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SPECIAL ARTICLE

The sense and nonsense of direct-to-consumer genetic testing for cardiovascular disease

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Abstract Expectations are high that increasing knowledge of the genetic basis of cardiovascular disease will eventually lead to personalised medicine—to preventive and therapeutic interventions that are targeted to at-risk individuals on the basis of their genetic profiles. Most cardiovascular diseases are caused by a complex interplay of many genetic variants interacting with many non-genetic risk factors such as diet, exercise, smoking and alcohol consumption. Since several years, genetic susceptibility testing for cardiovascular diseases is being offered via the internet directly to consumers. We discuss five reasons why these tests are not useful, namely: (1) the predictive ability is still limited; (2) the risk models used by the companies are based on assumptions that have not been verified; (3) the predicted risks keep changing when new variants are discovered and added to the test; (4) the tests do not consider non-genetic factors in the prediction of cardiovascular disease risk; and (5) the test results will not change recommendations of preventive interventions. Predictive genetic testing for multifactorial forms of cardiovascular disease clearly lacks benefits for the public. Prevention of disease should therefore remain focused on family history and on non-genetic risk factors as diet and physical activity that can have the strongest impact on disease risk, regardless of genetic susceptibility.

Keywords Genetic testing · Cardiovascular disease · Direct-to-consumer · Predictive ability · Risk assessment

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Expectations are high that increasing knowledge of the genetic basis of cardiovascular disease will eventually lead to personalised medicine—to preventive and therapeutic interventions that are targeted to at-risk individuals on the basis of their genetic profiles [1, 2]. Encouraged by these expectations, many companies already offer predictive genetic testing, mostly via the internet and directly accessing the general public. While intuitively it is clear that these direct-to-consumer genetic tests are too premature, it is a challenge to appreciate the seemingly conflicting claims.

Genome-based predictive testing and personalised medicine already exists for monogenic forms of cardiovascular disease. In the long-QT syndrome in particular, the genetic substrate impacts on prognosis and therapeutic choices. Furthermore, there is sound evidence that pre-symptomatic genetic testing in inherited primary arrhythmia syndromes leads to prophylactic therapy in a substantial number of patients [3]. In diseases without an easily discernable arrhythmogenic substrate such as familial idiopathic ventricular fibrillation, genetic testing might be the only way to identify individuals at risk [4]. In hypertrophic cardiomyopathy, genetic cascade testing is a cost-effective way to identify relatives at risk and for primary prevention of sudden cardiac death [5, 6]. Counselling and testing take

place in a medical setting, in the Netherlands located at the multidisciplinary cardiogenetics outpatient clinics [7]. Finally, cascade testing for familial hypercholesterolaemia is currently part of the Dutch population screening programme [8].

Most cardiovascular diseases are not monogenic but caused by a complex interplay of many genetic variants interacting with many non-genetic risk factors such as diet, exercise, smoking and alcohol consumption. In these complex forms of disease, each genetic variant has only a marginal impact on disease risk, and therefore, genetic prediction needs to consider multiple variants simultaneously. Their effects are combined in risk models using similar approaches, as for example, the Framingham Risk Score [9]. Empirical studies have demonstrated that the predictive ability of genetic risk models is still very modest [10–13].

Despite the modest predictive ability, genetic susceptibility testing for cardiovascular diseases has been offered via the internet directly to consumers since several years. In the early days, companies were offering cardiogenomic or heart health tests, which covered a limited number of genetic variants on the basis of which lifestyle recommendations were decided. These recommendations were based on each variant separately and usually included recommendation of nutrition supplements that could be bought from the same companies. The scientific basis for these tests was very limited, predominantly because tested variants were not robustly associated with disease risk at all or had very low effect sizes [14]. Most of these companies are now out of business, likely because for the same price others are offering genome-wide scans that predict multiple diseases simultaneously. For example, deCODEme tests six types of cardiovascular diseases, including myocardial infarction, abdominal aortic aneurysm, atrial fibrillation, peripheral arterial disease, intracranial aneurysm and venous thromboembolism, in addition to about 45 other diseases and traits. While the early commercial tests were based on variants for which there was insufficient scientific basis [14], companies like deCODEme, 23andMe, Navigenics and Pathway Genomics have adopted high scientific standards for the selection of genetic variants. Nevertheless, there are still five reasons why also their tests are not useful for predicting cardiovascular diseases at this moment.

First, the predictive performance of genetic variants for complex diseases in general is limited because only a relatively small number of the common variants involved have been identified and their effect sizes are generally low [15]. When tests only include a small number of variants with small effect sizes, most tested individuals have predicted risks that are very close to average. This implies that the majority of individuals receive approximately the same predicted risk, which consumers never realise, certainly not before buying the test. While the use of genome-wide scans suggests that prediction is based on a larger number of variants for each disease, this frequently is not the case. For example, deCODEme predicts abdominal aneurysm and peripheral artery disease on one genetic variant, atrial fibrillation on two, venous thrombosis and intracranial aneurysm on three and myocardial infarction on only seven variants and also 23andMe predicts myocardial infarction risk on the basis of one chromosome 9 variant alone (accessed 17 August 2010). It is clear that many more variants need to be identified to achieve appreciable predictive ability [16].

Second, the risk models used by the companies are based on assumptions that have not been verified. Companies do not obtain predicted risks from empirical studies, but rather calculate individual risks by multiplying a population average risk with the combined effects of the variants tested. More frequently than before, companies use age- and sex-specific average risks from epidemiological studies, but sometimes appropriate data are not available [17]. In addition, the odds ratios used in the calculation are obtained from meta-analyses of case–controls studies, which may overestimate the effects that are found in unselected populations. And finally, the algorithms used to calculate individual risks assume that genetic variants inherit independently and that their combined effects follow from multiplying the individual effects. While this may be the best strategy to date, it almost guarantees inaccurate risk estimates.

Third, predicted risks keep changing when new variants are discovered and added to the test. For consumers, this may imply that they are at increased risk of disease at one moment and at decreased risk at the next, which is confusing when the test result should impact decisions about prevention or treatment. Updating type 2 diabetes risk from 1 to 18 variants, we showed that half of the population changed at least once from decreased to increased risk or vice versa [18]. Thirty percent changed risk categories at least twice. Risks generally change when risk models are updated, but with the current speed of gene discoveries from genome-wide association studies, risk predictions may change too frequently to be of any practical utility.

Fourth, current commercial tests do not consider non-genetic factors in the prediction of cardiovascular disease risk. Several studies have shown that genetic risk models have substantially poorer predictive ability than conventional risk models based on clinical measures, lifestyle factors and family history and that genetic variants do not further improve prediction of disease beyond these risk factors [10–12, 19]. Recently, there has been substantial debate about the clinical utility of testing a variant in 9p21, a locus that has been consistently associated with cardiovascular conditions. Yet, also robustly associated variants do not necessarily improve prediction. The per-allele odds

ratio of 9p21 rs10757278 for risk of myocardial infarction is 1.26 [20], not spectacularly higher than many other variants, and two prospective studies showed that this polymorphism, as expected, did not markedly improve prediction of cardiovascular disease beyond traditional non-genetic risk factors [21, 22].

And finally, the results of direct-to-consumer cardiovascular genetic tests will not change recommendations of preventive interventions. Many preventive strategies such as healthy diet, physical activity, no smoking and moderate alcohol consumption are recommended to everyone, irrespective of one's exact cardiovascular disease risk. Some individuals may need to change their diet because of a genetic predisposition to cardiovascular disease, others because of type 2 diabetes, osteoporosis or cancer. Claims that genetic testing may enhance motivation and empower prevention [23] are not substantiated by empirical evidence, and evidence is also lacking for the preventive prescription of medication, such as aspirins or statins.

When genetic tests are unable to usefully predict cardiovascular disease to date, should we be concerned about these commercial developments? On the one hand, yes, because at least it may unnecessarily increase the workload of health care professionals. A recent survey showed that half of the individuals who bought a commercial test and three quarters of those who would consider buying one did or would consult a physician for help interpreting the results [24]. Some physicians even encourage their patients to use these tests (which are costly and not reimbursed), sharing the expectations of consumers that results will guide treatment. On the other hand, there are no appropriate empirical studies that demonstrate that these tests also have adverse psychological consequences for consumers, also because consumers' experiences with the early commercial tests cannot be simply extrapolated to these genome-wide scans. It is not clear whether consumers can handle and appropriately interpret all risk information from genome-wide scans, and whether they understand the relative importance of genetic information in contrast to non-genetic risk factors, particularly those lifestyle factors that can be changed. It has been suggested that individuals who learn that they are at increased genetic risk of disease may adopt fatalistic beliefs, thinking that there is nothing that they can do to prevent disease because it is already 'in their genes' or that those who learn that they are at decreased risk feel reassured and believe that in terms of their lifestyle they can do what they like because they are genetically protected.

In conclusion, most genetic tests for complex cardiovascular disease have minimal predictive ability and no clear benefits for consumers. Also for the future, it is uncertain whether DNA testing for cardiovascular diseases will yield useful information to guide decisions about preventive or therapeutic interventions [25, 26]. There will likely be promising exceptions, also for complex diseases. For example, in pharmacogenomics, where genetic variants are investigated for their impact on the degree of efficacy or the toxicity of medications, genetic testing may become useful to personalise medication regimens and doses. Yet, if such applications do prove useful, these genetic tests will undoubtedly be offered through the medical clinics and be reimbursed.

We have provided five reasons cardiologists can use to explain to patients why the direct-to-consumer cardiovascular tests are not useful. This information may hopefully lead to more realistic expectations about the impact of genetic variants on disease risk and put the focus of attention back to family history and to the non-genetic risk factors, diet and physical activity, which can have the strongest impact on disease risk, regardless of genetic susceptibility. Counselling and testing for monogenetic cardiovascular diseases should remain in the medical setting and should only be provided by those professionals that are knowledgeable and experienced in this field.

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