Corporate Medical Policy

Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

File Name: genetic_testing_for_lipoprotein_a_variant(s)_as_a_decision_aid_for_aspirin_treatment_and_or_cvd_risk_assessment

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Description of Procedure or Service

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL) which consists of a cholesterol bearing LDL – like particle (apolipoprotein B-100) bound to a plasminogen-like glycoprotein (apolipoprotein(a)) (Lu et al., 2015; Schmidt, Noureen, Kronenberg, & Utermann, 2016) and has been associated with increased risk for cardiovascular disease (CVD)(Tsimikas et al., 2018). Genetic variants of the apolipoprotein(a) gene, LPA, (rs3798220 and rs10455872) have been significantly associated with Lp(a) levels (Lu et al., 2015) and could serve as indicators of CVD risk (Lee et al., 2017). The genetic variant rs3798220 was found to have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin (Chasman et al., 2009). As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment (Shiffman, Slawsky, Fusfeld, Devlin, & Goss, 2012).

This policy only addresses the detection of specific variants of Lp(a) as a decision aid for aspirin therapy.

For information on serum measurement of Lp(a) levels see medical policy titled Cardiovascular Disease Risk Assessment AHS – G2050.

For information on testing for salicylate resistance see medical policy titled Measurement of Thromboxane Metabolites for ASA Resistance AHS – G2107.

Related Policies
Cardiovascular Disease Risk Assessment AHS – G2050
Measurement of Thromboxane Metabolites for ASA Resistance AHS – G2107

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Genetic testing for lipoprotein A variant as a decision aid for aspirin treatment and/or CVD risk assessment is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Lipoprotein A Variant as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment is covered

Not applicable.

When Genetic Testing for Lipoprotein A Variant as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment is not covered

The use of genetic testing for the rs3798220 allele (including proprietary testing such as LPA-Aspirin Check® and Cardio IQ® LPA aspirin Genotype) is considered investigational in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.

The use of genotyping of lipoprotein a (Lp(a)), including genetic testing for the rs3798220 single nucleotide polymorphism (SNP), the rs10455872 SNP, and/or the rs9457951 SNP, is considered investigational in all situations.

Policy Guidelines

Background

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality (Benjamin et al., 2018); with over 11.5% of American adults (27.6 million) diagnosed with heart disease, it claims more lives each year than cancer and chronic lower respiratory disease combined (Benjamin et al., 2018). While progression of CVD is multifactorial, pathophysiological, epidemiological, and genetic studies have provided substantial evidence that Lp(a) is a causal risk factor contributing to CVD (Berglund & Ramakrishnan, 2004; Boffa & Koschinsky, 2016; Chen et al., 2018; Clarke et al., 2009; Danesh, Collins, & Peto, 2000; Kamstrup & Nordestgaard, 2016; Kamstrup, Tybjærg-Hansen, Steffensen, & Nordestgaard, 2009; Nordestgaard & Langsted, 2016; Saleheen et al., 2017; Scanu, 1992; Schmidt et al., 2016; Tsimikas et al., 2018; Wang et al., 2016).

Since first described (Berg, 1963) as a genetic trait increased in patients with coronary heart disease (Berg, Dahlen, & Frick, 1974), Lp(a) has been characterized as a type of low density lipoprotein consisting of apolipoprotein B covalently bound to apolipoprotein(a) (Steyerer et al., 1994). The plasma level and size of Lp(a) are regulated through strict genetic control by the apolipoprotein(a) gene (LPA) on chromosome 6q26-27 with some influence from the APOE locus (Erhart et al., 2018; Lu et al., 2015; Moriartry, Varvel, Gordts, McConnell, & Tsimikas, 2017). The LPA gene is highly polymorphic based on the number of kringle IV repeats, therefore encoding >40 apo(a) isoforms (Marcovina, Hobbs, & Albers, 1996) of varying molecular weights.

As it is genetically controlled, the concentration of Lp(a) is generally stable, correlates inversely with molecular size (smaller size correlating with higher serum levels), and is minimally influenced by age, weight and diet (Enkhmaa, Anuurad, & Berglund, 2016; Tregouet et al., 2009). Genetic variants of apolipoprotein(a) have been found to have predictive value in CHD (Anderson et al., 2013; Cairns et al., 2017; Helgadottir et al., 2012; Lee et al., 2017; Zekavat et al., 2018; Zewinger et al., 2017). Beyond CHD, genetically lowered Lp(a) is also associated with a lower risk of peripheral vascular disease, stroke, heart failure, and aortic stenosis (Emdin et al., 2016).
However, the prevalence and association of these genetic variants with apolipoprotein(a) size and \text{Lp(a)} levels are highly variable and ethnicity-specific. Out of 118 SNPs identified, rs3798220 is most prevalent in Hispanics (42.38%), rs10455872 in whites (14.27%), and rs9457951 in blacks (32.92%). In Hispanics, where rs3798220 was present in 42.76% the variant was associated with large isoforms and lower \text{Lp(a)} levels, but in whites where it only present in 4.27%, it was associated with very small isoforms and higher \text{Lp(a)} levels (Lee et al., 2017).

Although its biology and pathophysiology is still incompletely understood (Tsimikas et al., 2018), \text{Lp(a)} is recognized as both atherogenic (Grainger et al., 1993; Hajjar, Gavish, Breslow, & Nachman, 1989; Helgadottir et al., 2012) and thrombogenic (Caplice et al., 2001; Marcovina & Koschinsky, 2003), possibly due to its structural homology with plasminogen (Hancock, Boffa, Marcovina, Nesheim, & Koschinsky, 2003; McLean et al., 1987). It is thought that \text{Lp(a)} could compete with plasminogen for fibrin binding, ultimately resulting in impaired fibrinolysis (Hervio, Durlach, Girard-Globa, & Angles-Cano, 1995).

A specific SNP rs3798220 in the \text{LPA} gene results in an isoleucine to methionine substitution within the inactive protease domain, a smaller number of kringle IV repeats, elevated \text{Lp(a)} levels and greater risk for CVD (Clarke et al., 2009; Helgadottir et al., 2012; Luke et al., 2007). The variant apolipoprotein(a) produced differs structurally, decreases coagulation time, increases fibrin clot lysis time, and increases fibrin fiber width (Scipione et al., 2017). Carriers of either rs3798220 or rs10455872 were found to have no difference in plasminogen concentration or clot lysis time (Wang et al., 2016). However, one study found a difference in phenotypic expression between different ethnic groups. Among non-Caucasians, carriers of rs3798220 had increased clot permeability and shorter lysis time; whereas among Caucasians, the trend was for decreased permeability and longer lysis time (Rowland et al., 2014).

An analysis of the Women’s Health Study, a randomized trial of low dose aspirin, found that rs3798220 was associated with elevated \text{lp(a)} and doubled cardiovascular risk which could be attenuated by aspirin. Carriers appeared to benefit more from aspirin than non-carriers (Chasman et al., 2009). The additional information obtained from the testing for \text{Lp(a)} genotype may aid physicians in better estimating the benefit/risk of aspirin therapy and therefore may aid in deciding whether to prescribe aspirin for individual patients. \text{LPA} genotyping in the context of the aspirin use guidelines for primary prevention of CVD was found to be potentially cost-effective (Shiffman et al., 2012). However, traditional plasma-based hemostasis-thrombosis laboratory testing, may better help manage venous thrombotic disease than a single DNA variant with a small effect size and no established mechanism linking aspirin with \text{Lp(a)} (Nagalla & Bray, 2016).

**Applicable Federal Regulations**

The \text{LPA-Aspirin Check®} that detects the presence of the rs3798220 allele is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Guidelines and Recommendations**

**American Association of Clinical Endocrinologists and American College of Endocrinology**

The AACE/ACE published guidelines for the management of Dyslipidemia an Prevention of Cardiovascular Disease (Jellinger et al., 2017) which state:
Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

“Testing for lipoprotein (a) is therefore not generally recommended, although it may provide useful information to ascribe risk in Caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.”

Genetic screening for lipoprotein(a) variants is not mentioned.

**National Heart, Lung, and Blood Institute**

The NHLBI published Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis (Tsimikas et al., 2018) which endorsed the European Society of Cardiology/European Atherosclerosis Society, Canadian Cardiovascular Society, and National Lipid Association Guidelines while making additional specific recommendations to facilitate basic, mechanistic, preclinical, and clinical research on Lp(a).

Genetic screening for lipoprotein(a) variants is not mentioned.

**American College of Cardiology/American Heart Association**

The ACC and AHA issued joint guidelines (Goff et al., 2014) on the assessment of cardiovascular risk based on a systematic review conducted by an expert panel appointed by the National Heart, Lung, and Blood Institute. The panel noted that LPA was considered as a risk predictor, but its contribution to risk assessment “awaits further consideration at a later time.”

The ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents (Lloyd-Jones et al., 2016) refer to elevated lipoprotein(a) as an comorbidity that increased ASCVD risk.

Genetic screening for lipoprotein(a) variants is not mentioned.

**The National Lipid Association**

The NLA published recommendations for the Patient-Centered Management of Dyslipidemia (Jacobson et al., 2015) which lists Lipoprotein (a) >50mg/dL as an additional risk indicator that physicians could consider, partially in patients with moderate risk.

Genetic screening for lipoprotein(a) variants is not mentioned.

**Choosing Wisely**

The American Society for Clinical Pathology (ASCP, 2016) as part of the Choosing Wisely Campaign recommended that “A standard lipid profile includes total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These lipids are carried within lipoprotein particles that are heterogeneous in size, density, charge, core lipid composition, specific apolipoproteins, and function. A variety of lipoprotein
Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

assays have been developed that subfractionate lipoprotein particles according to some of these properties such as size, density or charge. However, selection of these lipoprotein assays for improving assessment of risk of cardiovascular disease and guiding lipid-lowering therapies should be on an individualized basis for intermediate to high-risk patients only. They are not indicated for population based cardiovascular risk screening.”

Genetic screening for lipoprotein(a) variants is not mentioned.

U.S. Preventive Services Task Force (USPSTF) guidelines recommendation for aspirin

U.S. Preventive Services Task Force (USPSTF) guidelines from 2016 recommendation for aspirin do not mention lipoprotein(a) or genetic screening for lipoprotein (a).

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81479*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082


Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082


Kamstrup, P. R., & Nordestgaard, B. G. (2016). Elevated Lipoprotein(a) Levels, LPA Risk Genotypes, and Increased Risk of Heart Failure in the General Population. JACC Heart Fail, 4(1), 78-87. doi:10.1016/j.jchf.2015.08.006

Kamstrup, P. R., Tybjaerg-Hansen, A., Steffensen, R., & Nordestgaard, B. G. (2009). Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA, 301(22), 2331-2339. doi:10.1001/jama.2009.801


Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082


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Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082

(integrity of low density lipoproteins is a prerequisite for Lp(a) formation in human plasma. J Clin Invest, 94(6), 2330-2340. doi:10.1172/JCI117598


Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will not provide coverage for genetic testing for lipoprotein A variant as a decision aid for aspirin treatment because it is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

For the policy titled: Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment

4/1/2019 Policy title changed throughout to reflect the addition of Lp(A) testing for CVD; description section, policy guidelines and references updated. Related Policies section added. Added 2nd policy statement “The use of genotyping of lipoprotein a (Lp(a)), including genetic testing for the rs3798220 single nucleotide polymorphism (SNP), the rs10455872 SNP, and/or the rs9457951 SNP, is considered investigational”, to the When Not Covered section. Policy noticed 4/1/19, effective 6/1/19. Medical Director review 4/2019. (jd)

10/29/19 No change to policy statements. (hb)

2/11/20 Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change in policy intent. Medical Director review 12/2019. (jd)
Genetic Testing for Lipoprotein A Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment AHS – M2082


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.