



# CIGNA MEDICAL COVERAGE POLICY

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**Subject Carotid Intima-Media Thickness Measurement**

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## Coverage Policy

**CIGNA does not cover carotid intima-media thickness (CIMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment because it is considered experimental, investigational or unproven.**

## General Background

Cardiovascular disease is the leading cause of mortality and morbidity in the United States (American Heart Association, [AHA], 2007). Risk factor assessment plays the first step in primary prevention and guides therapeutic strategy. 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 thought that conventional risk factor assessment may not be sufficient to assess total risk of cardiovascular disease. In an effort to improve clinical outcomes, newer noninvasive imaging modalities have been proposed to measure and monitor atherosclerosis in asymptomatic individuals. These include techniques that may detect early structural changes in the coronary arteries, such as electron-beam computed tomography, magnetic

resonance imaging and intravascular ultrasound. Another method proposed that is intended to be a surrogate marker for coronary artery atherosclerosis is the measurement of the carotid intima-media thickness (CIMT). This 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 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 represents an independent marker, separate from the traditional risk factors for cardiovascular disease and stroke. It is not clear if the measurement of CIMT provides benefit above traditional risk factors or 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

There are disadvantages that have been identified to be associated with the use of this testing procedure. These 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**

Several observational studies have been published that correlate CIMT measurements with established risk factors for coronary heart disease.

Bots et al. (1997) used a nested case-control approach among 7983 subjects aged 55 years and older participating in the Rotterdam Study to examine whether common CIMT is related to future stroke and myocardial infarction (MI). The Rotterdam Study is a single-center, prospective, follow-up study on disease and disability in the elderly in 7983 subjects, aged 55 years or older, living in Rotterdam, Netherlands. Baseline data for each subject were collected from March 1990 through July 1993 in a home interview and two visits at the research center. At baseline, ultrasound images of the common carotid artery were stored on videotape. Determination of incident MI and stroke was predominantly based on hospital discharge records. Analysis was based on 98 MIs and 95 strokes that were registered before December 1994. The IMT was measured from videotape for all subjects and 1373 subjects who remained free from MI and stroke in the follow-up period. The mean duration of follow-up was 2.7 years. The results noted that stroke risk and MI increased gradually with increasing IMT. The authors concluded that, "the present study, based on a short follow-up period, shows that an increased common CIMT relates to future cardiovascular and cerebrovascular events. This study provides supportive evidence for the use of IMT measurements as an intermediate or proxy end point in observational studies and trials."

The atherosclerotic risk in communities (ARIC) study was a cohort study of 15,792 persons (7,289 women and 5,552 men), aged 45–64 years who were free of clinical CHD at baseline (Chambless, et al., 1997). In this study, an index of generalized atherosclerosis was defined as the mean of IMT measurements at six sites of the carotid arteries using B-mode ultrasound. This measurement was assessed in its relation to CHD incidence over four to seven years of follow-up (1987–1993). The study findings noted that there were 96 incident events for women and 194 for men. When the models were adjusted only for age, race, and center, the hazard rate ratio comparing extreme mean IMT (>1 mm) to not extreme (<1 mm) was 5.07 for women (95% confidence interval 3.08–8.36) and 1.85 for men (95% confidence interval 1.28–2.69). When major CHD risk factors were included, the strength of the association was reduced but remained elevated at higher IMT. The authors concluded that mean CIMT is a noninvasive predictor of future CHD incidence.

Hodis et al. (1998) conducted a long-term follow-up study of a previously studied cohort of individuals who had completed the two-year Cholesterol Lowering Atherosclerosis Study, which was a randomized arterial imaging trial designed to study the effects of lipid lowering on progression of atherosclerosis. The objective of the study was to determine whether CIMT predicts coronary events. The study included one hundred and forty-six men, aged 40–59 years who had previously had coronary artery bypass graft surgery. CIMT measurements were performed every six months with B-mode ultrasonography. Intrusive atherosclerosis in the coronary arteries was evaluated at baseline and at two years with quantitative coronary angiography. After the trial, the incidences of coronary events (i.e., nonfatal acute MI, coronary death, and coronary artery revascularization) were documented. Findings included that for each 0.03 mm increase per year in CIMT, the relative risk for non-fatal MI or coronary death was 2.2, and the relative risk for any coronary event was 3.1. Absolute IMT was also related to risk for clinical coronary events. Absolute thickness and progression in thickness predicted risk for coronary events beyond that predicted by coronary arterial measures of atherosclerosis and lipid measurements. The authors concluded that, “Noninvasive B-mode ultrasonographic measurement of progression of intima-media thickness in the distal common carotid artery is a useful surrogate end point for clinical coronary events.”

O’Leary et al. (1999) conducted an observational case study to examine the associations between the thickness of the carotid artery intima and media and the incidence of new MI or stroke in persons without clinical cardiovascular disease. CIMT measurements of the common and internal carotid artery were made in 5858 subjects 65 years of age or older. Outcome variables were cardiovascular events (i.e., new MI or stroke) in patients without clinical cardiovascular disease (4476 subjects) over a median follow-up of 6.2 years. The study found that the incidence of cardiovascular events correlated with measurements of CIMT. The relative risk of MI or stroke increased with the IMT. The authors concluded that, “Increases in the thickness of the intima and media of the carotid artery, as measured noninvasively by ultrasonography, are directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease.”

Iglesias del Sol et al. (2001) utilized a nested case-control study to examine the contribution of common CIMT in the prediction of future coronary heart disease and cerebrovascular disease when added to established risk factors. The study involved 374 subjects with either an incident stroke or MI and 1496 controls, 55 years of age or older, who had participated in the Rotterdam study. The mean follow-up was 4.2 years, with a range of 0.1 to 6.5 years. The study used logistic regression modeling and the area under the receiver operating characteristic curve (ROC area) to quantify the predictive value of the established risk factors and the added value of IMT measurements. The risk factors included in the study were: previous MI and stroke, diabetes mellitus, smoking, systolic blood pressure, diastolic blood pressure, and total and HDL cholesterol levels. The ROC area of a model with age and sex only was 0.65, and with the risk factors, the ROC area increased from 0.65 to 0.72. This model correctly predicted 17% of all subjects with CDH and cerebrovascular disease. When common CIMT was added to the previous model, the ROC area increased to 0.75. When only the IMT measurement was used, the ROC area was 0.71. When different measurement sites were used, they did not result in a difference in ROC area. The authors concluded that, “Adding IMT to a risk function for coronary heart disease and cerebrovascular disease does not result in a substantial increase in the predictive value when used as a screening tool.”

Gepner et al. (2006) conducted an observational study to identify predictors of patients for whom CIMT measurement and determinant of vascular age could change cardiovascular disease risk assessment. Five hundred six patients (287 men and 219 women) who were asymptomatic and non-diabetic were included in the study. Of these patients, 261 were not taking lipid lowering therapy. Advanced subclinical atherosclerosis was present in 77 (30%) of the patients. There were 62 (23.8%) with change in cardiovascular disease risk of 5% or more. Predictors of 5% or more change in cardiovascular disease risk were systolic blood pressure, total high-

density lipoprotein cholesterol ratio and male sex. Of the 97 patients at moderate or moderately high risk, 56.7% changed risk classification. The authors concluded that, "Measurement of CIMT (carotid IMT) and determination of vascular age can identify individuals with advanced subclinical atherosclerosis, resulting in clinically meaningful alterations in cardiovascular disease risk estimates." The study also noted that prospective studies are needed to determine if patient treatment guided by CIMT measurements improve cardiovascular disease outcomes.

Baldassarre et al. (2007) reported on results of a longitudinal observational study that investigated whether the measurement, in clinical practice, of carotid maximum intima-media thickness (Max-IMT) could be combined with the Framingham risk score (FRS) to improve the predictability of cardiovascular events in dyslipidemic patients who are at low or intermediate risk. The study included 1969 patients attending a lipid clinic. Max-IMT was measured by ultrasound in these patients. The "best threshold values" (BTVs) above which was considered the Max-IMT to be abnormally high were calculated for the dyslipidemic population for each 10-year age interval in men and women. Two hundred and forty-two patients (age  $54 \pm 10$  years; 43.8% women) with an FRS <20% (i.e., low or intermediate risk), were monitored for more than 5 years. Twenty-four of these patients experienced a cardiovascular event within  $5.1 \pm 2.3$  years. It was noted that both the FRS and Max-IMT proved to be independent outcome predictors ( $p < 0.04$  for both), with a hazard ratio (HR) of 6.7 (95% confidence interval [CI] 1.43, 31.04;  $p = 0.015$ ) in patients in whom the FRS was 10-20% and the Max-IMT was above the BTV. Utilizing Kaplan-Meier analysis, the study noted that the Max-IMT significantly improved the predictive value of the FRS ( $\chi^2 = 8.13$ ,  $p = 0.04$ ). Patients with FRS 10-20%, that are considered intermediate-risk, and with elevated Max-IMT values fell into the same high-risk category as patients with FRS 20-30%. The authors note that the CIMT measurement can enhance the predictability of cardiovascular events in the large number of patients who fall into the intermediate-risk category, which currently does not call for aggressive preventive measures.

Amato et al. (2007) conducted a study to investigate whether a stronger in vivo correlation between carotid and coronary arteries can be obtained by using homogenous variables such as carotid and coronary IMT, detected by external carotid ultrasound (ECU) and intravascular ultrasound (IVUS). Measurements of ECU, IVUS and quantitative coronary angiography (QCA) were made in 48 patients. CIMT was then correlated with both the angiographic and IVUS findings. The study noted a significant but weak correlation between ECU and QCA variables ( $p < 0.05$ ); the correlation between ECU and IVUS measurements of IMT was higher, with correlation coefficients ranging from 0.49 to 0.55. In patients with a QCA diagnosis of normal/intermediate coronary atherosclerosis, the presence of a CIMT (mean >1mm) was associated with an 18-fold increase in risk of having a positive IVUS test (OR = 17.99, 95% CI 1.83-177.14,  $p = 0.013$ ) and with a seven-fold increased risk of having a significant IVUS coronary stenosis (OR = 7.4, 95% CI 1.27-44.0,  $p = 0.028$ ). The authors noted that carotid atherosclerosis correlates better with coronary atherosclerosis when both circulations are investigated by the same technique (ultrasound) using the same parameter (IMT). This appears to support the concept that CIMT is a good surrogate marker of coronary atherosclerosis.

Kathiresan et al. (2007) reported on a study of a stratified random sample of 292 participants (mean age 59.5 years; 50% women) from the offspring cohort of the Framingham Heart Study who were free of clinically apparent cardiovascular disease. The authors note that screening for subclinical atherosclerosis has been advocated for individuals at intermediate global risk for coronary heart disease (CHD); however, the distribution of subclinical atherosclerosis test values across CHD risk strata is unknown. Abdominal and thoracic aortic plaque burden was assessed by cardiovascular magnetic resonance (CMR), coronary artery calcification (CAC) and thoracic aortic calcification (TAC) by electron beam computed tomography, and common carotid intima-media thickness (CIMT) by ultrasonography. The upper 20% of each measurement was classified as a high level of atherosclerosis and then these variables were evaluated across clinically relevant Framingham CHD risk score strata (low, intermediate, and high risk). In age-adjusted analyses in men and women, correlations across CMR aortic plaque, CAC, TAC, and CIMT were low (maximum  $r = 0.30$  for CAC: TAC in women,  $p < 0.005$ ). In men and women, it was noted that the proportion of subjects with high atherosclerosis test results for any of these measurements increased significantly across the Framingham CHD risk score strata (Kruskal-Wallis test,  $p < 0.0001$ ). Regarding the intermediate Framingham CHD risk score category, 14% of men and 25% of women had a high atherosclerosis result on  $\geq 2$  measurements. It was noted that different participants were identified as having high atherosclerosis by each modality — for example, in a comparison of the overlap across CMR aortic plaque, CAC, and CIMT, only 4% of men and 16% of women were classified as having high atherosclerosis on all three measurements. The authors concluded that correlations among subclinical atherosclerosis test results are low, and a substantial proportion has high levels of subclinical atherosclerosis detected on  $\geq 2$  imaging tests.

Kitagawa et al. (2007) conducted an investigation to determine the usefulness of CIMT measurements in high-risk patients in whom risk factors are managed clinically. The study included 900 outpatients with cardiovascular risk factors or established atherosclerosis. Calculation of CIMT was performed with the mean bilateral IMT of the common carotid artery, bifurcation, and internal carotid artery. At the time of enrollment, the following were recorded: baseline vascular risk factors, medications, and history of CVD. The incidence of CVD events was determined prospectively. There were 64 CVD events noted during a mean follow-up period of 2.6 years. The relative risk (RR) of a CVD event increased with increased IMT. Association between CVD events and CIMT was significant after adjustment for risk factors and history of CVD, and demonstrated an increased risk per IMT tertile from the middle tertile (RR, 2.5; 95% CI: 1.0-6.3) to the highest (RR, 3.6; 95% CI: 1.4-9.0). When patients with a history of CVD were excluded (n=574), the predictive value of IMT was found to be significant even after adjustment for risk factors (hazard ratio per 1 SD IMT increase was 1.57 [95% CI: 1.11-2.20]). The authors concluded that CIMT is an independent predictor of vascular events in high-risk patients in whom risk factors are managed clinically.

Kanwar et al. (2007) examined the role of carotid ultrasound in stratifying risk in symptomatic patients. They conducted a prospective study for the hypothesis that in symptomatic patients undergoing exercise (or pharmacologic) stress testing (EST), CIMT and carotid plaque will improve the ability to identify patients with  $\geq 50\%$  coronary diameter stenosis. The study included 50 symptomatic patients without known coronary artery disease (CAD) who were scheduled to undergo diagnostic angiography after EST with imaging. The mean and maximal CIMTs were measured in these patients. Fifty percent of patients were men, 32% were diabetic, 70% had hypertension, and 58% had dyslipidemia. The pretest probability of CAD was calculated for each patient based on age, gender, and nature of symptoms. The results noted that CAD  $\geq 50\%$  was associated with CIMT in the  $>75$ th percentile (74% vs. 44%,  $p=0.047$ ) and with presence of carotid plaque (96% vs. 59%,  $p=0.003$ ). For patients with an equivocal/negative EST result (n = 38), those with carotid plaque had a 46% (13 of 28) prevalence of significant CAD. In the smaller subset of patients without carotid plaque (n = 10), none had luminal stenosis  $\geq 50\%$  ( $p=0.007$ ). The pretest probability of CAD, presence of carotid plaque, moderately/severely abnormal EST result, and hypertension appear to be independent predictors of significant CAD. The authors concluded that carotid ultrasound appears to offer an incremental value to EST in predicting presence or absence of  $\geq 50\%$  coronary diameter stenosis in symptomatic patients with equivocal/negative EST result. Limitations of the study include the small number of patients and heterogeneity regarding optimum methods of measuring CIMT and plaque.

Takase et al. (2008) reported on a study that compared the predictive value of flow-mediated vasodilation (FMD), IMT, and stress electrocardiogram (ECG) for CAD prognosis. The study included 103 consecutive patients (62  $\pm$  9] years old; 79 men) with clinically suspected CAD that underwent FMD and nitroglycerin-induced dilation (NTG-D) in the brachial artery (BA), carotid artery IMT measurement using high-resolution ultrasound, and exercise treadmill testing. There were seventy-three patients with significant coronary artery disease (CAD group) and 30 patients without significant coronary artery stenosis (NCAD group). The patients were followed for 50 ( $\pm 15$ ) months. Coronary events were noted in 15 patients during this time: one cardiac death, two non-fatal myocardial infarctions, three acute heart failures, and nine unstable anginas. When compared to patients without cardiac events, the patients with cardiac events had significantly impaired FMD, and more severe exercise-induced myocardial ischemia. The patients with cardiac events were inclined to have higher CIMT, though this difference was not statistically significant. On Kaplan-Meier analysis, only FMD and stress ECG were significant predictors for cardiac events.

Baroncini et al. (2008) reported on findings from a study that evaluated the appropriateness of a carotid artery study that included the measurement of IMT, the presence of atherosclerotic plaque, and their correlation with cardiovascular risk factors. The study involved 555 patients (220 men; 67.06  $\pm$  12.44 years). One hundred twenty patients (21.62%) presented with carotid plaque. One hundred eight (19.45%) was noted in patients with at least one risk factor and 12 (2.1%) in patients without risk factors. The IMT medians were higher in males (0.0280; 95% CI, 0.0190 to 0.0592;  $p=0.0057$ ) and in hypertensive patients (0.0391; 95% CI, 0.0190 to 0.0592;  $p=0.001$ ). A linear increase in mean IMT was noted for each year and increased in age (0.0059; 95% CI, 0.0059 to 0.0067). Carotid plaque was more frequent in patients with CAD ( $p=0.0002$ ), diabetes ( $p=0.024$ ) and hypertension ( $p=0.036$ ).

**Meta-Analyses/Systematic Reviews:** 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. The studies included either those that utilized mean CIMT, determined from a number of IMT measurements at specific positions or by automated software over a segment of the artery, and those that use maximal CIMT, with the Rotterdam study being the only one in which IMT was determined by both methods in the same population. 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 analysis found that the age- and sex-adjusted overall estimates of the relative risk of myocardial infarction were 1.26 (95% confidence interval [CI], 1.21–1.30) per 1–standard deviation common carotid artery IMT difference and 1.15 (95% CI, 1.12–1.17) per 0.10-mm common carotid artery IMT difference. Regarding the age- and sex-adjusted relative risks of stroke, the review noted they were 1.32 (95% CI, 1.27–1.38) per 1–standard deviation common carotid artery IMT difference and 1.18 (95% CI, 1.16–1.21) per 0.10-mm common carotid artery IMT difference. 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.

Baldassarre et al. (2008) conducted a meta-analysis of 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]). The review included 107 articles. 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. An absence of an important publication bias was suggested by funnel plot analyses. 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. The degree of atherosclerotic disease in the population studied does not account for the heterogeneity of findings reported. 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. In regards of all other soluble markers considered, the number of groups was too small for this kind of statistical considerations. The heterogeneity in ultrasound methodologies and in statistical approach limited comparability between studies.

Paternoster et al. (2008) reported on a systematic review and meta-analysis to examine the association between apolipoprotein E genotype (APOE) and CIMT. APOE influences cholesterol levels and ischemic heart disease. While there is no association with ischemic stroke, it is thought that APOE may influence large artery (atherothrombotic) stroke and therefore have a relationship with CIMT. The review involved 22 studies (30,879 subjects). Study-specific and random effects pooled differences in mean CIMT between genotype groups were calculated. Heterogeneity between studies and predefined subgroups was assessed. Meta-analysis demonstrated a significant association between APOE and CIMT (95% CI 29 to 62;  $p < 0.00001$ ). There was evidence found of small study (mainly publication) bias, with a diminished (but still highly statistically significant) association in studies of  $>1000$  subjects (95% CI, 12 to 23;  $p < 0.00001$ ). The association was noted to be larger among high vascular risk and eastern Asian populations, but may reflect the smaller size of these studies.

### **Professional Societies/Organizations**

**American College of Cardiology:** The 34<sup>th</sup> Bethesda Conference, sponsored by the American College of Cardiology Foundation, was held in 2002 for the topic: Can Atherosclerosis Imaging Techniques Improve the Detection of Patients at Risk for Ischemic Heart Disease? The purpose of the conference was to review the current status and controversies within the integration of atherosclerosis imaging into clinical cardiovascular medicine. The report noted that additional testing, such as imaging, must provide incremental risk-prediction information to the Framingham Risk Score. In discussing the emerging techniques for noninvasive measurement of atherosclerosis, including measurement of CIMT, it is noted that “None of the available tests have yet been demonstrated to impact CHD management or outcomes.” Task Force 3 reviewed the existing and emerging noninvasive technologies for atherosclerosis imaging. The task force noted that different protocols and

standardization are used by different laboratories, and it is difficult to establish normal and abnormal values adjusted for gender and age. In addition, they noted that “None of these imaging technologies have been shown to make prevention more effective, although their integration into office-based risk factor assessment is under active study.” With regard to CIMT, they noted that (Redberg et al., 2003):

- Carotid ultrasonography can produce measurements for plaque or IMT; studies that have clearly distinguished IMT from plaque demonstrate that CHD risk is largely associated with the presence of nonobstructive or obstructive plaque rather than IMT.
- The current data available supports the use of this test mainly in middle-aged and older patients.

**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 Heart Association (AHA):** The AHA-sponsored Prevention Conference V: Beyond Secondary Prevention: Identifying the High-Risk Patient for Primary Prevention. Writing Group III, considered noninvasive tests of atherosclerotic burden. Regarding measurement of CIMT, the following was noted (Smith, et al., 2000):

- Cross-sectional associations between common carotid artery IMT and cardiovascular risk factors have been demonstrated in several studies.
- At least four published studies found that CIMT measurement was a viable predictor of the presence of coronary atherosclerosis and its clinical outcomes; thus, this test is an independent risk factor for coronary heart disease events and strokes.
- They concluded that in asymptomatic individuals older than 45 years of age, carefully performed carotid ultrasound examination with IMT measurement can add incremental information to traditional risk factor assessment and can be considered for further clarification of CHD assessment at the request of a physician.

**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.

**European Society of Cardiology (ESC):** The ESC published the European guidelines on cardiovascular disease prevention in clinical practice. With regard to CIMT the guidelines note that (De Backer, et al., 2003):

- CIMT is an independent predictor of cerebral and coronary events but seems to be more predictive in women than in men.
- Carotid ultrasound can add information beyond assessment with traditional risk factors which may help to make decisions about the necessity to institute medical treatment for primary prevention.
- One limitation of using carotid ultrasound for global risk assessment is the absence of reliable data relating IMT numbers to ten-year event rates.
- It is not currently clear how IMT measurements can be formally incorporated into existing risk algorithms used in asymptomatic persons.

**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).

**National Heart, Lung and Blood Institute (NHLBI):** The NHLBI sponsored the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) (National Institutes of Health [NIH], 2002). The ATP III report, in the section regarding tests for atherosclerotic plaque burden, notes the following regarding CIMT:

- The extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis
- Recent studies show that severity of IMT independently correlates with risk for major coronary events
- Measurement of CIMT theoretically could be used as an adjunct in CHC risk assessment.
- Its expense, lack of availability and difficulties with standardization preclude a current recommendation for its use in routine risk assessment for the purpose of modifying intensity of LDL-lowering therapy.

**Screening for Heart Attack Prevention and Education (SHAPE):** The SHAPE Task Force published a consensus paper regarding guidelines for screening for heart attack prevention and education (Naghavi, et al., 2006). The consensus paper recommends screening of the at-risk asymptomatic population (men 45–75 years of age and women 55–75 years of age) for subclinical atherosclerosis to more accurately identify and treat patients at high risk for acute ischemic events, as well as to identify those at lower risk who may be treated more conservatively. The guidelines recommend screening for atherosclerosis by utilizing two noninvasive tests: coronary artery calcification score (CACs) determined by CT and CIMT and plaque determined by ultrasound. All asymptomatic men 45–75 years of age and women 55–75 years of age who do not have very low-risk characteristics or a documented history of cardiovascular disease are encouraged to undergo screening for atherosclerosis. The very low-risk group is characterized by the absence of any traditional cardiovascular risk factors. Individuals with negative tests for atherosclerosis, defined as CACS = 0 and CIMT < 50th percentile without carotid plaque, are classified as lower risk (those without conventional risk factors) or moderate risk (those with established risk factors). Reassessment is recommended within 5–10 years unless otherwise indicated. Those who test positive for atherosclerosis are further stratified according to the magnitude of atherosclerotic burden: moderately high risk, high risk and very high risk. Treatment calls for aggressive lifestyle modifications.

### Summary

Carotid intima-media thickness (CIMT) measurement is a noninvasive test that serves as a surrogate marker for coronary atherosclerosis. There is a correlation between CIMT and traditional coronary risk factors. The clinical utility of measuring IMT for the purpose of predicting risk of coronary or cerebral events 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.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

### Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
0126T	Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment

ICD-9-CM Diagnosis Codes	Description
	Multiple/varied

\*Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	3/15/2008	0475	Carotid Intima-Media Thickness Measurement

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.