

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

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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

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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

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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.

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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

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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

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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

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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

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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 policies 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.

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VII. 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.

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

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IX. POLICY HISTORY

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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.

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	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.

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