evaluation of other complex congenital heart diseases;
C. Evaluation of sinus venosum atrial-septal defect;
D. Kawasaki's disease;
E. Person scheduled or being evaluated for surgical repair of tetralogy of Fallot or other congenital heart diseases;
F. Pulmonary outflow tract obstruction;
G. Suspected or known Marfan's syndrome.

V. Aetna considers cardiac CT angiography experimental and investigational for persons with any of the following contraindications to the procedure because its effectiveness for indications other than the ones listed above has not been established:

A. Body mass index (BMI) greater than 40.
B. Inability to image at desired heart rate (under 80 beats/min), despite beta blocker administration.

C. Person with allergy or intolerance to iodinated contrast material

D. Persons in atrial fibrillation or with other significant arrhythmia.

E. Persons with extensive coronary calcification by plain film or with prior Angiost score greater than 1,700.

Aetna considers cardiac CT angiography using less than 64-slice scanners experimental and investigational because the effectiveness of this approach has not been established.

VI. Aetna considers coronary CT angiography experimental and investigational for screening of asymptomatic persons, evaluation of atherosclerotic burden, evaluation of persons at high pre-test probability of coronary artery disease, evaluation of stent occlusion or in-stent restenosis, evaluation of persons with an equivocal PET rubidium study, identification of vulnerable plaques, monitoring of atheroma burden, and for all other indications (e.g., atrial angiosarcoma) because its effectiveness for these indications has not been established.

Note: The selection of CT angiography should be made within the context of other testing modalities such as stress myocardial perfusion images or cardiac ultrasound results so that the resulting information facilitates the management decision and does not merely add a new layer of testing.

VII. Aetna considers a single calcium scoring by means of low-dose multi-slice CT angiography, ultrafast [electron-beam] CT, or spiral [helical] CT medically necessary for screening the following: (i) asymptomatic persons age 40 years and older with diabetes; or (ii) asymptomatic persons with an intermediate (10% to 20%) 10-year risk of cardiac events based on Framingham Risk Scoring or Pooled Cohort Equations (see Appendix). Serial or repeat calcium scoring is considered experimental and investigational.

Aetna considers calcium scoring by means of low-dose CT angiography medically necessary for persons who meet
criteria for diagnostic cardiac CT angiography to assess whether an adequate image of the coronary arteries can be obtained.

VIII. Aetna considers calcium scoring (e.g., with ultrafast [electron-beam] CT, spiral [helical] CT, and multi-slice CT) experimental and investigational for all other indications because of insufficient evidence in the peer-reviewed published medical literature.

**Background**

**Cardiac CT Angiography**

Coronary computed tomography angiography (CCTA) is a noninvasive imaging modality designed to be an alternative to invasive cardiac angiography (cardiac catheterization) for diagnosing CAD by visualizing the blood flow in arterial and venous vessels. The gold standard for diagnosing coronary artery stenosis is cardiac catheterization.

Contrast-enhanced cardiac CT angiography (CTA) involves the use of multi-slice CT and intravenously administered contrast material to obtain detailed images of the blood vessels of the heart. It has been used as an alternative to conventional invasive coronary angiography for evaluating coronary artery disease and coronary artery anomalies.

The performance of cardiac CTA has been improved by increasing the number of slices that can be acquired simultaneously by increasing the number of detector rows (AHTA, 2006). As the number of slices that can be acquired simultaneously increases, the scanning time is shortened and the spatial resolution is increased. Initial cardiac CT imaging was conducted with 4-slice detector CT. Scanning times were reduced from 40 seconds down to 20 seconds with 16-slice detector CT and with the advent of 64-slice detector CT, scanning times have been reduced to a 10 second breath-hold.

Cardiac CTA using 64-slices has been shown in studies to have a high negative predictive value (93 to 100 %), using conventional
coronary angiography as the reference standard. Given its high negative predictive value, cardiac CTA has been shown to be most useful for evaluating persons at low to intermediate risk of coronary artery disease. This would include evaluation of asymptomatic low- to intermediate-risk persons with an equivocal exercise or pharmacologic stress test, and evaluation of low- to intermediate-risk persons with chest pain who have a contraindication to exercise and pharmacological stress testing. Cardiac CTA is also a useful alternative to invasive coronary angiography for pre-operative evaluation of persons undergoing non-coronary cardiac surgery or high-risk noncardiac surgery, where invasive coronary angiography would otherwise be indicated.

Substantial controversy over the appropriate indications for cardiac CTA is due, in part, to the relatively poor quality of available evidence. An assessment of cardiac CTA by the Duke Evidence-Based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) (Matchar et al, 2006) found that published studies of cardiac CTA were generally small, performed at single centers, and often did not include information that would serve to provide confident assessments of key questions of effectiveness. The reported noted: “In particular, we did not identify any studies evaluating the clinical impact of diagnostic strategies including NITs [noninvasive tests] of coronary anatomy compared with strategies that did not include these techniques.”

The BlueCross BlueShield Association’s Medical Advisory Panel (BCBSA, 2006) concluded that contrast-enhanced cardiac CTA as a substitute for invasive coronary angiography in the diagnosis of coronary artery stenosis does not meet the TEC criteria. The assessment found that “[t]he studies evaluating the use of CTA in comparison to angiography are relatively small studies from single centers. Their major failing is that they enrolled convenience samples of patients being referred for angiography. The results from these studies may not generalize to lower-risk populations.” The assessment explained that “in order to demonstrate improved patient outcomes, valid prognostication tied to improved management and outcomes must be
demonstrated. Clinical trials comparing patients undergoing CTA as part of their diagnostic work up compared to patients not undergoing CTA may be required to demonstrate improved patient outcomes.”

An assessment by the California Technology Assessment Forum (CTAF) found that cardiac CTA has generally not been compared with the established alternatives (Walsh, 2007). The assessment explained that cardiac CTA has relatively high sensitivity but a lower specificity than invasive coronary angiography. Thus, the negative predictive value of cardiac CTA is high, but there is a high false-positive rate, which then leads to additional testing. The assessment also found that, in several studies a high proportion of cardiac CTAs were unevaluable, which further limits the utility of this technology. The assessment reported that a precise estimate of the proportion of tests that are unevaluable is difficult to ascertain, because the absolute numbers of patients in each of the studies is small.

California Technology Assessment Forum also found only 1 study that compared cardiac CTA to the standard of care for the evaluation of chest pain. In that study, although cardiac CTA was accurate for ruling in or ruling out significant coronary artery disease in 75% of subjects, about 25% of subjects required additional diagnostic testing to clarify the diagnosis. The CTAF report noted, in addition, that important clinical outcomes that should be evaluated, such as the number of patients with acute coronary syndrome and the number of patients safely discharged from the emergency room, have not been evaluated in most of the studies. The CTAF assessment stated that, ideally, studies should demonstrate that cardiac CTA reduced the need for invasive procedures, accurately identified patients with acute coronary syndromes, and correctly identified patients who could safely be sent home from the emergency room.

An assessment by the Ontario Ministry of Long-Term Care Medical Advisory Secretariat (MAS, 2007) found insufficient evidence for the use of coronary CTA as a screening test for coronary artery disease (CAD) in asymptomatic individuals. The assessment found that coronary CTA exhibits only moderately
high sensitivity and specificity for detection of CAD in an asymptomatic population. If population-based screening were implemented, a high rate of false-positives would result in increased down-stream costs and interventions. Additionally, some cases of CAD would be missed, as they may not be developed, or not yet have progressed to detectable levels. The assessment noted that there is no evidence for the impact of screening on patient management. Cardiovascular risk factors are positively associated with the presence of coronary artery calcification and cardiovascular events; however, risk factor stratification to identify high-risk asymptomatic individuals is unclear given the current evidence-base. The assessment noted that the safety of coronary CTA screening is also an issue because of the introduction of increased radiation doses for the initial screening scan and possible follow-up interventions. The assessment found that no large randomized controlled trials of coronary CTA screening have been published. The assessment also found no evidence on the long-term implications of screening.

A decision memorandum from the Centers for Medicare & Medicaid Services (CMS, 2008) has concluded that there is uncertainty regarding any potential health benefits or patient management alterations from including coronary CTA in the diagnostic work-up of patients who may have CAD. The memorandum stated that no adequately powered study has established that improved health outcomes can be causally attributed to coronary CTA for any well-defined clinical indication, and the body of evidence is of overall limited quality and limited applicability to Medicare patients with typical co-morbidities in community practice. The memorandum noted that the primary safety concerns with cardiac CTA are the exposure to radiation and the use of contrast and beta blocker medications.

The CMS decision memorandum (CMS, 2008) explained that cardiac CTA is unlikely to benefit persons at high-risk for CAD, as these persons will likely need to have invasive coronary angiography regardless of the results of this test. The CMS decision memorandum also stated that there is no evidence that CTA will benefit persons with chest pain at low-risk of CAD. In
support of that conclusion, the decision memorandum cited a randomized clinical trial by Goldstein et al (2007) of low-risk patients presenting to the emergency room with chest pain. Study subjects were randomized to evaluation with cardiac CTA versus standard of care. At 6 months, there was no significant difference in the number of cumulative cardiac catheterizations (12 % in persons assigned to cardiac CTA versus 7 % in persons assigned to standard of care; p = 0.24). There were no significant differences between groups in cumulative angioplasty or coronary artery bypass surgery at 6 months. There were also no deaths or myocardial infarctions in either group at 6 months.

The decision memorandum observed that, in systematic reviews of coronary CTA, the overall reported sensitivity, specificity and predictive values are generally above 80 to 90 % (CMS, 2008). The decision memorandum stated, however, that these estimates have limitations in applicability and generalizability due to patient selection and potential bias. The decision memorandum found no published studies of the sensitivity and specificity of coronary CT angiography in persons at low or intermediate pre-test probability of CAD. Although available studies have not consistently reported the participants' pre-test probability of CAD, almost all persons enrolled in these studies are likely to be at relatively high-risk for CAD, since they were already scheduled for invasive coronary angiography. The decision memorandum noted that, in general, test sensitivity and specificity will be higher in patients with more severe disease. Thus, the sensitivity and specificity estimates for high-risk patients are not directly applicable to patients at low- or intermediate-risk. The sensitivity and specificity of coronary CTA for persons at intermediate- or low-risk are likely to be lower given the reduced severity of disease.

The CMS decision memorandum also explained that the reported positive and negative predictive values of coronary CTA based on high risk patients are not directly applicable to low- or intermediate-risk patients because the prevalence of disease is different (CMS, 2008). The predictive values would very likely be lower if calculated using data from low- or intermediate-risk patients since these populations have a lower prevalence of CAD.
The Institute for Clinical and Economic Review (ICER, 2008) completed a health technology assessment and cost-effectiveness analysis of coronary computed tomography angiography (CCTA) for coronary artery disease. ICER evaluated the cost-effectiveness of CCTA in the emergency department to evaluate persons with chest pain, and found, at base case, with costs based upon Medicare data, that CCTA is cost-saving, with about $296 in savings per patient in comparison with standard of care. The ICER assessment also evaluated the cost-effectiveness of the use of CCTA in the outpatient setting to evaluate persons at intermediate risk of CAD with stable chest pain. A number of strategies were evaluated involving CCTA, stress echocardiography, and myocardial perfusion imaging, used alone or in combination. Based on base case assumptions, the analysis found that all strategies were dominated except for CCTA alone and stress ECHO alone. Stress echocardiography was the least expensive strategy, and the incremental cost-effectiveness ratio of CCTA alone versus stress echocardiography was $178,000 per quality adjusted life year.

An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2011) concluded that CCTA meets the TEC criteria for patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes. The TEC assessment stated that evidence obtained in the emergency setting, similar to more extensive results among ambulatory patients, indicates a normal CCTA appears to provide a prognosis as good as other noninvasive tests.

In the outpatient setting, where the interest in the use of CCTA has been focused on the evaluation of patients with stable chest pain symptoms who are at low- to intermediate-risk of significant CAD, there are no published studies to date that have directly measured the impact of CCTA on clinical decision-making or on patient outcomes. The majority of available literature on 64-slice CCTA is limited to small, single-center studies of diagnostic accuracy compared to invasive coronary angiography (ICA), typically among consecutive patients at relatively high-risk of CAD.
who are already scheduled to undergo ICA.

The American College of Cardiology has published appropriateness criteria for cardiac CTA (Hendel et al, 2006). These criteria are based upon consensus of a technical panel, and not upon an explicit assessment of the available evidence.

Cardiac CTA requires high doses of ionizing radiation, with an average dose of 8.1 milliSieverts for patients weighing 75 kgs. This dose is approximately 2 to 3 times higher than the average radiation dose administered to patients during conventional coronary angiography (AHTA, 2006). Although the risk associated with a dose of this size is minimal, it may raise concerns about repeated doses, or in children and women of child-bearing age. In addition, a greater volume of contrast media is required for CCTA (150 mls) compared to conventional coronary angiography (approximately 20 mls).

Einstein and colleagues (2007) ascertained the lifetime attributable risk (LAR) of cancer incidence associated with radiation exposure from a 64-slice computed tomography coronary angiography (CTCA) study and evaluated the influence of age, sex, and scan protocol on cancer risk. Organ doses from 64-slice CTCA to standardized phantom (computational model) male and female patients were estimated using Monte Carlo simulation methods, using standard spiral CT protocols. Age- and sex-specific LARs of individual cancers were estimated using the approach of BEIR VII and summed to obtain whole-body LARs. Main outcome measures were whole-body and organ LARs of cancer incidence. Organ doses ranged from 42 to 91 mSv for the lungs and 50 to 80 mSv for the female breast. Lifetime cancer risk estimates for standard cardiac scans varied from 1 in 143 for a 20-year old woman to 1 in 3,261 for an 80-year old man. Use of simulated electrocardiographically controlled tube current modulation (ECTCM) decreased these risk estimates to 1 in 219 and 1 in 5,017, respectively. Estimated cancer risks using ECTCM for a 60-year old woman and a 60-year old man were 1 in 715 and 1 in 1911, respectively. A combined scan of the heart and aorta had higher LARs, up to 1 in 114 for a 20-year old woman. The highest organ LARs were for lung cancer and, in younger women,
breast cancer. The authors concluded that these estimates derived from simulation models suggested that use of 64-slice CTCA is associated with a non-negligible LAR of cancer. This risk varies markedly and is considerably greater for women, younger patients, and for combined cardiac and aortic scans.

In a study published in the New England Journal of Medicine, Miller et al (2008) stated that the accuracy of multi-detector CTA involving 64 detectors has not been well-established. These investigators conducted a multi-center study to examine the accuracy of 64-row, 0.5-mm multi-detector CTA as compared with conventional coronary angiography in patients with suspected coronary artery disease. Nine centers enrolled patients who underwent calcium scoring and multi-detector CT angiography before conventional coronary angiography. In 291 patients with calcium scores of 600 or less, segments 1.5 mm or more in diameter were analyzed by means of CT and conventional angiography at independent core laboratories. Stenoses of 50 % or more were considered obstructive. The area under the receiver-operating-characteristic curve (AUC) was used to evaluate diagnostic accuracy relative to that of conventional angiography and subsequent revascularization status, whereas disease severity was assessed with the use of the modified Duke Coronary Artery Disease Index. A total of 56 % of patients had obstructive coronary artery disease. The patient-based diagnostic accuracy of quantitative CTA for detecting or ruling out stenoses of 50 % or more according to conventional angiography revealed an AUC of 0.93 (95 % confidence interval [CI]: 0.90 to 0.96), with a sensitivity of 85 % (95 % CI: 79 to 90), a specificity of 90 % (95 % CI: 83 to 94), a positive predictive value of 91 % (95 % CI: 86 to 95), and a negative predictive value of 83 % (95 % CI: 75 to 89). Computed tomographic angiography was similar to conventional angiography in its ability to identify patients who subsequently underwent re-vascularization: the AUC was 0.84 (95 % CI: 0.79 to 0.88) for multi-detector CTA and 0.82 (95 % CI: 0.77 to 0.86) for conventional angiography. A per-vessel analysis of 866 vessels yielded an AUC of 0.91 (95 % CI: 0.88 to 0.93). Disease severity ascertained by CT and conventional angiography was well-correlated ($r = 0.81; 95 \% \text{ CI}: 0.76 to 0.84$). Two patients had important reactions to contrast medium after CT angiography.
The authors concluded that multi-detector CTA accurately identifies the presence and severity of obstructive coronary artery disease and subsequent re-vascularization in symptomatic patients. However, the negative and positive predictive values indicate that multi-detector CTA can not replace conventional coronary angiography at present.

An accompanying editorial commenting on the study by Miller et al stated that this study exemplifies current research in the field (Redberg and Walsh, 2008). The editorialists stated that, although this study was carefully done and provides more data on diagnostic accuracy, it does not advance our knowledge of the appropriate use and possible benefits of the technology. The editorialists explained that Miller et al sought to identify "patients with suspected coronary artery disease who should be referred for conventional coronary angiography." However, because all patients received both cardiac CTA and conventional coronary angiography and no data on outcomes are reported, the study does not answer this important question. The editorialists commented that, with respect to risks, Miller et al claimed that the new technology compares favorably to conventional coronary angiography, even though in their study the radiation exposure with cardiac CTA was significantly greater than that with conventional coronary angiography. The editorialists noted, in any event, that Miller et al concluded that cardiac CTA is not accurate enough to replace the older technology for patients with chest pain, adding to the body of research failing to prove a benefit of the new procedure.

The editorialists noted that the use of cardiac imaging has been increasing despite a lack of evidence of outcome benefit (Redberg and Walsh, 2008). The editorialists said that there is some evidence that cardiac imaging leads to additional unnecessary procedures, such as additional diagnostic testing, re-vascularizations, or biopsies for "incidental findings." The editorialists also noted that cardiac CT angiographic equipment exposes patients with radiation many orders of magnitude greater than that of traditional radiographs -- poses a risk that has never been studied in depth. The editorialists cited evidence that estimates that 1.5 to 2.0 % of all cases of cancers in the
United States may be attributable to CT radiation.

Cardiac CT angiography often produces non-cardiac incidental findings. To evaluate the incidence, clinical importance, and costs of these incidental findings, MacHaalany, et al (2009) studied 966 consecutive patients who underwent CTA. Incidental findings were noted in 401 patients (41.5 %); of these, 12 were deemed to be clinically significant (e.g., 5 thrombi, 1 aortic dissection that was not clinically suspected, 1 ruptured breast implant), and 68 were deemed to be indeterminate (e.g., 34 non-calcified pulmonary nodules less than 1 cm, 11 larger lung nodules, 9 liver nodules/cysts). After a mean 18-month follow-up, no indeterminate finding became clinically significant, although 3 malignancies were diagnosed after subsequent diagnostic tests. Non-cardiac and cancer death rates were not significantly different between patients with and without incidental findings. In all, 164 additional diagnostic tests and procedures were performed in the 80 patients with indeterminate or clinically significant incidental findings, including 1 patient who suffered empyema and abdominal abscesses as a complication of transthoracic biopsy.

Weustink et al (2010) compared the accuracy and clinical utility of stress testing and CTCA for identifying patients who require ICA. A total of 517 patients referred by their treating physicians for evaluation of chest symptoms by using stress testing or ICA were included in this study. Diagnostic accuracy of stress testing and CTCA were compared with ICA; pre-test probabilities of disease by Duke clinical score; and clinical utility of non-invasive testing, defined as a pretest or posttest probability that suggests how to proceed with testing (no further testing if less than or equal to 5 %, proceed with ICA if between 5 % and 90 %, and refer directly for ICA if greater than or equal to 90 %). Stress testing was not as accurate as CTCA; CTCA sensitivity approached 100 %. In patients with a low (less than 20 %) pre-test probability of disease, negative stress test or CTCA results suggested no need for ICA. In patients with an intermediate (20 % to 80 %) pre-test probability, a positive CTCA result suggested need to proceed with ICA (post-test probability, 93 % [95 % CI: 92 % to 93 %]) and a negative result suggested no need for further testing (post-test
Physicians could proceed directly with ICA in patients with a high (greater than 80 %) pre-test probability (91 % CI: 90 % to 92 %). The authors concluded that CTCA seems most valuable in patients with intermediate pre-test probability of disease, because the test can distinguish which of these patients need invasive angiography. The authors stated that additional studies, including cost-benefit analyses, are needed to confirm these findings before CTCA is accepted as a 1st-line diagnostic test in patients with an intermediate pre-test probability of CAD.

The American College of Cardiology's 2010 expert consensus document on CTCA listed the following as emerging applications: (i) evaluation of atherosclerotic burden, (ii) identification of vulnerable plaques, and (iii) monitoring of atheroma burden. Furthermore, the document also noted that the use of CTCA in asymptomatic high-risk individuals is an area that has been the subject of some empirical research, but the data overall are not yet sufficiently clear to support the development of a consensus.

Alsheikh-Ali et al (2010) reviewed the scope of recent literature on the concept of "vulnerable plaque" by examining 463 abstracts of primary and review articles identified through MEDLINE (2003 to April 2010). Proposed definition criteria of vulnerable plaque included active inflammation, a thin cap with a large lipid core, endothelial denudation, fissured cap, severe stenosis, or combinations of these findings. In 242 primary studies, histopathology, biomarkers, and imaging of carotid and coronary artery plaques were evaluated for features suggestive of vulnerability. Notably, 89 % of these studies were cross-sectional in design and were exclusively conducted in patients with known cardiovascular disease. None of the imaging studies documented whether the identified lesions were responsible for cardiovascular events. Cross-sectional design precludes evaluation of the predictive utility of biomarkers. Because vulnerable plaque is not an established medical diagnosis, no studies have been done that explicitly evaluate the treatment of vulnerable plaques. Few studies examined potential systemic treatments (e.g., statins) to modify vulnerability features. The authors stated that large prospective studies in patients with and without previous
cardiovascular events during long follow-up are required to validate this concept. They also stated that the value of the available literature is further limited by the use of imaging characteristics that have not been validated as reliable surrogates for histologic markers of plaques vulnerability (e.g., echolucency and plaque deformability).

von Ballmoos et al (2011) reviewed current evidence about the ability of low-dose coronary CT angiography to rule out CAD in symptomatic adults. Online databases, including MEDLINE, EMBASE, and the Cochrane Library, from inception through 31 October 2010; abstract databases; gray literature; reference lists of identified articles; and experts were searched. No language restrictions were applied. All investigators screened and selected studies that compared prospective electrocardiography-gated coronary CT angiography with catheter coronary angiography (the reference standard) in symptomatic patients with suspected CAD were selected. Two investigators independently extracted patient and study protocol characteristics and rated methodological quality; differences were resolved by consensus or by a third reader. Multi-variate random-effects models were used to obtain pooled estimates. A total of 16 studies, comprising 960 patients, were found (7 studies of single-source, 64-slice CT; 4 of dual-source, 64-slice CT; 2 of single-source, 320-slice CT; 1 dual-source, 128-slice CT; 1 of single-source, 128-slice CT; and 1 of single-source, 256-slice CT). On average, 2.4 % of the coronary arterial segments were of non-diagnostic image quality, and 1 or more segments were non-diagnostic in 9.5 % of the patients. The patient-level sensitivity and specificity of CT angiography were 1.00 (95 % CI: 0.98 to 1.00) and 0.89 (CI: 0.85 to 0.92), respectively. The pooled vessel- and segment-level estimates showed lower sensitivity and higher specificity than the patient-level estimates. Statistically significant heterogeneity was found between studies for vessel- and segment-level estimates, which seemed to be associated with body mass index and prevalence of CAD but not with CT scanner characteristics. The authors concluded that early evidence suggested that low-dose coronary CT angiography matches the sensitivity of catheter-based angiography, has low radiation exposure, and is a potentially valid alternative to catheter angiography for triaging
symptomatic patients with a clinical suspicion of CAD. Limitations of this meta-analysis included a small number of studies, 50% of which were from a single tertiary center, limits generalizability. The potential harms of the imaging tests were not well-evaluated. The authors stated that further studies are needed before widespread diffusion of the technology can be recommended.

Arbab-Zadeh et al. (2012) evaluated the impact of patient population characteristics on accuracy by CTA to detect obstructive CAD. For the CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) study, a total of 371 patients underwent CTA and cardiac catheterization for the detection of obstructive CAD, defined as greater than or equal to 50% luminal stenosis by quantitative coronary angiography (QCA). This analysis includes 80 initially excluded patients with a calcium score greater than or equal to 600. Area under the receiver-operating characteristic curve (AUC) was used to evaluate CTA diagnostic accuracy compared to QCA in patients according to calcium score and pre-test probability of CAD. Analysis of patient-based quantitative CTA accuracy revealed an AUC of 0.93 (95% CI: 0.90 to 0.95). The AUC remained 0.93 (95% CI: 0.90 to 0.96) after excluding patients with known CAD but decreased to 0.81 (95% CI: 0.71 to 0.89) in patients with calcium score greater than or equal to 600 (p = 0.077). While AUCs were similar (0.93, 0.92, and 0.93, respectively) for patients with intermediate, high pre-test probability for CAD, and known CAD, negative predictive values were different: 0.90, 0.83, and 0.50, respectively. Negative predictive values decreased from 0.93 to 0.75 for patients with calcium score less than 100 or greater than or equal to 100, respectively (p = 0.053). The authors concluded that both pre-test probability for CAD and coronary calcium scoring should be considered before using CTA for excluding obstructive CAD. For that purpose, CTA is less effective in patients with calcium score greater than or equal to 600 and in patients with a high pre-test probability for obstructive CAD. CTA is most useful as a rule-out test in patients with low-intermediate pre-test probability of disease and mild coronary calcification or those with a calcium score of zero". 
In an editorial that accompanied the afore-mentioned study, Nissen (2012) stated that "[t]he current study by Arbab-Zadeh et al helps us understand what must be expected in subsequent studies examining the clinical utility of CTA. Future studies must evaluate important clinical outcomes, not just the extent of stenoses, in a wide spectrum of patients, not selected because they represent the ideal candidates for CTA. Pending such evaluation, coronary imaging using CTA should be used sparingly, with full recognition of the radiation burdens and risks of misdiagnosis".

In an observational study, Kim and colleagues (2013) evaluated the prevalence and characteristics of coronary atherosclerosis in asymptomatic subjects classified as low-risk by National Cholesterol Education Program (NCEP) guideline using CCTA. A total of 2,133 (49.2 %) subjects, who were classified as low-risk by the NCEP guideline, of 4,339 consecutive middle-aged asymptomatic subjects who underwent CCTA with 64-slice scanners as part of a general health evaluation were included in this study. Main outcome measures were the incidence of atherosclerosis plaques and significant stenosis. In the subjects at low-risk, 11.4 % (243 of 2,133) of subjects had atherosclerosis plaques, 1.3 % (28 of 2,133) of subjects had significant stenosis, and 0.8 % (18 of 2,133) of subjects had significant stenosis caused by non-calcified plaque (NCP). Especially, 75.0 % (21 of 28) of subjects with significant stenosis and 94.4 % (17 of 18) of subjects with significant stenosis caused by NCP were young adults. Mid-term follow-up (29.3 ± 14.9 months) revealed 4 subjects with cardiac events: 3 subjects with unstable angina requiring hospital stay and 1 subject with percutaneous coronary intervention. The authors concluded that although an asymptomatic population classified as low-risk by the NCEP guideline has been regarded as a minimal risk group, the prevalence of atherosclerosis plaques and significant stenosis were not negligible. However, considering very low event rate for those patients, CTA should not be performed in low-risk asymptomatic subjects, although CTA might have the potential for identification of high-risk groups in the selected subjects regarded as a minimal-risk group by NCEP guideline.
Dorr and associates (2013) stated that clinical studies have consistently shown that there is only a very weak correlation between the angiographically determined severity of CAD and disturbance of regional coronary perfusion. On the other hand, the results of randomized trials with a fractional flow reserve (FFR)-guided coronary intervention (DEFER, FAME I, FAME II) showed that it is not the angiographically determined morphological severity of CAD but the functional severity determined by FFR that is critical for prognosis and the indications for re-vascularization. A non-invasive method combining the morphological image of the coronary anatomy with functional imaging of myocardial ischemia is therefore particularly desirable. An obvious solution is the combination of CCTA with a functional procedure, such as perfusion positron emission tomography (PET), perfusion single photon emission computed tomography (SPECT) or perfusion magnetic resonance imaging (MRI). This can be performed with fusion imaging or with hybrid imaging using PET-CT or SPECT-CT. First trial results with PET-CCTA and SPECT-CCTA carried out as cardiac hybrid imaging on a 64-slice CT showed a major effect to be a decrease in the number of false-positive results, significantly increasing the specificity of CCTA and SPECT. The authors concluded that although the results are promising, due to the previously high costs, low availability and the additional radiation exposure, current data are not yet sufficient to give clear recommendations for the use of hybrid imaging in patients with a low-to-intermediate risk of CAD. Moreover, they stated that ongoing prospective studies such as the SPARC or EVINCI trials will bring further clarification.

In a retrospective study, Kang et al (2014) evaluated coronary arterial lesions and assessed their correlation with clinical findings in patients with Takayasu arteritis (TA) by using coronary CT angiography. A total of 111 consecutive patients with TA (97 females, 14 males; mean age of 44 years ± 13.8 [standard deviation]; age range of 14 to 74 years) underwent CT angiography of the coronary arteries and aorta with 128-section dual-source CT. Computed tomography angiographic, clinical, and laboratory findings of each patient were retrospectively reviewed. Statistical differences between coronary CT angiographic findings
and clinical parameters were examined with uni-variate analysis. Of 111 patients, 32 (28.8 %) had cardiac symptoms and the remaining 79 (71.2 %) had no cardiac symptoms; 59 patients (53.2 %) had coronary arterial lesions at coronary CT angiography. Three main radiologic features were detected: (i) coronary ostial stenosis (n = 31, 28.0 %), (ii) non-ostial coronary arterial stenosis (n = 41, 36.9 %), and (iii) coronary aneurysm (n = 9, 8.1 %). Coronary artery ostial or luminal stenosis of 50 % or more or coronary aneurysms were observed in 26 (23.4 %) patients with TA. Patients with coronary arterial abnormalities at coronary CT angiography had higher incidences of hypertension (p = 0.02), were older at the time of CT (p = 0.01), and had longer duration of TA (p = 0.02) than those without coronary artery abnormalities. The presence of cardiac symptoms, disease activity, and other co-morbidities was not associated with differences in coronary artery involvement. The authors concluded that in patients with TA, there is a high prevalence of coronary arterial abnormalities at coronary CT angiography, regardless of disease activity or symptoms. Thus, these researchers noted that coronary CT angiography may add information on coronary artery lesions in patients with TA.

Noninvasive Fractional Flow Reserve (HeartFlow FFRCT)

HeartFlow FFRCT (HeartFlow, Inc, Redwood City, CA) is a coronary physiologic simulation software used for the clinical qualitative and quantitative analysis of previously acquired computerized tomography Digital Imaging and Communications in Medicine (DICOM) data. The software provides a non-invasive method of estimating fractional flow reserve using standard coronary CT angiography (CCTA) image data (NICE, 2017).

FFR is the ratio between the maximum blood flow in a narrowed artery and the maximum blood flow in a normal artery. FFR is currently measured invasively using a pressure wire placed across a narrowed artery. An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2011) concluded that invasive fractional flow reserve guideded
percutaneous coronary intervention (PCI) results in better outcomes than an angiography alone guided strategy for persons who are undergoing revascularization. The assessment concluded that "The evidence is consistent with prior physiologic data and long-held beliefs that identifying stenoses is insufficient to determine when revascularization is likely to have benefit. If revascularization is anticipated in patients with angina, evidence supports a conclusion that FFR-guided PCI results in better outcomes than an angiography alone-guided strategy."

A medical consultation technology document from the National Institute for Health and Care Excellence (NICE, 2016) found that "[t]he case for adopting HeartFlow FFRCT for estimating fractional flow reserve from coronary CT (CCT) angiography is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy." The consultation stated that HeartFlow FFRCT should be considered as an option for patients with stable, recent onset chest pain of suspected cardiac origin and a clinically determined intermediate (10% to 90%) risk of coronary artery disease. The consultation technology document found that, using HeartFlow FFRCT may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFRCT requires access to 64-slice (or above) coronary CT angiography facilities.

NICE guidance (2017) states that "[t]he case for adopting HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. . . . HeartFlow FFRCT 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 FFRCT may avoid the need for invasive coronary angiography and revascularisation." The guidance notes that, for correct use, HeartFlow FFRCT requires access to 64-slice (or above) CCTA facilities. Because the safety and effectiveness of FFRCT analysis has not been evaluated in other patient subgroups, HeartFlow FFRCT is not recommended in patients who have an acute coronary syndrome or have had a coronary stent, coronary bypass surgery or myocardial infarction in the past month.
The American College of Cardiology CathPCI Registry (Messenger, et al., 2017) has announced that they will allow FFRCT as an acceptable noninvasive method of documenting ischemia around the time of revascularization. Documentation of ischemia around the time of revascularization is important to the appropriate use criteria (AUC) for percutaneous coronary interventions (PCI).

**Calcium Scoring**

Coronary artery calcium (CAC) scoring is a noninvasive test that has been reported to detect the presence of subclinical coronary artery disease (CAD) by measuring the location and extent of calcium in the coronary arteries. Purportedly, the presence of (CAC) has been shown to be strongly correlated with the extent of atherosclerotic plaque as well as the severity of CAD. Tests to determine CAC scoring include multi-slice computed tomography, and electron beam computed tomography (EBCT), also known as ultrafast computed tomography (UFCT).

Ultrafast computed tomography (also known as electron-beam computed tomography [EBCT]) has been shown to be able to quantify the amount of calcium in the coronary arteries, and thus has been primarily investigated as a tool to predict risk of CAD. In ultrafast CT, an electron-beam is magnetically steered along stationary tungsten rings to produce a rotating X-ray beam.

Research has indicated that EBCT is highly sensitive in detecting coronary artery calcification in comparison to other types of CT. Moreover, various studies have shown a strong correlation between EBCT calcium scores and quantities of atherosclerotic plaque. However, there is skepticism about the relationship between EBCT calcium scores and the likelihood of coronary events because of the following factors:

- Calcium does not collect exclusively at sites with severe stenosis
- EBCT calcium scores do not identify the location of specific vulnerable lesions
- Substantial non-calcified plaque is frequently present in the absence of coronary artery calcification
- There are no proven relationships between coronary artery calcification and the probability of plaque rupture.

Some advocates have argued that EBCT scores could be an effective substitute for standard risk factors in predicting the risk of coronary artery disease. However, citing evidence that shows that only a small proportion of asymptomatic individuals with calcified coronary arteries ultimately develop symptomatic coronary artery disease, a 1996 American Heart Association (AHA) scientific statement on coronary artery calcification concludes that the presence of coronary artery calcium is a poor predictor of coronary artery disease risk, and that there is no role for ultrafast CT as a general screening tool to detect atherosclerosis in people who have no symptoms of the disease and no risk factors. More importantly, although a negative scan may mean a low probability of significant artery blockage in asymptomatic people with or without a previous cardiac event (e.g., myocardial infarction, bypass surgery, angioplasty, etc.), an unstable or vulnerable plaque may go undetected by ultrafast CT, and may rupture and cause thrombosis and obstruction of the coronary artery. Detrano (1999) demonstrated that the addition of EBCT data provided no added value to the risk of coronary artery disease risk determined by the Framingham and National Cholesterol Education Program risk models.

Several investigators have examined the potential role of ultrafast CT measurements of coronary artery calcium in ruling out coronary artery disease in patients with atypical anginal symptoms. The AHA report estimates that the negative predictive value of an ultrafast CT scan in these patients ranges from 90 to 95%, and suggests that a negative study may be useful in determining the need for further work-up with exercise stress testing and/or angiography. It must be realized, however, that ultrafast CT provides only anatomic and not physiologic information. Although ultrafast CT can be used to determine whether calcium is present in the coronary arteries, it can not replace stress testing and angiography in determining whether lesions result in significant coronary artery obstruction and ischemia. Ultrafast CT is being investigated for this proposed use.
The AHA does not recommend ultrafast CT as a replacement for stress testing and/or angiography in patients with conventional risk factors and in patients with typical anginal chest pain. The increased predictive value of ultrafast CT of the coronary arteries relative to traditional risk factor assessment is not yet defined. Although a greater amount of calcium may indicate a greater likelihood of obstructive disease, studies have shown that site-specificity and exact 1:1 correlations are not well predicted, that is, ultrafast CT cannot define the location or amount of obstruction with sufficient accuracy to be of use in predicting risk of coronary artery disease, in diagnosing coronary artery disease, or in planning surgical treatment.

Several studies have shown a variability in repeated measures of coronary calcium by ultrafast CT; therefore, use of serial ultrafast CT scans in individual patients to track the progression or regression of calcium is problematic. Although there is emerging evidence that ultrafast CT may help in identifying the presence of early coronary artery disease in people with known heart disease risk factors, there is no definitive evidence that ultrafast CT can substitute for coronary angiography because the absence of calcific deposits on an ultrafast CT scan does not imply the absence of atherosclerosis. Conversely, the presence of calcium does not secure a diagnosis of significant angiographic narrowing. There is still a need for further clarification regarding the relationship between calcification, atherosclerosis, and risk of plaque rupture.

The critical issue that defines the utility (or lack thereof) of ultrafast CT is its prognostic value. The evidence in the peer-reviewed medical literature linking detectable coronary calcium to event outcomes such as future coronary bypass surgery, angioplasty, myocardial infarction, and coronary death is limited. Large-scale prospective studies are still needed to define a role for ultrafast CT.

In a review on coronary artery calcium scoring by means of EBCT, Thomson and Hachamovitch (2002) stated that studies have indicated that the very early detection of a coronary artery burden is possible with EBCT. However, both the Prevention
Conference V and the ACC/AHA Expert Consensus Document on EBCT have recommended against the routine use of EBCT for screening for CAD in asymptomatic individuals. Moreover, there is no evidence so far to support using the results of EBCT in an asymptomatic patient to select a therapy or to guide referral to invasive investigations. The clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment. Electron beam computed tomography is highly sensitive, but its specificity is low. In fact, when referral to angiography is based on the results of EBCT, referrals will be made for very few patients with normal results while many referrals will be made for those with abnormal results. The outcome will be that, in clinical practice, the observed sensitivity of EBCT will be increased, and the observed specificity will be reduced. To date, there are no well-conducted studies that clearly demonstrate the incremental value of calcium scoring over traditional assessments of risk factors, and the clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment. The authors’ view is shared by Redberg and Shaw (2002) who stated that widespread use of EBCT is not recommended. More research is needed to establish the effectiveness of EBCT in the role of risk factor reduction and prevention of cardiovascular disease. Furthermore, Greenland (2003) stated that "To date, most research on EBT [electron-beam computed tomography] has been observational in nature, based entirely on self-referred patients” and that the "role of EBT remains uncertain" and that "additional randomized trials to define specific roles for EBT in risk prediction" are needed.

These conclusions are consistent with those of the U.S. Preventive Services Task Force (2004), which stated that there is "insufficient evidence to recommend for or against routine screening with ... EBCT [electron beam CT] scanning for coronary calcium for either the presence of severe [coronary artery stenosis] or the prediction of [coronary heart disease] events in adults at increased risk for coronary heart disease.” The USPSTF reaffirmed their position in 2009, stating that the evidence is insufficient to assess the balance of benefits and harms of using coronary artery calcification (CAC) score on electron-beam computed tomography (EBCT) to screen asymptomatic men and
women with no history of CHD to prevent CHD events.

Guidelines from the American College of Cardiology and the American Heart Association on assessment of cardiovascular risk (Goff et al, 2014) concluded that CAC score may be considered to inform decision making if, after quantitative risk assessment, a risk-based treatment decision is uncertain. This was a grade E recommendation (expert opinion), meaning that “[t]here is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.” The guidelines state that, on the basis of current evidence, it is the Work Group’s opinion that assessments of CAC “show some promise for clinical utility among the novel risk markers, based on limited data.” The Work Group noted that a review by Peters et al. (2012) provides evidence to support the contention that assessing CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment. Further research is recommended in this area.

American College of Cardiology/American Heart Association guidelines (Greenland et al, 2010) have two Class IIa recommendations for screening with calcium scoring, where Class IIa recommendations are defined as those for which “[t]he weight of evidence or opinion is in favor of the procedure or treatment.” Class IIa recommendations for calcium scoring are for asymptomatic patients with an intermediate (10% to 20%) 10-year risk of cardiac events based on the Framingham risk score (FRS) or other global risk algorithm, and for asymptomatic patients 40 years and older with diabetes mellitus. The guidelines state that there are no data demonstrating that serial CAC testing leads to improved outcomes or changes in therapeutic decision making.

Multi-slice (or multi-row detector) CT and spiral (or helical) CT has also been used to quantify calcium in the coronary arteries. Spiral or helical CT differs from conventional CT in that the patient is continuously rotated as he is moved. Multi-slice CT is a technical advance over spiral CT, and uses multiple rows of detector arrays to rapidly obtain multiple slices with one pass.
Multi-slice CT differs from ultrafast CT in that the latter has no moving parts, and ultrafast CT scans are faster than with multi-slice CT. One study examined the accuracy of spiral CT in evaluating coronary calcification, using ultrafast CT as the gold standard for comparison, in 33 asymptomatic individuals who were referred for calcium scans. Spiral CT was reported to have a sensitivity of 74 % and a specificity of 70 % compared to ultrafast CT. An assessment of spiral CT and multi-slice CT in screening persons with coronary artery disease by the Canadian Coordinating Office for Health Technology Assessment (2003) found no adequate long-term studies on clinical outcomes of people screened with multi-slice CT or spiral CT. In addition, the assessment failed to identify studies that compared spiral CT and multi-slice CT with established screening modalities like risk factor algorithms. The authors noted that the low specificity of spiral CT and multi-slice CT gives rise to concern over false-positive results, and that false-positives may cause harm and expense due to inappropriate and invasive follow-up. The assessment concluded that “[t]here is insufficient evidence at this time to suggest that asymptomatic people derive clinical benefit from undergoing coronary calcification screening using MSCT [multislice CT] or spiral CT scanning.”

In an editorial accompanying a meta-analysis of electron-beam CT for CAD by Pletcher et al (2004), Ewy (2004) explained that "the clinical utility of fast computed tomography (CT) scanners (i.e., the electron beam [EB] and double helical CT scanner) is still limited. Electron beam CT is not ready for prime time."

An assessment of the literature on calcium scoring by the German Agency for Health Technology Assessment (DAHTA, 2006) concluded that measuring coronary calcium is a "promising" tool for risk stratification, but that many questions remain unanswered about the targeted use in medical practice, including which patient groups should be screened, which calcium score threshold should be applied, and which scoring method should be used.

An assessment prepared for the National Coordinating Centre for Health Technology Assessment (Waugh et al, 2006) found: "CT
examination of the coronary arteries can detect calcification indicative of arterial disease in asymptomatic people, many of whom would be at low risk when assessed by traditional risk factors. The higher the CAC score, the higher the risk. Treatment with statins can reduce that risk. However, CT screening would miss many of the most dangerous patches of arterial disease, because they are not yet calcified, and so there would be false-negative results: normal CT followed by a heart attack. There would also be false-positive results in that many calcified arteries will have normal blood flow and will not be affected by clinically apparent thrombosis: abnormal CT not followed by a heart attack." The NCCHTA assessment concluded: "For CT screening to be cost-effective, it has to add value over risk factor scoring, by producing sufficient extra information to change treatment and hence cardiac outcomes, at an affordable cost per quality-adjusted life-year. There was insufficient evidence to support this. Most of the NSC [National Screening Committee] criteria were either not met or only partially met."

An assessment by the Institute for Clinical Effectiveness and Health Policy (Bardach, 2005) concluded: "Most consensus consider EBCT, SCT and MSCT still at their investigational stage for the following: a) detection of coronary artery calcifications as a screening method for asymptomatic subjects with coronary disease; b) detection of coronary artery calcifications in symptomatic patients; and c) assessment of coronary graft viability. No study reported that calcification measuring (plaque characterization) reduces the incidence of coronary events or death."

Detrano and associates (2008) noted that in white populations, computed tomographic measurements of coronary artery calcium (CAC) predict coronary heart disease (CHD) independently of traditional coronary risk factors. However, it is unclear if CAC predicts coronary heart disease in other racial or ethnic groups. These researchers collected data on risk factors and performed scanning for CAC in a population-based sample of 6,722 men and women, of whom 38.6 % were white, 27.6 % were black, 21.9 % were Hispanic, and 11.9 % were Chinese. The study subjects had no clinical cardiovascular disease at entry and were followed for a
median of 3.8 years. There were 162 coronary events, of which 89 were major events (myocardial infarction or death from coronary heart disease). In comparison with participants with no CAC, the adjusted risk of a coronary event was increased by a factor of 7.73 among participants with coronary calcium scores between 101 and 300 and by a factor of 9.67 among participants with scores above 300 (p < 0.001 for both comparisons). Among the 4 racial and ethnic groups, a doubling of the calcium score increased the risk of a major coronary event by 15 to 35 % and the risk of any coronary event by 18 to 39 %. The AUCs for the prediction of both major coronary events and any coronary event were higher when the calcium score was added to the standard risk factors. The authors concluded that the coronary calcium score is a strong predictor of incident coronary heart disease and provides predictive information beyond that provided by standard risk factors in 4 major racial and ethnic groups in the United States. No major differences among racial and ethnic groups in the predictive value of calcium scores were detected. While there were some interesting differences in the prevalence of CAC among the 4 racial and ethnic groups, what remains unclear is how this test should best be employed, or if it should be used at all, to attain better health outcomes for patients.

Calcium scoring may be useful when performed with an otherwise indicated muti-slice cardiac CTA to assess the calcium burden of the coronary arteries to determine whether an adequate scan can be obtained. The calcium score may be estimated with a scout scan, and the injection of contrast withheld if it appears that the patient has a prohibitively high calcium score. This allows one to avoid exposing the patient to unnecessary radiation from contrast if it is clear that the patient's calcium score is so high that an adequate image of the coronary vessels can not be obtained. In such cases, the patient may need invasive angiography to adequately assess the coronary vessels.

Baig and colleagues (2009) stated that CAD is present in 38 % to 40 % of patients starting dialysis. Both traditional and chronic kidney disease-related cardiovascular risk factors contribute to this high prevalence rate. In patients with end-stage renal disease, CAD, especially acute myocardial infarction, is under-
diagnosed. Dobutamine stress echocardiography and, to a lesser extent, stress myocardial perfusion imaging have proved useful in screening for CAD in such patients. Coronary artery calcium scoring is less useful. Acute myocardial infarction is associated with high short- and long-term mortality in dialysis patients. Cardiac troponin I appears to be more specific than cardiac troponin T or creatine kinase MB subunits in the diagnosis of acute myocardial infarction.

Ma and colleagues (2010) examined the relationship between coronary calcium score (CCS) and angiographic stenosis on a patient-based or vessel-based analysis. A total of 91 consecutive patients underwent both low-dose 64-slice CT calcium scoring scan as well as conventional angiography of the heart. The total CCS of abnormal coronary angiogram (n = 45) was 297.38 +/- 416.93, whereas that of normal coronary angiogram (n = 46) was 5.37 +/- 9.35 (p < 0.001). The CCS and degree of stenosis were moderately correlated on patient-based or vessel-based analysis (r = 0.517, 0.521, respectively; both p < 0.001). The authors concluded that CCS could reflect the degree of vessel stenosis to some extent, but CCS of zero could not rule out CAD.

Cademartiri et al (2010) compared the coronary artery calcium score (CACS) and CTCA for the assessment of non-obstructive/obstructive CAD in high-risk asymptomatic subjects. A total of 213 consecutive asymptomatic subjects (113 males; mean age of 53.6 +/- 12.4 years) with more than 1 risk factor and an inconclusive or unfeasible non-invasive stress test result underwent CACS and CTCA in an out-patient setting. All patients underwent conventional coronary angiography (CAG). Data from CACS (threshold for positive image: Agatston score 1/100/1,000) and CTCA were compared with CAG regarding the degree of CAD (non-obstructive/obstructive; less than/greater than or = 50 % lumen reduction). The mean calcium score was 151 +/- 403 and the prevalence of obstructive CAD was 17 % (8 % 1-vessel and 10 % 2-vessel disease). Per-patient sensitivity, specificity, positive and negative predictive values of CACS were: 97 %, 75 %, 45 %, and 100 %, respectively (Agatston greater than or equal to 1); 73 %, 90 %, 60 %, and 94 %, respectively (Agatston greater than or equal to 100); 30 %, 98 %, 79 %, and 87 %, respectively.
%, respectively (Agatston greater than or equal to 1,000). Per-patient values for CTCA were 100 %, 98 %, 97 %, and 100 %, respectively (p < 0.05). Computed tomography coronary angiography detected 65 % prevalence of all CAD (48 % non-obstructive), while CACS detected 37 % prevalence of all CAD (21 % non-obstructive) (p < 0.05). The authors concluded that CACS proved inadequate for the detection of obstructive and non-obstructive CAD compared with CTCA. Computed tomography coronary angiography has a high diagnostic accuracy for the detection of non-obstructive and obstructive CAD in high-risk asymptomatic patients with inconclusive or unfeasible stress test results.

Hadamitzky et al (2011) compared CCTA with calcium scoring and clinical risk scores for the ability to predict cardiac events. Patients (n = 2,223) with suspected CAD undergoing CCTA were followed-up for a median of 28 months. The end point was the occurrence of cardiac events (cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary re-vascularization later than 90 days after CCTA). Patients with obstructive CAD had a significantly higher event rate (2.9 % per year; 95 % CI: 2.1 to 4.0) than those without obstructive CAD, having an event rate 0.3 % per year (95 % CI: 0.1 to 0.5; hazard ratio, 13.5; 95 % CI: 6.7 to 27.2; p < 0.001). Coronary computed tomography angiography had significant incremental predictive value when compared with calcium scoring, both with scores assessing the degree of stenosis (p < 0.001) and with scores assessing the number of diseased coronary segments (p = 0.027). The authors concluded that in patients with suspected CAD, CCTA not only detects coronary stenosis but also improves prediction of cardiac events over and above conventional risk scores and calcium scoring.

In a prospective population-based study, Kavousi et al (2012) evaluated if newer risk markers for CHD risk prediction and stratification improve Framingham risk score (FRS) predictions. A total of 5,933 asymptomatic, community-dwelling participants (mean age of 69.1 years [SD, 8.5]) were included in this analysis. Traditional CHD risk factors used in the FRS (age, sex, systolic blood pressure, treatment of hypertension, total and high-density
lipoprotein cholesterol levels, smoking, and diabetes) and newer CHD risk factors (N-terminal fragment of prohormone B-type natriuretic peptide levels, von Willebrand factor antigen levels, fibrinogen levels, chronic kidney disease, leukocyte count, C-reactive protein levels, homocysteine levels, uric acid levels, CACS, carotid intima-media thickness, peripheral arterial disease, and pulse wave velocity). Adding CACS to the FRS improved the accuracy of risk predictions (c-statistic increase, 0.05 [95% CI: 0.02 to 0.06]; net re-classification index, 19.3% overall [39.3% in those at intermediate-risk, by FRS]). Levels of N-terminal fragment of prohormone B-type natriuretic peptide also improved risk predictions but to a lesser extent (c-statistic increase, 0.02 [CI: 0.01 to 0.04]; net re-classification index, 7.6% overall [33.0% in those at intermediate-risk, by FRS]). Improvements in predictions with other newer markers were marginal. The authors concluded that among 12 CHD risk markers, improvements in FRS predictions were most statistically and clinically significant with the addition of CACS. Moreover, they stated that further investigation is needed to assess whether risk refinements using CACS lead to a meaningful change in clinical outcome.

Cho and colleagues (2012) stated that the predictive value of CCTA in subjects without chest pain syndrome (CPS) has not been established. These researchers investigated the prognostic value of CAD detection by CCTA and determined the incremental risk stratification benefit of CCTA findings compared with clinical risk factor scoring and CACS for individuals without CPS. An open-label, 12-center, 6-country observational registry of 27,125 consecutive patients undergoing CCTA and CACS was queried, and 7,590 individuals without CPS or history of CAD met the inclusion criteria. All-cause mortality and the composite of all-cause mortality and non-fatal myocardial infarction were measured. During a median follow-up of 24 months (interquartile range, 18 to 35 months), all-cause mortality occurred in 136 individuals. After risk adjustment, compared with individuals without evidence of CAD by CCTA, individuals with obstructive 2- and 3-vessel disease or left main coronary artery disease experienced higher rates of death and composite outcome (p < 0.05 for both). Both CACS and CCTA significantly improved the performance of
standard risk factor prediction models for all-cause mortality and the composite outcome (likelihood ratio p < 0.05 for all), but the incremental discriminatory value associated with their inclusion was more pronounced for the composite outcome and for CACS (C statistic for model with risk factors only was 0.71; for risk factors plus CACS, 0.75; for risk factors plus CACS plus CCTA, 0.77). The net re-classification improvement resulting from the addition of CCTA to a model based on standard risk factors and CACS was negligible. The authors concluded that although the prognosis for individuals without CPS is stratified by CCTA, the additional risk-predictive advantage by CCTA is not clinically meaningful compared with a risk model based on CACS. Therefore, at present, the application of CCTA for risk assessment of individuals without CPS should not be justified.

The American College of Radiology Expert Panel on Cardiac Imaging’s clinical guideline on “Chronic chest pain - low to intermediate probability of coronary artery disease” (Woodard et al, 2012) rendered a “3” rating for CT coronary calcium (a “3” rating denotes the procedure is usually not appropriate).

Dedic et al (2016) noted that it is uncertain whether a diagnostic strategy supplemented by early CCTA is superior to contemporary standard optimal care (SOC) encompassing high-sensitivity troponin assays (hs-troponins) for patients suspected of acute coronary syndrome (ACS) in the emergency department (ED). In a prospective, open-label, multi-center, randomized trial, these researchers examined if a diagnostic strategy supplemented by early CCTA improves clinical effectiveness compared with contemporary SOC. They enrolled patients presenting with symptoms suggestive of an ACS at the ED of 5 community and 2 university hospitals in the Netherlands. Exclusion criteria included the need for urgent cardiac catheterization and history of ACS or coronary re-vascularization. The primary end-point was the number of patients identified with significant CAD requiring re-vascularization within 30 days. The study population consisted of 500 patients, of whom 236 (47 %) were women (mean age of 54 ± 10 years). There was no difference in the primary end-point (22 [9 %] patients underwent coronary re-vascularization within 30 days in the CCTA group and 17 [7 %] in the SOC group [p =
Discharge from the ED was not more frequent after CCTA (65% versus 59%, p = 0.16), and length of stay was similar (6.3 hours in both groups; p = 0.80). The CCTA group had lower direct medical costs (€337 versus €511, p < 0.01) and less outpatient testing after the index ED visit (10 [4%] versus 26 [10%], p < 0.01). There was no difference in incidence of undetected ACS. The authors concluded that CCTA, applied early in the work-up of suspected ACS, is safe and associated with less out-patient testing and lower costs. However, they stated that in the era of hs-troponins, CCTA did not identify more patients with significant CAD requiring coronary re-vascularization, shorten hospital stay, or allow for more direct discharge from the ED.

**Appendix**


**Table 1: ACC Criteria for Pre-test Probability of CAD by Age, Gender and Symptoms:**

†
Substernal chest discomfort with a characteristic quality and duration that is provoked by exertion or emotional stress and relieved by rest or nitroglycerin.

<table>
<thead>
<tr>
<th>Age(yrs)</th>
<th>Gender</th>
<th>Typical / Definite Angina Pectoris</th>
<th>Atypical / Probable Angina Pectoris</th>
<th>Nonanginal Chest Pain</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>Men</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Intermediate</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>40-49</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>50-59</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>60-69</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
</tbody>
</table>

Key:
- High: greater than 90 % pre-test probability
- Intermediate: between 10 % and 90 % pre-test probability
- Low: between 5 % and 10 % pre-test probability
- Very low: less than 5 % pre-test probability

†No data exist for patients less than 30 years or greater than 69 years, but it can be assumed that prevalence of CAD increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range.

Source: Adapted from Hendel et al, 2006.

Table 2: Clinical Classification of Chest Pain:

Typical angina (definite):

(i) Substernal chest discomfort with a characteristic quality and duration that is (ii) provoked by exertion or emotional stress and (iii) relieved by rest or nitroglycerin
Atypical angina (probable):

Meets 2 of the above criteria.

Non-cardiac chest pain:

Meets 1 or none of the above criteria.


**Table 3: Contraindications to Exercise Stress Testing:**

The following contraindications to exercise stress testing are from the AHA/ACC guidelines:

- Acute aortic dissection
- Acute myocardial infarction (within 2 days)
- Acute myocarditis or pericarditis
- Acute pulmonary embolus or pulmonary infarction
- Symptomatic severe aortic stenosis
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
- Uncontrolled symptomatic heart failure
- Unstable angina not previously stabilized by medical therapy.

In addition, exercise stress testing is not useful in persons who are unable to exercise, persons on digoxin, persons who have a cardiac conduction abnormality that prevents achievement of an adequate heart rate response, persons on a medication (e.g., beta blockers, other negative chronotropic agents) that can not be stopped which prevent achievement of an adequate heart rate response, and persons with an uninterpretable electrocardiogram. The American College of Cardiology defines an uninterpretable electrocardiogram as a ventricular paced rhythm, complete left bundle branch block, ventricular preexcitation arrhythmia (Wolfe Parkinson White syndrome), or greater than 1 mm ST segment depression at rest.
Table 4: Contraindications to Pharmacological Stress Testing:

The following are contraindications to adenosine or dipyridamole (Persantine) stress testing:

- Active bronchospasm or reactive airway disease;
- Patients taking Persantine (contraindication to adenosine stress testing);
- Patients using methylxanthines (e.g., caffeine and aminophylline) (In general, patients should refrain from ingesting caffeine for at least 24 hours prior to adenosine or dipyridamole administration);
- Severe bradycardia (heart rate less than 40 beats/min); Sick sinus syndrome or greater than first-degree heart block (in persons without a ventricular-demand pacemaker);
- Systolic blood pressure less than 90 mm Hg.

The following are contraindications to *dobutamine* stress testing:

- Atrial tachyarrhythmias with uncontrolled ventricular response;
- History of ventricular tachycardia;
- Left bundle branch block;
- Recent (within the past week) myocardial infarction;
- Significant aortic stenosis or obstructive cardiomyopathy;
- Thoracic aortic aneurysm;
- Uncontrolled hypertension;
- Unstable angina.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
</tr>
<tr>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>75571</td>
</tr>
<tr>
<td>CPT Code</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>75572</td>
</tr>
<tr>
<td>75573</td>
</tr>
<tr>
<td>75574</td>
</tr>
</tbody>
</table>

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33250 - 33266</td>
<td>Cardiac tissue ablation procedures</td>
</tr>
<tr>
<td>33361 - 33369</td>
<td>Transcatheter aortic valve replacement with prosthetic valve (TAVR/TAVI)</td>
</tr>
<tr>
<td>93015 - 93024</td>
<td>Cardiovascular stress testing and ergonovine provocation test</td>
</tr>
<tr>
<td>93650 - 93657</td>
<td>Intracardiac catheter ablation procedures</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria is met (not all-inclusive):

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.00 - E09.9</td>
<td>Diabetes mellitus due to underlying conditions</td>
</tr>
<tr>
<td>E10.10 - E13.9</td>
<td>Type I and Type II diabetes mellitus</td>
</tr>
<tr>
<td>I37.0 - I37.9</td>
<td>Nonrheumatic pulmonary valve disorders [pulmonary outflow obstruction]</td>
</tr>
<tr>
<td>M30.3</td>
<td>Mucocutaneous lymph node syndrome [Kawasaki disease]</td>
</tr>
<tr>
<td>Q21.3</td>
<td>Tetrology of Fallot</td>
</tr>
<tr>
<td>ICD-10 codes</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Q26.0 - Q26.9</td>
<td>Congenital malformations of great veins</td>
</tr>
<tr>
<td>Q87.40 - Q87.43</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>R07.1 - R07.9</td>
<td>Chest pain</td>
</tr>
<tr>
<td>R94.39</td>
<td>Abnormal result of other cardiovascular function study [covered for evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease by Framingham risk scoring (see Appendix) who have an equivocal or uninterpretable exercise or pharmacological stress test]</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C38.0</td>
<td>Malignant neoplasm of heart [atrial angiosarcoma]</td>
</tr>
</tbody>
</table>

**ICD-10 codes contraindicated for this CPB (not all-inclusive):**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I25.700 - I25.729</td>
<td>Coronary atherosclerosis of bypass graft [stenocclusion or instent restenosis]</td>
</tr>
<tr>
<td>I25.760 - I25.799</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>I46.2 - I46.9</td>
<td>Paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia, paroxysmal tachycardia, unspecified</td>
</tr>
<tr>
<td>I48.1, I48.3 - I48.4, I48.92</td>
<td>Atrial flutter</td>
</tr>
<tr>
<td>T82.817+, T82.827+, T82.837+, T82.847+, T82.857+, T82.867+, T82.897+, T82.9xx+</td>
<td>Other specified complications of cardiac device, implant, and graft [stenocclusion or instent restenosis]</td>
</tr>
<tr>
<td>Z68.41 - Z68.45</td>
<td>Body mass index 40 and over, adult</td>
</tr>
</tbody>
</table>
Radiographic dye allergy status [iodinated contrast material]

**Calcium Scoring:**

**HCPCS codes covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S8092</td>
<td>Electron beam computed tomography (also known as ultrafast CT, cine CT)</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria is met (not all-inclusive):**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.00</td>
<td>Diabetes mellitus due to underlying condition [asymptomatic persons age 40 years and older]</td>
</tr>
<tr>
<td>E09.9</td>
<td>Diabetes mellitus [asymptomatic persons age 40 years and older]</td>
</tr>
<tr>
<td>E10.10</td>
<td>Diabetes mellitus [asymptomatic persons age 40 years and older]</td>
</tr>
<tr>
<td>E13.9</td>
<td>Encounter for screening for cardiovascular disorders</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


15. Committee on Advanced Cardiac Imaging and Technology, Council on Clinical Cardiology, and Committee on Newer Imaging Modalities, Council on Cardiovascular Radiology, American Heart Association. Potential value of ultrafast computed tomography to screen for coronary artery


66. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Contrast-enhanced cardiac computed tomographic angiography in the diagnosis of coronary artery stenosis or for evaluation of acute chest pain. TEC Assessment Program. Chicago, IL: BCBSA; August


69. German Agency of Health Technology Assessment (DAHTA) at German Institute for Medical Documentation and Information (DIMDI). Computed tomography for the measurement of coronary calcification in asymptomatic risk patients [summary]. Technology Assessment. Cologne, Germany; DIMDI; 2006.


76. Ontario Ministry of Long-Term Care, Medical Advisory Secretariat (MAS). Multidetector computed tomography for coronary artery disease screening in asymptomatic populations. Evidence-based Analysis. Toronto, ON: MAS; May 2007.


89. Machaalany J, Yam Y, Ruddy TD, et al. Potential clinical and economic consequences of noncardiac incidental findings


95. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Coronary computed tomographic angiography in the evaluation of patients with acute chest pain. TEC Assessment Program. Chicago, IL: BCBSA; November 2011;26(9).


118. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Fractional flow reserve and coronary artery revascularization. TEC Assessment Program. Chicago, IL: BCBSA; July 2011;26(2).


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Amendment to
Aetna Clinical Policy Bulletin Number:
0228 Cardiac CT, Coronary CT Angiography, Calcium Scoring and CT Fractional Flow Reserve

There are no amendments for Medicaid.