Genetic Testing for Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment

Policy # 00300
Original Effective Date: 06/15/2011
Current Effective Date: 07/12/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of genetic testing for the LPA rs3798220 allele (LPA-Aspirin Genotype) in patients who are being considered for treatment with aspirin to reduce the risk of cardiovascular events to be **investigational.***

Background/Overview

Lipoprotein(a)
Extensive epidemiologic evidence has determined that lipoprotein(a) (LPA) blood level is an independent risk factor for cardiovascular disease. 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 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 2013 final guidelines recommended aspirin for men "age of 45 to 79 years when the potential benefit due to reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage"; the Task Force made the same recommendation for women between the ages of 55 and 79 years. Given such guidelines that recommend individualizing the risk-benefit ratio of aspirin therapy, additional tools that could 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

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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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 non carriers. 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.

Supplemental Information

Practice Guidelines and Position Statements

A number of guidelines contain recommendations for testing of lipoprotein(a) serum levels, but none were identified with recommendations for genetic testing.

American College of Cardiology/American Heart Association

The American College of Cardiology and American Heart Association (2013) issued joint guidelines on the assessment of cardiovascular risk. The guidelines were based on a systematic review conducted by an expert panel appointed by the National Heart, Lung, and Blood Institute. The panel noted that lipoprotein(a) was considered a risk predictor, but its contribution to risk assessment "awaits further consideration at a later time."

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in July 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

References

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Policy History

Original Effective Date: 06/15/2011
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06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. New policy.
06/14/2012	Medical Policy Committee review

06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding updated
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Updated test name to LPA-Aspirin Genotype. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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Next Scheduled Review Date: 06/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.