MEDICAL POLICY – 2.04.509
Cardiovascular Risk Panels

BCBSA Ref. Policy: 2.04.100
Effective Date: Aug. 1, 2019
Last Revised: July 25, 2019
Replaces: N/A

RELATED MEDICAL POLICIES:
2.02.16 Ultrasonographic Measurement of Carotid Intimal-Medial Thickness as an Assessment of Subclinical Atherosclerosis

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Studies prove that certain blood tests can help predict who is at higher risk of developing heart disease. These tests include things like total cholesterol, low-density lipoproteins (LDL) and high-density lipoproteins (HDL) cholesterol, and triglycerides. There are other types of heart-risk tests that look at many other things. These are known as cardiovascular risk panels. These panels can test genes, markers that don’t relate to the heart, metabolism, and inflammation. Medical studies do not show there is enough evidence that these types of heart-risk panels will bring better health results than already proven tests. For this reason, cardiovascular risk panels are not medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
Cardiovascular risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels*) are considered not medically necessary.

- Some examples of commercially available cardiovascular risk panels include, but are not limited to, the following (see Evidence Review for more details):
  - Applied Genetics Cardiac Panel
  - Atherotech® Diagnostics Lab CVD Risk Panel and VAP Lipid Panel
  - Boston Heart Cardiovascular Risk Markers Panels
  - CardioVIP/Spectracell Metabolic Characterization Panel
  - Cleveland HeartLab CVD Inflammatory Profile
  - Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel
  - Genova Diagnostics CV Health Plus Genomics™ Panel, Cardiovascular Health Profile
  - Health Diagnostics Cardiac Risk Panel
  - Metametrix Cardiovascular Health Profile (now part of Genova Diagnostics. Genova Diagnostics, Inc. acquired Metametrix, Inc. in 2012)
  - Singulex® cardiac-related test panels
  - True Health Diagnostics Cardiovascular Lab Panel
  - Veridia Diagnostics SMC™ cardiac function

*Lipid Panels:

- A simple lipid panel is generally composed of the following lipid measures:
  - Total cholesterol
  - Low-density lipoprotein (LDL) cholesterol
  - High-density lipoprotein (HDL) cholesterol
  - Triglycerides

- Certain calculated ratios, such as the total/HDL cholesterol may also be reported as part of a simple lipid panel.

- Other types of lipid testing (ie, apolipoproteins, lipid particle number or particle size, lipoprotein a, etc.) are not considered components of a simple lipid profile.
### Medical Necessity

**Note:** This policy does not address the use of panels of biomarkers in the diagnosis of acute myocardial infarction.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT</td>
<td>Lipoprotein-associated phospholipase A2 (Lp-PLA2)</td>
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### Related Information

N/A

### Evidence Review

#### Description

Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate the risk of developing cardiovascular disease (CVD). There are numerous commercially available risk panels that include different combinations of lipids, noncardiac biomarkers, measures of inflammation, metabolic parameters, and/or genetic markers. Risk panels report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.
Background

Cardiovascular Disease

CVD remains the single largest cause of morbidity and mortality in the developed world. As a result, accurate prediction of CVD risk is a component of medical care that has the potential to focus and direct preventive and diagnostic activities. Current methods of risk prediction in use in general clinical care are not highly accurate and, as a result, there is a potential unmet need for improved risk prediction instruments.

Risk Assessment

Components of CVD risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. Also, numerous laboratory tests have been associated with CVD risk, most prominently lipids such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These clinical and lipid factors are often combined into simple risk prediction instruments, such as the Framingham Risk Score. The Framingham Risk Score provides an estimate of the ten-year risk for developing cardiac disease and is currently used in clinical care to determine the aggressiveness of risk factor intervention, such as the decision to treat hyperlipidemia with statins.

Many additional biomarkers, genetic factors, and radiologic measures have been associated with increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD risk. Some general categories of these potential risk factors are as follows:

- **Lipid markers.** In addition to LDL and HDL, other lipid markers may have predictive ability, including the apolipoproteins, lipoprotein (a) (Lpa), lipid subfractions, and/or other measures.

- **Inflammatory markers.** Many measures of inflammation have been linked to the likelihood of CVD. High-sensitivity C-reactive protein (hs-CRP) is an example of an inflammatory marker; others include fibrinogen, interleukins, and tumor necrosis factor.

- **Metabolic syndrome biomarkers.** Measures associated with metabolic syndrome, such as specific dyslipidemic profiles or serum insulin levels, have been associated with an increased risk of CVD.

- **Genetic markers.** A number of variants associated with increased thrombosis risk, such as the MTHFR variant or the prothrombin gene variants, have been associated with increased
CVD risk. Also, numerous single-nucleotide variants have been associated with CVD in large genome-wide studies.

**Risk Panel Testing**

CVD risk panels may contain measures from one or all of the previous categories and may include other measures not previously listed such as radiologic markers (carotid medial thickness, coronary artery calcium score). Some CVD risk panels are relatively limited, including a few markers in addition to standard lipids. Others include a wide variety of potential risk factors from a number of different categories, often including both genetic and non-genetic risk factors. Other panels are composed entirely of genetic markers.

Some examples of commercially available CVD risk panels follow:

- **CV Health Plus Genomics™ Panel (Genova Diagnostics):** apolipoprotein (apo)E; prothrombin; factor V Leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; Lp (a); lipoprotein-associated phospholipase A2 (Lp-PLA2); MTHFR gene; triglycerides; very low-density lipoprotein (VLDL); VLDL size; vitamin D; hs-CRP.

- **CV Health Plus™ Panel (Genova Diagnostics):** fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; lipid panel; Lp(a); Lp-PLA2; triglycerides; VLDL; VLDL size; vitamin D; hs-CRP.

- **CVD Inflammatory Profile (Cleveland HeartLab):** hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA2, F2-isoprostanes.

- **Applied Genetics Cardiac Panel:** genetic variants associated with coronary artery disease: cytochrome p450 variants associated with metabolism of clopidogrel, ticagrelor, warfarin, β-blockers, rivaroxaban, prasugrel (2C19, 2C9/VKORC1, 2D6, 3A4/3A5), factor V Leiden, prothrombin gene, MTHFR gene, APOE gene.

- **Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel:** factor V Leiden, factor V R2, prothrombin gene, factor XIII, fibrinogen-455, plasminogen activator inhibitor-1 (PAI-1), platelet GP IIIA variant HPA-1 (PLA1/2), MTHFR gene, angiotensin-converting enzyme insertion/deletion (ACE I/D), apo B, apo E.

- **Cardiac-Related Test Panels (Singulex):** Several panels of markers related to cardiac dysfunction, vascular inflammation and dysfunction, dyslipidemia, and cardiometabolic status are offered by Singulex. Some are offered in conjunction with a CVD testing and
wellness management service. The test panels use an immunoassay method referred to as “ultra-sensitive Single Molecule Counting [SMC] technology.”

- Cardiac Dysfunction Panel: SMC™ cTnl (high-sensitivity troponin), N-terminal-pro-B-type natriuretic peptide
- Vascular Inflammation and Dysfunction Panel: SMC™ IL-6, SMC™ IL-17A, SMC™ TNFα, SMC™ Endothelin, Lp-PLA2, hs-CRP, homocysteine, vitamin B12, folate.
- Dyslipidemia panel: total cholesterol, LDL-C (direct), apo B, small dense LDL, HDL cholesterol, apo A-1, HDL2b, triglycerides, Lp(a).
- Cardiometabolic panel: parathyroid, vitamin D, calcium, magnesium, leptin, adiponectin, ferritin, cortisol, cystatin C, hemoglobin A1C, glucose, insulin, thyroid stimulating hormone (TSH), T3 and free T4, uric acid, liver panel, renal panel, thyroid peroxidase antibody, and thyroglobulin antibody.

In addition to panels that are specifically focused on CVD risk, a number of commercially available panels include markers associated with cardiovascular health, along with a range of other markers that have been associated with inflammation, thyroid disorders and other hormonal deficiencies, and other disorders. Examples of these panels include:

- **Cardiometabolic Panel (Singulex):** described above.
- **WellnessFX Premium (WellnessFX):** total cholesterol, HDL, LDL, triglycerides, apo A1, apo B, Lp(a), Lp-PLA2, omega-3 fatty acids, free fatty acids, lipid particle numbers, lipid particle sizes, blood urea nitrogen(BUN)/creatinine, aspartate aminotransferase (AST) and alanine aminotransferase(ALT), total bilirubin, albumin, total protein, dehydroepiandrosterone (DHEA), free testosterone, total testosterone, estradiol, sex hormone binding globulin, cortisol, insulin-like growth factor (ILGF)-1, insulin, glucose, hemoglobin A1c, total T4, T3 uptake, free T4 index, thyroid-stimulating hormone(TSH), total T3, free T3, reverse T3, free T4, hs-CRP, fibrinogen, homocysteine, complete blood count (CBC) with differential, calcium, electrolytes, bicarbonate, ferritin, total iron binding capacity(TIBC), vitamin B12, red blood cell (RBC) magnesium, 25-hydroxy vitamin D, progesterone, follicle stimulating hormone (FSH), luteinizing hormone.(LH)

**Summary of Evidence**

For individuals who have risk factors for CVD who receive CVD risk panels, the evidence includes multiple cohort and case-control studies and systematic reviews of these studies. Relevant
outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with increased risk of CVD. However, it is not clear how the results of individual risk factors or panels impact management changes, so it is also uncertain how the panels will impact management decisions. Given the lack of evidence for clinical utility of any individual risk factor beyond simple lipid measures, it is unlikely that the use of CVD risk panels improves outcomes Studies that have evaluated the clinical validity of panels of multiple markers have not assessed management changes that would occur as a result of testing or demonstrated improvements in outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT03599531</td>
<td>A Pilot Study to Evaluate the Utility of the SomaLogic CVD Secondary Risk Panel as a Tool to Stratify Cardiovascular Risk</td>
<td>200</td>
<td>Dec 2018</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<tr>
<td>NCT00969865a</td>
<td>Individualized Comprehensive Atherosclerosis Risk-reduction Evaluation Program (iCARE)</td>
<td>170</td>
<td>Dec 2016 (completed)</td>
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<tr>
<td>NCT01685840</td>
<td>Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure</td>
<td>894</td>
<td>Sep 2016 (terminated)</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

American College of Cardiology and American Heart Association

The American College of Cardiology and the American Heart Association (2013) issued joint guidelines for the assessment of cardiovascular disease risk.26 These guidelines recommended that age- and sex-specific pooled cohort equations, which included total cholesterol and high-density lipoprotein to predict the ten-year risk of a first hard atherosclerotic cardiovascular disease event, be used in non-Hispanic blacks and non-Hispanic whites between 40 and 79 years of age (American Heart Association/American College of Cardiology class of recommendation I, American Heart Association/American College of Cardiology level of evidence B). Regarding newer risk markers after quantitative risk assessment, the guidelines stated the following: "If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of ≥1 of the following—family history, hs-CRP [high-sensitivity C-reactive protein], CAC [coronary artery calcium] score, or ABI [ankle-brachial index]—may be considered to inform treatment decision-making" (class of recommendation IIb; level of evidence B). The guidelines did not recommend other novel cardiac risk factors or panels of cardiac risk factors.

U.S. Preventive Services Task Force Recommendations

No recommendations specific to the use of cardiovascular risk panels were identified. The U.S. Preventive Services Task Force (2018) updated its recommendation on the use of nontraditional risk factors in coronary heart disease risk assessment:

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-brachial 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.27

Medicare National Coverage

There is no national coverage determination.
Regulatory Status

Multiple assay methods for cardiac risk marker components, such as lipid panels and other biochemical assays, have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process.

Other components of testing panels are laboratory-developed tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/11/13</td>
<td>New policy. Policy created with literature review through July 31, 2013. Cardiovascular risk panels consisting of multiple individual markers intended to assess cardiac risk are considered not medically necessary.</td>
</tr>
<tr>
<td>05/12/014</td>
<td>Clarification. Additional cardiovascular risk panels added to the list of panel examples: Berkeley Heart Lab Cardio IQ™ Lipid Panel and Atherotech® Diagnostics Lab CVD Risk Panel and VAP Lipid Panel. Add Related Policy 12.04.509.</td>
</tr>
<tr>
<td>09/03/14</td>
<td>Coding update. CPT code 83698 added to the policy; this code was previously included on 2.04.32 Measurement of Lp-PLA in the Assessment of CV risk that was archived.</td>
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<td>05/12/15</td>
<td>Interim Review. CardioVIP added to list of CV risk panels in Policy Guidelines.</td>
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<td>10/19/15</td>
<td>Update Related Policies. Remove 12.04.509 as it was archived.</td>
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<td>01/12/16</td>
<td>Annual review. No change to policy statement. Added references 5, 6, and 8.15.</td>
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<td>06/01/16</td>
<td>Interim Review, approved May 10, 2016. Added references 21, 22. Added information on KIF6 and 9p21 genotyping to rationale. No change to policy statements.</td>
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<td>01/01/17</td>
<td>Interim Review, approved December 13, 2016. True Health Cardiovascular Lab Panel added to list of CV risk panels. Added reference 23. No change to policy statement.</td>
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<tr>
<td>04/11/17</td>
<td>Policy moved into new format; no change to policy statements. Evidence Review section reformatted.</td>
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<tr>
<td>12/01/17</td>
<td>Annual Review, approved November 9, 2017. Added references 24 and 26. No change to policy statement.</td>
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<tr>
<td>01/04/19</td>
<td>Coding update, CPT Codes 81200, 81479, and 81599 removed. Removed 12.04.72 from related policies.</td>
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<tr>
<td>02/01/19</td>
<td>Annual Review, approved January 22, 2019. Policy updated with literature review through October 2018; references 11-12 and 27 added; references 5-6 updated. Policy statement unchanged. Removed CPT 84999.</td>
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<tr>
<td>08/01/19</td>
<td>Interim Review, approved July 25, 2019. Removed Quest Diagnostics™ Lipid Panel/ASCVD (Atherosclerotic Cardiovascular Disease) Risk Panel (CardioIQ®) from list of examples of cardiovascular risk panels.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
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