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Medical Policy Manual Genetic Testing, Policy No. 60

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

Effective: September 1, 2020

Next Review: May 2021
Last Review: July 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic testing for lipoprotein(a) (LPA) variant rs3798220 has been proposed as a method of identifying patients who have a higher risk for thrombosis and may derive benefit from aspirin therapy.

MEDICAL POLICY CRITERIA

The use of genetic testing for the rs3798220 allele (Cardio IQ® LAP Aspirin Genotype) is considered **investigational** in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BACKGROUND

Lipoprotein(a) (LPA) is a lipid-rich particle similar to low-density lipoprotein (LDL) and has been

determined to be an independent risk factor for coronary artery disease (CAD). Patients with a positive test for the LPA genetic variant rs3798220 have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

A large amount of epidemiologic evidence has determined that LPA blood level is an independent risk factor for cardiovascular disease. The overall degree of risk associated with LPA levels appears to be modest, and the degree of risk may be mediated by other factors such as LDL levels and/or hormonal status.

Levels of LPA are relatively stable in individuals over time but vary up to 1,000-fold between individuals, presumably on a genetic basis. A single nucleotide polymorphism (SNP), LPA rs3798220, has been identified in the LPA gene that has been associated with both elevated levels of lipoprotein(a) and an increased risk of cardiovascular disease. Mendelian randomization studies have supported the hypothesis that these genetic variants, 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 (CAD). It is also prescribed as primary prevention for some patients who are at increased risk of CAD. Current recommendations for primary prevention consider the future risk of cardiovascular events weighed against the bleeding risk of aspirin. U.S. Preventive Services Task Force (USPSTF) guidelines from 2016 recommend aspirin for adults between the ages of 50-59 years who have a 10-year risk of CVD of 10% or greater and who are not at increased risk for bleeding.[1] Given guidelines such as these 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 on aspirin therapy.

The Cardio IQ® LPA Aspirin Genotype from Quest Diagnostics (formally the LPA-Aspirin Check®, from Berkeley HeartLab) is a commercially available genetic test that detects the presence of the rs3798220 allele.[2] Additionally, other laboratories may also have a similar test. DNA is extracted from a buccal swab sample taken from the inner cheek. Genetic testing is performed by real-time polymerase chain reaction (PCR) in conjunction with several control samples. Real-time PCR is expected to be more accurate than traditional PCR, since it preserves the exquisite sensitivity of PCR, while reducing the probability of cross-contamination that can result in false-positive results.[3] According to these authors, the main limitations to real-time PCR accuracy are human factors such as improper assay development, incorrect data analysis, or unwarranted interpretation.

Patients with a positive test for rs3798220 have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin. It has been proposed that the additional information obtained from the LPA-Aspirin Check test 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.

REGULATORY STATUS

The Cardio IQ® LPA Aspirin Genotype genetic test analyses using PCR methodology are commercially available as laboratory-developed tests. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food

and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[4] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes

ANALYTIC VALIDITY

There were no published studies identified that evaluated the accuracy of real-time PCR testing for the specific rs3798220 allele.

CLINICAL VALIDITY

Cardiovascular Risk

There were no published studies identified that evaluated the diagnostic performance of real-time PCR testing for the specific rs3798220 allele. Several nonrandomized studies have evaluated whether LPA rs3798220 is an independent risk factor for coronary artery disease (CAD).

Koch (2013) published a case-control study of 2,136 cases and 1,211 controls that evaluated if SNPs rs3798220 and rs10455872 were associated with an increased risk of coronary disease.[5] Genotyping of these SNPs and seven other LPA variants believed to be associated with coronary disease was done by Taqman assay. After adjusting for conventional risk factors, the authors found an increased odds of myocardial infarction (MI) of 2.14 (95% CI 1.37 to 3.33, p=0.00080) and 1.45 (95% CI 1.36 to 2.24, p <0.00001) for rs3798220 and rs10455872, respectively. Two additional SNPs, rs3127599 and rs9346818, were also found to be associated with risk of MI, with odds ratios of 1.18 (95% confidence interval [CI] 1.06 to 1.32) and 0.88 (95% CI 0.79 to 0.97) respectively.

The risk associated with genetic variants of LPA in diabetic patients may be different from that in the general population. A large prospective study performed in 2011 evaluated 2,308 patients with diabetes for LPA variants.[6] There was no significant association between genetic variants and cardiovascular risk or mortality. Odds ratios (OR) for coronary heart disease,

cardiovascular disease, and cardiovascular death were 0.94 (95% CI 0.69 to 1.28), 0.97 (95% CI 0.72 to 1.29), and 1.23 (95% CI 0.79 to 1.92), respectively. The authors also examined the degree of variability in risk between the diabetic and non-diabetic populations and reported that there was significant heterogeneity between the two groups (p=0.006).

Clarke (2009) examined the association of rs3798220 with CAD in 3,145 case patients and 3,352 control subjects from four European countries.[7] They initially examined 48,742 SNPs in 2,100 genes that had some association with heart disease, including 40 SNPs from the lipoprotein(a) (LPA) gene. The rs3798220 SNP was found in 2% of patients and had the strongest association with CAD, with a hazard ratio (HR) of 1.92 (95% CI 1.48 to 2.49). This association was then replicated in three independent populations from cohort studies, with a total of 4,846 case patients and 4,594 controls. In these populations, the rs3798220 variant remained an independent risk factor for CAD, with odds that were somewhat lower than in the derivation population (OR 1.68, 95% CI 1.43 to 1.98).

Shiffman (2008a) used data from the Cardiovascular Health Study, a prospective cohort study of risk factors for MI in 4,522 individuals who were 65 years or older, to examine the association of rs3798220 with MI.[8] These authors tested 74 SNPs that had been genotyped as part of the Cardiovascular Health Study. After 13 years of follow-up, 539 patients (12%) had developed MI. There were eight SNPs that were independent predictors of MI, with HRs varying from 1.13 to 1.62. The rs3798220 variant was one of the independent predictors and had the highest HR (1.62, 95% CI 1.09 to 2.42). The authors also calculated the false-positive reporting rate for each SNP and estimated this to be 1% for rs3798220.

In another case-control design, Shiffman (2008b) examined the association between the rs3798220 allele and MI in three case-control studies totaling 762 cases and 857 controls.[9] Starting from a total of 1,949 SNPs associated with MI, the authors identified five SNPs that were mostly strongly associated with MI. One of these was rs3798220, which had ORs in the three separate study populations of 1.59 (95% CI 1.03 to 2.48), 1.72 (95% CI 1.19 to 2.49), and 3.52 (95% CI 1.85 to 6.69).

In 2008, a Danish cohort study of 8,720 participants was followed for 10 years to determine if LPA variants or lipoprotein(a) levels increased the risk of a first-time MI or coronary heart disease (CHD) event.[10] Genotyping of rs3798220, rs10455872 and LPA-KIV-2 repeat genotype was performed by PCR. The authors found that 21% of the total variation in lipoprotein(a) levels was explained by the LPA-KIV-2, that 5% of the variation was explained by rs3798220 genotype, and that 27% of the variation was explained by rs10455872 genotype. The HR for carriers of rs3798220 was 1.3 (95% CI 0.8 to 2.1) for MI and 1.4 (95% CI 1.1 to 1.9) for CHD compared to noncarriers. LPA rs10455872 carriers had HRs of 1.3 (95% CI 1.1 to 1.6) for MI and 1.1 (95% CI 0.9 to 1.3) for CHD compared to noncarriers, whereas homozygous rs10455872 patients had hazard ratios of 1.2 (95% CI 0.5 to 3.3) for MI and 1.1 (95% CI 0.5 to 2.1) for CHD compared to noncarriers.

Luke (2007) examined the association of SNPs with severe CAD as determined by coronary angiography.[11] The authors used populations from three case-control studies in sequence to determine the SNPs that were most strongly associated with severe CAD. Starting with over 12,000 SNPs, the authors identified 302 SNPs associated with severe disease; following verification in the second study, there were five SNPs that remained independent predictors; and after verification in the third study, only rs3798220 remained as the SNP most strongly associated with severe CAD. The adjusted OR for rs3798220 was 3.14 (95% CI 1.51 to 6.56).

Aspirin Therapy

The Women's Health Study (WHS) examined the efficacy of aspirin treatment versus placebo for primary prevention of cardiovascular events in healthy women. Chasman (2009) published a post hoc analysis of 28,345 participants in the WHS who were genotyped for the presence of the LPA rs3798220 minor allele.[12] The allele was present in 3.7% of the population, 3.6% who were heterozygotes and 0.06% who were homozygotes. As expected, LPA levels in carriers of the allele were markedly elevated compared to non-carriers, and carriers had a two-fold increased risk for subsequent cardiovascular events compared to non-carriers.

The authors reported an interaction between the presence of the LPA rs378220 allele and response to aspirin therapy. In carriers, there was a significant risk reduction associated with aspirin (ASA) treatment, with cardiovascular events occurring in 4.8% of patients in the placebo group compared to 2.1% in the aspirin group (HR 0.44, 95% CI 0.20 to 0.94, p=0.03). For non-carriers of the allele, there was no significant reduction in cardiovascular events associated with aspirin treatment, with cardiovascular events occurring in 2.3% of the placebo group compared to 2.1% of the aspirin group (HR 0.91, 95% CI 0.77 to 1.08, p=0.30).

Shiffman (2009) reported on the interaction of the LPA rs3798220 variant and aspirin use from the Atherosclerosis Risk in Communities (ARIC) study.[13] The ARIC study was a prospective cohort study of risk factors for CAD in 15,792 individuals. The LPA genetic substudy of ARIC included 6,752 individuals with data available for LPA genotype and ASA use, including 221 individuals with the LPA rs3798220 genotype. Among carriers of rs3798220, the risk of cardiovascular events was compared in aspirin users and non-users. The HR for non-aspirin users (n=168) was elevated at 1.57 but did not reach statistical significance (95% CI 0.92 to 2.69), while the HR for users of aspirin was not elevated at 0.86 (95% CI 0.38 to 1.95).

CLINICAL UTILITY

There were no published studies identified that evaluated changes in management or health outcomes based on rs3798220 allele testing.

PRACTICE GUIDELINE SUMMARY

No evidence-based clinical practice guidelines were identified that recommend rs3798220 gene testing.[14]

SUMMARY

There is not enough research to show that genetic testing for the lipoprotein(a) (LPA) rs3798220 variant can lead to improved health outcomes for patients being considered for aspirin therapy. Also, there are no clinical guidelines based on research that recommend this testing. Therefore, testing for the LPA rs3798220 variant as a decision aid for aspirin treatment is considered investigational.

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CODES

Codes	Number	Description
CPT	81479	Unlisted molecular pathology procedure
	84999	Unlisted chemistry procedure
HCPCS	None	

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