Medical Policy Manual

Genetic Testing, Policy No. 32

KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

Effective: December 1, 2018

Next Review: October 2019
Last Review: October 2018

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 to determine the KIF6 Trp719Arg variant status of patients is being evaluated as a prognostic test to predict risk of future cardiovascular events and/or as a pharmacogenetic test to predict response to statin therapy, particularly in high-risk patients.

MEDICAL POLICY CRITERIA

KIF6 genotyping is considered investigational for all indications, including but not limited to predicting cardiovascular risk and/or the effectiveness of statin therapy.

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

CROSS REFERENCES

1. Genetic Testing for Familial Hypercholesterolemia, Genetic Testing, Policy No. 11
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BACKGROUND
Analysis of prospective observational studies of cardiovascular health and of the placebo arm of randomized controlled trials (RCTs) of statin intervention in at-risk populations has suggested a significant association between the Trp719Arg single nucleotide polymorphism (SNV; rs20455) in KIF6 and the development of clinical coronary artery disease (CAD). Approximately 60% of the population carries the putative KIF6 high-risk 719Arg variant. Moreover, carriers of the 719Arg variant in the treatment arms of the statin trials appeared to be at no increased risk, or at decreased risk, of CAD or recurrent myocardial infarction (MI), depending on the intensity of the statin therapy. These results supported the development of a KIF6 Trp719Arg genotyping test for use as a predictor of CAD risk and of the likely effectiveness of statin therapy.

The kinesin-like protein 6 encoded by KIF6 belongs to the kinesin superfamily of proteins involved in intracellular transport. The exact function of the KIF6 gene product has not yet been determined. According to one article, the gene is not expressed in the vasculature, the primary site of atherosclerosis. Rather, it is expressed in low levels in the brain, connective tissue, colon, eye, pharynx, skin, and testes. In contrast, a study presented at the American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology 2010 Scientific Sessions reported data derived from tissue immunohistochemistry, locating KIF6 protein in macrophages surrounding neovessels and in foam cells in human atherosclerotic lesions. Nevertheless, there is as yet no strong evidence that KIF6 protein plays a biological role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction (MI).

REGULATORY STATUS

Celera Corporation, now a wholly owned subsidiary of Quest Diagnostics, Inc., holds a U.S. patent relating to methods of determining heart attack risk by detecting the KIF6 Trp719Arg variant and reduction of such increased risk by statin therapy, and offers the “Cardio IQ™ KIF6 Genotype” test. Celera’s Berkeley HeartLab (BHL) subsidiary has been offering KIF6 genotyping (KIF6-StatinCheck™ Genotype Test) since July 2008, and now offers it as part of a comprehensive cardiovascular risk screening program with other serum-based tests. San Francisco General Hospital’s Clinical Chemistry Laboratory (University of California, San Francisco), is the only non-Celera lab to obtain a license to develop a KIF6 LTD and a small number of clinical labs/health care groups have negotiated with Celera to offer the test by sending it to BHL (e.g., Aurora Health Care of Milwaukee, WI).

FDA Approval

In December 2010, Celera (now a subsidiary of Quest Diagnostics) submitted a Premarket Approval (PMA) application to the U.S. Food and Drug Administration (FDA) seeking approval for the KIF6 genotyping assay as an in vitro diagnostic test. On April 7, 2011, the FDA sent a letter to Celera indicating that its application is not approvable “without major amendment.” The peer-reviewed publications of retrospective analyses of large, prospective, completed trials submitted were deemed “insufficient to demonstrate the safety and effectiveness of the device for its proposed intended use.” Additional data on clinical utility may be required, which could include conducting a randomized controlled clinical trial.

EVIDENCE SUMMARY

The focus of the literature review is on evidence related to the ability of test results to:
• Guide decisions in the clinical setting related to either treatment, management, or prevention, and
• Improve health outcomes as a result of those decisions.

SYSTEMATIC REVIEWS

In a meta-analysis, the conflicting results regarding the \textit{KIF6} variant, cardiovascular disease (CHD), and treatment outcomes were described by Ference (2011).\cite{3} The authors included 37 case-control studies, prospective cohort studies, or randomized trial treatment allocation arms (each considered as a separate cohort), which together enrolled 144,931 participants and reported 27,465 CHD events. The \textit{KIF6} genotype, particularly the Trp719Arg SNV carrier status, was not associated with increased risk of CHD event. A new analysis resulted in evidence of \textit{KIF6} variant effect modification. For each mmol/L increase in LDL cholesterol, \textit{KIF6} variant carriers experienced a 15% greater increase in the relative risk of CHD as compared to non-carriers (risk ratio [RR] 1.15, 95% CI 1.06 to 1.25, \(p=0.001\)). Similarly, the decrease in risk for each mmol/L decrease in LDL was 13% greater for variant carriers. Also included in the meta-analysis were eight randomized trials of statin therapy, involving 50,060 participants and 7,307 CHD events. \textit{KIF6} variant carriers derived a greater clinical benefit for each mmol/L reduction in LDL cholesterol during treatment with a statin than did non-carriers (RR 0.87, 95% CI 0.77 to 0.99, \(p=0.038\)). Thus, the results suggest that the \textit{KIF6} Trp719Arg variant increases vulnerability to LDL cholesterol. This evidence supports why \textit{KIF6} variant carriers appear to derive greater clinical benefit from a statin though the variant does not appear to affect the ability of the statin to lower LDL cholesterol, nor does it appear to be independently associated with the risk of CHD. However, “the association between the \textit{KIF6} variant and the risk of CHD will vary according to average LDL cholesterol level of the population(s) under study,” This may help explain some of the conflicting reports of \textit{KIF6} genotype association with CHD.

One meta-analysis of 19 case-control studies (total of 17,000 CAD cases and 39,369 controls) found no association between the Trp719Arg SNV and coronary artery disease (CAD), even when the overall population was restricted to Europeans with early onset disease (less likely to be confounded by statin therapy), to Europeans with myocardial infarction (MI), or to Europeans with early onset MI.\cite{4} The authors of the meta-analysis noted that they examined only non-fatal MI. The meta-analysis could not examine whether the effect on risk was modified by statin therapy.

RANDOMIZED CONTROLLED TRIALS

There have been no published randomized controlled trials that address \textit{KIF6} genotyping for predicting risk of cardiovascular events or statin therapy effectiveness.

NONRANDOMIZED STUDIES

A prospective trial, Additional \textit{KIF6} Risk Offers Better Adherence to Statins (AKROBATS), was conducted to determine whether \textit{KIF6} genotyping resulted in improved patient management.\cite{5} The AKROBATS trial investigated the effect of providing \textit{KIF6} test results and risk information directly to 647 tested patients on six-month statin adherence (proportion of days covered, PDC) and persistence compared with concurrent non-tested matched controls. Adjusted six-month statin PDC was significantly greater in tested patients compared to controls (\(p<0.0001\)). Significantly more tested patients were adherent and persisted on therapy (\(p<0.0001\)). Similar results were observed in a secondary comparison with 779 unmatched patients who declined
testing. Authors suggested that the AKROBATS trial provides the first evidence that pharmacogenetic testing may modify patient adherence. Study limitations included that the measures of adherence were based on prescription claims data, therefore whether patients consumed medications is not known. Further, it is unknown whether adherence observed in the testing group with higher statin adherence and persistence was in response to the testing process or personalized KIF6 test results. In addition, a “healthy user” may have influenced study results since participation in the study was voluntary, thus may cause confounding of the measured variables.

A smaller prospective study by Ruiz-Iruela (2018) evaluated whether the Trp719Arg variant modulates the response to statin treatment.[6] The study included 344 patients who had not received prior lipid-lowering treatment. Individuals who were homozygous for the variant had a 7% smaller reduction in LDL, compared to others (p=0.015).

In a 2014 prospective study evaluating the association between KIF6 genotype status and serum lipids in a cohort of 235 Filipino-American women, there was no association between KIF6 variant status and likelihood of elevated LDL-C levels in both statin-treated and non-statin-treated patients.[7] The authors also reported that there was no difference in select cardiovascular risk factors and KIF6 genotype status.

In a study by Ridker (2011) on the effect of the KIF6 variant on outcomes for 8,781 JUPITER (Justification for Use of Statins in Primary Prevention, An Intervention Trial Evaluating Rosuvastatin) trial participants, the authors reported equal effects of rosuvastatin, regardless of KIF6 status and stated that “there appears to be no clinical utility to screening for KIF6 genotype.”[8]

Hopewell (2011) evaluated data from the Heart Protection Study which enrolled more than 18,000 patients with prior cardiovascular disease or high predisposing risk and compared outcomes after treatment with simvastatin or placebo. The authors reported no association of KIF6 variant status with outcome in the placebo arm, nor in the treatment arm. Simvastatin reduced the incidence of coronary events equally regardless of KIF6 status. The authors concluded that “the use of KIF6 genotyping to guide statin therapy is not warranted.”[9]

Hoffmann (2011) evaluated a narrowly focused population of patients with type 2 diabetes and less than two years previous treatment by hemodialysis, randomly assigned to double-blinded treatment with either 20mg of atorvastatin (n=619) or placebo (n=636).[10] In neither the placebo nor the statin group was there any association of KIF6 genotype with major cardiovascular events. This study was limited because statins did not achieve the expected improvement in survival despite significantly decreasing LDL cholesterol.

Arsenalult (2012) investigated whether carriers of the KIF6 variant obtain more benefit from high-dose statin therapy than do noncarriers by retrospective analysis of two prospective trials.[11] In the Treating to New Targets (TNT) study, 4,599 patients with stable coronary heart disease and LDL cholesterol levels less than 130 mg/dL, randomly assigned to receive either 10 or 80 mg of atorvastatin per day and followed up for a median of 4.9 years, were genotyped. KIF6 genotype did not affect risk for future events within treatment arms. Genotype subgroups had a similar benefit from 80 mg atorvastatin compared to 10 mg except for the homozygous variant subgroup, which was the only group with a statistically significant benefit from the higher statin dose, but interaction for genotype by treatment was not significant. The Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) study enrolled patients with a history of MI and randomized them to high-dose atorvastatin or usual
dose simvastatin and followed for a median of 4.8 years. Of the 8,888 enrolled, 6,541 were genotyped; there were no significant differences by KIF6 genotype in comparative response to statin treatment, and the interaction for genotype by treatment was not significant.

A retrospective evaluation of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial participants found a significant relationship between KIF6 variant homozygotes and fatal or non-fatal myocardial infarction or stroke only in women on pravastatin, which lost significance after correction for multiple comparisons.[12] The study authors also reported that homozygous carriers of the KIF6 variant were significantly less responsive to pravastatin, but did not recommend the use of KIF6 testing to determine statin use.

Case-control studies have shown mixed results. A 2015 study evaluating the association between KIF6 719Arg variant and coronary artery disease (CAD) in 510 South Indian cases and 532 controls found the high-risk 719Arg variant in an equal number of CAD cases and controls.[13] The authors also performed a meta-analysis using five non-European case-control studies (including the present study) with 3369 cases and 3919 controls and found no association between the KIF6 719Arg variant and CAD risk in these populations. Similarly, a study in Saudi Arabia found no association between the KIF6 719Arg variant and coronary artery disease in 1,986 participants,[14] and KIF6 genotype frequencies were the same in 1,889 cases of myocardial infarction and 1,191 controls in a study of Czech men.[15] A small study of 100 patients in Iran, however, found a significant association with coronary heart disease,[16] while another found an association with thoracic aortic dissection.[17]

EVIDENCE SUMMARY

None of the several, large genome-wide association studies for CAD or MI reported any SNVs at the KIF6 locus as significant.[18-22] For this reason, some have considered the possible candidate (i.e., pre-selected) gene approach to the KIF6 variant analysis as lacking biologic plausibility. The retrospective evaluations of prospective, randomized trials conducted in large patient populations indicate that noncarriers of the KIF6 variant benefit from statin therapy to the same degree as variant carriers, likely invalidating the rationale for genotyping and basing statin treatment recommendations on the genotyping result.[23] One nonrandomized study suggested that subjects who received KIF6 genotype results had greater adherence to statin therapy, but the study design, potential for participant bias and the baseline group differences limit the validity of the results. Taken together, the above studies show that in different populations with different levels of vascular risk, treated with different statin drugs and doses, there was no measurable effect of the KIF6 variant on statin response, nor any association with vascular risk.

PRACTICE GUIDELINE SUMMARY

There are no clinical practice guidelines that address the use KIF6 genotyping for predicting cardiovascular risk or statin therapy effectiveness.

SUMMARY

There is not enough research to show that using the KIF6 gene variant to predict CAD can improve health outcomes for patients, and most evidence shows that statin treatment is similarly effective in people with and without the KIF6 gene variant. Also, there are no clinical guidelines based on research that recommend KIF6 testing. Therefore, testing for KIF6
status is considered investigational for all indications, including predicting cardiovascular risk and determining statin treatment benefit.

REFERENCES

3. Ference, BA, Yoo, W, Flack, JM, Clarke, M. A common KIF6 polymorphism increases vulnerability to low-density lipoprotein cholesterol: two meta-analyses and a meta-regression analysis. PloS one. 2011;6(12):e28834. PMID: 22216121


22. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007 Jun 7;447(7145):661-78. PMID: 17554300


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td></td>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

**Date of Origin:** September 2011