Lipoprotein Subclass Testing in the evaluation of Cardiovascular disease

Effective Date: December, 2006

Subject: Lipoprotein Subclass Testing in the evaluation of Cardiovascular disease

Overview: Lipoproteins are spherical particles that carry lipids, particularly cholesterol and triglyceride, in the plasma. There is a well-established association between dyslipidemias, or disorders of lipoprotein metabolism, and coronary heart disease (CHD): elevated levels of blood cholesterol, especially low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) increase risk for CHD. The relationship between triglyceride levels and CHD is controversial, although it is known that some triglyceride-rich lipoproteins can be atherogenic. Examination of HDL subclasses could contribute to an improved understanding of the dynamic interaction between HDL-C metabolism and CHD.

Components of advanced lipoprotein analysis may include:

1) LDL-C gradient gel electrophoresis (GGE) for low-density lipoprotein (LDL) subclasses
2) HDL-C GGE for HDL subclasses
3) lipoprotein (a) [Lp(a)] assay
4) apo A-I
5) apo B
6) apoE isoforms (E2, E3, E4)
7) total plasma homocysteine

Policy and Coverage Criteria:

Lipoprotein Subclass testing in the evaluation of Cardiovascular disease is NOT covered. Harvard Pilgrim Health Care considers this testing investigational and unproven due to insufficient evidence of its efficacy and safety in current literature.

Exclusions: N/A

Supporting Information:

1. Technology Assessment:
   - Technology Evaluation Center (TEC): (May 2003) TEC reports in its special report that the benefits of C-reactive protein testing remain uncertain. At this point in time, there appears to be no scientific literature that directly and experimentally tests the hypothesis that measurement of C-reactive protein to assess CHD risk results in improved patient outcomes. Thus, assessing the potential utility of C-reactive protein screening lies in understanding a chain of logic and the evidence supporting those links in the chain. C-reactive protein is only one of many so-called “emerging risk factors” for CHD that ATP III has identified. Others include lipoprotein remnants, lipoprotein (a), small LDL particles, HDL subspecies, various apolipoproteins, homocysteine, ankle-brachial blood pressure index, carotid intimal medial thickening, and coronary calcium. The principles of evaluating C-reactive protein as a risk predictor for CHD prevention would also hold for the evaluation of these other factors.

   - Literature review:
     There is a lack of research evidence to guide clinical use of HDL subclass determination for screening, diagnosing, or treating dyslipidemia or coronary heart disease (CHD). Case series, cross-sectional
studies, case-control studies, and prospective studies of the relationship of high-density lipoprotein (HDL) subclasses to CHD have been reported. These studies, including the prospective studies, have provided mixed results. The evidence on the relative importance of HDL2 and HDL3 is conflicting, i.e., several studies have shown that HDL2 has a stronger association with high-density lipoprotein cholesterol (HDL-C) and disease, while other studies have shown that HDL3 has a stronger association with HDL-C and disease. Moreover, no study has been able to show that prediction of ischemic heart disease is improved by replacing total HDL-C with some combination of its subfractions. Finally, in a recent study of cholesterol treatment practices in a health maintenance organization (HMO) primary care setting, only 14% of patients who needed lipid-lowering interventions had ever had cholesterol-lowering regimens.

There are relatively few recent studies investigating the relationship between apo A-I and risk of coronary heart disease (CHD) and results of these studies are conflicting. 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 HDL-C and other conventional lipid risk factors. There are even fewer studies investigating the effects of drug interventions on apo A-I levels in hypercholesterolemic patients. Results of two studies reviewed suggest that changes in apo A-I levels are dependent on the specific lipid-lowering drug administered. Finally, there is no evidence from intervention studies that increasing plasma apo A-I levels reduces coronary risk.

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 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. However, these results also need confirmation in additional, larger, prospective, longer-term studies.

Findings from studies that addressed the use of low-density lipoprotein (LDL) subclass testing have been reviewed and indicate that the prevalence of the small, dense LDL phenotype varies with a number of factors, including age, gender, hormonal status, and possibly ethnic or racial background, being most common in adult males and in postmenopausal women. Three cohort studies from Canada and the United States provided information on the role of LDL particle size in the risk of CHD. In the study by Lamarche et al., there was a 3.6-fold increased risk for CHD in males with small, dense LDL. In the Physicians' Health Study, male cases with MI were more likely to have small, dense LDL and increased levels of triglycerides. However, after adjustment for other coronary risk factors, LDL particle size was not a significant predictor of disease, while an elevated triglyceride level was associated with a 2.5-fold increased risk for MI. The nested case-control study from the Stanford Five-City Project, which included both men and women, found a prospective association between small, dense LDL and (CHD). However, the ratio of total cholesterol to HDL-C was a stronger independent predictor for the combined sample and for men. Among women, smoking and systolic blood pressure were the best predictors of CHD. On the other hand, severity of arterial occlusion was not increased among those with small, dense LDL.

The results of several studies suggest that LDL subclass combined with other metabolic states may increase one's risk for CHD. For example, low concentrations of Lp A-I, a component of HDL,
elevated apo B, or elevated triglycerides, combined with a high concentration of small, dense LDL could contribute to a high-risk profile, reflecting an underlying metabolic abnormality.

In a separate analysis from the Stanford Coronary Risk Intervention Project, the Risk Reduction intervention was beneficial for subjects with small, dense LDL, but not for those with large-buoyant LDL. This result is consistent with other research that suggests that pattern B LDL may be more responsive to dietary and exercise interventions than other LDL phenotypes. However, it is unclear whether the result of this study would have a substantial clinical impact in the general population, given the inadequate implementation of current National Cholesterol Education Program (NCEP) guidelines based on conventional cholesterol/triglyceride testing.

Several other case-control studies provided evidence that the relationship between LDL subclasses and risk of CHD is complex and variable. In a study of normolipidemic men with CHD, the large LDL subclass, rather than small, dense LDL, was associated with increased very-low-density lipoprotein (VLDL) and CHD risk, and with decreased levels of HDL-C (30). Among subjects with a family history of CHD, compared with those without a history, small, dense LDL was associated with older CHD-positive offspring >31 years of age(31). In a study that included male and female subjects, small, dense LDL was not associated with increased risk of CHD; increased heterogeneity of LDL subclass patterns, rather than the small, dense LDL profile itself, was associated with CHD. In addition, males had significantly smaller LDL than women. Among men only, small, dense LDL was associated with increased body mass index, waist-to-hip ratio, total cholesterol, postprandial glucose, triglycerides, and insulin responses.

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. The Hopkins et al. study reported that elevated Lp(a) interacted with elevated total cholesterol or total cholesterol/HDL-C ratio, as well as with nonlipid risk factors such as homocysteine, to increase risk of disease in both men and women. According to Craig et al., since some studies have shown that interactions between Lp(a) and LDL-C may play a role in CHD risk, Lp(a) testing may be useful for identifying those individuals who might benefit from more aggressive LDL-C reduction therapy.

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 by Luc et al. (28) the measurements of Lp(a) were all performed in the same laboratory with fresh plasma. Luc et al. 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.

Three things must occur 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 (15). There also is a need for additional studies to confirm the association of low molecular weight apo(a) isoforms and CHD and for the development of strategies to manage patients with high-risk phenotypes. Finally, future
Research should 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. For example, individuals with elevated levels of Lp(a) and other lipid risk factors, such as high LDL-C and/or low HDL-C, may warrant more aggressive lipid lowering therapy. On the other hand, it can be argued that patients with these other risk factors should already be receiving aggressive therapy and measurement of Lp(a) levels would provide no additional information for risk assessment.

Research on the relationship of apoE to lipid metabolism and risk of CHD has been conducted in Canada, the United States, Europe and Asia. Subjects in these studies have included healthy males and females of all ages, persons diagnosed with mild hypercholesterolemia, and patients with CHD and familial hypercholesterolemia (FH). To date, studies have consistently identified relationships between apoE and variations in lipid metabolism and CHD. Research has provided information on variations in the prevalence of apoE genotypes or phenotypes and the risk of CHD among cases and controls. Prospective analyses of apoE and CHD incidence and mortality, as well as longitudinal analyses of the relation of apoE to serum lipid changes, have also supported a role for apoE in the natural history of atherosclerotic disease. Studies of the dietary response of patients by apoE genotype, and the effect of apoE on treatment outcomes with lipid-lowering drugs, have identified areas for further research. However, relationships between apoE and study outcomes have varied by age, gender, adiposity, national origin, and race. There have been no randomized controlled trials of apoE polymorphism and the prevention or treatment of dyslipidemia or CHD.

Overall, many interesting and complex relationships between apoE isoforms, lipid metabolism, and development of CHD have been described or hypothesized in the research literature. However, although apoE and other genetic diagnostics may eventually prove useful in a clinical setting, it is unclear what impact these tests will have on patient management, given the poor implementation of current NCEP guidelines based on conventional cholesterol/triglycerides testing. The May 2001 National Institute of Health's (NIH) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) includes the National Cholesterol Education Program's (NCEP) updated recommended guidelines for cholesterol testing. The NCEP continues its recommendation that the LDL-cholesterol level be the primary target for cholesterol-lowering therapy. A fasting lipoprotein profile of the major blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) should be obtained at least once every five years in adults age 20 and older. The Adult Treatment Panel III does not recommend routine measure of any of the emerging risk factors for the purpose of risk assessment because at the time of their research, the NCEP found these tests not readily available, not well standardized, relatively expensive, and required additional interpretive clinical knowledge. Some of the emerging risk factors contributing to CHD mentioned in the NCEP guidelines include elevations of Lp(a), remnant lipoproteins, small LDL, fibrinogen, homocysteine, high-sensitivity C-reactive protein and impaired fasting plasma glucose. These factors may be potential adjuncts to risk assessment, but they should not take priority over the major risk factors(50). The clinical significance of the testing for additional risk factor indications must be evaluated against 1) the significant predictive power that is independent of other major risk factors, 2) relatively high prevalence in the population, 3) the laboratory measurement is widely available, well standardized, accepted reference values, inexpensive, and stable biologically, and 4) clinical trials show risk reduction based on modification of risk factor(23).

The Adult Treatment Panel III of the NCEP acknowledged that apolipoprotein B is a potential marker for all atherogenic lipoproteins, but did not feel there was sufficient clinical evidence to justify replacing the LDL as the preferred target of therapy.

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 (24).

The large population for the Apolipoprotein-related Mortality Risk Study (AMORIS) included 175,553 Swedish men and women (32). The focus of this study was to evaluate whether 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. Of importance in this study was the use of internationally standardized measurements so the data could be used to compare with the World Health Organization (WHO) - International Federation of Clinical Chemistry (IFCC) standardized reference materials for measurement of concentrations of apoB and apoA. The results substantiated the already known risk prediction for acute MI identified with measurements of total cholesterol, triglycerides, and LDL-cholesterol and the anti-atherogenic effect associated with HDL-cholesterol. 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 (32).

In a prospective nested case-control study from the Women's Health Study, the median baseline levels of LDL particle concentration by NMR were higher among 130 women who subsequently had cardiovascular events than among 130 women who did not have cardiovascular events. However, this was not substantively different from that of the total cholesterol to HDL cholesterol ratio and was less than that of C-reactive protein(49).

Homocysteine may induce vascular damage by several mechanisms(34,35,36). Numerous cross-sectional and case-control studies, and several prospective studies were utilized in a meta-analysis designed to evaluate evidence of the relationship between homocysteine and CHD. This meta-analysis of 27 studies included research that was completed in the United States and Europe during the late 1980s and early 1990s. Using the data from these studies, which almost unanimously reported a positive association between increased homocysteine and disease, Boushey et al. calculated a summary odds ratio (OR) for the risk of atherosclerotic disease associated with increased homocysteine levels. The OR for CHD was 1.7 in 15 studies; the OR for stroke was 2.5 in 9 studies, and the OR for peripheral vascular disease was 6.8 in 5 studies. Although there is controversy regarding OR estimates that are constructed by meta-analysis, this study by Boushey provided a useful overview of risk estimates for the relationship between homocysteine and disease, estimates that need further testing. ORs similar to those determined by Boushey et al. were reported in the nine-country European Concerted Action Project, a retrospective case-control study of homocysteine and vascular disease risk. Ford et al., in their meta-analysis of 57 publications between 1974 and 1999 also concluded that even though case-control studies offer more support than prospective studies, more information from prospective studies and clinical trials is needed to support the role for homocysteine in the pathogenesis of cardiovascular disease(26).

Subsequent studies have resulted in various outcomes. Two found an association between homocysteine and an increased risk for ischemic heart disease in patients who had a baseline of heart disease, but not among those without a baseline of heart disease(37,45). Two other studies compared homocysteine levels and acute coronary events in populations with no prior history of heart disease and found no association between the two(38,40). A 10-year follow-up of a study using a nested case-control design did not find a significant association between homocysteine and coronary heart disease(39), however 2 cohort studies did find a significant association between homocysteine and ischemic heart disease(41,43). Another nested case-control study found a significant association between homocysteine and sudden cardiac death(44).
The Hordaland homocysteine study measured plasma total cysteine levels in 12,595 men and women 40 to 42 years of age and in 4766 men and women 65 to 67 years of age from 1992 to 1993. Data on cardiovascular hospitalizations were collected from hospital records through May 1998 and data on mortality were collected through 1999. The investigators reported a significant association between homocysteine and ischemic heart disease in 2001. Using the same data, they reassessed the relationship between plasma total cysteine and mortality from all causes, from cardiovascular and noncardiovascular conditions, and the association between plasma total cysteine levels and the risk of hospitalizations from cardiovascular disease in 2003. They concluded there was no association between homocysteine and mortality or cardiovascular hospitalizations(42,47).

A prospective cohort study assessed the 1-year risk of death and cardiovascular morbidity associated with peripheral arterial disease in 6880 patients 65 years of age or older. After 1 year, mortality from all causes was 2.8% in patients with peripheral arterial disease and 0.9% in patients without peripheral arterial disease. Mortality due to cardiovascular events was 1.6 versus 0.4%. Patients with peripheral arterial disease and high homocysteine values had a significantly increased risk of premature death(46).

Cesari et al. measured the left ventricular ejection fraction, plasma homocysteine levels, folate levels and quantified coronary artery disease with a modified Duke Index score in 936 consecutive patients. In this sample, they found that homocysteine predicts cardiovascular mortality and a low left ventricular ejection fraction regardless of the presence of coronary artery disease or a history of myocardial infarction in arterial hypertensive patients, but not in normotensive patients(48).

Despite many positive associations between higher levels of homocysteine and CHD, there is a lack of consistency in results from prospective studies. In addition, there is no consensus on target-levels or safe-levels of total homocysteine. Therefore, it is premature to conclude that homocysteine levels are predictive of the development of CHD.

Hackam and Anand published results of their review of available clinical evidence from January 1990 through January 2003 concerning the four emerging risk factors of C-reactive protein, lipoprotein(a), fibrinogen, and homocysteine(9). Attention was focused on assessing the clinical significance and additive predictive value of these four risk factors. These four measures were selected because there is substantial available evidence on their predictive abilities, modifying treatments have been identified, and/or these four factors are the subject of current or completed clinical trials. Although all four of these risk factors are associated with cardiovascular disease, it was concluded that further investigation and/or standardization of these measurements is needed before any of these emerging factors can be recommended for risk stratification.

- **Review of clinical evidence:**
  - Lipoprotein subclass testing detects elevated or reduced levels of lipoproteins, but there is lack of agreement on how this information would be used in clinical decision-making.
  - Lipoprotein subclass testing has not been defined accurately as an independent variable for diagnosis and identification of individuals at risk for cardiovascular disease.
  - The National Cholesterol Education Program (NCEP) identifies lipoprotein subclass testing as an emerging technology but does not recommend its routine use in identifying persons at risk of coronary heart disease.
  - Future research may identify a role in such testing for an identified subset of patients that will define clinical interventions based on clinical evidence.

- **The National Heart, Lung and Blood Institute (NHLBI) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) includes the National Cholesterol Education Program (NCEP) recommendation of a fasting lipid profile of the major blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) for risk stratification of coronary artery disease and that the LDL-cholesterol level is the primary target for cholesterol-lowering therapy.**
2. **Benchmarks:**
   - **Blue Cross Blue Shield of Mass.:** No public policy found
   - **Aetna:** (Aug 06)
     I. **High-sensitivity C-reactive protein (hs-CRP):**
        A. Aetna considers high-sensitivity C-reactive protein (hs-CRP) testing **medically necessary** for members who meet all of the following criteria: 1) member has 2 or more coronary heart disease (CHD) major risk factors*, and 2) member has low density lipoprotein (LDL) cholesterol levels between 100 to 130 mg/dL; and 3) member has been judged to be at an intermediate risk of cardiovascular disease by global risk assessment (i.e., 10 to 20 percent risk of CHD per 10 years using Framingham point scoring**).
        
        *Major risk factors include the following:
        - Current cigarette smoking
        - Hypertension (BP 140 mmHg or higher, or on antihypertensive medication)
        - Low HDL cholesterol (less than 40 mg/dL)
        - Family history of premature CHD (CHD in male first degree relative less than 55 years; CHD in female first degree relative less than 65 years)
        - Age (men age 45 years or older; women age 55 years or older).
        
        B. Aetna considers hs-CRP testing experimental and investigational for all other indications, including use as a screening test for the general population and for monitoring response to therapy.
   
   II. Aetna considers **any** of the following tests for assessing CHD risk **experimental and investigational:**
        - Apolipoprotein A-I (apo AI)
        - Apolipoprotein B (apo B)
        - Apolipoprotein E (apo E)
        - Homocysteine testing
        - Lipoprotein remnants: intermediate density lipoproteins (IDL) and small density lipoproteins
        - HDL subspecies (LpAI, LpAI/AII and/or HDL3 and HDL2)
        - LDL subspecies (small and large LDL particles)
        - LDL gradient gel electrophoresis
        - Lipoprotein(a) enzyme immunoassay
        - Angiotensin gene (CardiaRisk AGT)
        - Fibrinogen
        - Lipoprotein-associated phospholipase A2 (Lp-PLA2) (PLAC)
        - Measurement of long chain omega-3 fatty acids composition in red blood cell
        - Interleukin 6 -174 g/c promoter polymorphism

        The medical literature does not support the utility of the above tests for screening, diagnosis, or management of CHD.
   
   III. Aetna considers measurement of carotid medial intima thickness experimental and investigational for assessing CHD risk.
   
   IV. Aetna considers non-invasive measurements of arterial elasticity by means of blood pressure waveforms (e.g., HDI PulseWave, CVProfilor) experimental and investigational for assessing CHD risk.


   - **Tufts:** No public policy found
   - **NICE:** No public policy found
   - **Fallon Community Health plan:** No public policy found

3. **Governmental/Regulatory Agencies:**
• **FDA:** The US Food and Drug Administration (FDA) has approved an immunoturbidimetric test for the quantitative determination of apo A-I and apo B in serum and plasma. In addition, the FDA has approved the product Apolipoprotein Control Serum CHD for use as a quality control material to monitor accuracy and precision of human serum protein assays, such as tests for the quantitative immunochromatographic determination of apo A-I and apo B using RID, the Behring Nephelometer Systems, and the TurbiTime System.

The FDA has approved a number of devices and reagents for testing blood levels of Lp(a). However, these approvals neither imply that the tests used for measuring Lp(a) are standardized nor that they are of value for coronary heart disease (CHD) risk prediction and patient management.

LDL subclass testing, apoE testing, homocysteine testing and HDL subclass testing must be performed in accordance with the quality standard established in 1988 by the Clinical Laboratory Improvement Amendments (CLIA).

• **CMS:** Medicare allows coverage for diagnostic and therapeutic use of **standard lipoprotein analysis** including total cholesterol, LDL and HDL cholesterol and triglyceride measurement, in the presence of specified diagnoses. Electrophoretic or other quantitation of lipoproteins is covered only for primary disorder of lipid metabolism.

Medicare does not cover routine screening and prophylactic testing.

**Codes:**
- **002T:** Lipoprotein, direct measurement, intermediate density lipoproteins (IDL) (remnant lipoproteins)
- **82172:** Apolipoprotein, each
- **83090:** Homocysteine
- **83695:** Lipoprotein (a)
- **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 numbers and lipoprotein particle subclasses (eg, by nuclear magnetic resonance spectroscopy)
- **83718:** Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
- **83719:** Lipoprotein, direct measurement; VLDL cholesterol
- **83721:** Lipoprotein, direct measurement; LDL cholesterol
- **86140:** C-reactive protein
- **86141:** C-reactive protein; high sensitivity (hsCRP)

**References:**