EDITORIAL

Genetic profiling tests in screening for cardiovascular disease

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The study of the association between genes and cardiovascular disease (CVD) is an active field of scientific enquiry and a number of single-nucleotide polymorphisms (SNPs) have been found to be associated with an increased, or decreased, risk of CVD.

A recent study by Ripatti and others[1] proposed a genetic risk score for the prediction of CVD. The genetic profiling test is based on 13 SNPs and was evaluated in a cohort study of 30,725 healthy participants with an average follow-up of 10.7 years. Individuals in the top fifth of the distribution of risk scores had an odds ratio for CVD of 1.50 (95% confidence interval: 1.29 – 1.75) compared to people in the bottom fifth. Given this, it appears reasonable to ask how useful the genetic risk score might be as a screening test in the general population.

Screening performance is determined by the detection rate (the proportion of individuals who do have a future CVD event who are designated 'high risk') for a specified false-positive rate (proportion of individuals who do *not* have a future CVD event who are designated 'high risk'). This can be estimated from the odds ratio between the top and bottom fifths of the risk score. The conversion from odds ratio to screening performance can be performed online using a risk-screening converter.[2,3] The risk score has a detection rate of 13% for a 10% false-positive rate. The test is therefore virtually useless for predicting disease.

It is unlikely that a better screening performance will be achieved by adding more SNPs. A review by Palomaki and others identified over 600 studies which investigated the association between CVD and more than 3000 SNPs and found 58 statistically significant associations in 29 genes.[4] The largest odds ratio for the association between a given SNP and CVD was approximately 1.6, with most odds ratios lying between 0.8 and 1.2. Using all the identified SNPs to achieve the best possible theoretical screening performance, the authors calculated a 23% CVD detection rate for a 10% false-positive rate, so this 'best case' example would miss about three-quarters of all future cardiovascular disease events. Even this is probably an overestimate of the screening performance because it was assumed that all genes acted independently, even though this is recognized not to be the case.

The overall screening performance of genetic profiling tests is poor because associations between disease and the component SNPs are weak. As an example consider a genetic profiling test consisting of a single SNP where the test is positive if an individual is homozygous for the marker SNP and the test has a false-positive rate of 10% (equivalent to an allele frequency of approximately 33% because $0.33^2 \approx 0.1$). If the odds ratio for having CVD with a positive test result compared to having a negative test result is 1.5 the detection rate for the test is only 14%. To achieve a detection rate of 50% would require an odds ratio of 10 or more, far larger than the identified odds ratios in the Palomaki review.

It may be thought that risk factors that individually have poor screening performance can have considerably improved screening performance when combined. This is not the case. Combining multiple SNPs adds little to screening performance because each additional SNP will contribute less and less to the screening performance.[5] Figure 1 illustrates this. The false-positive rate for the test with a combination of SNPs is fixed at 10% and the curves show the relationship between the number of SNPs in the profiling test and the detection rate, where each individual SNP has an odds ratio of either 1.2 or 1.5 (plausible odds ratios given the data from Palomaki and associates). The proportion of the population with a positive test result for each individual SNP was set at 50% for all SNPs and it was assumed that all SNPs act independently on disease risk, which yields the most optimistic performance. An individual has an overall positive result for the multi-SNP test if the product of the

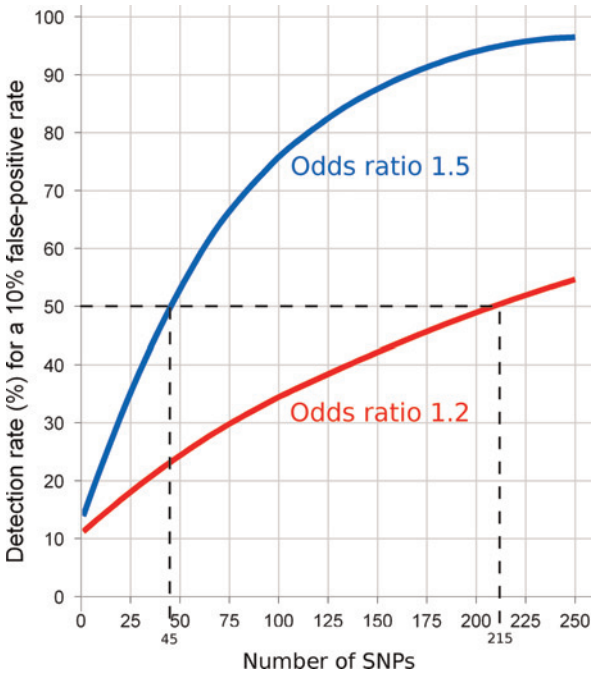

Figure 1 Detection rate for a 10% false-positive rate for a multi-SNP genetic profiling test with an odds ratio of 1.2 or 1.5 for each SNP, plotted against number of SNPs

odds from all the component SNPs exceeds the cut-off level needed to achieve a 10% false-positive rate. The figure shows that to achieve a 50% detection rate would require a test with 45 different SNPs if each SNP had an odds ratio of 1.5, and 215 SNPs if the odds ratio for each were 1.2, as illustrated by the dotted line.

For a genetic profiling test to be useful in screening for CVD there would have to be either a few SNPs with very strong associations with disease, or an extremely large panel of SNPs each with a modest association with disease. At present neither is the case.

Genetic profiling tests might be useful when combined with age and other traditional cardiovascular risk factors such as blood pressure and cholesterol. The Ripatti genetic risk score, when combined with such risk factors, was found to have a screening performance no better than using the risk factors without the genetic risk score.[1] Given the findings of the Palomaki review, using any genetic test in combination with other factors would increase the detection rate by no more than 1–2%. This is too small to justify their use.

Although genetic profiling tests are not useful in screening for cardiovascular disease it does not mean that knowledge of the causal associations between genetic polymorphisms and disease is not useful. Understanding the genetic causes of disease could be useful in research to prevent disease and to find useful treatments. This should be the aim of such genetic studies and not the creation of genetic profiling tests that may be commercially lucrative but give the false expectation that the tests can predict disease.

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