Healthy Blue

Medical Policy

Subject:	Advanced Lipoprotein Testing		
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Description/Scope

This document addresses the use of advanced testing of lipoproteins for cardiovascular disease (CVD) risk assessment and management, and all other indications. Lipoproteins are blood-borne complexes of lipids and proteins that allow the transport of cholesterol throughout the body. This document does not address the use of a basic lipid panel or lipoprotein genotyping.

Position Statement

Investigational and Not Medically Necessary:

Advanced lipoprotein testing (testing beyond that of a basic lipid panel), is considered **investigational and not medically necessary** for cardiovascular disease (CVD) risk assessment and management and for all other indications. Advanced lipoprotein testing includes, but is not limited to:

A. Apolipoprotein A-I (apoAI);
B. Apolipoprotein B (apoB);
C. Apolipoprotein E (apoE);
D. Intermediate density lipoproteins (IDL);
E. Lipoprotein(a) (Lp(a)) enzyme immunoassay;
F. Lipoprotein-associated phospholipase A2 (Lp-PLA2);
G. Small density lipoproteins.

Rationale

The primary categories of lipoproteins are classified as chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoprotein (LDL), intermediate density lipoprotein (IDL) and high-density lipoprotein (HDL). LDL is considered the most atherogenic component of serum cholesterol, and the National Cholesterol Education Program (NCEP) has designated total LDL cholesterol (LDL-C) as the primary target of therapy in the Adult Treatment Panel (ATP III, 2004) recommendations. However, LDL particles are not uniform in size or concentration, and measurement of particle size and concentrations have been proposed as a technique to further stratify individual risk beyond total LDL.

Particle size (for example, diameter) can be measured by a variety of techniques, including nuclear magnetic resonance (NMR). Small, dense lipoprotein particles have been extensively investigated in three distinct clinical contexts:

1. As an independent risk factor for coronary artery disease:
A nested case-control study from the Physician's Health Study, a prospective cohort study of almost 15,000 men, investigated whether LDL particle size was an independent predictor of coronary artery disease (CAD) risk, particularly in comparison to triglyceride levels (Stampfer, 1996). This study concluded that while LDL particle diameter was associated with risk of myocardial infarction, this association was not present after adjustment for triglyceride level. Only triglyceride level was significant independently.

The Quebec Cardiovascular Study (Lamarche, 1997) evaluated the ability of "nontraditional" lipid risk factors, including LDL size, to predict subsequent CAD events in a prospective cohort study of 2155 men followed up for 5 years. The presence of small LDL was associated with a 2.5 times increased risk for ischemic heart disease after adjustment for traditional lipid values, indicating a level of risk similar to total LDL. This study also suggested an interaction in atherogenic risk between LDL size and apolipoprotein B levels. In the presence of small LDL particles, elevated apolipoprotein B levels were associated with a 6-fold increased risk of CAD, whereas when small LDL particles were not present, elevated apolipoprotein B levels were associated with only a 2-fold increase in risk.

2. As a risk factor in individuals with "normal" total LDL and cholesterol levels:
A number of randomized trials have evaluated lipid-lowering therapy in individuals with dyslipidemia, but normal total cholesterol and total LDL levels. However, LDL size was not used as a selection criterion or as an outcome measure in these trials. Rather, other lipid parameters associated with dyslipidemia, such as high triglycerides and/or low HDL were used as individual selection factors and outcome measures (Gotto, 2000; Grundy, 2002).

3. As a predictor of response to treatment:
Individuals with subclass pattern B have been reported to respond more favorably to diet therapy compared to those with subclass pattern A (Kwiterovitch, 2002). Subclass pattern B has also been shown to respond more favorably to the drug gemfibrozil and niacin, with a shift from small, dense LDL particles to larger LDL particles (Grundy, 2002). While statin drugs lower the overall concentration of LDL cholesterol, there is no shift to the larger LDL particles (Superko, 1996).

In summary, small LDL size is one component of an atherogenic lipid profile that also includes increased triglycerides, increased apolipoprotein B, and decreased HDL. Some studies have reported that LDL size is an independent risk factor for CAD, and others have reported that a shift in LDL size may be a useful marker of treatment response. However, the direct clinical application of measuring small, dense lipoprotein particles is still unclear. An improved ability to predict cardiovascular risk and treatment response does not by itself result in better health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. This requires guidelines that incorporate emerging risk factors into existing risk prediction models that have been demonstrated to classify individuals into risk categories with greater accuracy. Predictive models also need to be accompanied by treatment guidelines that target interventions toward those who will get the most benefit.

Validated tools for linking levels of small dense LDL to clinical decision making, both in risk assessment and treatment response, are currently not available. Published data are inadequate to determine how such measurements should guide treatment decisions and whether these treatment decisions result in beneficial clinical outcomes beyond measurement of LDL and HDL. Other associated lipid parameters, such as triglycerides and HDL levels

may be more useful than LDL size in assessing risk and treatment response. The ATP III practice guidelines endorse clinical decision making tied to more conventional measures of a simple lipid panel, such as total cholesterol, LDL-C, and HDL-C (ATP III, 2004). Furthermore, in the most recently published 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, there is no recommendation of particle size in assessing risk or efficacy of treatments (Stone, 2014).

Similar to small dense lipoprotein particles, several epidemiologic studies have shown that the lipoprotein particle concentration is also associated with cardiac risk. In 2008, the American Diabetes Association (ADA) and the ACC released a joint consensus statement on lipoprotein management in individuals with cardiometabolic risk. The document extensively discusses the measurement of lipoprotein size and concentration via NMR. However, the discussion regarding the clinical utility and importance of these measures is accompanied by questions regarding the value of the measurement of lipoprotein size and concentration.

LDL particle concentration and LDL size are important predictors of CVD. However, the Multi-Ethnic Study of Atherosclerosis (MESA) suggested that in multivariate analyses, both small and large LDL were strongly associated with carotid intima-media thickness, while the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that both were significantly related to coronary heart disease (CHD) events. The association of small LDL and CVD may simply reflect the increased number of LDL particles in individuals with small LDL. Hence, it is unclear whether LDL particle size measurements add value to measurement of LDL particle concentration. There is a need for more independent data confirming the accuracy of the method and whether its CVD predictive power is consistent across various ethnicities, ages, and conditions that affect lipid metabolism.

The ADA/ACC (2008) summarized their recommendations at the end of the document. In that summary, LDL cholesterol, non-HDL cholesterol, and ApoB are mentioned as the only appropriate markers for the assessment of cardiovascular risk. No recommendation supporting the measurement of lipoprotein size or concentration is mentioned. While there may be some close associations between particle number or size and the propensity of some individual subgroups to develop atherosclerosis, it has not yet been conclusively demonstrated how to use NMR testing to incrementally improve outcomes for an individual as compared with current preventive, diagnostic, and treatment strategies including LDL, non-HDL cholesterol, or ApoB. The ADA published further guidance in 2016 on CVD risk management and although basic lipid panel measures are discussed, more advanced measurements are not.

In 2008, the Agency for Healthcare Research and Quality (AHRQ) released a comprehensive review of the clinical research available addressing the use of LDL (for example, β-lipoprotein) subfraction measurement in clinical practice. The technology assessment concludes with the following summary:

> In summary, despite a large number of studies evaluating the association of LDL subfractions and CVD (that have led to a very large number of studies of potential interventions to alter subfraction patterns), the clinically useful evidence regarding whether measurement of LDL subfractions may be a helpful tool for assessing cardiovascular risk (or altering treatment of cardiovascular risks) is lacking. This is largely due to the relative paucity of studies that have evaluated clinically available tests and their associations with incidence or progression of CVD.

Only one measure (LDL particle concentration measured by NMR) was consistently significantly associated with CVD events, after adjustment for lipoproteins and other cardiovascular risk factors. The strength of the associations varied, with RR or ranging from 1.11 to 2.90. Other NMR measures were not consistently associated with incident or progressive disease. LipoPrint® GE, the other clinically available test, has not been tested as a predictor for incident or progressive CVD. Studies of the remaining (not clinically available) tests are inconsistent, but mostly find no association with incident CVD (before or after adjustment for lipoproteins and other risk factors). More well conducted research is needed. Future studies should focus on the clinically available tests and incidence or progression of CVD, and should aim to use standard test metrics and classifications to allow for comparison across studies. The current evidence suggests that LDL subfractions is not a consistently strong predictor of CVD compared to other known risk factors, but this question has not been properly evaluated by any study.

The small number of trials of cardiovascular interventions that have been secondarily analyzed to evaluate LDL subfractions suggest a possible role for the subfractions in predicting outcomes with treatment, but fail to address the clinical question of whether treating patients based on LDL subfractions would reduce their risk of CVD.

The small number of studies that directly compared different tests generally found fair to good agreement, though not all studies consistently agreed. These studies need to be reproduced to assess their validity. This is particularly true for the one study that found a difference in size measurements between NMR and GE since this is frequently cited among other studies. Within-subject and within-sample variability have not been adequately evaluated to definitely determine the tests' accuracy. It is possible that the day-to-day variability found by one study may partly account for the heterogeneity of results regarding the value of the test as a predictor of CVD.

In 2009, the National Academy of Clinical Biochemistry Laboratory Medicine published a Practice Guideline regarding emerging biomarkers for primary prevention of cardiovascular disease. In the section of their guideline regarding lipoprotein subclasses and particle concentration and CVD risk they make three separate recommendations:

Recommendation 1: Lipoprotein subclasses, especially the number or concentration of small dense LDL particles, have been shown to be related to the development of initial coronary heart disease events, but the data analyses of existing studies are generally not adequate to show added benefit over standard risk assessment for primary prevention.

Recommendation 2: There are insufficient data that measurement of lipoprotein subclasses over time is useful to evaluate the effects of treatments.

Recommendation 3: Several methods are available to assess lipoprotein subclasses. Standardization is needed for this technology.

The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults includes the following recommendation related to the efficacy of lipoproteins and apolipoproteins (for example, ApoE).

> Class III: No Benefit
>
> Measurement of lipid parameters, including lipoproteins, apolipoproteins, particle size, and density, beyond a standard fasting lipid profile is not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: C)

This recommendation (Class III, Level of Evidence C) is the lowest recommendation possible and is defined as being based on only expert opinion, case studies or standard of care but having no empirically demonstrated usefulness/effectiveness and having the potential to cause harm. In summary, the empirical evidence for measuring the size and density of lipoproteins does not support the use of this method in CVD risk, treatment and management.

Results of two large-scale observational studies have suggested that Lp-PLA2, an enzyme mostly associated with LDL, is an independent risk factor for CHD in men. For example, the West of Scotland Coronary Prevention Study (WOSCOPS) was a 5-year case-control trial evaluating 6595 men with elevated cholesterol and no history of a heart attack (Packard, 2000). Researchers looked at a smaller population of this study group to determine if inflammatory markers such as Lp-PLA2 and high sensitivity C-reactive protein were correlated with CHD events. The 580 men who went on to have a myocardial infarction or revascularization were compared to 1160 age and smoking matched men who did not have an event. The results noted that those with the highest levels of Lp-PLA2 had twice the risk of an event, compared to those with the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators.

The Atherosclerosis Risk in Communities (ARIC) study was a trial that evaluated the various risk markers and their association with increased risk in a large, diverse population and has included over 12,000 individuals (Ballantyne, 2005). At enrollment in the study, subjects were free of CHD and were followed for the development of the disease for the next 9 years. The case-cohort component of the study examined two inflammatory markers, Lp-PLA2 and high sensitivity C-reactive protein in a subset of 609 cases and 741 controls. The results showed that elevated levels of Lp-PLA2 are higher in CHD. In individuals with non-elevated LDL levels (<130 mg/dL), Lp-PLA2 levels were independently associated with CHD, even after adjustment for traditional risk factors and C-reactive protein. As noted in the FDA press release accompanying the FDA approval for the PLAC® Test Reagent Kit (diaDexus, Inc, San Francisco, CA):

> An elevated PLAC test result with an LDL-cholesterol level of less than 130 mg/dL gives doctors increased confidence that patients have two to three times the risk of having coronary heart disease when compared with patients having lower PLAC test results.

However, the key outcome of cardiac risk assessment is an improvement in health outcomes. Improved risk prediction does not, by itself, result in improved health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. This requires guidelines that incorporate emerging risk factors into existing risk prediction models and that have been demonstrated to classify individuals into risk

categories with greater accuracy. Predictive models also need to be accompanied by treatment guidelines that target intervention toward those who will get the most benefit.

In 2008, the ADA and the ACC released a joint consensus statement on lipoprotein management in individuals with cardiometabolic risk. There is no mention of Lp-PLA2 testing in this document.

In another follow-up publication of the ARIC study, Nambi and colleagues report that Lp-PLA2 improves the area under the receiver operator characteristic curve for 5-year ischemic stroke risk (2009). However, this improvement was minimal, between 1 and 2%, and may not be clinically significant, an issue also raised by the authors themselves in the discussion section of the paper. Furthermore, they state that further studies are needed in other populations and investigation into whether or not changes in treatment as a result of Lp-PLA2 measurements result in improved clinical outcomes.

Similar findings associating abnormal Lp-PLA2 measurements with increased morbidity and mortality have been reported by several other authors (Oei, 2005). These papers conclude with recommendations similar to those posed by Nambi and colleagues (2009); that further investigation is required to show clinical utility prior to more widespread use in clinical practice (Ballantyne, 2005; Corson, 2008; Davidson, 2008; Elkind, 2006; Persson, 2008; Wassertheil-Smoller, 2008).

In 2010, the ACCF and AHA published updated guidelines related to CVD risk in asymptomatic adults. The following recommendation was released regarding Lp-PLA2: "Class IIb: Lipoprotein-associated phospholipase A2 (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults (Level of Evidence: B)." This recommendation (Class IIb, Level of Evidence B) is defined by the guideline as describing a topic where usefulness/efficacy is less well established due to conflicting evidence from multiple randomized trials or meta-analyses.

In 2011, a guideline was published by Davidson and colleagues entitled, "Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists." Although this guideline recommends testing of selected individuals with past cardiac events and family history for Lp-PLA2, it is not recommended that test results be taken into account when treatment decisions are being made. Therefore, the clinical utility of using the test for an assessment is unclear.

The National Heart, Lung, and Blood Institute's (NHLBI's) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2011) stated that:

> In terms of other lipid measurements: (i) at this time, most but not all studies indicate that measurement of apolipoprotein B (apoB) and apolipoprotein A-1 (apoA–1) for universal screening provides no additional advantage over measuring non-HDL–C, LDL–C, and HDL–C; (ii) measurement of lipoprotein(a) (Lp[a]) is useful in the assessment of children with both hemorrhagic and ischemic stroke; (iii) in offspring of a parent with premature CVD and no other identifiable risk factors, elevations of apoB, apoA–1, and Lp(a) have been noted; and (iv) measurement of lipoprotein subclasses and their sizes by advanced lipoprotein testing has not been shown to have sufficient clinical utility in children at this time (Grade B).

In the 2013 publication of the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Stone, 2013), only LDL-C, HDL-C and triglycerides are recommended as serum markers for assessing risk and managing disease. The guideline includes statements on "treatments proven to reduce ASCVD events" and do not include recommendations that include advanced lipoprotein testing. The guideline includes a critical question for future guidelines to determine "Whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions." Also in 2013, a related guideline was published by ACC/AHA on the assessment of CVD risk and stated that measurement of ApoB "is of uncertain value" (Goff, 2014).

In 2015, the American Association of Clinical Endocrinologists (AACE) in conjunction with the American College of Endocrinology (ACE) published clinical practice guidelines on a comprehensive care plan for diabetes mellitus (Handelsman, 2015). The guidelines include a recommendation for treatment goals for ApoB and low-density lipoprotein particles (LDL-P) in individuals with at least one major risk factor for CVD. However, these measurements are listed as *secondary* treatment goals to the primary treatment goals of a basic-lipid panel and graded with an evidence level of D/4 (that is, not evidence based). The AACE/ACE also released a consensus statement in 2016 recommending target treatment levels for CVD risk assessment in diabetes type 2 management using Apo B and LDL-P, but these recommendations are not graded and are only weakly endorsed by other specialty medical societies, such as the ACC, AHA or ADA. The US Department of Defense and Department of Veterans Affairs published clinical guidelines on management of dyslipidemia for CVD risk reduction and do not mention advanced lipoprotein testing.

The National Lipid Association (NLA) released its Annual Summary of Clinical Lipidology (2016). In it, the following statements and recommendations regarding advanced lipoprotein testing may be found:

- While some studies suggest apo B may be superior to LDL-C and non-HDL-C in predicting future ASCVD risk, the NLA Recommendations favor measuring non-HDL-C because it is universally available, requires no additional expense, can be measured either fasting or non-fasting, and clinical trial evidence has not always supported apo B as superior to non-HDL-C in predicting ASCVD risk.
- Among patients at low ASCVD risk, lipid treatment decisions are unlikely to be altered by use of LDL-P.
- For patients at higher ASCVD risk, especially those who with anticipated discordance between LDL-C and LDL-P, it is unclear if additional LDL-P information should alter initial therapeutic decisions.
- The following lower Lp(a); however, the clinical implications are unclear:
    - B PCSK9 inhibitors
    - B Niacin
    - B Mipomersen (apo B antisense)
    - B Lomitapide
    - B Lipoprotein apheresis
    - B Estrogen

The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) released guidelines for the management of dyslipidemias in 2016. These guidelines reported disadvantages of ApoB including that it has

not been evaluated as a primary treatment target in clinical trials, it is not included in algorithms for calculation of global risk, and it has not been a predefined treatment target in controlled trials.

In 2016, AHRQ issued an evidence report and systematic review (Lozano, 2016a) evaluating lipid screening in childhood and adolescence for detection of familial hypercholesterolemia (FH). There was no evidence found to quantify the association between intermediate outcomes (such as lipid concentrations or measures of atherosclerosis) in children or adolescents and myocardial infarction and stroke in adults. Long-term harms were noted to be unknown. The authors concluded:

> Randomized trials of screening for FH in U.S. youth are needed, as are longer-term treatment trials evaluating the benefits and harms of medications in children and adolescents with FH.

A separate AHRQ evidence report and systematic review (Lozano, 2016b) evaluated benefits and harms of screening children and adolescents for multifactorial dyslipidemia. The authors indicated that pediatric studies are needed that screen for abnormal non-HDL-C or apolipoprotein B concentrations and concluded:

> No direct evidence was identified for benefits or harms of childhood screening or treatment on outcomes in adulthood. Intensive dietary interventions may be safe, with modest short-term benefit of uncertain clinical significance.

In 2019, a report was published of the ACC/AHA Task Force on Clinical Practice Guidelines on the management of blood cholesterol. In it, the association between apoB and Lp(a) with increased risk for adverse health outcomes is acknowledged but the added clinical utility beyond LDL-C is also highlighted (Grundy, 2019).

A statement from the NLA (Wilson, 2019) was published regarding use of Lipoprotein(a) in clinical practice. While the statement asserts that "Meta-analyses of prospective, population-based studies of high Lp(a) demonstrate high risk of MI, CHD, and ischemic stroke," it also highlights aforementioned limitations, including "Measurement of Lp(a) is currently not standardized or harmonized... Evidence is incomplete regarding the utility of using different risk cut points of Lp(a) based on age, gender, ethnicity, or the presence of comorbid conditions."

In 2020, the US Department of Veterans Affairs and US department of Defense published clinical practice guidelines on the management of dyslipidemia for CVD risk reduction. In the guidelines, the following statement was made,

> Much effort has been made to improve these tools with additional testing, such as coronary artery calcium (CAC), high-sensitivity C-reactive protein, ankle–brachial index, and apolipoprotein evaluations. However, our updated review of the literature on the added prognostic value of these tests indicates that they are limited in further refining risk.

In 2021, the Canadian Cardiovascular Society published guidelines for the management of dyslipidemia in adults (Pearson, 2021). Lp(a) measurement is recommended once in a person's lifetime as part of initial lipid screening to assess cardiovascular risk. Either non-HDL-C or apoB measurements are recommended instead of LDL-C as the lipid level of interest in initial lipid screening and as a treatment target in all individuals with triglyceride level > 1.5 mmol/L. However, also in 2021, the ACC published an expert

analysis of the utilization of advanced lipoprotein testing in the setting of dyslipidemia (Farbaniec, 2021). In discussing assays for apoB and Lp(a), there was concern that "there are no current assays that have been standardized at this time." For Lp(a), variability in the size of the Lp(a) particle contributes to the difficulty in developing a well-standardized assay. The overall conclusion was that "advanced lipid testing is becoming more widely available, but these assays are not standardized and cross comparisons of advanced lipid assays are not well published at this time."

In addition to the above mentioned guidelines, several meta-analyses, reviews and clinical studies have been published assessing the association of lipoprotein with CVD risk and events and other conditions. Although consistently strong associations have been found between levels of lipoproteins and adverse cardiac health outcomes, evidence presented on the clinical utility of these measures above and beyond that of a basic lipid panel, continues to be inconsistent, conflicting and thus inconclusive (Arsenault, 2020; Cole, 2013; de Boer, 2021; Forbes, 2016; Gregson 2012; Holmes 2013; Holst-Albrechtesen, 2013; Kumar, 2021;Mattiuzzi, 2015; Melvin, 2013; O'Donoghue, 2014; Rosenson, 2013; Thanassoulis, 2014; Toth, 2014; Turgeon, 2016; Vittos, 2012). Numerous clinical studies are ongoing to further assess and define the role and clinical utility of advanced lipoprotein testing in the risk assessment, treatment and management of a variety of health conditions (Bittner, 2020; Mahmood, 2021; O'Donoghue, 2019; Paciullo, 2021; Pluimakers, 2021; Tsimikas, 2020).

Background/Overview

According to the Centers for Disease Control (CDC), about 647,000 individuals die of heart disease in the United States every year. CHD is the most common type of heart disease, killing approximately 366,000 individuals annually. A major risk factor for CHD is an elevated blood test known as LDL cholesterol.

Lipoproteins are molecules comprised mostly of proteins (including apoproteins), enzymes such as Lp-PLA2 also known as platelet-activating factor acetylhydrolase [PAF-AH] and fats. The role of plasma lipoprotein particles is to transport triglycerides and cholesterol throughout the body, and they have been suspected as having a key role in the pathophysiology of heart disease. The primary categories of lipoproteins are classified as chylomicrons, very-VLDL, LDL, DL and HDL. This nomenclature is based on the relative densities after ultracentrifugation (Feingold, 2021). IDLs' density falls between LDL and VLDL. IDL, also referred to as remnant lipoproteins, consist of partially degraded VLDLs which are rich in triglycerides and cholesterol. ApoE is a component of both VLDLs and IDLs.

A blood test can be done to measure specific types of plasma lipoproteins. Several lipoprotein ratios have surfaced in an attempt to optimize the predictive ability of lipid profiles with respect to a number of diseases, particularly CVD. LDL is considered the most atherogenic lipoprotein, and NCEP has designated total LDL-C as the primary target of therapy in the Adult Treatment Panel (ATP III) recommendations (ATP III, 2004). However, the LDL particles themselves are not uniform in size or density, and particle size/density has been proposed as a technique to further stratify patient risk beyond total LDL-C.

The recognition that atherosclerosis represents, in part, an inflammatory process, has created considerable interest in measurement of proinflammatory factors as part of CVD risk assessment. However, despite this association, the appropriate, safe and efficacious treatment approach for abnormal lipid level results from advanced testing remains

unclear. Neither the AHA nor the ACC recommends the advanced testing of lipoproteins in adults for CVD risk identification or management.

Definitions

Alpha-lipoprotein (α-lipoprotein): One with electrophoretic mobility equivalent to that of the α1-globulins, e.g., high-density lipoprotein.

Atherosclerosis: An accumulation of lipids (e.g., cholesterol) on the inner linings of arteries. The resulting blockage restricts blood flow to the heart.

Basic lipid panel: The basic lipid panel measures total cholesterol, triglyceride levels, HDL and LDL cholesterol levels.

Beta-lipoprotein (β-lipoprotein): One with electrophoretic mobility equivalent to that of the β-globulins, e.g., low-density lipoprotein.

Cholesterol: A fat-like substance that is made by the human body and eaten in animal products. Cholesterol is used to form cell membranes and process hormones and vitamin D. High cholesterol levels contribute to the development of atherosclerosis.

Coronary artery disease (CAD; coronary heart disease [CHD]): A disease characterized by narrowing or blockage of the blood vessels that supply blood to the heart.

High-density lipoprotein (HDL): A class of plasma lipoproteins that promote transport of cholesterol from extra-hepatic tissue to the liver for excretion in the bile; serum levels have been negatively correlated with premature CAD.

Intermediate-density lipoprotein (IDL): A class of lipoproteins formed in the degradation of very-low-density lipoproteins; some are cleared rapidly into the liver and some are degraded to low-density lipoproteins.

Lipoproteins: Blood-borne complexes of lipids and proteins that allow the transport of cholesterol throughout the body.

Low-density lipoprotein (LDL): A class of plasma lipoproteins that transport cholesterol to extra-hepatic tissues; high serum levels have been correlated with premature CHD.

Lp(a) lipoprotein: A lipoprotein particle containing apolipoprotein B-100 as well as an antigenically unique apolipoprotein; its occurrence at high levels in plasma has been correlated with increased risk of heart disease.

Very-high-density lipoprotein (VHDL): A class of lipoproteins composed predominantly of proteins and also containing a high concentration of free fatty acids.

Very-low-density lipoprotein (VLDL): A class of lipoproteins that transport triglycerides from the intestine and liver to adipose and muscle tissues; they contain primarily triglycerides with some cholesteryl esters.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
82172	Apolipoprotein, each
83695	Lipoprotein (a)
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
83700	Lipoprotein, blood; electrophoretic separation and quantitation
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)
83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
84999	Unlisted chemistry procedure [when specified as secretory type II phospholipase A2 (sPLA2-IIA)]
0052U	Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation VAP Cholesterol Test; VAP Diagnostics Laboratory, Inc.
0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables) Liposcale®, CIMA Sciences, LLC

ICD-10 Diagnosis	
	All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	03/29/2023	Updated Coding section with 04/01/2023 CPT changes; added 0377U.
Reviewed	05/12/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, Background/Overview and References sections.
	12/29/2021	Updated Coding section with 01/01/2022 CPT changes; added 84999 NOC code replacing 0423T deleted 12/31/2021.
Reviewed	05/13/2021	MPTAC review. Updated Rationale and References sections.

Reviewed	05/14/2020	MPTAC review. Updated Rationale, Background/Overview and References section.
Reviewed	06/06/2019	MPTAC review. Updated References section.
Reviewed	07/26/2018	MPTAC review. Updated References section.
	06/28/2018	Updated Coding section with 07/01/2018 CPT changes; added CPT 0052U.
	05/15/2018	The document header wording updated from "Current Effective Date" to "Publish Date."
Reviewed	08/03/2017	MPTAC review. Formatting of Investigational and Not Medically Necessary statement updated. Rationale, Background and References sections updated.
	01/01/2017	Updated Coding section with 01/01/2017 CPT descriptor revision for code 83704.
Reviewed	08/04/2016	MPTAC review. Updated Rationale and References sections.
Revised	11/05/2015	MPTAC review. Expanded scope of Criteria and Title to include "all indications." Updated Rationale, Background and Reference sections. Updated Coding section with 01/01/2016 CPT changes; also removed ICD-9 codes from Coding section.
New	05/07/2015	MPTAC review. Initial document development.