MASSACHUSETTS

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Medical Policy

Cardiovascular Risk Panels

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Policy Number: 664

BCBSA Reference Number: 2.04.100
NCD/LCD: N/A

Related Policies

- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease, #016
- Measurement of Lipoprotein-Associated Phospholipase A2 - Lp-PLA2- in the Assessment of Cardiovascular Risk, #558
- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease, #283
- Ultrasonographic Measurement of Carotid Intima-Medial Thickness as an Assessment of Subclinical Atherosclerosis, #547

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk, are **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.
Medicare HMO Blue℠	This is **not** a covered service.
Medicare PPO Blue℠	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

No specific CPT codes

Description

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.[1] 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.[2,3,4] 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 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 nongenetic 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 A_2 (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, F_2isoprostanes.

- **Applied Genetics Cardiac Panel:** genetic variants associated with coronary artery disease: cytochrome p450 variants associated with metabolism of clopidogrel, ticagrelor, warfarin, b-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.”[5]

    - Cardiac Dysfunction panel: SMC™ cTnI (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 B_{12}, folate

    - Dyslipidemia panel: total cholesterol, LDL-C (direct), apo B, small dense LDL, HDL cholesterol, apo AI, HDL_{2b}, triglycerides, Lp(a).

    - Cardiometabolic panel: parathyroid, vitamin D, calcium, magnesium, leptin, adiponectin, ferritin, cortisol, cystatin C, hemoglobin A_{1c}, glucose, insulin, thyroid-stimulating hormone, T3 and free T4, uric acid, liver panel, renal panel, thyroid peroxidase antibody, 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 AI, apo B, Lp(a), Lp-PLA2, omega-3 fatty acids, free fatty acids, lipid particle numbers, lipid particle sizes, blood urea nitrogen/creatinine, aspartate aminotransferase and alanine aminotransferase, total bilirubin, albumin, total protein, dehydroepiandrosterone, free testosterone, total testosterone, estradiol, sex hormone binding globulin, cortisol, insulin-like growth factor 1, insulin, glucose, hemoglobin A_{1c}, total T4, T3 uptake, free T4 index, thyroid-stimulating hormone, total T3, free T3, reverse T3, free T4, hs-CRP, fibrinogen, homocysteine, complete blood count with differential, calcium, electrolytes, bicarbonate, ferritin, total iron binding capacity, vitamin B_{12}, red blood cell magnesium, 25-hydroxy vitamin D, progesterone, follicle-stimulating hormone, luteinizing hormone.[6]

Summary

Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate the risk of 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.

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 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 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.

Policy History

Date	Action
2/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
3/2018	New references added from BCBSA National medical policy.
1/2016	New references added from BCBSA National medical policy.
12/2014	New References added from BCBSA National medical policy.
4/2014	New medical policy describing investigational indications. Effective 4/1/2014.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

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