MEDICAL POLICY

POLICY TITLE	LAB TESTS FOR CARDIAC RISK MANAGEMENT
POLICY NUMBER	MP-2.204

Original Issue Date (Created):	**7/1/2002**
Most Recent Review Date (Revised):	**10/17/2018**
Effective Date:	**2/1/2019**

I. POLICY

Cardiovascular risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels, see Policy Guidelines), are considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these tests.

Policy Guidelines

A simple lipid panel is generally composed of the following lipid measures:

- Total cholesterol
- LDL cholesterol
- 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 to be components of a simple lipid profile.

Cross-references:

MP-2.311 - Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm

MP-2.313 - Gene Expression Testing in Patients with Stable Ischemic Heart Disease

II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO - Refer to FEP Medical Policy Manual MP-2.04.65, Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease and MP 2.04.32, Measurement of A2 (lp-PLA2) in the Assessment of Cardiovascular Risk. The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate risk of cardiovascular (CV) disease. 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 one score.

Cardiovascular Disease

Cardiovascular disease remains the single largest cause of morbidity and mortality in the developed world. As a result, accurate prediction of cardiovascular 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 cardiovascular risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. In addition, numerous laboratory tests have been associated with cardiovascular (CV) 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 sore (FRS).[1] 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 CV disease. Over 100 emerging risk factors have been proposed as useful for refining estimates of cardiovascular risk.[2-4] 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 CV disease. High-sensitivity C-reactive protein (hs-CRP) is one 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 CV disease.
- **Genetic markers.** A number of mutations associated with increased thrombosis risk, such as the *MTHFR* mutation or the prothrombin gene mutations, have been associated with increased CV risk. In addition, numerous single nucleotide polymorphisms (SNPs) have been associated with CV disease in large genome-wide studies.

Risk Panel Testing

CV risk panels may contain measures from one or all of the above categories, and may include additional measures not listed above such as radiologic markers (carotid CMT, calcium score). Some cardiovascular 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 CV risk panels are as follows:

- **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 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."5
    - 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 AI, HDL2b, triglycerides, Lp(a).
    - Cardiometabolic panel: parathyroid, vitamin D, calcium, magnesium, leptin, adiponectin, ferritin, cortisol, cystatin C, hemoglobin A1c, 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 CV risk, a number of commercially available panels include markers associated with CV 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 (San Francisco, CA) Premium[6]:** total cholesterol, HDL, LDL, triglycerides, Apo AI, Apo B, LP(a), Lp-PLA_2, 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 A1c, total T4, T3 uptake, free T4 index, TSH, 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.

Regulatory Status

Multiple assay methods for cardiac risk marker components, such as lipid panels and other biochemical assays, have been cleared for marketing through 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 Act (CLIA). Laboratories that offer 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.

IV. RATIONALE

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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 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.

V. DEFINITIONS

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APOLIPOPROTEIN refers to proteins imbedded in the outer shell of lipoproteins.

ARTERIOSCLEROSIS is a disease of the arterial vessels marked by thickening, hardening, and loss of elasticity in the arterial walls.

ATHEROGENIC refers to the development of arteriosclerosis.

ATHEROSCLEROSIS is the most common form of arteriosclerosis marked by cholesterol-lipid-calcium deposits in the walls of the arteries.

HYPERLIPOPROTEINEMIA refers to any of a large group of inherited and acquired disorders of lipoprotein metabolism characterized by greater than normal amounts of certain protein-bound lipids and other fatty substances in the blood.

LOW DENSITY LIPOPROTEIN (LDL) refers to plasma lipids that carry the majority of the cholesterol in plasma. Bound to albumin, LDLs are a proven cause of atherosclerosis.

LIPOPROTEIN refers to conjugated chemicals in the bloodstream consisting of simple proteins bound to fat. Cholesterol, phospholipids, and triglycerides are all fatty components of lipoproteins.

SERUM is the thin, watery portion of the blood.

THROMBOTIC refers to that which is related to, caused by, or of the nature of a thrombus.

THROMBUS is a blood clot that occurs in a blood vessel or a cavity of the heart

TRIGLYCERIDE refers to a compound, which makes up most animal and vegetable fats and are the principal lipids in the blood, where they circulate, bound to protein, forming high and low-density lipoproteins**.**

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

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Cardiovascular risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels), are considered **investigational;** therefore, not covered:

CPT Codes®								
81291	81400	81401	81479	81599	83876	84999	0024U	0052U

Note: *Refer to Avalon Healthcare Solutions for all other tests used as an adjunct to LDL Cholesterol in risk assessment and management of cardiovascular disease.*

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.204	**CAC 6/28/05**
	CAC 6/27/06
	CAC 7/25/06
	CAC 9/25/07
	CAC 7/29/08
	CAC 7/28/09 Consensus Review
	CAC 11/30/10 Consensus review. Reference update.
	CAC 11/22/11 Consensus Review
	CAC 4/24/12 Consensus review; no changes, references updated.
	CAC 1/29/13 Medicare variation revised to refer to the new Novitas Solutions Local Coverage Determination (LCD) L32559 Lipid Profile/Cholesterol Testing for additional coverage indications related to lipid profile testing. Previously, the variation referred to NCD 190.23 Lipid Testing. References updated; no changes to the policy statements. Codes reviewed 11/26/12
	4/08/13- Admin code review
	CAC 11/26/13 Consensus. No change to the policy statements. Rationale section added for Medicare is silent project for code 82172 found on LCD L32559.
	1/1/14 Admin. Review. No change to policy statements. Rationale section added for Medicare is silent project for code 82172 found on L32559.
	CAC 1/28/14 Minor. B-type natriuretic protein, cystatin C, fibrinogen and leptin added to policy statement as investigational. Policy statement added indicating the use of panels that include lipid and non-lipid biomarkers would be considered not medically necessary.
	5/14 Administrative posting. Medicare variation removed as Novitas Local Coverage Determination (LCD) L32559 Lipid Profile/Cholesterol Testing was retired May 2014.
	CAC 1/27/15 Minor. Changed statement indicating "the use of panels that include lipid and non-lipid cardiovascular risk markers is considered not medically necessary".to "cardiovascular risk panels consisting of multiple individual markers intended to assess cardiac risk is investigational. References and rationale updated. Added Medicare variation to reference NCD 190.23 Lipid Testing. Coding reviewed.
	11/2/15 Administrative change. LCD number changed from L31686 to L35094 due to Novitas update to ICD-10.

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	1/26/16 Consensus review. No change to policy statements. References and rationale updated. Coding reviewed.
	Admin update 1/1/17: Product variation section reformatted. Added reference to LCD L34856 to Medicare variation to address 86141
	Admin Update 1/1/18: New code 0024U added; effective 1/1/18. Medicare variations removed from Commercial Policies
	11/28/17 Consensus review. Policy statements unchanged. Appendix added. Description/Background, Rationale and Reference sections updated. Coding reviewed.
	Admin Update 7/1/18: New Code 0052U added; effective 7/1/18**.**
	10/17/18 Consensus review. No change to policy statements. References updated. Rationale condensed. Admin revision to remove general labs, please refer to new Laboratory Service policies for coverage criteria effective 2/1/19.

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