CARDIOVASCULAR DISEASE RISK TESTS

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COVERAGE RATIONALE

Arterial compliance testing, using waveform analysis, is unproven as a method to determine risk for cardiovascular disease.
There is insufficient evidence to conclude that noninvasive arterial compliance testing is effective as a screening tool for the early detection of cardiovascular disease (CVD). There is inadequate clinical evidence from prospective studies that the use of this technology alters patient management and improves clinical outcomes. Additional research involving larger, better-designed studies is needed to establish the role of arterial compliance in the early identification, prevention and management of CVD.

Carotid intima-media thickness (CIMT) measurement is unproven as an effective screening tool for the management of cardiovascular disease.
There is insufficient evidence to conclude that noninvasive arterial compliance testing is effective as a screening tool for the early detection of cardiovascular disease (CVD). There is inadequate
cardiovascular disease. Clinical evidence from prospective studies that the use of this technology alters patient management and improves clinical outcomes.

**Advanced lipoprotein analysis (i.e., apolipoprotein or lipoprotein(a)) is unproven as a method to determine risk of cardiovascular disease.**

While advanced lipoprotein analysis detects elevated or reduced levels of lipoproteins, there is lack of agreement on how this information would be used in clinical decision-making. In addition, while the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III identifies lipoprotein (a) and apolipoprotein analysis as emerging technologies, it does not recommend their routine use in identifying persons at risk for cardiovascular disease or ischemic stroke.

**Tests that measure the lipoprotein-associated phospholipase A2 (Lp-PLA2) enzyme are unproven as a method to determine risk of cardiovascular disease or ischemic stroke.**

Additional well-designed clinical trials are necessary to establish the clinical utility of Lp-PLA2 for cardiovascular risk assessment and to determine the role of Lp-PLA2 as a potential adjunct to traditional risk assessment in the overall management of stroke in adults.

**Tests that measure long-chain omega-3 fatty acids are unproven as a method to determine risk for cardiovascular disease.**

There is insufficient evidence to conclude that measuring long-chain omega-3 fatty acids is effective as a screening tool for the early detection of cardiovascular disease (CVD). There is inadequate clinical evidence from prospective studies that the use of this technology alters patient management and improves clinical outcomes.

**Endothelial function assessment using tools such as peripheral arterial tonometry (PAT) (e.g., the EndoPAT 2000 device) or brachial artery pressure ultrasound is unproven as a prognostic indicator to determine risk of cardiovascular disease.**

There is insufficient evidence in the peer-reviewed medical literature to support the effectiveness and prognostic clinical utility of endothelial function assessment to establish the risk of cardiovascular disease. The majority of the identified studies reported some measure of statistical association of either PAT or brachial artery ultrasound with cardiovascular disease. However, these associations are insufficient to directly demonstrate their clinical utility to effectively predict cardiovascular morbidity. Well-designed studies that extend beyond measures of simple statistical association are needed to demonstrate the clinical usefulness of such assessment tools to effectively predict cardiovascular events and classify patients according to their individual cardiovascular risk.

**BENEFIT CONSIDERATIONS**

State mandates should be reviewed when determining benefit coverage for early detection of cardiovascular disease. In certain limited circumstances, the state of Texas may mandate coverage for computed tomography (CT) scanning or ultrasonography when performed as a screening test for atherosclerosis and abnormal artery structure and function.

**BACKGROUND**

Cardiovascular diseases (CVD), including coronary artery disease, stroke and hypertension, are the leading causes of morbidity and mortality in the United States. Vascular disease is the major contributor to cardiovascular morbid events and ideally is identified early, before symptoms are detected or irreversible damage has occurred. Arterial compliance (elasticity), carotid intima-media thickness (CIMT) and advanced lipoprotein analysis are tests used to measure and monitor atherosclerosis.

Arterial endothelial dysfunction and endothelial damage, which play an important role in the **Cardiovascular Disease Risk Tests: Medical Policy (Effective 01/01/2014)**

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atherosclerotic process, may result in reduced arterial compliance (elasticity) or increased arterial stiffness, especially in the smaller arteries. Arterial compliance can be measured by several techniques, many of which are invasive or clinically inappropriate. Direct methods include magnetic resonance imaging and ultrasound. Indirect methods include pulse wave velocity and augmentation index. At this time, there is no gold standard for its measurement. Cardiovascular profiling using blood pressure waveform analysis (the rate at which pressure rises and falls during the cardiac cycle), provides a noninvasive assessment of arterial compliance. It is used for both large and small arteries by calculating pulse pressure, body surface area (BSA) and body mass index (BMI) to determine arterial compliance indices. These indices may be used as an early indication of CVD. Other noninvasive prognostic tools to assess endothelial functioning have been introduced as adjuncts to standard cardiovascular disease risk assessments (Roman et al., 2006). Specifically, these tools attempt to further stratify the risk of cardiovascular morbidity, while refining disease prevention measures. Two such assessment approaches involve the use of artery ultrasound testing and peripheral arterial tonometry using a fingertip pulse amplitude tonometry (PAT) device. Brachial artery ultrasound uses high-resolution ultrasound to assess changes in vascular dimensions, while the PAT records finger arterial pulse wave amplitude in response to reactive hyperemia. Increased finger pulse amplitude is posited to be a complex response to ischemia and reflects changes in digital flow and digital vessel dilation (Kuvin et al., 2007; Hamburg et al., 2008).

Carotid intima-media thickness (CIMT) is based on the theory that the extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis. CIMT is a noninvasive test using ultrasound to capture images of the carotid artery and computer software to analyze the measurements.

Cholesterol is a fat-like substance (lipid) that is present in cell membranes, and travels in the blood in distinct particles containing both lipid and proteins (lipoproteins). Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). LDL cholesterol typically makes up 60 - 70 percent of the total serum cholesterol and contains a single apolipoprotein, namely apo B-100 (apo B). HDL cholesterol normally makes up 20 - 30 percent of the total serum cholesterol. The major apolipoproteins of HDL are apo A-I and apo A-II. The VLDL are triglyceride-rich lipoproteins, but contain 10 - 15 percent of the total serum cholesterol. Apolipoprotein, lipoprotein (a) and lipoprotein-associated phospholipase A2 are emerging risk factors being evaluated for their ability to predict cardiovascular disease or ischemic stroke (NHLBI, 2002).

Lipoprotein-associated phospholipase A2 (Lp-PLA2), a vascular inflammatory enzyme, has been investigated as a surrogate biomarker of increased coronary heart disease and stroke risk. Lp-PLA2 testing has been used as an adjunct to conventional risk assessment in healthy or asymptomatic adults to determine who might benefit from specific risk-reducing interventions, such as pharmacological therapies and behavior modification strategies (Hayes, 2011; updated 2013).

**CLINICAL EVIDENCE**

**Arterial Compliance**

In a small, randomized, controlled trial (n=30), Woodman et al. (2005) compared large and small artery compliance (C1 and C2, respectively), stroke volume/pulse pressure (SV/PP), augmentation index (AIx), central pulse pressure (CPR), stiffness index (SI), systemic arterial compliance (SAC) and brachial pulse pressure to central pulse wave velocity (PWV). The authors concluded that C1, C2, SV/PP, and SAC showed poor agreement with central PWV, an established measure of central arterial stiffness. In comparison, SI, AIx, and CPP are more closely related to central arterial stiffness.

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In a prospective, single-center study of moderate size (n=298), Duprez et al. (2004) studied 206 male and 92 female healthy subjects with a mean age of 50 +/- 12 years. Noninvasive radial artery pressure waveforms were acquired with a piezoelectric transducer and analyzed for 1) diastolic indices of C1 and C2 from the CR-2000 CVProfilor, and 2) systolic indices of augmentation as defined by augmentation pressure (AP), augmentation index (Alx), and systolic reflective index (SRI = P2/P1). These indices were then correlated to each other as well as to individual traditional risk factors and the Framingham Risk Score. The results indicate that the diastolic indices were significantly and inversely correlated to systolic indices with C2 showing a stronger inverse association than C1. C2 and Alx were significantly correlated with height, weight, and body mass index in men but not in women. All indices correlated better to blood pressure in women than men. In women, only systolic indices were significantly correlated to HDL cholesterol and only diastolic indices were significantly correlated to LDL cholesterol. All indices were significantly correlated to the Framingham Risk Score, which was stronger in women than men, but when adjusted for age only diastolic indices remained significant in women. The authors concluded that diastolic and systolic indices of pulse contour analysis correlate differently with traditional risk factors in men and women.

Wilson et al. (2004) compared small and large arterial elasticity (SAE/C2, LAE/C1), endothelial function as measured by flow mediated dilation (FMD), carotid intima-medial thickness (IMT), ankle brachial index (ABI), pulse pressure (PP) and pulse wave velocity (PWV) for assessing arterial function in low and high vascular disease risk groups. Twenty healthy subjects (HS) and 20 older subjects with type 2 diabetes mellitus (DM) were studied with all techniques at a single sitting by a single operator. C2 assessed by pulse wave analysis correlated with endothelial function measured by FMD in young apparently healthy subjects and older subjects with type 2 diabetes. Systolic BP and PP correlated with C2 and FMD in older diabetic subjects but not healthy subjects. The interrelationships between arterial function measures are different in high and low risk populations. This variability needs to be considered when applying these techniques to individuals in different populations.

Three prospective, multicenter studies, of moderate sample size (n=212, n=230, n=178), were conducted by the same research group and used the same study population of normotensive and hypertensive individuals. In these groups of individuals, blood pressure was measured using a mercury manometer and arterial compliance or elasticity was determined using the CVProfilor CardioVascular Profiling System. These parameters were measured in triplicate 3 minutes apart in a random sequence, with the patient in a supine position.

The objective of the first study was to determine arterial elasticity in normotensive and hypertensive individuals using the CVProfilor. An evaluation of large artery and small artery elasticity in 212 normotensives (with and without a family history of hypertension) and hypertensives (treated and controlled or untreated and uncontrolled) demonstrated that both large artery and small artery elasticity indices were significantly higher (P<0.0001) in normotensives without a family history compared with untreated and uncontrolled hypertensives. After controlling for age and BSA, there was a significant linear trend (P=0.0001) across the four groups in these elasticity indices. As hypertension status worsened, large and small artery elasticity decreased, suggesting a potential for the diagnostic use of arterial elasticity determinations (Prisant, 2001a).

The aim of the second study was to assess and compare the accuracy of sequential same arm blood pressure measurement by the mercury sphygmomanometer with oscillometric blood pressure measurements using the CVProfilor, which also determines arterial elasticity. Sequential single-arm blood pressure measurements performed in 230 normotensives and hypertensives (in which the sequence of testing was randomized) showed that the CVProfilor, which uses a dynamic linear deflation oscillometric method, measures blood pressure with reasonable agreement to that obtained manually using a mercury sphygmomanometer as reference method. For systolic and diastolic blood pressure, 60.9% and 70.4% of sequential measurements were within mm Hg, respectively, and 85.2% of systolic and 92.6% of diastolic blood pressure
measurements were within mm Hg agreement (Prisant, 2001b).

The third study examined arterial elasticity by ethnicity in normotensive and hypertensive individuals to determine whether there were racial differences. An evaluation of large and small artery elasticity indices in 178 normotensives and hypertensives confirmed that these are reduced as hypertension status worsens. While age and height were important covariates of small and large artery elasticity, and hypertension status was a significant predictor of small and large artery elasticity, race was not found to be a significant predictor of either small or large artery elasticity. That is, large and small artery elasticity indices do not differ between white and black individuals with varying degrees of hypertension after adjusting for covariates (Prisant, 2002).

**Carotid Intima-Media Thickness**

There is some evidence, from observational studies, that a one-time carotid intima-media thickness (IMT) measurement in adults adds incremental information to traditional risk factor assessments in the prediction of future vascular events. However, there is a lack of evidence that change in carotid IMT over time is related to the risk of subsequent vascular events. Standardized protocols for scanning and monitoring IMT assessments and patient selection criteria have not been established (Hayes, 2009; updated 2012).

van den Oord et al. (2013) conducted a systematic review and meta-analysis of the published evidence on the association of carotid intima-media thickness (CIMT) with future cardiovascular events and its additional value to traditional cardiovascular risk prediction models. Fifteen studies were included in the analysis. The authors concluded that CIMT was associated with future cardiovascular events. However, the addition of CIMT to traditional cardiovascular risk prediction models did not lead to a statistically significant increase in performance of those models.

Den Ruijter et al. (2012) conducted a meta-analysis to determine whether the addition of common carotid intima-media thickness (CIMT) measurements to the Framingham Risk Score added value in 10-year risk prediction of first-time myocardial infarctions or strokes. Individual data from studies were combined into one data set and a meta-analysis was performed on individuals without existing cardiovascular disease. Fourteen population-based cohorts of 45,828 individuals were included. During a median follow-up of 11 years, 4007 first-time myocardial infarctions or strokes occurred. The authors concluded that adding common CIMT measurements to the Framingham Risk Score was associated with a small improvement in 10-year risk prediction of first-time myocardial infarction or stroke, but this improvement is unlikely to be of clinical importance.

Costanzo et al. (2010) performed a meta-analysis to verify whether intima-media thickness (IMT) regression is associated with reduced incidence of cardiovascular events. Carotid IMT increase is associated with a raised risk of coronary heart disease (CHD) and cerebrovascular (CBV) events; however, it is undetermined whether favorable changes of IMT reflect prognostic benefits. Forty-one trials enrolling 18,307 participants were included. Despite significant reduction in CHD, CBV events and all-cause death induced by active treatments, there was no significant relationship between IMT regression and CHD events, CBV events and all-cause death. In addition, 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 regression or slowed progression of carotid IMT, induced by cardiovascular drug therapies, do not reflect reduction in cardiovascular events.

Carotid intima-media thickness (CIMT) is increasingly being used as a surrogate end point in randomized control trials (RCTs) of novel cardiovascular therapies. However, it remains unclear whether changes in CIMT that result from these therapies correlate with nonfatal myocardial infarction (MI). Goldberger et al. (2010) performed a meta-analysis of 28 randomized controlled trials (RCT) with 15,598 patients. Differences in mean change in CIMT over time between treatment and control groups correlated with developing nonfatal MI during follow-up. However,
there was no significant relationship between mean change in CIMT and nonfatal MI in RCTs evaluating statin therapy or those with high CIMTs at baseline. The authors concluded that less progression in CIMT over time is associated with a lower likelihood of nonfatal MI in selected RCTs; however, these findings were inconsistent at times, suggesting caution in using CIMT as a surrogate end point.

In a multicenter, comparative study, Nambi et al. (2010) evaluated whether carotid intima-media thickness (CIMT) and the presence or absence of plaque improved coronary heart disease (CHD) risk prediction when added to traditional risk factors (TRF). Risk prediction models considered included TRF only, TRF plus CIMT, TRF plus plaque and TRF plus CIMT plus plaque. Of 13,145 eligible subjects (5,682 men, 7,463 women), approximately 23% were reclassified by adding CIMT plus plaque information. The authors concluded by stating that traditional CHD risk prediction schemes need further improvement as the majority of the CHD events occur in the "low" and "intermediate" risk groups. Adding plaque and CIMT to TRF improves CHD risk prediction in the ARIC (Atherosclerosis Risk In Communities) study.

Folsom et al. (2008) assessed whether maximum carotid intima-media thickness (IMT) or coronary artery calcium (CAC) is the better predictor of incident cardiovascular disease (CVD) in a prospective cohort study of subjects aged 45 to 84 years who were initially free of CVD (n = 6698). The main outcome measure was the risk of incident CVD events (coronary heart disease, stroke, and fatal CVD) over a maximum of 5.3 years of follow-up. The investigators found that there were 222 CVD events during follow-up. Coronary artery calcium was associated more strongly than carotid IMT with the risk of incident CVD. The hazard ratio was only 1.2 for the association between carotid IMT and risk of incident CVD. A receiver operating characteristic curve analysis also suggested that CAC score was a better predictor of incident CVD than was IMT. The investigators concluded that although the use of bioimaging tests of subclinical atherosclerosis remains a topic of debate, this study found that CAC score is a better predictor of subsequent CVD events than carotid IMT.

Lorenz et al. (2007) evaluated eight studies and concluded that CIMT is a strong predictor of future vascular events. The relative risk per CIMT difference is slightly higher for the end point stroke than for myocardial infarction. In future CIMT studies, ultrasound protocols should be aligned with published studies. Data for younger individuals are limited and more studies are required.

Brohall et al. (2006) performed a systematic review of 23 studies of CIMT that included patients with Type 2 diabetes. They concluded that Type 2 diabetes was associated with a 0.13 mm increase in IMT compared with control subjects. In patients with IGT, the increase in CIMT was about one-third of that observed in diabetes. The observed difference in CIMT can be interpreted as if the diabetes patients were more than 10 years older than the control groups, and that the relative risks of myocardial infarction and stroke were increased by almost 40%, respectively.

Espeland et al. (2005) performed a meta-analysis of an unspecified number of studies that evaluated CIMT as a surrogate for clinical events in trials of HMG-CoA reductase inhibitors and concluded that CIMT progression meets accepted definitions of a surrogate for cardiovascular disease endpoints in statin trials. This does not, however, establish that it may serve universally as a surrogate marker in trials of other agents.

The Mannheim Carotid Intima-Media Thickness Consensus (2004-2006) consensus concluded that there is no need to ‘treat IMT values’ nor to monitor IMT values in individual patients. 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 the 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 (Touboul, 2007).
The U.S. Preventive Services Task Force (USPSTF) concluded that the evidence is insufficient to assess the balance of benefits and harms of using nontraditional risk factors, such as carotid intima-media thickness (IMT) or lipoprotein(a) levels, to screen asymptomatic men and women with no history of CHD to prevent CHD events. Fair-quality evidence indicates that carotid IMT predicts CHD independent of Framingham risk factors in asymptomatic persons (Chambless, 1997; O'Leary, 1990; van der Meer, 2004). Adding carotid IMT scores to a risk prediction equation based on traditional risk factors modestly improved the prediction of subsequent CHD among healthy adults. However, the studies that show an association of carotid IMT with CHD outcome have all been done in research settings, and the ability to conduct carotid IMT with precision in non-research settings has not been established. No information is available about the prevalence or applicability of carotid IMT to populations at intermediate risk for CHD events (USPSTF, 2009).

In the National Cholesterol Expert Panel (NCEP) Adult Treatment Panel III (ATP III) Report, carotid intimal medial thickening is listed as an emerging risk factor. The report states that some studies show that severity of IMT independently correlates with risk for major coronary events. Thus, measurement of carotid IMT theoretically could be used as an adjunct in CHD risk assessment. However, 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. If carried out under proper conditions, carotid IMT could be used to identify persons at higher risk than that revealed by the major risk factors alone (NCEP, 2002).

Advanced Lipoprotein Analysis

Di Angelantonio et al. (2012) assessed whether adding various emerging lipid markers to total cholesterol and high-density lipoprotein cholesterol (HDL-C) improved cardiovascular disease (CVD) risk prediction. Records were evaluated from 165,544 individuals without baseline CVD from 37 cohort studies in which apolipoprotein B (apoB) and apoA1, lipoprotein(a) (Lp[a]) or lipoprotein-associated phospholipase A2 (Lp-PLA2) were measured. Participants received follow-up for 10 years, during which 15,126 CVD-related fatal and nonfatal outcomes occurred. Main outcome measures were CVD outcomes and low (<10%), intermediate (10% to <20%) and high risk (≥20%) prediction. The authors concluded that replacing information on total cholesterol and HDL-C with various lipid parameters did not significantly improve CVD risk prediction.

Apolipoproteins

In review of the published, scientific literature there are inconsistent results with regards to the usefulness of apolipoprotein testing. Research has shown a lack of universal, standardized testing modalities and patient-selection criteria.

There are relatively few studies investigating the relationship between apoA-I and risk of coronary heart disease (CHD) and results of these studies are conflicting. There are even fewer studies investigating the effects of drug interventions on apo A-I levels in hypercholesterolemic patients. Additional large, prospective studies that include both men and women are needed to establish whether measurement of apo A-I will be more predictive of CHD than conventional lipid risk factors.

The MONICA/KORA Augsburg cohort study included 1414 men and 1436 women aged 35 to 64 years. It concluded that the predictive power of the apoB/apoA-I ratio was similar to that of the total cholesterol/HDL cholesterol ratio in men and women (Meisinger, 2004).

The studies that evaluated the association of apo B with CHD, with the exception of the early report from the Physicians’ Health Study, were, for the most part, positive studies. While there is some evidence from these studies that apo B levels, either singularly or in combination with other metabolic abnormalities, may be more predictive of CHD risk than conventional risk factors such as age, sex, family history, and HDL-C.
as low-density lipoprotein cholesterol (LDL-C) and the ratio of total cholesterol to HDL-C, for most patient groups these results need confirmation in additional, large, prospective studies. However, there is strong evidence from the very large AFCAPS/TexCAPS trial that in certain patient groups, such as those with average total cholesterol and LDL-C levels and low HDL-C levels, apo B may be a more accurate predictor of CHD than LDL-C. The intervention studies established that lipid-lowering therapy produces angiographic benefits as well as reductions in clinical cardiovascular events. Moreover, there was some evidence that therapy reduces levels of apo B and apo B-containing lipoproteins. Evidence from one small intervention study suggested that patients with elevated apo B levels and lower LDL-C levels may benefit from lipid-lowering therapy, confirming the results of the AFCAPS/TexCAPS trial (Gotto et al. 2000). However, these results also need confirmation in additional, larger, prospective, longer-term studies.

The large population for the Apolipoprotein-related Mortality Risk Study (AMORIS) included 175,553 Swedish men and women. This study evaluated if apolipoprotein B (apoB) and apolipoprotein A-1 (apoA-1) can better predict the risk of acute myocardial infarctions (MI) than the conventional risk factor analysis of total cholesterol, triglycerides, and LDL-cholesterol measurements. The study reported that total cholesterol, triglycerides, apoB and apoB/apoA-1 ratio were strong positive predictors of increased risk of fatal MI in both men and women. ApoB proved to be a stronger predictor of cardiac risk than LDL-cholesterol, but there may have been a methodological error in the calculation of LDL-cholesterol in the study. The study outcome suggests that the measurement of apoB, apoA-1 and the apoB/apoA-1 ratio could improve the prediction of cardiac risk and be useful in the assessment of risk and decision making of initiating lipid-lowering treatment (Wallidius, 2001).

In the National Cholesterol Expert Panel (NCEP) Adult Treatment Panel III (ATP III) Report, apolipoproteins are listed as an emerging risk factor. The NCEP acknowledges that apolipoprotein B is a potential marker for all atherogenic lipoproteins, but did not conclude there was sufficient clinical evidence to justify replacing the LDL as the preferred target of therapy. The measurement of apolipoprotein A-I is not recommended due to lack of standardized methodology (NCEP, 2002).

Lipoprotein (a)
There are three requirements for Lp(a) testing to be of value for risk prediction and patient management: 1) standardization of Lp(a) assays, 2) development of additional treatments to reduce Lp(a) levels and 3) intervention trials to establish the benefit of Lp(a) reduction. Future research must investigate further the interactions of Lp(a) with other CHD risk factors and the value of using the combination of Lp(a) and other risk factors to predict risk and manage patients.

There have been many studies investigating the relationship between Lp(a) and CHD. In some studies, risk of disease was increased by the interaction of Lp(a) with other lipid factors. A cross-sectional analysis of 750 men and 403 women concluded that, although neither Lp(a) nor homocysteine were individually associated with risk of CHD in women, the two factors interacted to increase risk; and the size of this effect was greater than what would be expected if the risk factors were operating either additively or exponentially. In men, both elevated Lp(a) and homocysteine appeared to be independent risk factors for CHD, but the presence of both factors did not confer additional risk (Foody, 2000).

The PRIME study was a prospective five-year cohort study of 9,133 French and Northern Irish men who were between the ages of 50-59 at the start of the study, had no history of coronary heart disease and were not on any lipid lowering drug therapy. On entry in the study, the Lp(a) was measured along with other traditional laboratory cardiovascular risk factors such as LDL and HDL cholesterol, and triglycerides. Previous comparisons of different studies looking at the relationship of Lp(a) and CHD were inconsistent due to various procedures for determining plasma Lp(a) and the absence of standardization of Lp(a) measurement. In the study, the measurements of Lp(a) were all performed in the same laboratory with fresh plasma. The authors
reported the association between Lp(a) and CHD to be independent of other risk factors but that there was also a significant interaction between high levels of Lp(a) and increasing LDL-cholesterol. The study results concluded that Lp(a) was significant in predicting increased risk of myocardial infarction and angina pectoris (Luc, 2002).

The Atherosclerosis Risk in the Communities (ARIC) Study reported a follow-up after ten years in which 725 coronary heart disease (CHD) events occurred in 12,339 middle-aged participants who were initially identified as free of CHD. The conclusions indicated that LDL-C, HDL-C, triglycerides (TG) and Lp(a), without additional apolipoproteins or lipid subfractions, were substantial predictors of CHD. Unlike other apolipoprotein evaluation, Lp(a) was found to have independently risk prediction significance. The clinical value of the Lp(a) needs to be judged against the cost of the test, what treatment plan would be initiated based on the Lp(a) measurement, and whether the Lp(a) measurement adds significant predictive value when included with the other lipid measurements (Sharrett, 2001).

The U.S. Preventive Services Task Force (USPSTF) concluded that the evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors, such as lipoprotein(a), to screen asymptomatic men and women with no history of CHD to prevent CHD events. Fair-quality evidence indicates that lipoprotein(a) level predicts CHD events after adjustment for some Framingham risk factors, but no studies calculated a Framingham risk score, assessed predictive value beyond Framingham risk scoring or assessed whether lipoprotein(a) contributes to reclassification from intermediate to another risk category (USPSTF, 2009).

In the National Cholesterol Expert Panel (NCEP) Adult Treatment Panel III (ATP III) Report, lipoprotein (a) is listed as an emerging risk factor. Some studies report a strong association between Lp(a) levels and CHD risk, while others do not confirm independent predictive power. Issues related to measurement of Lp(a) in clinical practice have not been resolved, and standardized methods are available only in a few reference laboratories. Despite these limitations, some groups advocate measuring Lp(a) in individuals with a strong family history of premature CHD or those with genetic causes of hypercholesterolemia. ATP III did not find strong evidence to support this approach, but accepts it as an option for selected persons (NCEP, 2002).

**Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)**

The Rotterdam study (Oei, 2005) is a population-based follow-up study of 7983 subjects >55 years of age. The authors performed a case-cohort study, including 308 coronary heart disease cases, 110 ischemic stroke cases, and a random sample of 1820 subjects. Compared with the first quartile of Lp-PLA2 activity, multivariate-adjusted hazard ratios for coronary heart disease for the second, third, and fourth quartiles were 1.39, 1.99, and 1.97, respectively. Corresponding multivariate-adjusted hazard ratios for ischemic stroke were 1.08, 1.58, and 1.97. The relation between Lp-PLA2 and coronary heart disease was present in both subjects with non-HDL cholesterol levels below the median and those with non-HDL cholesterol levels above the median. The authors concluded that Lp-PLA2 activity is an independent predictor of coronary heart disease and ischemic stroke in the general population.

**Cardiovascular Disease**

Evidence from a number of large prospective group and case-control studies consistently demonstrate a positive association of lipoprotein-associated phospholipase A2 (Lp-PLA2) with coronary heart disease (CHD) events. This association appears to be independent of most other risk factors. Increasing levels of Lp-PLA2 indicate increasing risk of CHD events. However, the overall magnitude of these associations varied considerably and the evidence was weakened by several methodological limitations, such as heterogeneity across trials, varying approaches to measuring levels of Lp-PLA2, differences in patient populations and variability in length of follow-up.
Given the low-quality evidence and absence of important evidence, no conclusions can be drawn regarding the clinical utility of Lp-PLA2 alone or in combination with other traditional biomarkers and/or risk assessments to determine the risk of CHD events in healthy or asymptomatic individuals. Additional well-designed clinical trials are necessary to establish the clinical utility of Lp-PLA2 and to determine the role of Lp-PLA2 as a potential adjunct to traditional risk assessment in the overall management of CHD in adults (Hayes, 2010; updated 2013).

An expert consensus panel (Davidson, 2008), evaluated how Lp-PLA2 might be used for determining CVD risk and concluded that testing is not recommended for the general population or for persons who are at low risk. The panel defined a simplified approach to determining criteria for testing of persons who are at least moderate-risk for CHD and includes the following individuals:

- any age with two major risk factors
- age greater than or equal to 65 years with one major risk factor
- cigarette smoking
- fasting blood glucose greater than or equal to 100 mg/dl
- metabolic syndrome

Lp-PLA2 levels greater than 200 mg/dl warrants risk reclassification and reduction of LDL levels. The authors suggest annual testing for individuals with levels greater than 200 mg/dl. The evidence reviewed by the panel lends some support to further stratify risk in select individuals and there is some evidence in the published medical literature that statin drugs and fibrates may reduce Lp-PLA2 levels. It is not presently known whether lowering Lp-PLA2 levels will decrease the incidence of CHD or stroke and improve clinical health outcomes. Treatment for elevated Lp-PLA2 is targeted at lowering LDL levels.

Corsetti et al. (2006) performed a factor analysis on blood markers and lipoprotein-associated phospholipase A2 (Lp-PLA2) for 766 patients of the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) postinfarction study. Their multivariable analysis concluded Lp-PLA2 is related to both hypercholesterolemia and high triglyceride-low HDL dyslipidemia in their study population.

Koenig et al. (2006) determined plasma concentrations and activity of Lp-PLA2 in 1051 patients aged 30 to 70 years old who had coronary heart disease and were followed for four years. In multivariable analyses, Lp-PLA2 mass and activity were strongly associated with cardiovascular events after controlling for traditional risk factors. They concluded that increased levels of Lp-PLA2 predicts future cardiovascular events in patients who already exhibit heart disease.

May et al. (2006) investigated Lp-PLA2 as an independent predictor of angiographic diagnosis of coronary artery disease and coronary death. Lp-PLA2 and C-reactive protein were measured in 1493 consecutive patients enrolled in the registry of the Intermountain Heart Collaborative Study. All patients underwent coronary angiography for coronary artery disease and were followed for 6.7 years for cardiovascular events. Lp-PLA2 was confirmed to predict the risk of coronary artery disease related death, but not all-cause death.

While these studies suggest that Lp-PLA2 is an independent risk factor for CHD, there is a lack of agreement on how this information would be used in clinical decision-making. The key outcome of risk assessment for coronary heart disease (CHD) or ischemic stroke prediction is an improvement in health outcomes, i.e., reduced morbidity and mortality. Improved risk prediction does not by itself result in improved health outcomes. At the present time, measurements of Lp-PLA2 are not a component of the guidelines developed by the National Cholesterol Education Program Adult Treatment Panel III. While studies have suggested that statin drugs and fibrates may reduce levels of Lp-PLA2, it is not known whether such drug therapy in patients not already considered candidates based on other well established risk factors will ultimately decrease the incidence of coronary heart disease or ischemic stroke.
Stroke

A Hayes literature search identified 11 studies that reported results from 12 trials assessing the ability of Lp-PLA₂ to predict risk of stroke in adults (Ballantyne et al., 2005; Oei et al., 2005; Elkind et al., 2006; Sabatine et al., 2007; Olson et al., 2008; Persson et al., 2008; Robins et al., 2008; Wassertheil-Smoller et al., 2008; Elkind et al., 2009; Nambi et al., 2009; Caslake et al., 2010). Two trials had overlapping patient populations (Elkind et al., 2006; Elkind et al., 2009). Of the 12 identified studies, 11 were prospective observational or prospective cohort studies, and 1 was a case-control study. Across studies, stroke events generally referred to fatal or nonfatal ischemic stroke events. Patient populations were described as middle-aged adult men and women, older than 50 years of age, who were either apparently healthy at baseline, or presented with a variety of diseases, including diabetes, coronary heart disease (CHD), and/or previous incidence of stroke.

Evidence from these prospective group and case-control studies demonstrated a positive, though modest, association of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) with stroke events. However, not all studies found a significant association between increasing levels of Lp-PLA₂ and increasing risk of stroke. There was no evidence from the reviewed studies regarding the diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value) of Lp-PLA₂ to predict the presence of incident stroke events, the risk of experiencing a future stroke event or the risk of experiencing a stroke event in individual patients. Most importantly, there was no evidence in the literature regarding how the use of Lp-PLA₂ might lead to appropriate preventive and/or therapeutic measures in at-risk patients. Given the low-quality evidence and absence of important evidence, no conclusions can be drawn regarding the clinical utility of Lp-PLA₂ alone or in combination with other traditional biomarkers and/or risk assessment scores to accurately assess the risk of stroke events in adult patients. Additional well-designed clinical trials are necessary to establish the clinical utility of Lp-PLA₂ and to determine the role of Lp-PLA₂ as a potential adjunct to traditional risk assessment in the overall management of stroke in adults (Hayes, 2011; updated 2013).

In a prospective case-cohort (n=949), using a subset of participants in the Atherosclerosis Risk in Communities (ARIC) study, Nambi et al. (2009) found that Lp-PLA₂ improved ischemic stroke risk prediction. The improvement was most enhanced when Lp-PLA₂ was combined with high sensitivity C-reactive protein levels and provided the most benefit in individuals at intermediate risk of ischemic stroke. The authors state that it would be ideal to validate these findings in other cohorts and conduct studies to examine if changes in therapy based on such risk stratification improve ischemic stroke prevention.

Neither the National Cholesterol Expert Panel (NCEP) Adult Treatment Panel III (ATP III) Report nor the U.S. Preventive Services Task Force (USPSTF) recommendations address lipoprotein-associated phospholipase A₂.

Long-chain omega-3 fatty acids


While there are many published studies addressing the potential benefits of adding omega-3 fatty acids to one’s diet, no studies were identified evaluating the clinical application of measuring long-chain omega-3 fatty acids to determine risk of cardiovascular disease.

Endothelial Function Assessment

Rubenstein et al. (2010) examined whether endothelial dysfunction, as detected by non-invasive peripheral arterial tonometry (EndoPAT), can predict late cardiovascular events (n=270). Once reactive hyperaemia (RH) was manually induced, patients were evaluated over a 7-year follow-up.
period for subsequent cardiovascular adverse events, such as cardiac death, myocardial infarction (MI), revascularization or cardiac hospitalization. Cox regression models were used to estimate the association of EndoPAT results with adverse events, adjusted for age. Univariate predictors of adverse events were LRHI, advancing age, and prior coronary bypass surgery. Multivariate analysis identified LRHI value of less than 0.4 as an independent predictor of cardiovascular events.

In a correlation study of Framingham Heart Study participants (n=1957), Hamburg et al. (2008) evaluated the relationship between digital pulse amplitude using a fingertip peripheral arterial tonometry (PAT) device and cardiovascular disease risk factors. Initial findings demonstrated that manually induced, reactive hyperemia resulted in a time-dependent increase in fingertip pulse amplitude. Based on a stepwise, multivariate, linear regression model, a number of risk factors were inversely related to the hyperemic response (PAT ratio), including being male, body mass index (BMI), total/high density lipoprotein (HDL) cholesterol, diabetes, smoking, and lipid-lowering treatment. Conversely, increasing age was positively correlated with PAT ratio (P<0.01). These results may suggest a link between certain risk factors and lower digital hyperemic response. However, a causal relationship between these risk factors and digital vascular function could not be established. Given the homogenous nature of the study participants (Caucasian individuals of European descent), the preliminary results are also not generalizable to different ethnic or racial groups. Despite these positive preliminary findings, the clinical utility and predictive value of digital pulse amplitude have yet to be established.

Professional Societies/Government Organizations
American College of Cardiology (ACC)/American Heart Association (AHA)
An ACC/AHA Task Force makes the following recommendations on assessing cardiovascular risk in asymptomatic adults: (Greenland et al., 2010)

1. Arterial Compliance
ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that measures of arterial stiffness outside of research settings are not recommended. Class III, Level of Evidence C recommendation – no benefit; very limited populations evaluated.

2. Carotid intima media thickness
ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that measurement of carotid artery IMT is reasonable for asymptomatic adults at intermediate risk. Published recommendations on required equipment, technical approach and operator training and experience for performance of the test must be carefully followed to achieve high-quality results. Class IIa, Level of Evidence B recommendation - conflicting evidence but the panel recommends in favor of testing.

3. Advanced lipoprotein analysis
ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that measurement of lipid parameters, including lipoproteins and apolipoproteins beyond a standard fasting lipid profile is not recommended. Class III, Level of Evidence C recommendation – no benefit; very limited populations evaluated.

4. Lipoprotein-associated phospholipase A2
ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that lipoprotein-associated phospholipase A2 (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults. The report also states that, at this time, there is no information indicating that Lp-PLA2 levels are clinically effective for motivating patients, guiding treatment or improving outcomes. Class IIb, Level of Evidence B – conflicting evidence and usefulness/efficacy of test is less well established.

5. Long-chain omega-3 fatty acids
Cardiovascular Disease Risk Tests: Medical Policy (Effective 01/01/2014)
ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults do not address this test as a measure of cardiovascular risk.

6. **Brachial/Peripheral Flow-Mediated Dilation**

ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that peripheral arterial flow-mediated dilation (FMD) studies are not recommended for cardiovascular risk assessment in asymptomatic adults. Class III, Level of Evidence B – no benefit. The guideline also states that it is unclear whether measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors.

**American Diabetes Association and the American College of Cardiology Foundation (ADA/ACCF)**

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 risk for cardiovascular disease 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 (CMR) is unclear.

The clinical utility of routine measurement of lipoprotein (a) is unclear, although more aggressive control of other lipoprotein parameters may be warranted in those with high concentrations of Lp(a) (Brunzell, 2008).

**American Heart Association (AHA)/American Stroke Association Stroke Council (ASA)**

The AHA/ASA updated the guideline on primary prevention of stroke in 2011. The guideline states that measurement of inflammatory markers such as Lp-PLA2 in patients without cardiovascular disease may be considered to identify patients who may be at increased risk of stroke, although their effectiveness (i.e., usefulness in routine clinical practice) is not well established (Goldstein et al., 2011).

**Additional Search Terms**
carotid sonography, contour wave analysis, intimal, Lp (a), profile screening, pulse contour analysis, pulse wave analysis, waveform profiling

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

The CVProfilor® System received 510(k) approval (K001948) from the FDA on November 1, 2000 as a Class II device for the noninvasive measurement of blood pressure and pulse rate. It is classified as a noninvasive blood pressure measurement system providing a signal from which systolic, diastolic, mean, or any combination of the three pressures can be derived through the use of transducers placed on the surface of the body. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/K001948.pdf. Accessed September 12, 2013.

Measurement of CIMT is a procedure, and not subject to FDA regulation. B-mode ultrasound equipment used to measure CIMT is regulated by the FDA, but products are too numerous to list. See the following web site for more information (use product code IYO). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfm. Accessed September 12, 2013.

Advanced lipoprotein analysis must be performed in accordance with the quality standard established in 1988 by the Clinical Laboratory Improvement Amendments (CLIA).

Products used to measure lipoprotein (a) are too numerous to list. See the following web site for more information (use product code DFC). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfm. Accessed September 12, 2013.

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Products used to measure apolipoproteins are too numerous to list. See the following web site for more information (use product code DER or MSJ). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfm. Accessed September 12, 2013.

The diaDexus PLAC® Test for Lp-PLA₂ received initial 510(k) approval (K030477) from the FDA on July 18, 2003. It was approved at that time as an enzyme immunoassay for the quantitative determination of Lp-PLA₂ in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfm?ID=10908. Accessed September 12, 2013.

On June 15, 2005, a second 510(k) approval (K050523) was issued for the PLAC Test for the same indications but also incorporating approval for prediction of risk of ischemic stroke associated with atherosclerosis. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfm?ID=17692. Accessed September 12, 2013.

The EndoPAT 2000 received FDA 510(k) clearance (K032519) on November 12, 2003. According to the clearance summary, the Endo PAT 2000 device is a non-invasive device intended for use as a diagnostic aid in the detection of coronary artery Endothelial Dysfunction (positive or negative) using a reactive hyperemia procedure. The Endo PAT 2000 has been shown to be predictive of coronary artery Endothelial Dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The Endo PAT 2000 device is not intended for use as a screening test in the general patient population. See the following Web Site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfm?ID=12698. Accessed August 19, 2013.


**Additional Product Information**

HDI/PulseWave CR-2000 (HDI, Inc.): Available in the United States for research purposes only

CVProfilor® DO-2020 (HDI, Inc.)

CVProfilor® MD-3000 (HDI, Inc.): Not available in the United States

SphygmoCor (AtCor Medical)

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) for arterial compliance testing, using waveform analysis. Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Category III CPT Codes, Non-Covered Category III CPT Codes, Noncovered Services, Non-Covered Services and Services That Are Not Reasonable and Necessary.

Medicare does not have a National Coverage Determination (NCD) for carotid intima-media thickness (CIMT) testing. Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Non-Covered Category III CPT Codes, Non-Covered Services, Noncovered Services, and Services That Are Not Reasonable and Necessary.

Medicare does not have a National Coverage Determination (NCD) for measurement of long-chain omega-3 fatty acids as a tool for determining cardiovascular disease risk. Local Coverage Cardiovascular Disease Risk Tests: Medical Policy (Effective 01/01/2014)
Determinations (LCDs) do exist. Refer to the LCDs for Category III CPT Codes, Non-Covered Category III CPT Codes, Noncovered Services, Non-Covered Services and Services That Are Not Reasonable and Necessary.

Medicare covers lipid testing as appropriate for evaluating atherosclerotic cardiovascular disease. Refer to the National Coverage Determination for Lipid Testing (190.23). Local Coverage Determinations (LCDs) exist for lipid profile cholesterol testing. Refer to the LCDs for Lipid Profile/Cholesterol Testing.

Medicare does not have a National Coverage Determination (NCD) for Apolipoprotein testing. Local Coverage Determinations (LCDs) exist. Refer to the LCDs for Lipid Profile/Cholesterol Testing, Non-Covered Services and Non-covered Services.

Medicare does not have a National Coverage Determination (NCD) for Lipoprotein-associated phospholipase A2, (Lp-PLA2) testing. Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Assays for Vitamins and Metabolic Function.

Medicare does not have a National Coverage Determination (NCD) for unlisted cardiovascular services or procedures. Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Noncovered Services, Cardiovascular Stress Testing and Cardiac Event Detection. (Accessed July 23, 2013)

### APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

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<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
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<tr>
<td>0111T</td>
<td>Long-chain (C20-22) omega-3 fatty acids in red blood cell (RBC) membranes</td>
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<tr>
<td>0126T</td>
<td>Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment</td>
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<tr>
<td>0311T</td>
<td>Non-invasive calculation and analysis of central arterial pressure waveforms with interpretation and report</td>
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<tr>
<td>0337T</td>
<td>Endothelial function assessment, using peripheral vascular response to reactive hyperemia, non-invasive (eg, brachial artery ultrasound, peripheral artery tonometry), unilateral or bilateral</td>
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<td>Apolipoprotein, each</td>
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<td>83695</td>
<td>Lipoprotein (a)</td>
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<td>83698</td>
<td>Lipoprotein-associated phospholipase A2, (Lp-PLA2)</td>
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<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure</td>
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### REFERENCES


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POLICY HISTORY/REVISION INFORMATION

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<th>Date</th>
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<tbody>
<tr>
<td>01/01/2014</td>
<td>• Updated description of services to reflect most current clinical evidence and references</td>
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<td>• Revised coverage rationale; added language to indicate endothelial function assessment using tools such as peripheral arterial tonometry (PAT) (e.g., the EndoPAT 2000 device) or brachial artery pressure ultrasound is unproven as a prognostic indicator to determine risk of cardiovascular disease</td>
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<td>• Updated list of applicable CPT codes to reflect annual code edits (effective 01/01/2014); added 0337T</td>
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