Medical Coverage Policy

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Carotid Intima-Media Thickness Measurement

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Atherosclerotic Cardiovascular Disease Risk Assessment: Emerging Laboratory Evaluations

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Overview

This Coverage Policy addresses carotid intima-media thickness (CIMT) testing, a noninvasive test, where the lining of the carotid arteries is measured with the use of B-mode ultrasound.

Coverage Policy

Coverage of carotid intima-media thickness (CIMT) testing may be governed by state mandates.

Carotid intima-media thickness (CIMT) testing for any indication including the evaluation of atherosclerotic burden or coronary heart disease risk factor assessment is considered experimental, investigational or unproven.

General Background

Measurement of the carotid intima-media thickness (CIMT) is a noninvasive test, where the lining of the carotid arteries is measured with the use of B-mode ultrasound. The intima is the innermost layer of the artery, and the media is the middle layer of the artery. Carotid ultrasound has been routinely used for evaluation of ischemic

cerebrovascular signs and symptoms. In the utilization of carotid ultrasound in the context of risk stratification, the intima-media thickness is measured for the objective of detecting preclinical or subclinical cardiovascular disease. Measurement of the CIMT is considered to be a surrogate marker for the measurement of atherosclerosis, which correlates with the presence of coronary atherosclerosis. This has led to the theory that it may represent an independent marker, separate from the traditional risk factors for cardiovascular disease and stroke. The major independent risk factors are cigarette smoking, elevated blood pressure, elevated serum total and LDL cholesterol, low serum HDL cholesterol, diabetes mellitus, and advancing age. Additional risk factors include obesity, family history of premature coronary heart disease (CHD), and physical inactivity (Pearson, 2000). It is not clear if the measurement of CIMT provides benefit above traditional risk factors or if treatment guided by this test has an effect on clinical outcomes.

The wall thickness can be measured at a single site, such as the far wall of common carotid artery or at several sites including near and far walls of the left and right common carotid arteries, bifurcation, and internal carotid artery (Crouse, 2006). CIMT has been widely used in research as an outcome measurement in studies, including tests involving the following (Simon and Levenson, 2002):

- testing the value of new or emerging risk factors by means of observational or epidemiological studies in groups of patients or in general populations
- evaluating effects of risk factor modifications by various drugs on progression of early arterial wall alteration in therapeutic trials

Disadvantages that have been identified to be associated with the use of this testing procedure include (Nissen, 2004):

- A high level of technical expertise is needed for precise quantification. In particular, this is needed when the measurement is used in for multicenter studies, since the precision of the studies depends upon the measurement of extremely small differences in thickness.
- There is an incomplete standardization of equipment, with various devices and frequencies employed at different centers.

Difficulties that have been identified with CIMT testing include: poor image quality, drifting, improper machine settings and difficult patient anatomy (e.g., high bifurcations of the carotid artery and deep vessels) (Mitchell, et al., 2004). At this time, there is a lack of standardization of measurement and imaging protocols. It is not clear whether generalized IMT or focal plaque formation is of more importance (Mancini, et al., 2004). The literature indicates that there are gender- and age-related differences with IMT. A definition of what is considered expected normal limits that take into account these differences has not been established. It is not evident from the literature that CIMT is able to improve on risk prediction above what is provided by utilization of traditional risk factors or the effect of these measurements on patient outcomes.

Literature Review

Systematic reviews: van den Oord et al. (2013) reported on a systematic review and meta-analysis of the published evidence on the association of CIMT with future cardiovascular events and its additional value to traditional cardiovascular risk prediction models. The association of CIMT with future cardiovascular events and the additional value of CIMT were calculated using random effects analysis. The review included 15 articles that provided sufficient data for the meta-analysis. A one standard deviation (SD) increase in CIMT was predictive for myocardial infarction (HR 1.26, 95% CI 1.20 e1.31) and for stroke (HR 1.31, 95% CI 1.26e1.36). A 0.1 mm increase in CIMT was predictive for myocardial infarction (HR 1.15, 95% CI 1.12e1.18) and for stroke (HR 1.17, 95% CI 1.15e1.21). It was found that the overall performance of risk prediction models did not significantly increase after addition of CIMT data. The areas under the curve increased from 0.726 to 0.729 (p ¼ 0.8). The authors concluded that CIMT as measured by B-mode ultrasound is associated with future cardiovascular events; however, the addition of CIMT to traditional cardiovascular risk prediction models does not lead to a statistically significant increase in performance of those models.

Den Ruijter et al. (2012) conducted a meta-analysis to determine whether common CIMT has added value in 10-year risk prediction of first-time myocardial infarctions or strokes, above that of the Framingham Risk Score. The review included 14 population-based cohorts with data for 45,828 individuals. The studies included participants

were drawn from the general population, common CIMT was measured at baseline, and individuals were followed up for first-time myocardial infarction or stroke. Individual data were combined into one data set and an individual participant data meta-analysis was performed on individuals without existing cardiovascular disease. During a median follow-up of 11 years, 4,007 first-time myocardial infarctions or strokes occurred. The risk factors of the Framingham Risk Score were refitted and then the model with common CIMT measurements was extended to estimate the absolute 10-year risks to develop a first-time myocardial infarction or stroke in both models. The added value of common CIMT measurements to the Framingham Risk Score in the general population was found to be minor (0.8% were correctly reclassified). In individuals at intermediate risk, the added value was 3.2% in men and 3.9% in women. The authors concluded that the addition of common CIMT measurements to the Framingham Risk Score was associated with small improvement in 10-year risk prediction of first-time myocardial infarction or stroke, but this improvement is unlikely to be of clinical importance. The findings of this study indicate that there is little clinical utility of using CIMT for cardiac risk assessment.

Lorenz et al. (2012) conducted a meta-analysis to test the association between changes in CIMT and cardiovascular risk (PROG-IMT collaborative project). The review included 16 studies with 36,984 participants. The review identified general population cohort studies that assessed CIMT at least twice and followed up with participants for myocardial infarction, stroke, or death. During a mean follow-up of seven years, 1,519 myocardial infarctions, 1,339 strokes, and 2,028 combined endpoints (myocardial infarction, stroke, vascular death) occurred. Individual participant data meta-analysis was performed. After excluding individuals with previous myocardial infarction or stroke, the association was assessed between CIMT progression and the risk of cardiovascular events (myocardial infarction, stroke, vascular death, or a combination of these) for each study with Cox regression. Yearly CIMT progression was derived from two ultrasound visits 2–7 years apart. No evidence of an association between individual CIMT progression and the risk of subsequent cardiovascular events, irrespective of definition of CIMT, endpoint, and adjustment. The authors strongly advocate further validations and improvements of ultrasound protocols. The authors concluded that the association between CIMT progression assessed from two ultrasound scans and cardiovascular risk in the general population remains unproven. Further studies are needed to determine how the association between CIMT progression and cardiovascular risk and the assessment of CIMT will affect health outcomes.

Lorenz et al. (2018) conducted a meta-analysis to assess the relation between CIMT change and events in individuals at high cardiovascular risk (results from the PROG-IMT collaboration above). From 31 cohorts with two CIMT scans (n = 89070) on average 3.6 years apart and clinical follow-up, subcohorts were drawn: A) individuals with at least three cardiovascular risk factors without previous CVD events; B) individuals with carotid plaques without previous CVD events; and C) individuals with previous CVD events. Cox regression models were fit to estimate the hazard ratio (HR) of the combined endpoint (myocardial infarction, stroke or vascular death) per standard deviation (SD) of CIMT change, adjusted for CVD risk factors. These HRs were pooled across studies. In groups A, B and C it was observed 3483, 2845 and 1165 endpoint events, respectively. The average common CIMT was 0.79mm (SD 0.16mm), and annual common CIMT change was 0.01mm (SD 0.07mm), both in group A. The pooled HR per SD of annual common CIMT change (0.02 to 0.43mm) was 0.99 (95% confidence interval: 0.95-1.02) in group A, 0.98 (0.93-1.04) in group B, and 0.95 (0.89-1.04) in group C. The HR per SD of common CIMT (average of the first and the second CIMT scan, 0.09 to 0.75mm) was 1.15 (1.07-1.23) in group A, 1.13 (1.05-1.22) in group B, and 1.12 (1.05-1.20) in group C. The authors concluded that although common CIMT is associated with future CVD event risk, this is not apparently true for common CIMT change over time; it is theorized that reasons may include the complexity of atherosclerotic process, and technical limits of current CIMT measurement.

Costanzo et al. (2010) reported on a systematic review conducted with the aim to assess, using a meta-regression analysis of randomized trials whether reduced progression or regression of IMT is associated with a reduced incidence of major cardiovascular events in subjects at intermediate to high cardiovascular risk. The review included 41 trials with 18,307 participants that assessed carotid IMT at baseline, at the end of follow-up, and reporting clinical end points. The influence of baseline patients' characteristics, cardiovascular risk profile, IMT at baseline, follow-up, and quality of the trials was also examined. Although there was a significant reduction in coronary heart disease (CHD) and cerebrovascular (CBV) events, and all-cause death induced by active treatments (for CHD events, odds ratio [OR]: 0.82, 95% confidence interval [CI]: 0.69 to 0.96, p=0.02; for CBV events, OR: 0.71, 95% CI: 0.51 to 1.00, p=0.05; and for all-cause death, OR: 0.71, 95% CI: 0.53 to 0.96,

p=0.03), there was no significant relationship between IMT regression and CHD events, CBV events, and all-cause death. It was also noted that subjects' baseline characteristics, cardiovascular risk profile, IMT at baseline, follow-up, and quality of the trials did not significantly influence the association between IMT changes and clinical outcomes. The authors concluded that the regression or slowed progression of CIMT, induced by cardiovascular drug therapies do not reflect reduction in cardiovascular events.

Wald et al. (2009) reported on a meta-analysis of studies that assessed the screening performance of CIMT and carotid plaque in identification of individuals with CHD. The review included 18 case-control and cohort studies that involved 2,920 individuals with CHD and 41,941 without. An assessment of screening performance (detection rates [DRs] for specified false positive rates [FPRs]) was carried out from the relative Gaussian distributions of IMT among individuals with and without CHD and from the proportion of affected and unaffected individuals with plaque. Findings included: for plaque that the DR was 62% for an FPR of 30%; and for IMT, the DR was 65% for the same 30% FPR. The authors concluded that neither carotid plaque nor IMT has a CHD screening performance that is sufficiently discriminatory between affected and unaffected individuals to be considered a worthwhile screening test.

Baldassarre et al. (2008) conducted a meta-analysis of 107 studies addressing the association between CIMT and soluble markers and to investigate whether these observed inconsistencies could be explained by the characteristics of the patients included in different studies (e.g., the prevalence of atherosclerotic disease, gender, age, or occurrence of specific vascular risk factors [VRFs]). Regardless of the marked heterogeneity of results presented in the literature, the meta-analysis demonstrated that studies showing positive associations between CIMT and plasma levels of C-reactive protein (CRP) or fibrinogen are in the majority. The data regarding the relationships between CIMT and other soluble markers are by contrast noted to be scanty, contradictory, or unconfirmed by multivariate (as opposed to univariate) analyses, and the freedom from publication bias here cannot be assured. Gender, noninsulin-dependent diabetes mellitus (NIDDM) and hypercholesterolemia appeared to influence the association between CIMT and CRP. Blood pressure and hypercholesterolemia appeared to influence the association between CIMT and fibrinogen. The heterogeneity in ultrasound methodologies and in statistical approach limited comparability between studies.

Lorenz et al. (2007) conducted a systematic review of the literature to provide an overview of the relevant studies, critically appraise the methods used and, where possible, to perform a meta-analysis to gain more robust estimates of the predictive value of increased IMT to predict future clinical cardiovascular end points. The review included eight observational studies with general population based samples for which CIMT was measured and follow-up for clinical end points were provided. The studies represented 37,197 subjects followed for a mean of 5.5 years. Major sources of heterogeneity were age distribution, carotid segment definition and IMT measurement protocol. The review found that CIMT is a strong predictor of future vascular events. In addition, it was noted that the relative risk per IMT difference is slightly higher for the end point of stroke than for MI. The review also noted heterogeneity between the studies regarding the details of the ultrasound protocols. These details included: the precise definitions of the carotid segments investigated, the use of mean or maximal IMT, the measurement of near and far wall or IMT, and whether IMT is measured on one side or both sides. It is recommended that in future studies of IMT, ultrasound protocols should be aligned with published studies. It appears that data for younger individuals is limited, and additional studies are required.

Studies: Jeevarethinam et al. (2015) reported on a study that examined whether increased carotid intima–media thickness (cIMT) and prevalence of carotid plaque (CP) are predictive of prevalence and severity of coronary atherosclerosis. The retrospective study included 150 consecutive patients with no history of coronary artery disease (CAD), who underwent both carotid ultrasound and computed tomographic coronary angiography. The mean cIMT was higher in patients with CAD than in those without CAD (0.76 vs 0.66 mm, P<.003). Backward selection analysis demonstrated higher mean cIMT measurement correlated well with prevalence of any coronary plaque (P=.03) and obstructive coronary plaque disease (P=.05), whereas presence of CP was a good predictor of both obstructive (>50% stenosis P=.003) and any coronary plaque (P=.003). This study was limited by small sample size, predominantly middle-aged males and the retrospective nature of the study.

Polak et al. (2011) conducted a study that examined if the intima–media thickness of the walls of the common carotid artery and internal carotid artery could add to the Framingham risk score for predicting cardiovascular events. The mean intima–media thickness of the common carotid artery and the maximum intima–media

thickness of the internal carotid artery were measured in 2,965 members of the Framingham Offspring Study cohort. Cardiovascular disease outcomes were evaluated for an average follow-up of 7.2 years. Multivariable Cox proportional hazards models were generated for intima–media thickness and risk factors. Reclassification was performed of cardiovascular disease on the basis of the 8-year Framingham risk score category (low, intermediate, or high) after adding intima–media thickness values. A total of 296 participants had a cardiovascular event with the risk factors of the Framingham risk score predicting these events , with a C statistic of 0.748 (95% confidence interval [CI], 0.719–0.776). The adjusted hazard ratio for cardiovascular disease with a 1-SD increase in the mean intima–media thickness of the common carotid artery was 1.13 (95% CI, 1.02–1.24), with a nonsignificant change in the C statistic of 0.003 (95% CI, 0.000–0.007); the corresponding hazard ratio for the maximum intima–media thickness of the internal carotid artery was 1.21 (95% CI, 1.13–1.29), with a modest increase in the C statistic of 0.009 (95% CI, 0.003–0.016). The net reclassification index increased significantly after addition of intima–media thickness of the internal carotid artery (7.6%, p<0.001) but not intima–media thickness of the common carotid artery (0.0%, P = 0.99). With the presence of plaque, defined as intima–media thickness of the internal carotid artery of more than 1.5 mm, the net reclassification index was 7.3% (p=0.01), with an increase in the C statistic of 0.014 (95% CI, 0.003–0.025). The authors concluded that the maximum internal and mean common carotid-artery intima–media thicknesses both predict cardiovascular outcomes, but only the maximum intima–media thickness of (and presence of plaque in) the internal carotid artery had a modest effect of improving the classification of risk of cardiovascular disease in this cohort. Limitations of the study included that the population only included white race and the results may not be applicable to other races or ethnic groups; the follow-up period was 7.2-years up period, which is shorter than the 10-year period for which the Framingham risk score is calculated; and a single experienced and supervised sonographer to was used to obtain high-quality measurements during carotid artery ultrasonography, which may affect the implementation of our findings in primary prevention.

There are several observational, longitudinal studies published that demonstrate a correlation between CIMT measurement and established risk factors for heart disease (Villines, et al., 2017; Geisel, et al., 2017; Nambi, et al., 2010; Kathiresan,, et al., 2007; Amato, et al., 2007; O'Leary, et al., 1999; Hodis, et al., 1998; Bots, et al., 1997; Chambless, et al., 1997).

Although there appears to be an association with established risk factors for heart disease, cohort and case-control studies have not demonstrated that use of this test results in a substantial increase in predictive value when utilized as a screening tool in addition to established risk factors or if patient treatment guided by CIMT improves cardiovascular outcomes (Bot, et al., 2014; Jain, et al., 2011; Folsom et al., 2008; Baldassare, et al., 2007; Kitagawa, et al., 2007; Kanawar, et al., 2007; Gepner, et al., 2006; Iglesias del Sol, et al., 2001).

Lorenz, et al. (2010) published results of a ten-year follow-up of a cohort of 4,904 patients without pre-existing vascular disease in the Carotid Atherosclerosis Progression Study (CAPS). The usefulness of CIMT in individual risk prediction beyond the Framingham and the SCORE models was investigated. The authors found that while CIMT was predictive for cardiovascular endpoints, it did not consistently improve the risk classification of individuals.

Professional Societies/Organizations
American Association of Clinical Endocrinologists (AACE): the AACE published updated guidelines for management of dyslipidemia and prevention of cardiovascular disease (Jellinger, et al., 2017). The guidelines include the following recommendation: Carotid intima media thickness (CIMT) may be considered to refine risk stratification to determine the need for more aggressive atherosclerotic cardiovascular disease preventive strategies. (Grade B; best evidence level [BEL] 2).

American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines: The ACC/AHA published updated 2013 ACC/AHA guidelines, in collaboration with National Heart, Lung, and Blood Institute (NHLBI) on the assessment of cardiovascular risk (Goff, et al., 2014). The guidelines include the following regarding CIMT:

CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.

NHLBI grade: (Grade N*, No Recommendation For or Against)
ACC/AHA Class III*: No Benefit, LOE B*
Based on new evidence reviewed during ACC/AHA update of the evidence.

* Grade N: No recommendation for or against
There is insufficient evidence or evidence is unclear or conflicting.")
Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

Class III/LOE B: recommendation that procedure or treatment is not useful/effective and may be harmful; evidence from single randomized trial or nonrandomized studies

American College of Preventive Medicine (ACPM): the ACPM published position statement for atherosclerotic cardiovascular disease screening in adults (Lim, et al., 2011). The statement notes that the ACPM "recommends CHD risk assessment using the FRS [Framingham Risk Score] to guide risk-based therapy. ACPM does not recommend routine screening of the general adult population using electrocardiogram, exercise-stress testing, computed tomography scanning, ankle-brachial index, carotid intima medial thickness, or emerging risk factors, including high-sensitivity C-reactive protein (hs-CRP)."

American Diabetes Association and American College of Cardiology Foundation: A consensus statement from these two organizations was published regarding lipoprotein management in patients with cardiometabolic risk (Brunzell, et al., 2008). The report included the following statements regarding CIMT measurement:

- The presence of so-called subclinical vascular disease may be determined by measuring coronary calcification, carotid intima-media thickness, or the ankle-brachial index. Patients with documented subclinical atherosclerosis are at increased cardiovascular disease risk and may be considered candidates for more aggressive therapy
- Whether such tests improve prediction or clinical decision making in patients with diabetes or cardiometabolic risk is unclear.

American Society of Echocardiography (ASE) American and the Society of Vascular Medicine and Biology: A report published in 2006 by these two organizations, Clinical Application of Noninvasive Vascular Ultrasound in Cardiovascular Risk Stratification, notes that numerous carotid artery imaging protocols have been proposed. The protocols and methodological aspects are reviewed in the report. The report notes that protocols may vary in the number of segments in which IMT is measured, whether the near wall is measured in addition to the far wall, and whether IMT measurements are derived from B-mode or M-mode ultrasound images (Roman, et al., 2006).

In 2008, these two organizations published a consensus statement—Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Endorsed by the Society for Vascular Medicine (Stein, et al., 2008). In order to address the issues of standardization and assist in improving the availability of experienced clinical laboratories that can perform high-quality CIMT studies, the societies have provided recommendations for carotid ultrasound scanning protocol. It is noted that since a randomized controlled trial studying the effectiveness of carotid ultrasound imaging as a tool to modify preventive therapies and improve cardiovascular disease outcomes has not been performed, the clinical practice recommendations are based on observational data. The guidelines note that additional research is required in order to determine whether improved risk prediction observed with CIMT or carotid plaque imaging translates into improved patient outcomes. The recommendations for performing CIMT include:

- Measuring CIMT and identifying carotid plaque by ultrasound are most useful for refining cardiovascular risk assessment in patients at intermediate cardiovascular risk (i.e., Framingham risk score 6-20% without established coronary heart disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus or abdominal aortic aneurysm).
- CIMT assessment and carotid plaque detection may also be considered in the following situations:

- patients with family history of premature cardiovascular disease in a first degree relative (i.e., men <55 years old, women <65 years old)
- individuals younger than 60 years old with severe abnormalities in a single risk factor (e.g., genetic dyslipidemia) who otherwise would not be candidates for pharmacotherapy
- women younger than 60 years old with at least two cardiovascular risk factors

- Imaging should not be performed in the following situations:
  - with established atherosclerotic vascular disease
  - if the results would not be expected to alter therapy
- Serial studies of CIMT to address progression or regression are not recommended.

Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council Cardiovascular Radiology and Intervention, American Heart Association: A consensus statement from these groups was published regarding the role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease (Mieres, et al., 2005). The consensus statement makes the following notations regarding CIMT:

- CIMT is one of several emerging imaging modalities in the detection of subclinical atherosclerotic heart disease in women that has not amassed the wealth of evidence that would clearly define the role in the clinical evaluation of women with suspected atherosclerotic heart disease.
- The advantages of CIMT include the wide availability of ultrasound technology, absence of ionizing radiation or incidental scan findings and well-validated nature of the test results.
- The limitations of the test include the lack of accepted technical standards for IMT testing and the absence of published population distributions of IMT. Further precise documentation of what defines an abnormal level of IMT and measurement guidelines are needed.
- The clinical use of CIMT for risk stratification in asymptomatic women has not been shown to result in improved outcomes.

Mannheim Carotid Intima-Media Thickness Consensus (2004-2006): The Mannheim Consensus was convened to standardize methods used in the measurement of CIMT. The consensus statement notes that, “Although IMT has been suggested to represent an important risk marker, according to the current evidence it does not fulfill the characteristics of an accepted risk factor. Standardized methods recommended in this consensus statement will foster homogenous data collection and analysis. This will help to improve the power of randomized clinical trials incorporating IMT measurements and to facilitate the merging of large databases for meta-analyses.” It is noted that there is no need to “treat IMT values nor to monitor IMT values in individual patients.” (Touboul, et al., 2007)

US Preventive Services Task Force (USPSTF): The USPSTF Recommendation Statement on Using Nontraditional Risk Factors In Coronary Heart Disease Risk Assessment concluded that the current evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events (USPSTF, October 2009). (Grade: I [Insufficient] Statement, current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.) The nontraditional risk factors included in this recommendation are high-sensitivity C-reactive protein (hs-CRP), ankle–brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima–media thickness (carotid IMT), coronary artery calcification (CAC) score on electron-beam computed tomography (EBCT), homocysteine level, and lipoprotein(a) level. (USPSTF, 2009). The 2018 update to the 2009 USPSTF recommendations does not include carotid IMT. The update concluded that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events (USPSTF, 2018).

Use Outside of the US

European Society of Cardiology (ESC): The ESC published updated guidelines on cardiovascular disease prevention in clinical practice. With regard to CIMT the guidelines note that, “The lack of standardization regarding the definition and measurement of IMT, its high variability and low intra-individual reproducibility have

raised concerns. A recent meta-analysis failed to demonstrate any added value of IMT compared to the Framingham Risk Score in predicting future CVD, even in the intermediate risk group. Thus, the systematic use of carotid ultrasound IMT to improve risk assessment is not recommended." (Piepoli, et al., 2016)

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation, bilateral
93998†	Unlisted noninvasive vascular diagnostic study
0126T	Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment (Code deleted 12/31/2020)

†**Note: Considered Experimental/Investigational/Unproven when used to report common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment**

References

1. American Academy of Family Physicians (AAFP). Summary of recommendations for clinical preventive services. July 2017. Accessed March 31, 2021. Available at URL address: https://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/cps-recommendations.pdf

2. Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM, et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. Eur Heart J. 2007 Sep;28(17):2094-101.

3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e596-e646.

4. Baldassarre D, Amato M, Pustina L, Castelnuovo S, Sanvito S, Gerosa L, et al. Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events. Atherosclerosis. 2007 Apr;191(2):403-8. Epub 2006 May 8.

5. Baldassarre D, De Jong A, Amato M, Werba JP, Castelnuovo S, Frigerio B, et al. Carotid intima-media thickness and markers of inflammation, endothelial damage and hemostasis. Ann Med. 2008;40(1):21-44.

6. Bard RL, Kalsi H, Rubenfire M, Wakefield T, Fex B, Rajagopalan S, Brook RD. Effect of carotid atherosclerosis screening on risk stratification during primary cardiovascular disease prevention. Am J Cardiol. 2004 Apr 15;93(8):1030-2.

7. Bernard S, Serusclat A, Targe F, Charriere S, Roth O, Beaune J, et al. Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. Diabetes Care. 2005 May;28(5):1158-62.

8. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation. 1997 Sep 2;96(5):1432-7.

9. Bots ML, Baldassarre D, Simon A, de Groot E, O'Leary DH, Riley W, et al. Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? Eur Heart J. 2007 Feb;28(4):398-406.

10. Bots ML, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engström G. Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. Hypertension. 2014 Jun;63(6):1173-81.

11. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL; American Diabetes Association; American College of Cardiology Foundation. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. 2008 Apr;31(4):811-22.

12. Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. Circulation. 2007 Jul 3;116(1):32-8.

13. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. 1997 Sep 15;146(6):483-94.

14. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol. 2010 Dec 7;56(24):2006-20.

15. Crouse JR 3rd. Thematic review series: patient-oriented research. Imaging atherosclerosis: state of the art. J Lipid Res. 2006 Aug;47(8):1677-99.

16. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation. 2001 Dec 4;104(23):2815-9.

17. de Groot E, Kastelein JP, Duivenvoorden R. Carotid intima-media thickness. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Last updated: May 23, 2019 (Accessed on March 31, 2021).

18. del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Grobbee DE, et al. Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. Stroke. 2001 Jul;32(7):1532-8.

19. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012 Aug 22;308(8):796-803.

20. Dijk JM, van der Graaf Y, Bots ML, Grobbee DE, Algra A. Carotid intima-media thickness and the risk of new vascular events in patients with manifest atherosclerotic disease: the SMART study. Eur Heart J. 2006 Aug;27(16):1971-8.

21. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008 Jun 23;168(12):1333-9.

22. Geisel MH, Bauer M, Hennig F, Hoffmann B, Lehmann N, Möhlenkamp S, et al.; Heinz Nixdorf Recall study. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. Eur Heart J. 2017 Jun 14;38(23):1815-1822.

23. Gepner AD, Keevil JG, Wyman RA, Korcarz CE, Aeschlimann SE, Busse KL, Stein JH. Use of carotid intima-media thickness and vascular age to modify cardiovascular risk prediction. J Am Soc Echocardiogr. 2006 Sep;19(9):1170-4.

24. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2935-59.

25. Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. Am Heart J. 2010 Oct;160(4):701-14.

26. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al.; American College of Cardiology Foundation; American Heart Association. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010 Dec 14;56(25):e50-103.

27. Helfand M, Buckley D, Fleming C, Fu R, Freeman M, Humphrey L, et al. Screening for Intermediate Risk Factors for Coronary Heart Disease: Systematic Evidence Synthesis. Evidence Synthesis No. 73. AHRQ Publication No. 10-05141-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality, October 2009.

28. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med. 1998 Feb 15;128(4):262-9.

29. Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J. 2002 Jun;23(12):934-40.

30. Jain A, McClelland RL, Polak JF, Shea S, Burke GL, Bild DE, et al. Cardiovascular Imaging for Assessing Cardiovascular Risk in Asymptomatic Men Versus Women: The Multi-Ethnic Study of Atherosclerosis (MESA). Circ Cardiovasc Imaging. 2011 Jan 1;4(1):8-15.

31. Jeevarethinam A, Venuraju S, Weymouth M, Atwal S, Lahiri A. Carotid intimal thickness and plaque predict prevalence and severity of coronary atherosclerosis: a pilot study. Angiology. 2015 Jan;66(1):65-9.

32. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al.. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. Endocr Pract. 2017 Apr;23(Suppl 2):1-87.

33. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, et al.; AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012 Mar-Apr;18 Suppl 1:1-78.

34. Kathiresan S, Larson MG, Keyes MJ, Polak JF, Wolf PA, D'Agostino RB, et al. Assessment by cardiovascular magnetic resonance, electron beam computed tomography, and carotid ultrasonography of the distribution of subclinical atherosclerosis across Framingham risk strata. Am J Cardiol. 2007 Feb 1;99(3):310-4.

35. Kitagawa K, Hougaku H, Yamagami H, Hashimoto H, Itoh T, Shimizu Y, et al.; OSACA2 Study Group. Carotid intima-media thickness and risk of cardiovascular events in high-risk patients. Results of the Osaka Follow-Up Study for Carotid Atherosclerosis 2 (OSACA2 Study). Cerebrovasc Dis. 2007;24(1):35-42.

36. Lim LS, Haq N, Mahmood S, Hoeksema L; ACPM Prevention Practice Committee; American College of Preventive Medicine. Atherosclerotic cardiovascular disease screening in adults: American College Of Preventive Medicine position statement on preventive practice. Am J Prev Med. 2011 Mar;40(3):381.e1-10.

37. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007 Jan 30;115(4):459-67.

38. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). Eur Heart J. 2010 Aug;31(16):2041-8.

39. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, et al.; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet. 2012 Jun 2;379(9831):2053-62.

40. Lorenz MW, Gao L, Ziegelbauer K, et al. Predictive value for cardiovascular events of common carotid intima media thickness and its rate of change in individuals at high cardiovascular risk - Results from the PROG-IMT collaboration [published correction appears in PLoS One. 2018 Sep 20;13(9):e0204633]. PLoS One. 2018;13(4):e0191172. Published 2018 Apr 12.

41. Mancini GB, Dahlof B, Diez J. Surrogate markers for cardiovascular disease: structural markers. Circulation. 2004 Jun 29;109(25 Suppl 1):IV22-30.

42. Mieres JH, Gulati M, Bairey Merz N, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association [published correction appears in Circulation. 2014 Jul 22;130(4):e86]. Circulation. 2014;130(4):350–379.

43. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, et al.; Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on

Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation. 2005 Feb 8;111(5):682-96.

44. Mitchell CK, Aeschlimann SE, Korcarz CE. Carotid intima-media thickness testing: technical considerations. J Am Soc Echocardiogr. 2004 Jun;17(6):690-2.

45. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, et al.; SHAPE Task Force. From vulnerable plaque to vulnerable patient--Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol. 2006 Jul 17;98(2A):2H-15H.

46. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010 Apr 13;55(15):1600-7.

47. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999 Jan 7;340(1):14-22.

48. Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: the Atherosclerosis Risk in Young Adults (ARYA) Study. Arch Intern Med. 2003 Aug 11-25;163(15):1787-92.

49. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation. 2002 Jul 16;106(3):388-91.

50. Peters SA, den Ruijter HM, Grobbee DE, Bots ML. Results from a carotid intima-media thickness trial as a decision tool for launching a large-scale morbidity and mortality trial. Circ Cardiovasc Imaging. 2013 Jan 1;6(1):20-5. doi: 10.1161/CIRCIMAGING.112.978114. Epub 2012 Nov 30.

51. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al; Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;37(29):2315-81.

52. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011 Jul 21;365(3):213-21.

53. Raiko JR, Magnussen CG, Kivimäki M, Taittonen L, Laitinen T, Kähönen M, et al. Cardiovascular risk scores in the prediction of subclinical atherosclerosis in young adults: evidence from the cardiovascular risk in a young Finns study. Eur J Cardiovasc Prev Rehabil. 2010 Oct;17(5):549-55.

54. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003 Nov 5;290(17):2277-83.

55. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E; American Society of Echocardiography; Society of Vascular Medicine and Biology. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of

Echocardiography and the Society of Vascular Medicine and Biology. J Am Soc Echocardiogr. 2006 Aug;19(8):943-54.

56. Saba L, Jamthikar A, Gupta D, et al. Global perspective on carotid intima-media thickness and plaque: should the current measurement guidelines be revisited?. *Int Angiol*. 2019;38(6):451–465.

57. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens. 2002 Feb;20(2):159-69.

58. Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease). Circulation. 1999 Aug 31;100(9):951-7.

59. Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. Eur Heart J. 2007 Dec;28(24):2967-71.

60. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. ASE consensus statement: Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. Feb 2008.

61. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the advisory board of the 3rd and 4th watching the risk symposium 13th and 15th European stroke conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis. 2007;23(1):75-80.

62. Touboul PJ, Hernandez-Hernandez R, Kucukoglu S, Woo KS, Vicaut E, Labreuche J, et al. for the PARC-AALA Investigators. Carotid artery intima media thickness, plaque and framingham cardiovascular score in Asia, Africa/Middle East and Latin America: the PARC-AALA Study. Int J Cardiovasc Imaging. 2006 Dec 21.

63. Touboul PJ, Labreuche J, Vicaut E, Belliard JP, Cohen S, Kownator S,et al.; PARC Study Investigators. Country-based reference values and impact of cardiovascular risk factors on carotid intima-media thickness in a French population: the 'Paroi Artérielle et Risque Cardio-Vasculaire' (PARC) Study. Cerebrovasc Dis. 2009;27(4):361-7.

64. U.S. Preventive Services Task Force. Using Nontraditional Risk Factors In Coronary Heart Disease Risk Assessment: Recommendation Statement. October 2009. Agency for Healthcare Research and Quality, Rockville, MD. Accessed March 31, 2021. (archived) Available at URL address: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/coronary-heart-disease-screening-using-non-traditional-risk-factors

65. U.S. Preventive Services Task Force. Risk Assessment for Cardiovascular Disease with Nontraditional Risk Factors: Recommendation Statement. July 2018. Accessed March 31, 2021. Available at URL address: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/cardiovascular-disease-screening-using-nontraditional-risk-assessment.

66. van den Oord SC, Sijbrands EJ, ten Kate GL, van Klaveren D, van Domburg RT, van der Steen AF, Schinkel AF. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. Atherosclerosis. 2013 May;228(1):1-11.

67. Villines TC, Hsu LL, Blackshear C, Nelson CR, Griswold M. Relation of Carotid Intima-Media Thickness to Cardiovascular Events in Black Americans (From the Jackson Heart Study). Am J Cardiol. 2017 Nov 1;120(9):1528-1532.

68. Wald DS, Bestwick JP. Carotid ultrasound screening for coronary heart disease: results based on a meta-analysis of 18 studies and 44,861 subjects. J Med Screen. 2009;16(3):147-54.

69. Wilson PWF. Cardiovascular disease risk assessment for primary prevention in adults: Our approach. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Last updated: May 29, 2020 (Accessed on April 9, 2021).