Cardiac Disease Risk Screening

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COVERAGE CRITERIA 2
POLICY CROSS REFERENCES 4
POLICY GUIDELINES 4
REGULATORY STATUS 10
CLINICAL EVIDENCE AND LITERATURE REVIEW 10
HEALTH EQUITY CONSIDERATIONS 14
BILLING GUIDELINES AND CODING 14
REFERENCES 17
POLICY REVISION HISTORY 19

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

PHA members must also the testing criteria governed by the Oregon Health Plan (OHP) - OHP Diagnostic Procedure Codes / Procedure Group 1119. Diagnostic services needed to establish a diagnosis are covered regardless of where the ultimate diagnosis appears. Once the diagnosis is determined, coverage of further treatment is reimbursed if the service appears funded by the OHA for that condition. Medicaid members must also meet the genetic testing criteria governed by the Oregon Health Plan (OHP) Prioritized List Guideline Notes D1 and D17.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Notes:

- This policy does not address simple lipid panels (CPT 80061) including total serum cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, which may be considered medically necessary.
- This policy does not address testing for *F2* (prothrombin, coagulation factor II) and *F5* (coagulation factor V) gene analysis (CPTs 81240 and 81241), which are reviewed under medical policy, *Genetic Testing for Inherited Thrombophilia (Company)*.

Measurement of Biomarkers for the Assessment of Cardiovascular Disease Risk

I. The measurement of the following biomarkers for the assessment of cardiovascular disease risk (not including those in a simple lipid panel) is considered **not medically necessary**:
   A. Apolipoprotein A1 (ApoA1)
   B. Apolipoprotein B (Apo B)
   C. Apolipoprotein E (Apo E)
   D. Cystatin C
   E. Fibrinogen mass
   F. GlycA

G. Homocysteine
H. Intermediate density lipoproteins (IDL)
I. Lipoprotein-associated phospholipase A2 (Lp-PLA2)
J. Lipoprotein (a) (LP(a))
K. Long-chain omega-3 fatty acids in red blood cells
L. Microalbumin
M. Myeloperoxidase (MPO)
N. Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP)
O. Very low-density lipoprotein (VLDL) particles, small dense low-density lipoprotein (sdLDL), small dense LDL.

Genotyping for the Assessment of Cardiovascular Disease Risk

II. Genotyping for the assessment of cardiovascular disease risk is considered **not medically necessary** including, but not limited to, the following genes, unless requested as part of a multi-gene panel that meets criteria per the Medical Policy, "Next Generation Sequencing for Cancer":

A. Apolipoprotein E genotype
B. CYP2C19 genotype
C. Kinesin-like protein 6 (KIF6)
D. Lipoprotein (a) (LPA) aspirin genotype
E. Lipoprotein (a) (LPA) intron 25 genotype
F. Methylenetetrahydrofolate reductase (MTHFR)
G. 4q25 atrial fibrillation risk genotype
H. 9p21 genotype

Cardiovascular Disease Risk Panels

III. Laboratory panels to assess cardiovascular disease risk (other than a simple lipid panel) consisting of one or more biomarkers or genes listed above (criteria I. and II.) are considered **not medically necessary**, unless requested as part of a multi-gene panel that meets criteria per the Medical Policy, "Next Generation Sequencing for Cancer." Examples of commercially available cardiovascular disease risk panels include, but are not limited to, the following:

***Note:** If any component of the panel test is considered not medically necessary, then the entire panel test will be denied as **not medically necessary.**

A. Boston Heart HDL Map®
B. Boston Heart Fatty Acid Balance™ Test
C. Cleveland HeartLab® NMR LipoProfile®
D. CardioDX® Corus® CAD
E. Genova Diagnostics® CV Health Plus Genomics™
F. Genova Diagnostics® Comprehensive Cardiovascular Assessment
G. LabCorp Heart Disease and Stroke Risk Profile
H. Mayo Clinic Cardiovascular Risk Marker Panel

I. Quest Diagnostics™ Cardio IQ®, including:
   1. Cardio IQ® Advanced Lipid Panel
   2. Cardio IQ® Advanced Lipid Panel and Inflammation Panel
   3. Cardio IQ® Apolipoprotein Evaluation
J. SmartHealth Vascular Dx™
K. SpectraCell Laboratories Advanced Lipoprotein Particle Profile (LPP)™ Basic
L. SpectraCell Laboratories Advanced Lipoprotein Particle Profile (LPP)™ Plus
M. VAP (Vertical Auto Profile)+Lipid Panel by VAP® Diagnostics Laboratory (previously Atherotech Diagnostics Lab)
N. HART CADhs, Complete Omics, Prevencio, Inc.
O. HART CVE, Complete Omics, Prevencio, Inc.
P. HART KD, Complete Omics, Prevencio, Inc.
Q. Epi+Gen CHD™,Cardio Diagnostics, Inc.
R. PrecisionCHD™, Cardio Diagnostics, Inc.

Link to Evidence Summary

POLICY CROSS REFERENCES

- Next Generation Sequencing for Cancer, MP352

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

Cardiovascular Disease (CVD)

Cardiovascular disease (also known as heart disease or heart and blood vessel disease) includes numerous health problems, most of which are related to atherosclerosis. Atherosclerosis is the buildup of plaque on the walls of arteries; therefore, narrowing the arteries and making it harder for blood to flow through. If a blood clot form, this can cause a heart attack or stroke. Other conditions associated with CVD include congestive heart failure (the heart is not pumping blood as well as it should), arrhythmias (abnormal heart rhythms), and stenosis (when heart valves do not open enough to allow for adequate blood flow).

Cardiovascular Disease (CVD) Risk Assessment

CVD risk assessment includes the measurement of serum cardiovascular lipids (i.e., simple lipid panel) and the use of a standardized cardiovascular risk calculator (e.g., Framingham risk calculator) to further estimate CVD risk.[1,2] A simple lipid panel is generally composed of the following lipid measures:

- Low-density lipoprotein (LDL) cholesterol
- High-density lipoprotein (HDL) cholesterol
- Triglycerides (a type of fat in the blood)

- Total cholesterol (LDL + HDL + [triglycerides/5])

The results of this CVD risk assessment help to inform decision making around lifestyle changes (e.g., weight loss) and/or medical therapy (e.g., statins) in order to reduce CVD risk. Several other biomarkers (e.g., apolipoproteins, lipoproteins, homocysteine) and genetic testing (e.g., apolipoprotein E genotype, CYP2C19 genotype, KIF6 genotype) have been purported as indicators for CVD. These biomarkers and genes are not components of a simple lipid profile and standard CVD risk assessment.

Biomarkers and Genotyping for Assessing Cardiovascular Disease Risk[3]

Biomarker	Description
Apolipoprotein A1 (ApoA1)	ApoA-I is a protein produced in both the liver and intestine. It provides structure to HDL particles as well as activates enzymes that add a fatty acid to cholesterol (esterifies cholesterol) and allows it to enter the core of HDL.
Apolipoprotein B (ApoB)	ApoB is a protein produced in both the liver and intestine that provides structure to the triglyceride (TG) carrying atherogenic lipoprotein particles. Each particle carries only one apoB protein. Thus, apoB is a direct measure of the number of atherogenic particles in the circulation. ApoB is also a surrogate marker for LDL particle concentration or LDL particle number. ApoB is found on: • Very low-density lipoproteins (VLDL) • Intermediate-density lipoproteins (IDL) • Low-density lipoproteins (LDL) • Lp(a) • Chylomicrons
Apolipoprotein E (apo E)	ApoE is a critical protein component of very low-density lipoprotein (VLDL) and chylomicrons. ApoE is important for: • Cholesterol absorption from the intestine • Uptake of triglyceride-rich lipoproteins by the liver
Cystatin C	Cystatin C is a low molecular weight (13,250 kD) cysteine proteinase inhibitor that is produced by all nucleated cells and found in body fluids, including serum. Since it is formed at a constant rate and freely filtered by the kidneys, its serum concentration is inversely correlated with the glomerular filtration rate (GFR); that is, high values indicate low GFRs while lower values indicate higher GFRs, similar to creatinine.
Fibrinogen mass	Fibrinogen or Factor I is an acute phase inflammatory plasma protein synthesized by the liver and is an essential component in the clotting cascade.
Homocysteine	Homocysteine is a thiol-containing amino acid formed from methionine. Values >15 µmol/L have been associated with increased risk of cardiovascular disease.

Intermediate density lipoproteins (IDL)	(IDL) is a class of lipoproteins formed in the degradation of very-low-density lipoproteins; some are cleared rapidly into the liver and some are degraded to low-density lipoproteins.
Lipoprotein-associated phospholipase A2 (Lp-PLA2)	LpPLA2 is an enzyme produced by monocytes/macrophages that breaks down phospholipids. Increased blood levels of LpPLA2 are associated with soft, active growing plaque.
Lipoprotein (a) (LP(a))	Lp(a) is a plasma lipoprotein that is composed of two parts: • LDL-like particle • Apolipoprotein (a) [apo(a)], a protein made in the liver and attached to the apoB portion of this particle
Long-chain (LC) omega-3 fatty acids	LC omega-3 fatty acids are a specific group of polyunsaturated fatty acids (PUFA) that are the building blocks of most fats and oils. LC omega-3 includes eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA).
Microalbumin	Albumin is a protein in the body that is necessary for cell growth and tissue repair. A level of microalbumin in the urine is indicative of kidney damage.
Myeloperoxidase (MPO)	This is an enzyme made by white blood cells in the artery wall. Elevated levels of MPO indicate the presence of unstable plaque or buildup in the arterial wall.
Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP)	Natriuretic peptides (NPs) are hormones which are mainly secreted from the heart. B-type NPs (BNPs) are purported to have important diagnostic value in heart failure.
Very low-density lipoprotein (VLDL) particles, small dense low-density lipoprotein (sdLDL), small dense LDL	VLDL-C is a calculation that indicates the amount of VLDL lipoproteins in the bloodstream.

Gene	Description
Apolipoprotein E genotype[4]	The genetic test identifies individuals with altered lipid transport. The APOE gene has three common alleles (e2, e3, e4) that encode for three protein isoforms (E2, E3, E4). ApoE3 is the most common form of apoE. Population frequencies for these APOE alleles are: • e2 (15%) • e3 (65%) • e4 (20%)
CYP2C19 genotype[4]	CYP2C19 polymorphisms are inherited variations in the DNA sequence of the gene that codes for the cytochrome P450 (CYP) enzyme 2C19. This enzyme is found in the liver and converts the pro-drug clopidogrel (PLAVIX®) to its active form.

Kinesin-like protein 6 (KIF6)[5]	This gene encodes a member of a family of molecular motors which are involved in intracellular transport of protein complexes, membrane organelles, and messenger ribonucleic acid along microtubules. This gene is ubiquitously expressed in coronary arteries and other vascular tissue. A naturally occurring mutation in this gene is associated with coronary heart disease.
Lipoprotein (a) (LPA) genotyping[6]	Two single nucleotide polymorphisms (SNPs) have been identified at the Lp(a) locus (LPA) on chromosome 6q26 –27 (rs3798220 and rs10455872) that are associated Lp(a) levels and possible coronary artery disease.
Methylenetetrahydrofolate reductase (MTHFR)[4]	MTHFR (methylenetetrahydrofolate reductase) is the enzyme responsible for metabolizing folate which, in turn, is essential for converting homocysteine to methionine. Homocysteine is a necessary amino acid that plays an important role in metabolism, but high levels are related to a higher risk of coronary heart disease, stroke and peripheral vascular disease. The intended use of MTHFR genetic testing is, along with assessing homocysteine levels, to assess and minimize a patient's risk for cardiovascular disease (CVD) through nutritional therapy and possibly clot prevention with low dose aspirin.
4q25 atrial fibrillation (AF) risk genotype[7]	Common single nucleotide polymorphisms (SNPs) at chromosome 4q25 (rs2200733, rs10033464) are associated with both lone and typical AF. Risk alleles at 4q25 have recently been shown to predict recurrence of AF.
9p21 genotype[8]	Multiple variants in the 9p21 locus (ie, the p21 locus on chromosome 9) are associated with risk of coronary heart disease (CHD). These variants are highly correlated and can be used to define the at-risk alleles. About 50% of individuals (ie, risk variant heterozygous carriers) carry one copy of an at-risk allele and 23% of individuals (risk variant homozygous carriers) carry 2 copies of an at-risk allele.

Cardiovascular Disease Risk Panels

Panel	Measures
Boston Heart HDL Map®[9]	• 5 HDL subclasses • Apolipoprotein A-I
Boston Heart Fatty Acid Balance™ Test[4,9]	Measures all the major fatty acids in plasma and reports: • Saturated Fatty Acid Index • Trans Fatty Acid Index • Monounsaturated Fatty Acid Index • Unsaturated/Saturated Ratio Index • Omega-3 Fatty Acid Index • Omega-6 Fatty Acid Index • EPA/AA Ratio Index • Omega-3/Omega-6 Ratio Index

	• Levels of all the major omega-3 fatty acids including EPA, DHA and ALA as well as the two major omega-6 fatty acids, AA and LA
Cleveland HeartLab® Lipoprotein Fractionation, NMR[10]	Simple lipid panel plus lipoprotein subclasses (e.g., very low density lipoproteins)
CardioDX® Corus® CAD[11]	23 genes, including: L18RAP, TNFAIP6, CASP5, IL8RB, KCNE3, TLR4, TNFRSF10C, S100A8, S100A12, CLEC4, RPL8 (men), NCF4, AQP9 (women), SLAMF7, KLRC4, TMC8, CD3D, SPIB, CD79B, AF289562 (not yet described), TSPAN16 (men), TFCP2, and HNRPF
Genova Diagnostics® CV Health Plus Genomics™[12]	Lipid Markers • LDL, HDL, Total Cholesterol, Triglycerides • LDL – Particle Number and Size • HDL – Particle Number and Size • Lipoprotein (a) Independent Risk Factors • High Sensitivity CRP (hs-CRP) • Lp-PLA2 (PLAC) • Fibrinogen • Homocysteine Insulin Resistance Score by Lipid Fractionation, combining: • Small LDL – Particle Number • LDL Size • Large VLDL – Particle Number • VLDL Size • Large HDL – Particle Number • HDL Size Genotyping • APOE • MTHFR • Factor II (prothrombin) • Factor V (Leiden)
Genova Diagnostics® Comprehensive Cardiovascular Assessment[13]	• HDL • LDL • total cholesterol (including ratios) • triglycerides • lipoprotein(a) • homocysteine • apolipoprotein A1 • apolipoprotein B • fibrinogen • C-reactive protein

LabCorp Heart Disease and Stroke Risk Profile[14]	• C-reactive protein, cardiac • fibrinogen activity • lipoprotein (a) • von Willebrand factor antigen
Mayo Clinic Cardiovascular Risk Marker Panel[15]	Simple lipid panel, plus: • Lipoprotein (a) • high sensitivity C-reactive protein
Quest Diagnostics™ Cardio IQ® Advanced Lipid Panel[16]	Simple lipid panel, plus: • lipoprotein subfractions (e.g., small density LDL) • apolipoprotein B • lipoprotein (a)
Quest Diagnostics™ Cardio IQ® Advanced Lipid Panel and Inflammation Panel[17]	Simple lipid panel, plus: • lipoprotein subfractions (e.g., small density LDL) • apolipoprotein B • lipoprotein (a) • high sensitivity C-reactive protein • Lp-PLA2 activity
Quest Diagnostics™ Cardio IQ® Apolipoprotein Evaluation[18]	• apolipoprotein A1 • apolipoprotein B • apolipoprotein B/A1 ratio
SmartHealth	•
SpectraCell Laboratories Advanced Lipoprotein Particle Profile (LPP)™ Basic[19]	• Lipoprotein Fractionation • Lipoprotein Particle Numbers • Total Cholesterol • HDL Cholesterol • LDL Cholesterol • Triglycerides • Lipoprotein (a)
SpectraCell Laboratories Advanced Lipoprotein Particle Profile (LPP)™ Plus[19]	• Lipoprotein Fractionation • Lipoprotein Particle Numbers • Total Cholesterol • HDL Cholesterol • LDL Cholesterol • Triglycerides • hs-CRP • Homocysteine • Apolipoprotein A-1 • Apolipoprotein B • Lipoprotein (a) • Insulin

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

Clinical Utility

Clinical utility is defined as, "the ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results."[20] A test must have established the following components to demonstrate clinical utility:

- Leads to changes in clinical management of the patient that improve outcomes
- Eliminates the need for further clinical workup or invasive testing
- Leads to discontinuation of interventions that are unnecessary and/or ineffective
- Leads to initiation of effective medication(s) and/or changes in dosing of a medication that is likely to improve outcomes
- Leads to discontinuation of medications that are ineffective or harmful
- Provides prognostic information not revealed by standard laboratory and/or clinical testing that reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies

Of note, in order to receive FDA approval a test or assay must demonstrate analytical and clinical validity. However, the FDA does not review clinical utility; therefore, FDA approval does not indicate clinical utility and subsequent medical necessity.

Biomarkers for Assessing Cardiovascular Disease Risk

Biomarker	Evidence
Apolipoprotein A1 (ApoA1)	The 2016 Centers for Disease Control and Prevention and Laboratory Medicine Best Practices (LMBP) systematic review and evidence-based guideline for lipoprotein biomarkers and risk of cardiovascular disease stated, "(b)ecause of the insufficient available evidence, no recommendations could be made for or against the effectiveness of apo A-1 practices to predict the CVD events."[21]
Apolipoprotein B (ApoB)	The 2013 American College of Cardiology/American Heart Association evidence-based guideline for cardiovascular risk

	assessment states that the contribution of ApoB for risk assessment for a first ASCVD event is uncertain at present.[22]
Apolipoprotein E (ApoE)	The 2010 American College of Cardiology/American Heart Association evidence-based guideline for cardiovascular risk assessment states, "(m)easurement of lipid parameters, including lipoproteins, apolipoproteins, particle size, and density, beyond a standard fasting lipid profile is not recommended for cardiovascular risk assessment in asymptomatic adults. (Level of Evidence: C)"[23] The 2013 ACC/AHA guideline provides no recommendation for or against the use of ApoE screening in symptomatic adults.
Cystatin C	The National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease stated, "(c)ystatin C may be a more powerful predictor of cardiovascular events than estimated GFR (eGFR) calculation based on creatinine. Research should be conducted to examine if interventions based on cystatin C measurements for risk stratification in individuals with diminished estimated GFR will provide added clinical benefit. (Classification of recommendation: IIa; Level of evidence: C)"[24]
Fibrinogen mass	The National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease stated, "(t)here are sufficient data that fibrinogen is an independent marker of CVD risk; however, because of analytical concerns, insufficient assay standardization, and uncertainty in identifying treatment strategies, measurement is not recommended for this application. (Classification of recommendation: III; Level of evidence: A)"[24]
GlycA	GlycA, a nuclear magnetic resonance composite marker of systemic inflammation, reflects serum concentration and glycosylation state of main acute phase reactants. The biomarker reflects the integrated concentrations and glycosylation states of several abundant acute-phase inflammatory proteins, including α1-acid glycoprotein, haptoglobin, α1-antitrypsin, α1-antichymotrypsin, and transferrin.[25]
Homocysteine	The National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease stated, "(t)he clinical application of homocysteine measurement for risk assessment or primary prevention of CVD is uncertain."[24]
Intermediate density lipoproteins (IDL) Lipoprotein-associated phospholipase A2 (Lp-PLA2) Lipoprotein (a) (LP(a)) Very low-density lipoprotein (VLDL) particles, small dense	The National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease gave the following recommendations for lipoprotein subclasses and the estimation of CVD risk: • Lipoprotein subclasses, especially the number or concentration of small dense LDL particles, have been shown to be related to the development of initial coronary heart disease events, but the data analyses of existing studies are generally not adequate

low-density lipoprotein (sdLDL), small dense LDL	to show added benefit over standard risk assessment for primary prevention. (Classification of recommendation: III (lipoprotein subclass determination is not recommended); Level of Evidence: A) • LP(a) screening is not warranted for primary prevention and assessment of cardiovascular risk. (Classification of recommendation: III (against measurement); Level of evidence: A)[24]
Long-chain (LC) omega-3 fatty acids	A 2016 Agency for Healthcare Research and Quality (AHRQ) systematic review on omega-3 fatty acids and cardiovascular disease concluded the following: • Higher intakes of LC omega-3s (primarily EPA and DHA from foods such as fish and seafood as well as dietary supplements) lower triglyceride levels and raise high-density lipoprotein levels, but also raise low-density lipoprotein levels. However, LC omega-3s do not affect major adverse cardiovascular events or rates of coronary revascularization, sudden cardiac death, or all-cause death. • LC omega-3s have inconsistent effects on the risk of cardiac death based on the results of five randomized controlled trials.[26]
Microalbumin	The 2013 American College of Cardiology/American Heart Association evidence-based guideline for cardiovascular risk assessment states that the contribution of albuminuria for risk assessment for a first ASCVD event is uncertain at present.[22]
Myeloperoxidase (MPO)	Few studies have purported an association between myeloperoxidase levels and CVD risk in prepubescent obese children.[27-29] However, no studies have evaluated how this may affect disease management and patient health outcomes.
Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP)	The National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease gave the following recommendations regarding natriuretic peptides and CVD risk: • Increased BNP or NT-proBNP concentrations are associated with increased mortality in the next 2–7 years in community-based populations. However, the benefits of therapy based on these measurements are uncertain. Measurement for CVD risk assessment in the primary prevention setting is unwarranted. (Classification of recommendation: III (against measurement); Level of evidence: B) • More research should be performed to determine if BNP and NT-proBNP measurements are useful in identifying individuals who are at increased risk of developing heart failure and might benefit from therapies for prevention of heart failure and cardiovascular disease. (Classification of recommendation: I; Level of evidence: C)[24]

Cardiovascular Disease Risk Panels

The following panels are considered not medically necessary because they include one or more of the biomarkers and/or genes described above (see Description for specific measures included in each panel):

A. Boston Heart HDL Map®
B. Boston Heart Fatty Acid Balance™ Test
C. Cleveland HeartLab® NMR LipoProfile®
D. CardioDX® Corus® CAD
E. CARDIOinCodeSchore, GENinCode US Inc.
F. Genova Diagnostics® CV Health Plus Genomics™
G. Genova Diagnostics® Comprehensive Cardiovascular Assessment
H. KawasakiDx, OncoOmicsDx Laboratory, mProbe
I. LabCorp Heart Disease and Stroke Risk Profile
J. Mayo Clinic Cardiovascular Risk Marker Panel
K. Quest Diagnostics™ Cardio IQ®, including:
    1. Cardio IQ® Advanced Lipid Panel
    2. Cardio IQ® Advanced Lipid Panel and Inflammation Panel
    3. Cardio IQ® Apolipoprotein Evaluation
L. SpectraCell Laboratories Advanced Lipoprotein Particle Profile (LPP)™ Basic
M. SpectraCell Laboratories Advanced Lipoprotein Particle Profile (LPP)™ Plus
N. VAP®(Vertical Auto Profile)+Lipid Panel by VAP® Diagnostics Laboratory (previously Atherotech Diagnostics Lab)

CLINICAL PRACTICE GUIDELINES

Genotyping for Assessing Cardiovascular Disease Risk

The 2010 American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines evidence-based guidelines for cardiovascular risk assessment do not recommend the use of genotype testing for CHD risk assessment (Level of Evidence: B).[30] The guidelines states, "(g)iven the very small OR [odds ratio] and the small incremental risk information of the individual polymorphisms, the writing committee judged that genomic tests for CHD risk currently offer no proven benefit in risk assessment when added to a global basic risk score such as the FRS [Framingham Risk Score]." Additionally, "(s)tudies assessing whether genotype testing enhances motivation and success with adherence to recommended lifestyle and medical therapies demonstrate mixed results." There is also a lack of data to determine whether genotype testing alters disease management or improves patient health outcomes in the prevention of cardiovascular disease. For these reasons, genotyping for assessing cardiovascular disease risk is considered not medically necessary.

EVIDENCE SUMMARY

There is insufficient evidence to establish the clinical utility of biomarkers beyond simple lipid panels to assess cardiovascular disease (CVD) risk. There is also insufficient evidence to support genotyping

specific individual targets. Genetic molecular analysis by way of larger CVD risk panels are not designed to be specific to an individual's risk, and will lack clinical utility when applied to the general population. Additional studies of good methodological quality are required to determine if assessment of these biomarkers and genes included in CVD risk panels improves disease management and patient health outcomes. Therefore, biomarker testing including genotyping of individual genes listed in this policy and panels containing one or more of the specific listed genes is considered not medically necessary.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
CPT	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
	81400	Molecular Pathology Procedure Level 1
	81401	Molecular Pathology Procedure Level 2
	81406	Molecular Pathology Procedure Level 7
	80061	Lipid panel This panel must include the following: Cholesterol, serum, total (82465) Lipoprotein, direct measurement, high density cholesterol (HDL cholesterol) (83718) Triglycerides (84478)
	82172	Apolipoprotein, each
	82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
	82397	Chemiluminescent assay

	82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
	82570	Creatinine; other source
	82610	Cystatin C
	82725	Fatty acids, nonesterified
	82777	Galectin-3
	82947	Glucose; quantitative, blood (except reagent strip)
	83036	Hemoglobin; glycosylated (A1C)
	83090	Homocysteine
	83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
	83525	Insulin; total
	83695	Lipoprotein (a)
	83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
	83700	Lipoprotein, blood; electrophoretic separation and quantitation
	83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)
	83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
	83719	Lipoprotein, direct measurement; VLDL cholesterol
	83721	Lipoprotein, direct measurement; LDL cholesterol
	83722	Lipoprotein, direct measurement; small dense LDL cholesterol
	83880	Natriuretic peptide
	84484	Troponin, quantitative
	84681	C-peptide
	85246	Clotting; factor VIII, VW factor antigen
	85384	Fibrinogen; activity
	85385	Fibrinogen; antigen
	86141	C-reactive protein; high sensitivity (hsCRP)
	0024U	Glycosylated acute phase proteins (GlycA), nuclear magnetic resonance spectroscopy, quantitative
	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
	0308U	Cardiology (coronary artery disease [CAD]), analysis of 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]) with 3 clinical parameters (age, sex, history of cardiac intervention), plasma, algorithm reported as a risk score for obstructive CAD

	0309U	Cardiology (cardiovascular disease), analysis of 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for major adverse cardiac event
	0310U	Pediatrics (vasculitis, Kawasaki disease [KD]), analysis of 3 biomarkers (NTproBNP, C-reactive protein, and T-uptake), plasma, algorithm reported as a risk score for KD
	0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables)
	0389U	Pediatric febrile illness (Kawasaki disease [KD]), interferon alphainducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1), RNA, using reverse transcription polymerase chain reaction (RT-qPCR), blood, reported as a risk score for KD
	0401U	Cardiology (coronary heart disease [CAD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event
	0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide 25 polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site (TSS200) of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD
	0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1, cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD
	0466U	Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease
	0541U	Cardiovascular disease (HDL reverse cholesterol transport), cholesterol efflux capacity, LC-MS/MS, quantitative measurement of 5 distinct HDL-bound apolipoproteins (apolipoproteins A1, C1, C2, C3, and C4), serum, algorithm reported as prediction of coronary artery disease (pCAD) score
	81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
	81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score
	83876	Myeloperoxidase (MPO)

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
4/2023	Added 0377U to coding table.
7/2023	Changed the denial for genotyping for the assessment of cardiovascular disease (CPT 81291 and 81493) to "not medically necessary." Q3 codes added to policy.
9/2023	Changed denial language in criteria I. and III. from "investigational" to "not medically necessary." Added non-covered biomarker and corresponding code.
4/2024	Quarterly code set update.
7/2024	Annual update and Q3 2024 code set update. No changes to criteria.
4/2025	Q2 2025 code set update. New code added, code revisions.
7/2025	Annual update. No changes.
7/2026	Annual update. No changes.