COMMENTARY

Urge Caution With Cardiac Risk Genetic Testing

Dr. Matthew Taylor recently discussed the "step backward" that occurred in genetic risk prediction of coronary artery disease with the discovery that variations in the KIF6 gene might not be clinically associated with CAD after all. More research and vigorous discussion about the role of this gene in this disease – and about early clinical adoption of newly discovered risk factors in general – are sure to follow.

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Of course, KIF6 is only one of many genetic markers that have been linked to CAD risk. Many are already in the public domain and available clinically through health care providers and via direct-to-consumer marketing.

What are we to do with these?

One approach to answering such questions is to turn to an evidence review. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative seeks to evaluate genetic tests and innovations with respect to implementation in clinical practice and public health. Much like the U.S. Preventive Services Task Force, EGAPP commissions evidence reviews and then issues recommendations based upon the evidence. More information, as well as evidence reviews and recommendations reports, is available at www.egappreviews.org.

In December, EGAPP published a report on genomic profiling to assess cardiovascular risk (Genet. Med. 2010;12:839-43). The overarching question was whether genomic profiling to identify undiagnosed individuals who are at increased risk for cardiovascular disease (CVD) leads to improved cardiovascular outcomes.

Overall, the assessment was that there is insufficient evidence to support such testing in the general population. The net health benefit was deemed to be low, and clinical use was discouraged unless improved clinical outcomes are demonstrated in future research.

It is worth exploring the report further to understand the current state of knowledge and anticipate potential new developments. The evidence review looked at all eight genetic testing panels marketed for CVD risk prediction that were commercially available in February 2008. Collectively, 58 genetic variants were identified among 29 genes. Of these, 38 were reported to have some association with risk for coronary heart disease (CHD), consisting of coronary artery disease, ischemic heart disease, or myocardial infarction. Data for association with stroke were weaker.

Only two test manufacturers (deCODE Genetics and Interleukin Genetics) indicated that they are Clinical Laboratory Improvement Amendments–certified and provided detailed test method and validation information. For the other tests, there was frequently insufficient information to identify even the specific genetic variants being tested, much less the analytic validity of the approach. Nonetheless, the existing scientific technology was considered adequate to allow satisfactory accuracy and reliability of the tests for detecting genetic variation.

Regarding sensitivity and specificity for predicting CHD, of the 38 genetic markers identified, only the one located at chromosome position 9p21 was graded as highly credible and statistically significant. The odds ratio for developing heart disease among people carrying two copies of the high-risk variant, compared with those carrying two copies of the low-risk variant, was 1.56. Although the tumor suppressor genes CDKN2A and CDKN2B are located in this region, the specific gene(s) and/or biological mechanism underlying this risk association is still unknown.

Among all the markers, 24 were deemed to have some degree of credibility and/or statistical significance. However, combining them in a statistical model did not provide a clinically useful stand-alone predictive test. Even the 9p21 genetic marker, when combined with traditional cardiac risk factors, provided only 0%-5% improvement in risk assessment for CHD.

Regarding clinical utility, there are no published data on the long-term outcomes associated with genetic testing for CHD risk prediction. The anticipated benefit is improved identification of those at higher risk of disease, which could lead to improved clinical outcomes by virtue of increased efforts at risk reduction (through behavior change and pharmacologic treatment) and more aggressive screening for and management of manifest disease.

Potential harms must be considered, too. Among false positives – those identified incorrectly as being at increased risk for CHD – there may be unnecessarily increased anxiety and treatment-associated adverse events, without any reduction in morbidity or mortality. There also are financial costs associated with false positives.

An additional risk is false reassurance for those who are at increased risk, but who are not identified by genetic testing. There is room for optimism, as early data suggest at least short-term cardiac risk reduction without clinical harms, but additional and longer-term studies are still needed.

There are notable limitations to this report. Most of the data so far were obtained in whites of European ancestry. Gene-disease associations and effect sizes may be quite different in other populations. In addition, many of the studies are relatively small and underpowered. Larger and newer studies are still identifying additional candidate genes and markers.

Even more challenging is that we still do not know how to combine multiple genetic factors to develop a composite risk assessment, nor do we know how to combine a genetic risk assessment with traditional cardiac risk predications. Most models assume complete independence and simply multiply the odds ratio of each identified variant. However, this approach has not been validated and could yield falsely elevated or diminished risk scores.

The true power of genetic association studies to identify risk factors for common diseases may in fact not lie in better identification of those at increased risk. Rather, elucidation of the biological basis of such associations holds the promise of improving our understanding and eventual treatment of the underlying disease process.

So, how should a physician deal with the availability of cardiac risk assessment tests? Clearly, these are best suited for people who consider themselves early adopters. The 9p21 marker appears to be the most clinically relevant marker at this point. Indeed, the risk associated with this genetic variant appears highest in younger individuals. So, perhaps it might be appropriate to consider obtaining such information in a person under age 55 years who needs further encouragement to modify his or her cardiac risks.

Ideally, patients and their providers will engage in a discussion of the potential risks and benefits prior to any testing. Then, in the truest and oldest model of personalized medicine, they can decide together if pursuing such testing is appropriate on a case-by-case basis. ■

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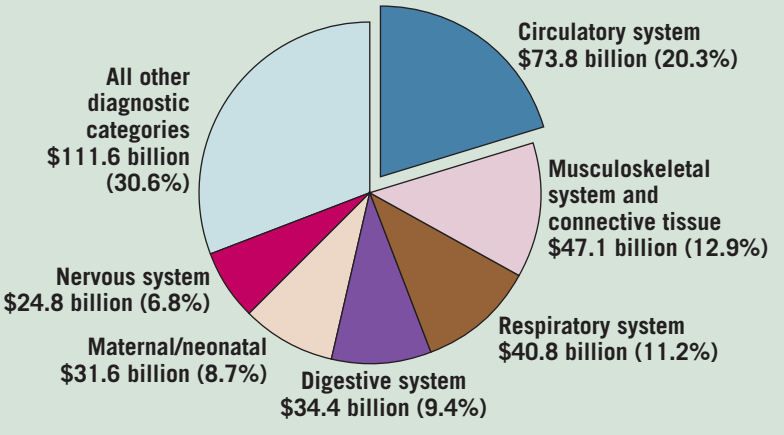

Note: Based on data from the Healthcare Cost and Utilization Project.
Source: Agency for Healthcare Research and Quality