

**MEDICAL POLICY**

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

<b>CLINICAL BENEFIT</b>	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
<b>Effective Date:</b>	<b>1/1/2025</b>

[POLICY RATIONALE](#)  
[DISCLAIMER](#)  
[POLICY HISTORY](#)

[PRODUCT VARIATIONS](#)  
[DEFINITIONS](#)  
[CODING INFORMATION](#)

[DESCRIPTION/BACKGROUND](#)  
[BENEFIT VARIATIONS](#)  
[REFERENCES](#)

**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**

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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

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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. BENEFIT VARIATIONS**

[TOP](#)

The existence of this medical policy does not mean that this service is a covered benefit under the member’s health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member’s health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member’s health benefit plan for information or contact Capital Blue Cross for benefit information.

**MEDICAL POLICY**

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<b>POLICY NUMBER</b>	<b>MP 2.310</b>

**VII. DISCLAIMER**

[TOP](#)

*Capital Blue Cross' 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. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

**VIII. 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							

**IX. REFERENCES**

[TOP](#)

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**MEDICAL POLICY**

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<b>POLICY NUMBER</b>	<b>MP 2.310</b>

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**MEDICAL POLICY**

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

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**X. POLICY HISTORY**

[Top](#)

<b>MP 2.310</b>	<b>03/09/2020 Consensus Review.</b> No change to policy Statement. References updated.
	<b>02/01/2021 Consensus Review.</b> No change to policy statement. Cross reference removed; policy referenced was retired. Reference and coding reviewed.
	<b>08/31/2022 Consensus Review.</b> No changes to policy statement. Updated FEP, references. Coding reviewed.
	<b>08/17/2023 Consensus Review.</b> No changes to policy statement. Updated background, references. Coding reviewed, no changes.
	<b>01/19/2024 Administrative Update.</b> Clinical benefit added.
	<b>09/16/2024 Consensus Review.</b> No changes to policy statement. Coding reviewed, no changes.

[Top](#)

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