BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.100 Cardiovascular Risk Panels

Effective Policy Date: April 1, 2023

Original Policy Date: March 2015

Related Policies:

None

Cardiovascular Risk Panels

Description

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.

Cardiovascular disease risk panels may contain measures from 1 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 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, F_2 isoprostanes.
- **Applied Genetics Cardiac Panel:** genetic variants associated with coronary artery disease: cytochrome p450 variants associated with the 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, platelet glycoprotein (GP) IIIA variant human platelet antigen (HPA)-1 (PLA1/2), *MTHFR* gene, angiotensin-converting enzyme insertion/deletion, 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:

- **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 A1c, 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 B12, red blood cell magnesium, 25-hydroxy vitamin D, progesterone, follicle-stimulating hormone, luteinizing hormone.[6,]

OBJECTIVE

The objective of this evidence review is to determine whether the use of cardiovascular risk panels improves the net health outcome in individuals who have risk factors for cardiovascular disease.

POLICY STATEMENT

Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels, see Policy Guidelines section), are considered **investigational**.

POLICY GUIDELINES

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

- Total cholesterol
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol
- Triglycerides

Certain calculated ratios (eg total/high-density lipoprotein 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]) are not considered components of a simple lipid profile.

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have risk factors for cardiovascular disease (CVD) who receive CVD risk panels, the evidence includes multiple cohorts and case-control studies and systematic reviews of these studies. 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' 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 and the American Heart Association issued joint guidelines for the assessment of cardiovascular disease (CVD) risk.[30,]These guidelines recommended that age- and sex-specific pooled cohort equations, which included total cholesterol and high-density lipoprotein to predict the 10-year risk of a first hard atherosclerotic CVD 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.

In 2019, the American College of Cardiology/American Heart Association issued a special report on the use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic CVD.[31,] Although the report did not recommend specific novel cardiac risk factors or panels of cardiac risk factors, it discusses features of current US-based cardiovascular (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.[32,] This guideline contains updated recommendations for lipid analyses for CV disease risk estimation. Beyond traditional lipid markers (ie, total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [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 patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk" [Class I!a 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.[33,] 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 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."

U.S. Preventive Services Task Force Recommendations

No recommendations specific to the use of CVD risk panels were identified. In 2018, the U.S. 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 (hs-CRP) 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."[34,]

Medicare National Coverage

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

REFERENCES

1. Niakouei A, Tehrani M, Fulton L. Health Disparities and Cardiovascular Disease. Healthcare (Basel). Mar 22 2020; 8(1). PMID 32235705
2. D'Agostino RB, Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. Jul 11 2001; 286(2): 180-7. PMID 11448281
3. Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. Oct 06 2009; 151(7): 496-507. PMID 19805772
4. Brotman DJ, Walker E, Lauer MS, et al. In search of fewer independent risk factors. Arch Intern Med. Jan 24 2005; 165(2): 138-45. PMID 15668358
5. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Dec 14 2010; 56(25): e50-103. PMID 21144964
6. WellnessFX. Premium: The Deluxe Deep Dive. n.d.; https://www.wellnessfx.com/premium. Accessed October 25, 2022.
7. Antonopoulos AS, Angelopoulos A, Papanikolaou P, et al. Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication: A Meta-Analysis. JACC Cardiovasc Imaging. Mar 2022; 15(3): 460-471. PMID 34801448
8. van Holten TC, Waanders LF, de Groot PG, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. PLoS One. 2013; 8(4): e62080. PMID 23630624
9. Gottlieb SS, Harris K, Todd J, et al. Prognostic significance of active and modified forms of endothelin 1 in patients with heart failure with reduced ejection fraction. Clin Biochem. Mar 2015; 48(4-5): 292-6. PMID 25541019
10. Patterson CC, Blankenberg S, Ben-Shlomo Y, et al. Which biomarkers are predictive specifically for cardiovascular or for non-cardiovascular mortality in men? Evidence from the Caerphilly Prospective Study (CaPS). Int J Cardiol. Dec 15 2015; 201: 113-8. PMID 26298350
11. Malachias MVB, Jhund PS, Claggett BL, et al. NT-proBNP by Itself Predicts Death and Cardiovascular Events in High-Risk Patients With Type 2 Diabetes Mellitus. J Am Heart Assoc. Oct 20 2020; 9(19): e017462. PMID 32964800
12. Schoe A, Schippers EF, Ebmeyer S, et al. Predicting mortality and morbidity after elective cardiac surgery using vasoactive and inflammatory biomarkers with and without the EuroSCORE model. Chest. Nov 2014; 146(5): 1310-1318. PMID 24992322
13. Wallentin L, Eriksson N, Olszowka M, et al. Plasma proteins associated with cardiovascular death in patients with chronic coronary heart disease: A retrospective study. PLoS Med. Jan 2021; 18(1): e1003513. PMID 33439866
14. Wuopio J, Hilden J, Bring C, et al. Cathepsin B and S as markers for cardiovascular risk and all-cause mortality in patients with stable coronary heart disease during 10 years: a CLARICOR trial sub-study. Atherosclerosis. Nov 2018; 278: 97-102. PMID 30261474
15. Winkel P, Jakobsen JC, Hilden J, et al. Prognostic value of 12 novel cardiological biomarkers in stable coronary artery disease. A 10-year follow-up of the placebo group of the Copenhagen CLARICOR trial. BMJ Open. Aug 20 2020; 10(8): e033720. PMID 32819979
16. Welsh P, Kou L, Yu C, et al. Prognostic importance of emerging cardiac, inflammatory, and renal biomarkers in chronic heart failure patients with reduced ejection fraction and anaemia: RED-HF study. Eur J Heart Fail. Feb 2018; 20(2): 268-277. PMID 28960777
17. Harari G, Green MS, Magid A, et al. Usefulness of Non-High-Density Lipoprotein Cholesterol as a Predictor of Cardiovascular Disease Mortality in Men in 22-Year Follow-Up. Am J Cardiol. Apr 15 2017; 119(8): 1193-1198. PMID 28267961
18. Kunutsor SK, Bakker SJ, James RW, et al. Serum paraoxonase-1 activity and risk of incident cardiovascular disease: The PREVEND study and meta-analysis of prospective population studies. Atherosclerosis. Feb 2016; 245: 143-54. PMID 26724525
19. Di Angelantonio E, Gao P, Pennells L, et al. Lipid-related markers and cardiovascular disease prediction. JAMA. Jun 20 2012; 307(23): 2499-506. PMID 22797450
20. Keller T, Boeckel JN, Gross S, et al. Improved risk stratification in prevention by use of a panel of selected circulating microRNAs. Sci Rep. Jul 03 2017; 7(1): 4511. PMID 28674420
21. de Lemos JA, Ayers CR, Levine BD, et al. Multimodality Strategy for Cardiovascular Risk Assessment: Performance in 2 Population-Based Cohorts. Circulation. May 30 2017; 135(22): 2119-2132. PMID 28360032
22. Greisenegger S, Segal HC, Burgess AI, et al. Biomarkers and mortality after transient ischemic attack and minor ischemic stroke: population-based study. Stroke. Mar 2015; 46(3): 659-66. PMID 25649803
23. Cho S, Lee SH, Park S, et al. The additive value of multiple biomarkers in prediction of premature coronary artery disease. Acta Cardiol. Apr 2015; 70(2): 205-10. PMID 26148381
24. Wilsgaard T, Mathiesen EB, Patwardhan A, et al. Clinically significant novel biomarkers for prediction of first ever myocardial infarction: the Tromso Study. Circ Cardiovasc Genet. Apr 2015; 8(2): 363-71. PMID 25613532
25. Guarrera S, Fiorito G, Onland-Moret NC, et al. Gene-specific DNA methylation profiles and LINE-1 hypomethylation are associated with myocardial infarction risk. Clin Epigenetics. 2015; 7: 133. PMID 26705428
26. Lara J, Cooper R, Nissan J, et al. A proposed panel of biomarkers of healthy ageing. BMC Med. Sep 15 2015; 13: 222. PMID 26373927
27. Paynter NP, Chasman DI, Pare G, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. Feb 17 2010; 303(7): 631-7. PMID 20159871
28. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. Feb 14 2007; 297(6): 611-9. PMID 17299196
29. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med. May 15 2008; 358(20): 2107-16. PMID 18480203

30. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. Jun 24 2014; 129(25 Suppl 2): S49-73. PMID 24222018
31. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report From the American Heart Association and American College of Cardiology. Circulation. Jun 18 2019; 139(25): e1162-e1177. PMID 30586766
32. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. Jan 01 2020; 41(1): 111-188. PMID 31504418
33. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. Sep 07 2021; 42(34): 3227-3337. PMID 34458905
34. U.S. Preventive Services Task Force. Cardiovascular disease: risk assessment with nontraditional risk factors. 2018; https://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-summary--html/cardiovascular-disease-screening-using-nontraditional-risk-assessment. Accessed October 25, 2022.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2015	New policy	Cardiovascular risk panels consisting of multiple individual markers intended to assess cardiac risk are considered investigational.
March 2018	Replace policy	Policy updated with literature review through October 26, 2017; references 11-12, 16, 18-19, and 25 added; references 24 updated. Policy statement unchanged.
March 2019	Replace policy	Policy updated with literature review through October 18, 2018; references 11-12 and 27 added; references 5-6 updated. Policy statement unchanged.
March 2020	Replace policy	Policy updated with literature review through October 14, 2019; no references added. Policy statement unchanged.
March 2021	Replace policy	Policy updated with literature review through October 19, 2020; references added. Policy statement unchanged.
March 2022	Replace policy	Policy updated with literature review through November 10, 2021; references added. Policy statement unchanged.
March 2023	Replace policy	Policy updated with literature review through October 25, 2022; references added; DEI refinements added. Policy statement unchanged.