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Medical Policy Manual

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

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Section: Genetic Testing

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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.

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 (SNP; rs20455) in kinesin-like protein 6 (*KIF6*) and the development of clinical coronary artery disease (CAD). Approximately 60% of the population carries the putative *KIF6* high-risk 719Arg allele. Moreover, carriers of the 719Arg allele 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 *KIF6* protein belongs to the kinesin superfamily of proteins involved in intracellular transport. The exact function of the *KIF6* gene product is as yet undetermined. 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.[1] 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.[2] Nevertheless, there is as yet no strong evidence that KIF*6* protein plays a biological role in atherosclerosis, lipid metabolism, coronary artery disease (CAD), or myocardial infarction (MI).

Regulatory Status

The *KIF6*-StatinCheck™ genotyping test (Celera Corporation) is a laboratory-developed test (LDT), offered by clinical laboratories licensed under Clinical Laboratory Improvement Amendments (CLIA) for high-complexity testing. Celera Corporation offers the test via Celera's Berkeley HeartLab (BHL).

FDA Approval

In December, 2010, Celera 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.

MEDICAL POLICY CRITERIA

KIF6 genotyping is considered **investigational** for predicting cardiovascular risk and/or the effectiveness of statin therapy.

SCIENTIFIC EVIDENCE

The focus of the scientific background 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.

Clinical Validity

The clinical validity of the *KIF6* genotyping has not been firmly established.

Systematic Review/Meta-analyses

- A recent systematic review analyzed the evidence for the role of pharmacogenetics in cardiovascular disease.[3] The review described the genetic evidence for the pharmacogenetics of

statins as mediocre, and concluded that functional studies are needed to explore the role of KIF6. Further, authors note that despite the clinical effectiveness of statins, interindividual variation translates to failure of some patients to achieve adequate reduction in cholesterol levels.

- In a recent meta-analysis, the conflicting results regarding the KIF6 variant, cardiovascular disease (CHD), and treatment outcomes was described by Ference et al.[4] 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 KIF6 genotype, and in particular the Trp719Arg SNP carrier status, was not associated with increased risk of CHD event. A new analysis resulted in evidence of KIF6 variant effect modification. For each mmol/L increase in LDL cholesterol, KIF6 variant carriers experienced a 15% greater increase in the relative risk of CHD as compared to non-carriers (ratio of RR: 1.15, 95% CI: 1.06–1.25, 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 8 randomized trials of statin therapy, involving 50,060 participants and 7,307 CHD events. 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 (ratio of RR: 0.87, 95% CI: 0.77–0.99, p = 0.038). Thus, the results suggest that the KIF6 Trp719Arg variant increases vulnerability to LDL cholesterol. This evidence supports why 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 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 KIF6 genotype association with CHD.
- One meta-analysis of 19 case-control studies found no association between the Trp719Arg SNP 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.[5] 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.

Non-randomized trials

- In the published analysis by Ridker et al. of the JUPITER (Justification for Use of Statins in Primary Prevention, An Intervention Trial Evaluating Rosuvastatin) study and the effect of the *KIF6* variant on outcomes of 8,781 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."[6]
- Hopewell et al. 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."[7]
- Hoffmann et al. 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).[8] 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. Nevertheless, taken

together, these three studies show that in different populations with different levels of vascular risk and treated with different statin drugs, there was no measureable effect of the *KIF6* variant on statin response, nor any association with vascular risk.

- Arsenault et al. 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.[9] In the Treating to New Targets (TNT) study, 4,599 patients with stable coronary heart disease and LDL cholesterol levels <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.[10] 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.

Conclusion

In addition to the findings of the meta-analysis, none of the several, large genome-wide association studies for CAD or MI reported any SNPs at the *KIF6* locus as significant.[11-15] For this reason, some have considered the possible candidate (i.e., pre-selected) gene approach to the *KIF6* variant analysis by the test developers as potentially flawed, given the current lack of biologic plausibility. 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.

Clinical Utility

Technology Assessments

Hayes, Inc. conducted an assessment of *KIF6* p.Trp719Arg testing and concluded that the evidence is currently insufficient to determine clinical utility of the test.[16]

Non-randomized trials

In a recent prospective trial, Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS), determined whether *KIF6* genotyping resulted in improved patient management.[17] The AKROBATS trial investigated the effect of providing KIF6 test results and risk information directly to 647 tested patients on 6-month statin adherence (proportion of days covered (PDC)) and persistence compared with concurrent non-tested matched controls. Adjusted 6-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.

However, the retrospective evaluations of prospective, randomized trials (discussed above), 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 test result.[18]

Clinical Practice Guidelines

The 2010 American College of Cardiology Foundation/American Heart Association Practice Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults is silent on KIF*6* testing.[19,20]

Summary

The data supporting the association of the *KIF6* Trp719Arg SNP with coronary artery disease (CAD) outcomes are contradictory. The biologic function of the *KIF6* protein is currently unknown. Evidence from large populations at different levels of vascular risk does not support a significant association with future CAD outcomes. The most recent results of treatment trials suggest that the efficacy of statin treatment appears to be similar in both carriers and non-carriers of the mutation. A large meta-analysis shows that KIF6 variant carriers derive greater clinical benefit from LDL cholesterol reduction compared to non-carriers by about 13%. One prospective non randomized observational trial with methodological limitations suggests that patients modified adherence rates to medication based on their KIF6 results. Because clinical validity or clinical utility has not been established, and it has not been determined whether the results of *KIF6* genotyping can be used to improve patient management, testing for *KIF6* status to predict cardiovascular risk and/or determine statin treatment benefit is considered investigational.

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CROSS REFERENCES

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

CODES	NUMBER	DESCRIPTION
CPT	81479	Unlisted molecular pathology procedure
	84999	Unlisted chemistry procedure
HCPCS	None	