Subject: Cardiovascular Disease Risk Tests

Background: Management of risk factors for cardiovascular disease (CVD) may be considered primary prevention for those who have not previously experienced an atherosclerotic vascular event, and there are several diagnostic tests designed to help assess non-traditional risk factors for cardiovascular disease.

The purpose of serum high-sensitivity C-reactive protein (hs-CRP) testing is to predict the risk of recurrent events in those with coronary artery disease (CAD) so that applicable interventions can be introduced and improved.

Policy and Coverage Criteria:

Harvard Pilgrim Health Care (HPHC) considers high sensitivity C-reactive protein testing as reasonable and medically necessary for assessment of cardiovascular disease risk for individuals at intermediate risk of coronary heart disease (ten-year risk of 10-20% using professionally accepted risk assessment tools) when documentation confirms ALL the following:

- Member is metabolically stable; AND
- Member does not have inflammatory or infectious conditions; AND
- Member has 2 or more of the following coronary heart disease (CHD) major risk factors:
    - Men who are 45 years of age or older or Women who are 55 years of age or older, OR
    - Current cigarette smoker, OR
    - Type I or Type II Diabetes, OR
    - Family history of premature CHD (CHD, specifically in father or brother who has been diagnosed before the age of 55 years or in mother or sister who has been diagnosed before the age of 65 years), OR
    - Hypertension (blood pressure of 140 mm Hg or higher, or individual is on anti-hypertensive medication), OR
    - Low high-density lipoprotein (HDL) cholesterol (less than 40 mg/dL for males, less than 50 mg/dL for females); AND
- Member has low-density lipoprotein (LDL) cholesterol levels between 100 to 130 mg/dL

Exclusions: Harvard Pilgrim Health Care (HPHC) considers cardiovascular disease risk tests as not medically necessary for all other indications. In addition, HPHC does not cover:

- Arterial compliance testing using waveform analysis
- Carotid intima-media thickness (CIMT) measurements
- Endothelial function assessment tools (e.g. peripheral arterial tonometry, brachial artery pressure ultrasound)
- Measurement of novel lip and non-lipid risk factors (as an adjunct to measurement of LDL cholesterol)
- Panels that include lipid and non-lipid cardiovascular risk markers
- Tests for risk assessment of cardiovascular disease, such as:

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- Angiotensin II
- Apolipoproteins
- B-type Natriuretic Peptide
- Cystatin C
- Cystine and homocysteine, urine, qualitative
- Fibrinogen; antigen
- Glycosylated acute phase proteins (GlycA)
- HDL subclass (e.g. Boston Heart HDL Map®)
- Homocysteine
- Human A_2 phospholipases
- Interleukin 6, 17, 18
- Long-chain omega-3 fatty acids
- Leptin
- LDL subclass (e.g. Boston Heart Cholesterol Balance® Test)
- Lipoprotein (e.g. direct measurement, intermediate density lipoproteins (IDL) remnant lipoproteins)
- Lipoprotein, blood:
    - Electrophoretic separation and quantitation
    - High resolution fractionation and quantitation of lipoproteins including (when performed) lipoprotein subclasses
    - Quantitation of lipoprotein particle numbers and lipoprotein particle subclasses
- Lipoprotein- associated phospholipase (LP-PLA_2)
- Mid-regional pro-atrial natriuretic peptide
- Molecular lipid/metabolic profiling (e.g. lipidomic, metabolomics)
- Pregnancy-associated plasma protein-A (PAPP-A)
- Protein C
- Prothrombotic factors (e.g. antithrombin III, PAI-1, tPA, Factor V Leiden)
- Group II Secretory Phospholipase A2 (sPLA_2-IIA)
- Soluble cell adhesion molecules (e.g. VCAM-1, ICAM-1)
- Transforming growth factor beta
- Troponin
- VLDL cholesterol

Supporting information:

There is some evidence to suggest that lipoproteins may be helpful in determining cardiovascular disease (CVD) risk and targeting therapy. A number of authors have investigated using testing on populations identified as moderate and high-risk. Comprehensive lipoprotein analysis tests have been developed to help evaluate patients at risk for CVD. The analyses may include tests for LDL subclasses, HDL, subclasses, lipoprotein(a) immunoassay, apolipoprotein A-1, B and E, total homocysteine plasma levels, prothrombotic factors and lipoprotein-associated phospholipase A2. Researchers continue to evaluate different cardiovascular tests to assess the predictive risk of CVD. Evidence supporting tests such as LDL subclasses, HDL, subclasses, lipoprotein(a), etc., remains limited. Further studies are needed to illustrate the risk predicted by these tests is comparable to more traditional risk prediction methods. Also, more studies are needed showing the testing influencing therapeutic decisions and clinical outcomes.

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Connelly et al. (2017) assessed studies of the protein glycosylation (GlycA) biomarker in regards to systemic inflammation and cardiovascular disease risk. As GlycA is positively correlated with body mass index (BMI), markers of metabolic syndrome, and insulin resistance, it may be a reliable biomarker of cardiometabolic risk. However, it was concluded that larger prospective studies and randomized trials are necessary to measure the impact of GlycA tests.

von Haehling et al. (2013) evaluated pregnancy-associated plasmas protein-A (PAPP-A) based on observational studies and systematic reviews. There was a consensus that the efficacy of standardization of assays was not yet established and optimal cut off values have not been determined. The authors concluded clinical utility of PAPP-A was unproven and additional studies were necessary to confirm its effectiveness.

Data from more than 30 epidemiologic studies have shown a significant association between elevated serum or plasma concentrations of CRP and the prevalence of underlying atherosclerosis, the risk of recurrent cardiovascular events among patients with established disease, and the incidence of first cardiovascular events among individuals at risk for atherosclerosis. Pearson et al. (2003) endorsed the optional use of hs-CRP to identify people without known cardiovascular disease who are at intermediate risk. Those with the testing results may help guide considerations of further evaluation or therapy. Yeh (2005) noted that hs-CRP testing enhances information provided by lipid screening or global risk assessment. In a randomized controlled trial, Ridker et al. (2005) found patients with low CRP levels after statin therapy had better clinical outcomes than those who had higher CRP levels, regardless of LDL cholesterol levels.

Additional studies support the theory that increased levels of hs-CRP are associated with increased risk of CVD, sudden death, and peripheral arterial disease (Ridker et al., 2000; Yin et al., 2004; Laberrere and Zaloga, 2004).

While the angiotensin gene polymorphisms have shown some association with cardiovascular disease risk and certain forms of hypertension, there is not enough evidence in clinical literature demonstrating improved outcomes and management due to testing.

Some research suggests apolipoprotein measurement improves overall risk prediction compared to standard lipid testing. However, opinions are varied and the clinical utility of apolipoprotein testing in the general population is uncertain. In most studies, patient-selection criteria are not clearly established. Available evidence consists of both retrospective and prospective case series, cohort studies, and randomized controlled clinical trials, including a few systematic reviews and meta-analyses. Many study populations involve large subsets of patients evaluating outcomes over several years. Some proponents report the predictive power of apolipoprotein testing (apo A–1 and apo B) is comparable to or better than traditional measurements (Sniderman, et al., 2003a; Kastelein, et al., 2008; Khadem-Ansari, et al., 2009; Benderly, et al., 2009) while other studies did not (Stampfer, et al., 1991; Sharrett, et al., 2001; Ingelsson, et al, 2007; Ray, et al., 2009). Moreover, some studies strongly support the association of apo B with CVD and provide evidence that apo B may have more clinical utility than conventional measurements, including LDL (Lamarche, et al., 1996; Gotto, et al., 2000; Khadem-Ansari, et al., 2009; Sierra-Johnson, et al., 2009).

Literature lends some support that the ratios of total cholesterol to HDL and of apo B: apo A–1 are more highly correlated with severity and extent of cardiovascular disease (Wallach, et al., 2007; Lau and Smith, 2009; Sierra-Johnson, et al., 2009). Yet, Wallach et al. (2007) noted the apo B: apo A–1 ratio showed greater sensitivity/specificity for CVD than LDL-C:HDL-C ratio, HDL-C: triglyceride ratio, or any of the individual

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components. Few studies have evaluated the effect of lipid lowering agents on apolipoproteins, but there is some evidence to suggest a positive effect (Ray, et al., 2009; Holme, et al., 2008).

Rosenson et al. 2013 stated that there are no clinical trials that have adequately tested the hypothesis that Lp(a) reduction reduces the incidence of first or recurrent CVD events. Therefore, widespread screening for Lp(a) excess is not indicated and treatment of Lp(a) excess should only be considered in specific circumstances, when the treating clinician believes that the possible CVD benefits of Lp(a) reduction or more aggressive LDL cholesterol reduction outweigh the potential risks of therapy.

Guidelines:

The American Association of Clinical Endocrinologists (AACE, 2017) guidelines identified major risk factors (i.e. high LDL, high non-HDL, low HDL) in relation to optimal lipid levels. The guidelines support the use of apolipoprotein B level ad LDL particle concentration to achieve LDL-C lowering. However, the conclusion specified that consistency in these methods for LDL particle testing has not been established currently. Routine measurement of homocysteine, uric acid, or other inflammatory markers was also not recommended due to lack of sufficient evidence.

The United States Preventive Services Task Force (USPSTF, 2016) guidelines published recommendations for screening for dyslipidemia in younger adults. Clotting inhibitors or anticoagulants have been suggested as risk factors of cardiovascular disease (CVD). Nevertheless, the correlation between these factors have not been clearly identified and there is a lack of clinical evidence surrounding this association.

According to the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice guidelines, biomarkers may be beneficial in specific subgroups. However, this has only been addressed in a number of studies, and the efficacy of these biomarkers have not been fully determined.

The National Lipid Association (NLA, 2015) evaluated the clinical utility of lipoprotein testing (i.e. apolipoprotein B, lipoprotein a) to improve cardiovascular risk prediction. For those at intermediate risk (5-20%) or those with a family history of coronary heart disease (CHD), testing was reasonable. However, for low risk patients, the guidelines stated testing was not recommended.

The 2013 Practice Guideline for Assessment of Cardiovascular Risk (AAC/AHA) does not recommend the measurement of lipid parameters, including lipoproteins, apolipoproteins, particle size, and density, beyond a standard fasting lipid profile. It was also noted that there is no evidence that the assessment of additional lipid parameters leads to improved net health outcomes. Therefore, the cost effectiveness also cannot be assessed.

They also recommended the measurement of c-reactive protein in the following instances:

- In men 50 years of age or older or women 60 years of age or older with LDL cholesterol less than 130 mg/dL; not on lipid lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy.
- In asymptomatic intermediate-risk men 50 years of age or younger or women 60 years of age or younger, measurement of CRP may be reasonable for cardiovascular risk assessment.

While the American Heart Association (AHA) does not classify elevated homocysteine levels as a major cardiac disease risk factor, some researchers have suggested in clinical literature that reducing elevated levels reduces

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cardiac risk. In a consensus statement Davidson et al. (2008) noted that biomarkers, including homocysteine, have been evaluated as factors that may be considered in the evaluation of persons with lipoprotein abnormalities, although their independent predictive power and clinical utility are still unclear. There is limited evidence that lowering homocysteine levels improves clinical outcomes. Literature does not clearly define patient selection criteria or target and safe levels of homocysteine (Mangoni and Jackson, 2002; Linton and Fazio, 2003; Splaver et al., 2004; Giacobbe et al., 2004; Cesari et al., 2005; Myers et al., 2009). The USPSTF (2009) found insufficient evident to support the use of homocysteine levels in the assessment of CHD.

The National Heart, Lung and Blood Institute (NHLBI, 2011) guidelines do not support universal screening at this time as studies indicate measurement of apolipoprotein B (apoB) and apolipoprotein A-1 (apoA-1) do not provide additional advantage over non-HDL-C or LDL-C measurements.

The American College of Cardiology Foundation and American Heart Association (ACCF/AHA, 2010) guidelines do not recommend cardiovascular risk assessment based on lipoprotein-associated phospholipase A2 (Lp-PLA2) as the usefulness and efficacy is not well established due to conflicting evidence from multiple randomized trials and meta-analyses. The foundation also found no association between high-sensitivity cardiac troponin (hs-cTnI and hs-cTnT) concentration and cardiovascular disease (CVD) outcomes.

The American Heart Association (AHA, 2009) guidelines reviewed a meta-analysis on B-type natriuretic peptides (BNP) and its association with cardiovascular disease (CVD). Although prospective studies showed strong associations between BNP and CVD, further investigation was deemed necessary, especially in large general population studies, to refine the utility of the markers.

The National Academy of Clinical Biochemistry Laboratory (NACBL, 2009) guidelines also do not support LDL subclass testing. The guideline notes the analyses of the existing studies are generally not adequate to show added benefit when compared to standard risk assessment. There some evidence in the medical literature supporting the theory LDL particle size and concentration is associated with atherosclerosis and coronary artery disease (Cromwell and Otvos, 2006; Otvos, et al., 2006; Mora, et al. 2007; Biswas, et al., 2008; Koba, et al., 2008, California Technology Assessment Forum [CTAF], 2008). The effects of niacin on lipoprotein particle distribution has also been studied and has shown to reduce the number of circulating particles of the more atherogenic subtypes of LDL, despite having no effect on total LDL levels (Jafri, et al., 2009). Other studies suggest increased LDL particles and small LDL size (smaller, more dense LDL particles) are more atherogenic and predict cardiac risk better than total LDL levels. However, within a technology assessment report, the CTAF (2008) noted there were no studies addressing whether or not treated LDL particle levels affected clinical outcomes. The ATP III guidelines also do not support measurement of small LDL particles in routine practice. According to the ADA/ACC consensus statement (Brunzell, et al., 2008), measuring LDL particles using NMR may be more accurate, and “many cross sectional and prospective studies show LDL particle number is a better discriminator of risk than is LDL cholesterol.” However, the report also notes the lack of data confirming the accuracy of the method and question whether its CVD predictive power is consistent across various ethnicities, ages, and conditions that affect lipid metabolism.

A report from Agency for Healthcare Research and Quality (AHRQ, 2008) regarding LDL subfraction (subclass) measurement suggests it has yet to be determined if cardiac disease risk assessment and treatment decisions would be improved by adding LDL subclass measurements.

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The Journal of the American Medical Association (JAMA, 2006) assessed incremental coronary risk prediction with C-reactive proteins and other markers. Utilizing various case-cohort studies, the Atherosclerosis Risk in Communities (ARIC) study evaluated the connection between 19 risk markers with congenital heart disease (CHD). The authors concluded, however, that routine measurement of these markers did not affirm risk assessment of CHD.

The National Cholesterol Education Program Adult Treatment Panel (Adult Treatment Panel III [ATP III], 2001) guidelines do not recommend the use of routine measurement of risk factors for the sole purpose of risk assessment. Studies were inadequate and measurement of specific assays for lipoprotein was not advised for routine observation.

Lipoprotein remnants, including intermediate density lipoproteins (IDLs) and VLDLs have been shown to be atherogenic (ATP III). Yet, the panel concluded there are limited studies, and measurement with specific assays for lipoprotein remnants are not recommended for routine practice.

HDL subclass testing has been investigated for information regarding CVD risk in addition to total cholesterol, HDL cholesterol and low-density lipoprotein cholesterol. Some studies suggest HDL subclasses may be more closely associated with risk than is total HDL and may provide additional risk information for those individuals identified as low- or intermediate-risk by standard lipoprotein tests. According to the ATP III panel, the literature does not support improved clinical outcomes with the use of HDL subclass testing, and it has not been recommended as a routine measurement of cardiac risk

Coding:

Codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible.

Not medically necessary ICD-10 codes

CPT® Codes	Description
86141	C-reactive protein; high sensitivity

CPT codes not covered when billed with the diagnoses above:

CPT® Codes	Description
82163	Angiotensin II
82172	Apolipoprotein, each
82610	Cystatin C
82615	Cystine and homocysteine, urine, qualitative
83090	Homocysteine
83695	Lipoprotein (a)
83698	Lipoprotein associated phospholipase A2
83700	Lipoprotein, blood; electrophoretic separation and quantitation
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed

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83704	Lipoprotein, blood; quantitation of lipoprotein particle numbers and lipoprotein particle subclasses
83719	Lipoprotein, direct measurement; VLDL cholesterol
83880	Natriuretic peptide
85384	Fibrogen, activity
85385	Fibrinogen; antigen
93050	Arterial pressure waveform analysis for assessment of central arterial pressures includes waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation, bilateral
93998	Unlisted noninvasive vascular diagnostic study
0111T	Long-chain (C20-22) omega-3 fatty acids in red blood cell (RBC) membranes
0126T	Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment
0423T	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

Billing Guidelines:

Member's medical records must document that services are medically necessary for the care provided. Harvard Pilgrim Health Care maintains the right to audit the services provided to our members, regardless of the participation status of the provider. All documentation must be available to HPHC upon request. Failure to produce the requested information may result in denial or retraction of payment.

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Summary of Changes:

Date	Changes
3/21	Annual review; no changes
3/20	References and supporting information updated; Coding and coverage criteria updated

Approved by Medical Policy Committee: 2/16/21
Approved by Clinical Policy Operational Committee: 4/10, 4/12, 4/14, 6/14, 6/16, 4/20, 3/21
Policy Effective Date: 3/08/21
Initiated: 12/06

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