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MEDICAL POLICY – 2.04.509

Cardiovascular Risk Panels

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Effective Date:	May 1, 2024	RELATED MEDICAL POLICIES:
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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

Panel	Medical Necessity

Cardiovascular risk panels	**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
	  ○ Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel
	  ○ CV Health Plus Genomics Panel (Genova Diagnostics)
	  ○ CV Health Plus Panel (Genova Diagnostics)
	  ○ CVD Inflammatory Profile (Cleveland Heart Lab),
	  ○ Cardio Check Profile (Genova Diagnostics)
	  ○ Quest Diagnostics Cardio IQ (advanced lipid panel)
	  ○ Quest Diagnostics/Cleveland HeartLab it inflammation testing (inflammatory biomarkers)
	  ○ Singulex SMC Cardiac function and Inflammation testing
	  ○ 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

Note: There is no specific CPT code for cardiovascular risk panels. Some of the components of the testing may be reported with the codes below.

Code	Description
CPT	
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
82465	Cholesterol, serum or whole blood, total
82652	Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed
83090	Homocysteine
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
83721	Lipoprotein, direct measurement; LDL cholesterol
83722	Lipoprotein, direct measurement; small dense LDL cholesterol
83880	Natriuretic peptide
84478	Triglycerides
86141	C-reactive protein; high sensitivity (hsCRP)
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
0119U	Cardiology, ceramides by liquid chromatography–tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events

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. Mortality from CVD has accounted for 1 in 4 deaths in the United States, and there are numerous socio-economic factors that affect CVD mortality rates.[1] Lower-income, race, age, and behavioral factors all have a significant impact on health outcome disparities associated with CVD.

As a result, accurate prediction of CVD risk is a component of medical care that has the potential to focus on 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.[2] 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 an increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD risk.[3-5] 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 5,10-methylene tetrahydrofolate reductase (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 are as follows:

- **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 the 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.

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. An example of these panels is:

- **Advanced Health Panel (Thorne):** total cholesterol, HDL, LDL, triglycerides, HDL ratios, non-HDL cholesterol, LDL particle number, small LDL, medium LDL, LDL pattern, LDL peak size, large HDL, apo A1, apo B, Lp(a), cortisol, hs-CRP, homocysteine, glucose, hemoglobin A1c, insulin, homeostatic model assessment for insulin resistance, free T4, free T3, thyroid-stimulating hormone, reverse T3, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin, total testosterone, free testosterone, albumin, globulin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, total bilirubin,

total serum protein, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine ratio, estimated glomerular filtration rate form creatinine, estimated glomerular filtration rate from cystatin C, cystatin C, fibrinogen, platelet count, white cell count, absolute neutrophils, lymphocytes, absolute lymphocytes, monocytes, absolute monocytes, eosinophils, absolute eosinophils, basophils, absolute basophils, red blood cell count, hemoglobin, hematocrit, mean platelet volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, folate, vitamin B12, vitamin D, red blood cell magnesium, calcium, carbon dioxide, chloride, potassium, sodium, ferritin, iron total iron binding capacity, omega-3 index, omega-6 to omega-3 ratio, arachidonic acid, eicosapentaenoic acid, eicosapentaenoic acid/arachidonic acid ratio, docosahexaenoic acid, free fatty acids.[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. The relevant outcomes are test 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 an increased risk of CVD. However, it is not clear how the results of individual risk factors impact management changes, so it is also uncertain how the panels will impact management decisions. Given the lack of evidence for the 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 that the technology results in an improvement in the net health outcome.

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT03599531	A Pilot Study to Evaluate the Utility of the SomaLogic CVD Secondary Risk Panel as a Tool to Stratify Cardiovascular Risk	244	Oct 2020

NCT: national clinical trial.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology / American Heart Association

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued joint guidelines for the assessment of CVD risk.[33] 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 (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 did not recommend other novel cardiac risk factors or panels of cardiac risk factors.

In 2019, the ACC/AHA issued a special report on the use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic CVD.[34] Although the report did not recommend specific novel cardiac risk factors or panels of cardiac risk factors, it discusses features of current US-based CV risk assessment tools including the Reynolds Risk Score, which includes hs-CRP level as one of its variables, mentions risk-enhancing factors for a clinician-patient risk discussion including elevated hs-CRP, lipoprotein(a), and apolipoprotein B levels, and the use of CAC measurement to reclassify CVD risk.

European Society of Cardiology/European Atherosclerosis Society

In 2019, the European Society of Cardiology and European Atherosclerosis Society published a guideline for the management of dyslipidaemias: lipid modification to reduce CV risk.[35] This guideline contains updated recommendations for lipid analyses for CV disease risk estimation. Beyond traditional lipid markers (i.e., total cholesterol, HDL, LDL, and triglycerides), the guideline recommends non-HDL-C "for risk assessment, particularly in people with high triglyceride levels, diabetes mellitus, obesity, or very low LDL-C levels" [Class I recommendation: Level C evidence (consensus of opinion of the experts and/or small studies, retrospective studies, registries)]. Apolipoprotein B is recommended "for risk assessment, particularly in people with high triglyceride levels, diabetes mellitus, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high triglyceride levels, diabetes mellitus, obesity, or very low LDL-C levels" [Class I recommendation: Level C evidence]. Additionally, the guideline states that lipoprotein(a) measurement "should be considered at least once in each adult person's lifetime to identify those with very high inherited lipoprotein(a) levels > 180 mg/dL who may have a lifetime risk of atherosclerotic CVD equivalent to the risk associated with heterozygous familial hypercholesterolemia" and "should be considered in selected individuals with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk" [Class IIa recommendation; Level C evidence].

In 2021, the European Society of Cardiology published a guideline on CVD prevention, however, the guideline did not recommend specific novel cardiac risk factors or panels of cardiac risk factors for the assessment of CVD risk.[36] The guideline states that "main causal and modifiable ASCVD [atherosclerotic cardiovascular disease] risk factors are blood apolipoprotein-B-containing lipoproteins, high BP [blood pressure], cigarette smoking, and DM [diabetes mellitus]". The guideline also states that the ankle brachial index (ABI) may be considered as a risk modifier in CVD risk assessment but the "routine collection of other potential modifiers,

such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended."

US Preventive Services Task Force Recommendations

No recommendations specific to the use of cardiovascular disease risk panels were identified. In 2018, the US Preventive Services Task Force updated its recommendation on the use of nontraditional risk factors in CVD risk assessment:

> The USPSTF concludes that there are insufficient adequately powered clinical trials evaluating the incremental effect of the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score in risk assessment and initiation of preventive therapy. Furthermore, the clinical meaning of improvements in measures of calibration, discrimination, and reclassification risk prediction studies is uncertain."[37]

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 US 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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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History

Date	Comments
03/01/20	New policy, approved February 4, 2020. This policy replaces 2.04.509 (originally effective November 2013) which is now deleted effective March 1, 2020. Policy created with literature review through October 2019. Policy statement unchanged from previous policy.
03/01/21	Annual Review, approved February 2, 2021.Policy updated with literature review through October 19, 2020; references added. Policy statement unchanged.
03/01/22	Annual Review, approved February 7, 2022. Policy updated with literature review through November 10, 2021; references added. Policy statement unchanged.
02/01/23	Annual Review, approved January 23, 2023. Policy updated with literature review through October 25, 2022; references added; DEI refinements added. Policy statement unchanged. Added examples to list of cardiovascular risk panels considered not medically necessary: Quest Diagnostics Cardio IQ, Quest Diagnostics/Cleveland HeartLab it inflammation testing, Singulex SMC cardiac function and inflammation testing.
05/01/24	Policy renumbered from 2.04.100 to 2.04.509 Cardiovascular Risk Panels, approved April 9, 2024. Policy updated with literature review through October 16, 2023; references added. Policy statement unchanged. Codes from policy 2.04.65 moved to this policy to match BCBSA coding list.
08/02/24	Minor update made to Related Policies section. Removed archived policy 2.02.16 Ultrasonographic Measurement of Carotid Intimal-Medial Thickness as an Assessment of Subclinical Atherosclerosis.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.