MEDICAL POLICY – 2.04.509
Cardiovascular Risk Panels

BCBSA Ref. Policy: 2.04.100
Effective Date: Feb. 1, 2018
Last Revised: Jan. 30, 2018
Replaces: N/A

RELATED MEDICAL POLICIES:
2.02.16 Ultrasonographic Measurement of Carotid Intimal-Medial Thickness as an Assessment of Subclinical Atherosclerosis
12.04.72 Gene Expression Testing to Predict Coronary Artery Disease

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, LDL and 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

<table>
<thead>
<tr>
<th>Panel</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular risk panels</td>
<td>Cardiovascular risk panels, consisting of multiple individual</td>
</tr>
</tbody>
</table>
**bkomarkers 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)
  - Quest Diagnostics™ Lipid Panel/ASCVD (Atherosclerotic Cardiovascular Disease) Risk Panel (Cardio IQ®)
  - 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, i.e., apolipoproteins, lipid particle number or particle size, lipoprotein (a), etc., are not considered components of a simple lipid profile.
Panel 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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</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>83698</td>
<td>Lipoprotein-associated phospholipase A2 (Lp-PLA2)</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

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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 individual results of multiple tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

Background

**Cardiovascular Disease**

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 that are used 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 (FRS). The Framingham Risk Score provides an estimate of the 10-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) (Lp[a]), 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 above 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:

• **Cardiac Risk Panel (Health Diagnostics):** MTHFR gene analysis, common variants; vitamin D, 1,25 dihydroxy; B-type natriuretic peptide; lipoprotein-associated phospholipase A2 (Lp-PLA2); myeloperoxidase; apolipoprotein (apo); immune complex assay; lipoprotein, blood; electrophoretic separation and quantitation; very long chain fatty acids; total cholesterol; HDL; LDL; triglycerides; hs-CRP; Lp(a); insulin, total; fibrinogen; multiple SNVs associated with coronary artery disease.

• **CV Health Plus Genomics™ Panel (Genova Diagnostics):** apo E; prothrombin; factor V Leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; Lp (a); 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 CAD: cytochrome p450 mutations 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 variantHPA-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.”

  o Cardiac Dysfunction Panel: SMC™ cTnl (high-sensitivity troponin), N-terminal-pro-B-type natriuretic peptide

  o Vascular Inflammation and Dysfunction Panel: SMC™ IL-6, SMC™ IL-17A, SMC™ TNFα, SMC™ Endothelin, Lp-PLA2, hs-CRP, homocysteine, vitamin B12, folate.

  o Dyslipidemia panel: total cholesterol, LDL-C (direct), apo B, small dense LDL, HDL cholesterol, apo A-1, HDL2b, triglycerides, Lp(a).

  o 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, ApoA1, ApoB, 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)/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)6

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 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 outcome. 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. As a result, the use of cardiac risk panels for predicting risk of CVD disease is considered not medically necessary.

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>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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<td>NCT No.</td>
<td>Trial Name</td>
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<td>Completion Date</td>
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<tr>
<td>NCT00969865*</td>
<td>Individualized Comprehensive Atherosclerosis Risk-reduction Evaluation Program (iCARE)</td>
<td>170</td>
<td>Dec 2016 (completed)</td>
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</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

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

In 2013, the ACC and the AHA issued joint guidelines for the assessment of cardiovascular disease risk in non-Hispanic blacks and non-Hispanic whites between 40 and 79 years of age. These guidelines recommend that age- and sex-specific pooled cohort equations, including total cholesterol and high-density lipoprotein, be used to predict the 10-year risk of a first atherosclerotic cardiovascular disease event in these groups (AHA/ACC class of recommendation: I; AHA/ACC 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 do 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. In 2009, U.S. Preventive Services Task Force (USPSTF) made the following recommendation about using nontraditional risk factors in coronary heart disease risk assessment:

The USPSTF concludes that the evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors studies to screen asymptomatic men and women with no history of CHD to prevent CHD events. Grade: I

The nontraditional risk factors included in this recommendation are high-sensitivity C-reactive protein (hs-CRP), ankle-brachial index (ABI), leukocyte count, fasting blood glucose
level, periodontal disease, carotid intima-media thickness (carotid IMT), coronary artery calcification (CAC) score on electron beam computed tomography (EBCT), homocysteine level, and lipoprotein (a) level.

This USPSTF recommendation is currently being updated.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests (LDTs) must be licensed by CLIA 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**


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<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>05/12/14</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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<tr>
<td>05/12/15</td>
<td>Interim Review. CardioVIP added to list of CV risk panels in Policy Guidelines.</td>
</tr>
<tr>
<td>10/19/15</td>
<td>Update Related Policies. Remove 12.04.509 as it was archived.</td>
</tr>
<tr>
<td>01/12/16</td>
<td>Annual review. No change to policy statement. Added references 5, 6, and 8-15.</td>
</tr>
<tr>
<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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<tr>
<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>
</tr>
<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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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S9FF, HHH Building
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