Clinical Policy: Cardiac Risk Assessment Laboratory Tests

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Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

This policy describes the medical necessity requirements for cardiac risk assessment laboratory blood tests. They are proposed to help to determine the risk for coronary artery disease (CAD), myocardial infarction (MI), plus other cardiac conditions and guide the individual's treatment.

Policy/Criteria

I. It is the policy of Health Net of California that for following tests are medically necessary when the indications are met:
   A. High-sensitivity C-reactive protein (hs-CRP) testing for the assessment of CAD when the member has undergone previous noninvasive tests for cardiac risk stratification and been found to be at intermediate risk, as evidenced by meeting all of the following:
      1. LDL cholesterol levels between 100 to 130 mg/dL;
      2. Patient has ≥ 2 coronary heart disease (CHD) major risk factors, such as:
         i. Hypertension (BP ≥ 140 mmHg or on an antihypertensive medication),
         ii. Low HDL cholesterol (< 40 mg/dL),
         iii. Diabetes,
         iv. Family history of premature CHD in male first degree relative < 55 years; CHD in female first degree relative < 65 years,
         v. Man ≥ 45 years or woman ≥ 55 years,
         vi. Current cigarette smoking;
      3. Global risk assessment such as the Framingham point scoring (ie 10 to 20% risk of CHD per 10 years).
   B. Apolipoprotein B (a-poB) in high risk individuals with hypercholesterolemia to assess if additional intense interventions are necessary when LDL cholesterol goals are reached. Persons with diabetes, known cardiovascular disease, family history of premature CVD and smoking are considered high risk.

II. It is the policy of Health Net of California that any of the following tests are considered investigational to assess cardiac risk because the medical literature is inconclusive regarding the utility of these tests for screening, diagnosis or management of CHD:
   A. hs-CRP testing for members at high-risk for CAD,
   B. hs-CRP as a screening test for the general population or for monitoring response to therapy,
   C. Complete profiles of cardiac risk,
   D. Apolipoprotein A-I,
   E. Apolipoprotein B for the general population,
   F. Apolipoprotein E,

G. Lipoprotein remnants: intermediate density lipoproteins and small density lipoproteins (NMR LipoProfile),
H. High density lipoprotein subclasses (LpAI, LpAI/AII and/or HDL3 and HDL2),
I. Low density lipoprotein subclasses (small and large LDL particles) Lipoprotein(a) enzyme immunoassay,
J. Fibrinogen,
K. Lipoprotein-associated phospholipase A2 (Lp-PLA2) (PLAC), secretory phospholipase A2 (sPLA2-IIA),
L. Noninvasive measurements of arterial elasticity by means of blood pressure
    a. waveforms (e.g., HDI PulseWave, CVProfilor),
M. Vertical auto profile: cholesterol test,
N. Measurement of B-type natriuretic peptides,
O. Carotid intima-media thickness (CIMT)

Background

CAD develops when the coronary arteries become damaged or diseased with plaque development. Myocardial ischemia occurs when blood flow to the heart is reduced, preventing it from receiving enough oxygen. This reduced blood flow is usually the result of a partial or complete blockage of the coronary arteries. This condition may be chronic, narrowing of the coronary artery over time and limiting of the blood supply to part of the muscle; or it can be acute, resulting from a sudden rupture of a plaque and formation of a thrombus.

CHD is the most common form of heart disease affecting seven million Americans. It could lead to a MI or other cardiac issues and is the result of CAD, which can begin earlier in an individual's life. Preventive measures are thought to delay the progression of CAD. Therefore, it is imperative to understand not only how to diagnose heart disease but also how to stratify its risk, an important factor in treatment decision making in patients with CAD. Once the initial diagnosis has been made, various cardiac tests can be used to obtain pertinent information about risk level and the appropriateness of medical versus more invasive treatments.

Biomarkers of CVD have been identified and evaluated as potential adjuncts to standard risk assessment strategies. For CHD, biomarkers must reflect the underlying biology of the vessel walls and the atherosclerotic process. Various markers include hs-CRP, homocysteine, and Lp-PLA2, which have been investigated as a tool for determining the risk of CVD in apparently healthy and asymptomatic individuals, thereby presenting the opportunity for targeted preventive efforts based on an individual’s predicted risk profile. [4]

Hs-CRP is a laboratory test developed to evaluate a patient's risk of MI or other heart conditions. Studies suggest that hs-CRP is useful in detecting the small amounts of CRP in patients with atherosclerosis. Current data suggest that the addition of hs-CRP to standard lipid screening can improve the ability to detect absolute coronary risk. This is a critical issue because one-half of all MIs and strokes occur among individuals without overt hyperlipidemia. In addition, it was theorized that risk assessment based on hs-CRP levels might provide a superior prediction of response to statin therapy.

Several meta-analyses, reviews and clinical studies have been published assessing the association of lipoprotein with CVD risk and events. 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 continues to be inconsistent, conflicting and thus inconclusive. Clinical studies are ongoing to further assess and define the role and clinical utility of lipoprotein testing in CVD risk assessment, treatment and management.

Advanced lipoprotein analysis is being studied to determine if this method is superior to standard testing but currently indicate inconsistent results and a lack of universal, standardized testing modalities and patient-selection criteria. Researchers note that additional large, prospective studies are needed to establish whether measurement of these emerging markers will be more predictive of CVD than conventional lipid risk factors.

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.

Zhang et al (2021) studied 823 individuals at high risk for stroke to determine the association between cardiovascular disease and Lp-PLA2. Screening took place at 3,6,12 and 24 months. Among the 823 participants, 286 had varying degrees of carotid artery stenosis and 18 had cerebrovascular events. The level of Lp-PLA2 was higher in the group with cerebrovascular events than in the group without cerebrovascular events. No statistical difference was found between the other parameters of the event group, such as HDL, LDL, and the no event group. The authors concluded that the level of Lp-PLA2 was positively correlated with the degree of carotid artery stenosis and predicted cerebrovascular events. However, the authors noted a number of study limitations such as small sample size, brief follow-up period, single center and the study was not representative of the population as it included those >40 with a high risk of stroke. Additionally, the study did not address how integrating measurements of Lp-PLA2 to clinical care alters patient management and improves clinical outcomes.

Hu et al. (2019) conducted a meta-analysis to determine whether elevated Lp-PLA2 is a risk factor for stroke. Twenty-two studies involving 157,693 participants were included for analysis. The authors concluded that elevated Lp-PLA2 levels are associated with higher stroke risk but also identified some study limitations such as the test methods for Lp-PLA2 were not uniform in the included studies, which is a potential source of bias and there was a lack of studies in individuals ≥ 65 years. Lp-PLA2 as a therapeutic target to prevent stroke requires further investigation. Furthermore, the study did not address how integrating measurements of Lp-PLA2 to clinical care alters patient management and improves clinical outcomes.

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 LpPLA2 and sPLA2-IIA for cardiovascular risk assessment and to determine the role of Lp-PLA2 as a potential adjunct to traditional risk assessment in the management of cardiovascular disease or stroke in adults.

Other studies include Sang et al. (2021) investigated the association of lipoprotein(a) with long-term poor prognosis following acute coronary syndromes (ACS) in advanced-age patients. The study included 536 patients aged ≥ 80 years hospitalized for ACS. The primary outcomes were hard CHD events (a composite of fatal or non-fatal myocardial infarction, and CHD death). The secondary outcomes included major adverse cardiovascular events (MACEs), all-cause death and cardiac death. During a median 66-month follow-up, 89 hard CHD events occurred. Kaplan-Meier curves showed higher cumulative incidence of hard CHD events, MACEs, all-cause death and cardiac death in high lipoprotein(a) group than that in low lipoprotein(a) group. The authors concluded that elevated lipoprotein(a) levels were associated with an increased risk of hard CHD events, MACEs, all-cause death and cardiac death in the advanced-age patients with ACS, which indicated that routine screening for lipoprotein(a) might aid prognosis and risk assessment. This study did not address how integrating these measurements to clinical care alters patient management and improves clinical outcomes.

Kouvari and Panagiotakos (2019a) conducted a systematic review regarding the role of Lp(a) in primary and secondary CVD prevention. Searches resulted in the selection of n = 19 studies. In the context of primary CVD prevention, n = 9 cohorts, n = 2 case-cohorts, and n = 2 retrospective studies were identified, the majority of which suggested a significant positive association between Lp(a) and CVD onset. In terms of secondary CVD prevention, n=5, cohorts and n = 1 case-cohort were considered as eligible highlighting from a positive to a neutral association between Lp(a) and CVD progression. The authors concluded that a positive association between Lp(a) and CVD seemed to be supported by a large body of evidence, yet it is comparatively moderate in magnitude and differentiates according to study population and the examined endpoints. This fact along with the lack of a definitive functional mechanism limits the potential connotation of Lp(a) in daily clinical practice.

Guidelines from the American College of Cardiology (ACC) and the American Diabetes Association (ADA) recommend the use of apoB in persons at elevated cardiometabolic risk to assess whether additional intense interventions are necessary when LDL cholesterol goals are reached (Brunzell et al, 2008). According to these guidelines, high-risk persons are those with known CVD, diabetes, or multiple CVD risk factors (i.e., smoking, hypertension, family history of premature CVD). The American Association of Clinical Chemistry has issued similar recommendations regarding the use of apoB (Contois et al, 2009). Guidelines from the American Association of Clinical Endocrinologists (2012) recommend apo B measurements to assess the success of LDL-C–lowering therapy. The guidelines note that LDL particle number as reflected by apo B is a more potent measure of cardiovascular disease (CVD) risk than LDL-C and LDL particle size (e.g., small, dense LDL).

The clinical evidence is insufficient to show an added benefit of Carotid intima-media thickness (CIMT) testing beyond traditional lipid risk assessment. 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, well-designed studies is needed to establish the role of arterial compliance in the early identification, prevention and management of CVD.

American Heart Association

High-sensitivity C-reactive protein (hsCRP) and coronary artery calcium (CAC) are the leading novel markers of cardiovascular risk and are most commonly suggested for use in a tailored treatment approach.

American College of Cardiology (ACC) and American Heart Association (AHA).

A 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease identifies the following "Risk-Enhancing Factors for Clinician–Patient Risk Discussion".

1) Lipids/biomarkers associated with increased ASCVD risk:
   a) Persistently elevated primary hypertriglyceridemia (≥ 175 mg/dL, nonfasting)
   b) If measured:
      i) Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
      ii) Elevated lipoprotein(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)
      iii) Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
      iv) Ankle-brachial index (< 0.9)

National Institute of Health Care Excellence (NICE)

NICE has guidelines on 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. However, these guidelines do not mention the laboratory testing for cardiac risks.

U.S. Preventive Services Task Force (USPSTF 2018)

- USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population. (D recommendation).
- The USPSTF also concluded that the evidence is insufficient to assess the balance of benefits and harms of using nontraditional risk factors, such as CIMT to screen asymptomatic men and women with no history of CHD to prevent CHD events.
- 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
- The USPSTF notes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events

A 2020 Consensus Statement by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) on the management of dyslipidemia and prevention of cardiovascular disease algorithm makes the following recommendation:

Measurement of Lp(a) in individuals should be considered in the following settings:

- All individuals with clinical ASCVD, especially premature or recurrent ASCVD despite LDL-C lowering
- Individuals with a family history of premature ASCVD and/or increased Lp(a)
- Individuals with South Asian or African ancestry, especially with a family history of ASCVD or increased Lp(a)
- Individuals with a 10-year ASCVD risk ≥ 10% (primary prevention setting), in order to stratify risk
- Patients with a personal or family history of aortic valve stenosis
- Patients with refractory elevations of LDL-C despite aggressive LDL-C-lowering therapy (i.e., statin resistance). (Handelsman et al., 2020)

The 2017 AACE guidelines for management of dyslipidemia and prevention of cardiovascular disease make the following recommendations:

- Carotid Intima Media Thickness: CIMT may be considered to refine risk stratification to determine the need for more aggressive atherosclerotic cardiovascular disease (ASCVD) preventive strategies (Intermediate level of evidence and recommendation grade).
- Apolipoprotein B: For individuals at increased risk of ASCVD, including those with diabetes, an optimal apolipoprotein B (apo B) goal is < 90 mg/dL, while for individuals with established ASCVD or diabetes plus 1 or more additional risk factor(s), an optimal apo B goal is < 80 mg/dL, and for individuals at extreme risk, an optimal apo B goal is < 70 mg/dL (Strong level of evidence and recommendation grade).
- Lipoprotein (a): Testing for lipoprotein(a) is not generally recommended, although it may provide useful information to assign risk in Caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.
- Lipoprotein-Associated Phospholipase A2: Measuring lipoprotein-associated phospholipase A2 (Lp-PLA2) in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of hsCRP elevations (Strong level of evidence and recommendation grade).

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2015, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
82172	Apolipoprotein, each
83695	Lipoprotein (a)
83698	Lipoprotein-associated phosolipase 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 Numbers And Lipoprotein Particle Subclasses (Eg, By Nuclear Magnetic Resonance Spectroscopy
83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
83721	LDL cholesterol
83722	Lipoprotein, direct measurement; small dense LDL cholesterol
83695	Lipoprotein (a) enzyme immunoassay
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
83880	Natriuretic peptide
84999	Unlisted chemistry procedure
86140	C-reactive protein
86141	C-reactive protein; high sensitivity (hsCRP)
93799	Unlisted cardiovascular service or procedure
93895	Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment

HCPCS Codes	Description
N/A	

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
E10.9	Type I diabetes mellitus without complication
E11.9	Type II diabetes mellitus without complication
E78.0-E78.89	Disorders of lipoprotein metabolism and other lipidemias
I24.0	Acute coronary thrombosis not resulting in MI
I24.8	Other forms of acute ischemic heart disease
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I25.110-	Atherosclerotic heart disease of native coronary artery with angina pectoris

ICD-10-CM Code	Description
I25.119	
I25.810-I25.9	Other forms of chronic ischemic heart disease
Z13.1	Encounter for screening for diabetes mellitus
Z13.220	Encounter for screening for lipoid disorders
Z13.6	Encounter for screening for cardiovascular disorders

Reviews, Revisions, and Approvals	Date	Approval Date
Policy adopted from Health Net NMP 203, Cardiac Risk Assessment Laboratory Tests	10/16	10/16
Updated references, no changes	10/17	10/17
Added secretory phospholipase A2 (sPLA2-IIA) and Carotid intima-media thickness (CIMT) to investigational section. Updated references and background information	10/18	10/18
Added Apolipoprotein B as medically necessary for high risk individuals but not for general population Removed homocysteine as there is a separate Centene Clinical Policy	10/19	10/19
Updated society and college recommendations, codes and references	10/20	10/20
Revised T code for CIMT (93895) Formatting changes	10/21	10/21
Removed gene tests and other outdated tests. Updated References and guideline section with current literature	10/22	10/22

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and

LCDs should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.