MEDICAL POLICY

POLICY TITLE	**GENETIC TESTING FOR LIPOPROTEIN(A) VARIANT(S) AS A DECISION AID FOR ASPIRIN TREATMENT**
POLICY NUMBER	**MP 2.310**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

I. POLICY

The use of genetic testing for the *LPA* rs3798220 allele (*LPA*-Aspirin Genotype) is considered **investigational** in patients who are being considered for treatment with aspirin to reduce the risk of cardiovascular events. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .
Note* - The Federal Employee Program (FEP) Service Benefit Plan does not have a medical policy related to these services.

III. DESCRIPTION/BACKGROUND

TOP

Lipoprotein (a) (LPA) is a lipid-rich particle similar to low-density lipoprotein and has been determined to be an independent risk factor for coronary artery disease. Patients with a positive test for the *LPA* genetic variant, rs3798220, have a higher risk for thrombosis and therefore may derive greater benefit from the antithrombotic properties of aspirin. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR LIPOPROTEIN(A) VARIANT(S) AS A DECISION AID FOR ASPIRIN TREATMENT
POLICY NUMBER	MP 2.310

Extensive epidemiologic evidence has determined that lipoprotein (a) (LPA) blood level is an independent risk factor for cardiovascular disease (CVD). The overall risk associated with LPA appears to be modest, and the degree of risk may be mediated by other factors such as low-density lipoprotein (LDL) levels and/or hormonal status.

Over time, a person's LPA levels remain relatively stable; however, levels have been known to vary up to 1000-fold between different people, and this is most likely due to genetics. A single-nucleotide variant in the *LPA* gene, *LPA* rs3798220, has been associated with both elevated LPA levels and an increased risk of cardiovascular disease. This variant substitutes methionine for isoleucine at amino acid position 4399 and is also called I4399M. Mendelian randomization studies have supported the hypothesis that this genetic variant, and the subsequent increase in LPA levels, are causative of cardiovascular disease.

Aspirin is a well-established treatment for patients with known coronary artery disease. It also is prescribed as primary prevention for some patients who are at increased risk of coronary artery disease. Current recommendations for primary prevention consider the future risk of cardiovascular events weighed against the bleeding risk of aspirin. The U.S. Preventive Services Task Force 2009 Guidelines recommended aspirin for men between the ages of 45 and 79 years when the benefit in reducing myocardial infarction exceeds the risk of bleeding, particularly gastrointestinal hemorrhage; and for women between the ages of 55 and 79 years when the benefit in reducing stroke exceeds the risk of gastrointestinal bleeding. USPSTF updated these guidelines in 2022 stating the following: The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit. (C recommendation) The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older. (D recommendation). Given such guidelines that recommend individualizing the risk-benefit ratio of aspirin therapy, additional tools that would aid in better defining the benefits of aspirin, and/or the risk of bleeding, have potential utility for clinicians who are making decisions about aspirin therapy.

The Cardio IQ® LPA Aspirin Genotype test is a commercially available genetic test (Berkeley HeartLab, a Quest Diagnostics service) that detects the presence of the rs3798220 allele. Patients with a positive test for rs3798220 have a higher risk for thrombosis and therefore may derive more benefit from the antithrombotic properties of aspirin. It has been proposed that the additional information obtained from the test may aid physicians in better estimating the benefit and risk of aspirin therapy and therefore may aid in deciding whether to prescribe aspirin for individual patients.

Regulatory Status

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. Berkeley HeartLab/Quest Diagnostics is certified under the auspices 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 U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

TOP

SUMMARY OF EVIDENCE

For individuals who have a high risk of thrombosis who receive genetic testing for *LPA* rs3798220 variant, the evidence includes observational studies. Relevant outcomes are test validity, medication use, and morbid events. The *LPA* minor allele, rs3798220, is associated with higher levels of LPA and a higher risk for cardiovascular events. This allele is infrequent in the population and is associated with a modest increase in cardiovascular risk in the general population. Testing for this allele is commercially available, but performance characteristics are uncertain, and standardization of testing has not been demonstrated. Several observational studies have reported that this variant is an independent risk factor for cardiovascular disease, but some studies have not reported a significant association. Evidence from a post hoc analysis of the Women's Health Study reported that carriers of the allele might derive greater benefit from aspirin therapy compared with noncarriers. It is unclear whether this information, which derives from genetic testing, leads to changes in management; in particular, it cannot be determined from available evidence whether deviating from current guidelines on aspirin therapy based on *LPA* genetic testing improves outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

TOP

GENOTYPE refers to the pair of genes present for a particular characteristic or protein.

POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. DISCLAIMER

TOP

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

TOP

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.

The following codes are investigational when used to report genetic testing for lipoprotein (a) variant as a decision aid for aspirin therapy as outlined in the policy statement:

Procedure Codes								
81479								

VIII. REFERENCES

TOP

1. *Wang Y, Wang L, Liu X, et al. Genetic variants associated with myocardial infarction and the risk factors in Chinese population. PLoS One. Jan 2014;9(1):e86332. PMID 24475106*
2. *Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. Sep 11-17 2004;364(9438):937-952. PMID 15364185*
3. *Koch W, Mueller JC, Schrempf M, et al. Two rare variants explain association with acute myocardial infarction in an extended genomic region including the apolipoprotein(A) gene. Ann Hum Genet. Jan 2013;77(1):47-55. PMID 23278389*
4. *Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. J Am Coll Cardiol. Mar 19 2013;61(11):1146-1156. PMID 23375930*
5. *Anderson JL, Knight S, May HT, et al. Validation and quantification of genetic determinants of lipoprotein-a levels and predictive value for angiographic coronary artery disease. Am J Cardiol. Sep 15 2013;112(6):799-804. PMID 23735648*
6. *Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. Dec 24 2009;361(26):2518-2528. PMID 20032323*
7. *Shiffman D, Kane JP, Louie JZ, et al. Analysis of 17,576 potentially functional SNPs in three case-control studies of myocardial infarction. PLoS One. Aug 06 2008;3(8):e2895. PMID 18682748*
8. *Qi Q, Workalemahu T, Zhang C, et al. Genetic variants, plasma lipoprotein(a) levels, and risk of cardiovascular morbidity and mortality among two prospective cohorts of type 2 diabetes. Eur Heart J. Feb 2012;33(3):325-334. PMID 21900290*
9. *Shiffman D, O'Meara ES, Bare LA, et al. Association of gene variants with incident myocardial infarction in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. Jan 2008;28(1):173-179. PMID 17975119*

10. *Luke MM, Kane JP, Liu DM, et al. A polymorphism in the protease-like domain of apolipoprotein(a) is associated with severe coronary artery disease. Arterioscler Thromb Vasc Biol. Sep 2007;27(9):2030-2036. PMID 17569884*
11. *Chasman DI, Shiffman D, Zee RY, et al. Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. Atherosclerosis. Apr 2009;203(2):371-376. PMID 18775538*
12. *Shiffman D, Chasman DI, Ballantyne CM, et al. Coronary heart disease risk, aspirin use, and apolipoprotein(a) 4399Met allele in the Atherosclerosis Risk in Communities (ARIC) study. Thromb Haemost. Jul 2009;102(1):179-180. PMID 19572086*
13. *Anderson TJ, Gregoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. Feb 2013;29(2):151-167. PMID 23351925*
14. *Goff DC, Jr., 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. J Am Coll Cardiol. Jul 01 2014;63(25 Pt B):2935-2959. PMID 24239921*
15. *American College of Cardiology/American Heart Association, Assessment of Cardiovascular Risk Full Work Group. 2013 report on the assessment of cardiovascular risk: full work group report supplement. 2013;*
16. *O'Sullivan, J. W., Raghavan, S., Marquez-Luna, C., Luzum, J. A., Damrauer, S. M., Ashley, E. A., O'Donnell, C. J., Willer, C. J., & Natarajan, P. (2022, July). Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. professional.heart.org.*
17. *U.S. Preventive Services Task Force. Archived Final Recommendation Statement: Aspirin for the Prevention of Cardiovascular Disease: Preventive Medication. 2022;*
18. *Genetic Variants in the Apolipoprotein(a) Gene and Coronary Heart Disease | Circulation: Cardiovascular Genetics (ahajournals.org)*
19. *Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., & Hahn, E. J. (2019, September). 2019 ACC/AHA guideline on the primary prevention of cardiovascular ... Journal of the American College of Cardiology.*
20. *US Preventive Services Task Force. (2022, April 26). USPSTF RECOMMENDATION: Aspirin use to prevent cardiovascular disease. JAMA.*

IX. POLICY HISTORY

TOP

MP 2.310	**03/09/2020 Consensus Review.** No change to policy Statement. References updated.
	02/01/2021 Consensus Review. No change to policy statement. Cross reference removed; policy referenced was retired. Reference and coding reviewed.
	08/31/2022 Consensus Review. No changes to policy statement. Updated FEP, references. Coding reviewed.

MEDICAL POLICY

POLICY TITLE	**GENETIC TESTING FOR LIPOPROTEIN(A) VARIANT(S) AS A DECISION AID FOR ASPIRIN TREATMENT**
POLICY NUMBER	**MP 2.310**

	08/17/2023 Consensus Review. No changes to policy statement. Updated background, references. Coding reviewed, no changes.
	01/19/2024 Administrative Update. Clinical benefit added.
	09/16/2024 Consensus Review. No changes to policy statement. Coding reviewed, no changes.
	08/15/2025 Consensus Review. No changes to policy statement.
	09/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/09/2026 Retirement Review. EviCore Delegation.

Top