

# Genomic profiling to promote a healthy lifestyle: not ready for prime time

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**Genomic profiling has the potential to usher in a revolution of personalized healthcare and disease prevention. But evidence to support genomic profiling is inconsistent, and data on the health outcome benefits based on such testing are lacking. For genomic profiling to become valid and useful, well designed epidemiologic studies and thorough clinical evaluations of recommended interventions based on genotype are required.**

Advances in genetics and the sequencing of the human genome will ultimately result in a comprehensive understanding of the molecular underpinnings of human development, health and disease. Hundreds of reports of gene-disease associations have already been published, and knowledge about the interactions between genetic and environmental factors is increasing daily. Genomic profiling, the newest approach to personalized medicine, consists of the concurrent detection of multiple gene variants that have been associated with greater risk or predisposition to a particular disease or condition. The profiles are proposed as a means to identify individual risk, for the purpose of tailoring specific risk-reducing actions, typically involving vitamins, environmental exposures, diet or other lifestyle changes that are expected to prevent disease. The assumption driving this approach is that individuals will be able to use their genomic profiles to reduce their risk of common conditions, such as heart disease, diabetes and obesity, or to improve overall health and well-being.

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Experts have predicted that future medical care and disease prevention will be based on genetic risk profiles that identify individual risks for various diseases and for drug response<sup>1,2</sup>. But physicians and consumers can already order personalized genomic profiles to promote healthy lifestyles or guide preventive care. A number of companies in the US and the UK offer genomic profiles, such as the Oxidative Stress Profile, Oxidative Stress for Skin Health and Aging Profile, Obesity Susceptibility Profile, Osteopenia Susceptibility Profile, CardioGenomic Profile, DetoxiGenomic Profile, Immuno Genomic Profile, Tissue Repair Screen and Alcohol Metabolism Screen (see <http://www.genovations.com>, <http://www.sciona.com> and <http://www.bankdna.com> for more information). The combination of specific gene variants screened in these profiles is not always disclosed on their websites or advertisements.

This lack of disclosure is important because the scientific and clinical data on which genomic profiling is currently based are questionable. In this commentary, we address four concerns in evaluating the utility of genomic profiling: (i) the need for a thorough evaluation and interpretation of the outcomes of testing, (ii) the need to address labeling and promotion of such tests, (iii) the need for robust epidemiological and clinical data and (iv) the need to identify and implement appropriate consensus procedures to evaluate emerging data to determine when a genomic profile has met an acceptable threshold for clinical use.

## Genomic profiling today

At present, the evidence to support genomic profiling is weak at best owing to limited data. It has become increasingly clear that many initial gene-disease associations prove on follow-up to be spurious or much weaker than originally predicted<sup>3,4</sup>. Because of the observational nature of such studies<sup>5</sup>, the association between a single gene variant and disease state can often be confounded by a number of factors, including variation in other genes, exposures, population stratification and other individual differences between cases and controls. Even if replicated, association studies per se do not necessarily imply causality.

To demonstrate the complexity involved in deciphering the clinical effect of a genetic variant, we consider the test for polymorphisms of the gene encoding methylene tetrahydrofolate (THF) reductase (*MTHFR*), which is included in some cardiovascular risk profiles (see <http://www.genovations.com> for more information). *MTHFR* catalyzes the reduction of methylene-THF (a cofactor involved in methylation of dUMP to dTMP in DNA synthesis) to methyl-THF (a cofactor in methylating homocysteine to methionine). Two variants of *MTHFR*, 677C→T and 1,298A→C, result in reduced enzyme activity, but only 677C→T leads to elevated plasma homocysteine levels and lowered plasma folate levels<sup>6–8</sup>. Compound heterozygosity results in an even lower *MTHFR* activity than heterozygosity with respect to either variant alone, resulting in significantly higher plasma homocysteine levels and lower folate levels<sup>8</sup>.

Elevated plasma homocysteine levels have been independently associated with greater risk for coronary heart disease (CHD). Numerous studies have analyzed the association between *MTHFR* gene variants and risk of CHD, but the results have been conflicting<sup>9–12</sup>. A recent meta-analysis of studies linking the *MTHFR* 677C→T variant and CHD indicated only a modestly greater risk of CHD, particularly in individuals with low folate levels<sup>13</sup>. Although other gene variants are included in the cardiovascular risk profile, it is unclear whether the results are reported as individual risks for each gene analyzed or if a cumulative risk is calculated based on all the genes analyzed in the profile, as has been shown possible for Factor V Leiden<sup>14</sup>.

Even if the association between *MTHFR* 677C→T and CHD were robust, increasing folate intake in carriers of this allele has not been shown to reduce the risk of CHD. At present, population-based studies strongly suggest that greater folate intake may be beneficial in treating heart disease<sup>15–17</sup>, but there are insufficient outcome data to make any recommendations about folate intake based on genotype. Therefore, the combined effect of gene variants in enzymes of a metabolic pathway, diet and multiple disease endpoints warrant further studies to clarify the complex relationships and impact on health<sup>18</sup> before conclusions about clinical use of testing can be made.

The uncertain efficacy of the recommended dietary change based on *MTHFR* genotype contrasts with the probable benefits of tailoring drug therapy based on genotype. For example, carriers of reduced-activity allelic variants of the gene encoding thio-purine S-methyltransferase should be prescribed 15–50% lower dosages of standard thiopurine therapy to minimize risk of drug toxicity and maximize efficacy<sup>19–22</sup>. Another emerging example suggesting promise for pharmacogenomic testing is the assessment of *CYP2C9* gene variants before the use of warfarin for anticoagulation therapy; a recent observational study found a higher rate of bleeding complications and difficulties in maintaining a stable anticoagulation dose in people with *CYP2C9* 2\* and 3\* alleles (as compared with the more common 1\* allele; ref. 23). This genetic test is not yet ready for clinical use: outcome data are needed to confirm that adjusting dosage according to genotype reduces complications of therapy, but the association data suggest benefit and justify clinical trials. Many other pharmacogenetic tests are under active study<sup>2</sup>, suggesting that tests that lead to tailoring of drug therapy on the basis of genotype will provide important benefits in future health care.

### Evaluation of genomic profiling

Genomic profiling will probably have an important role in future health care practice. Genomic profiling and lifestyle assessment will be essential tools in helping to shift the current medical paradigm from a reactive to a proactive or preventive approach. Acceptance of genomic profiling by the medical and public health community, health care payers and consumers, however, depends largely on the verification that an individual's genomic profile can contribute to improved health outcomes. Determining whether genomic profiling can improve health outcomes requires careful assessment of three main areas: (i) the validity of the testing process, (ii) the utility of the test information, based on the availability of safe and effective interventions to reduce risk, and (iii) the accurate labeling and promotion of such tests. The associated ethical, legal and social issues should also be carefully considered.

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The validity of the testing process can be measured in terms of analytical validity and clinical validity<sup>24–26</sup>. Analytical validity refers to how well a test measures the property or characteristic it is intended to measure and can be defined as the sensitivity, specificity and reproducibility of the test's measurement of a particular genetic variant. Sample type and quality, testing protocol, reagents and equipment, and personnel are among the many factors that can influence analytical validity. Because few data have been published regarding the assays used in the genomic profiles currently offered, and consensus-based standards have yet to be established, it is difficult to evaluate their analytical validity at this time.

Clinical validity refers to the accuracy with which a test predicts the presence or absence of a certain disease or predisposition<sup>24–26</sup>. Clinical validity data ideally should be based on strong epidemiologic study design and may be presented as the sensitivity, specificity or positive and negative predictive value of a test for a particular clinical outcome. Many genetic tests have uncertain clinical validity because of limited and potentially biased study populations, low genotype penetrance, variable expressivity, lack of understanding of

phenotypic modifiers and multiple or ambiguous clinical endpoints<sup>25</sup>. For gene variants associated with common diseases, low predictive value is expected as many other genetic and non-genetic factors also contribute to clinical outcomes. Thus, caution is advisable in evaluating scientific claims for tests based on studies of gene-disease associations that do not include robust clinical data and consideration of other risk factors. Because some laboratories offering genomic profiling have elected not to disclose which gene variants are included in their profiles, it is not possible to evaluate the clinical validity of their tests. And as there is no independent regulatory review of the clinical validity of genetic testing provided as a laboratory service in the US<sup>24,26</sup>, the medical and public health community and the general public must be vigilant in questioning the scientific basis for the claims of genetic testing.

Clinical utility refers to the likelihood that use of a test will result in improved health outcomes<sup>24–26</sup>. The clinical utility of a test will depend on the availability, safety and effectiveness of preventive or therapeutic measures offered to individuals with positive test results. When a gene variant predicts greater risk that could be ameliorated through a change in lifestyle, three questions must be addressed to determine clinical utility of the test: (i) Will people with a positive test result make the indicated lifestyle changes that lead to improved health outcomes? (ii) Will people with a negative test result have less motivation to pursue healthy lifestyles? and (iii) Are lifestyle recommendations dependent on the genotype information? If all would benefit from a healthy diet, exercise, smoking cessation or prudent alcohol intake, regardless of genotype, the added value of the test is unclear unless it can be shown to motivate compliance in those who test positive without reducing compliance in those who test negative. Unfortunately, current data suggest little reason for optimism concerning the potential for genetic test results to motivate behavioral change<sup>27</sup>.

In our view, the efficacy and risks of interventions recommended for those with positive results from genomic profiling, and therefore the rationale for the use of these tests in medical decision-making, are uncertain. The medical profession's long experience indicates that there are no interventions without harm and therefore, the benefits and risks of any new test must be carefully weighed. When both harms and efficacy of the recommended interventions are unknown, the wisest choice of action may be inaction. One can argue that the harm of increasing the daily



intake of vitamins and natural supplements to reduce risk of disease or improve overall health is probably minimal. This may indeed be true for some interventions recommended for individuals with positive results from genomic profiling, but even these 'harmless' interventions provide false hope and could distract test-takers from considering proven interventions. There is also a potential conflict of interest when a laboratory that does the testing is the source of the recommended course of action, as a suggestion to use test results as the basis for lifestyle changes may falsely inflate the value of the test.

### Labeling and promotion of genomic profiling

Another concern is the labeling and promotion of genomic profiling to promote healthy lifestyles. A recent review of advertisements for genetic tests found them to be potentially misleading, exaggerating claims and emphasizing genetic determinism<sup>28</sup>. Health professionals and consumers need complete information about what a test can and cannot provide so that they may make an informed decision. Therefore, test offerers should disclose what is known and not known about a test. At present, the implications of results of genomic profiling might be unclear even to health professionals capable of prescribing effective interventions.

Genomics will continue to be hampered for some time by a lack of knowledge about its clinical implications, so the limitations of testing should be clearly described. The complexity of information provided by genetic testing, public misperceptions and lack of clinical utility have, so far, limited the educational value of advertising for genetic tests<sup>28</sup>. These issues will be of particular concern as marketing of genomic profiling is directed to consumers. In response to public and government concerns, the UK Human Genetics Commission recently recommended enhanced controls and safeguards over the provision of genetic tests directly to the public<sup>29</sup>.

### From epidemiologic association to clinical relevance

What steps should be taken to develop valid and useful genomic profiles? The scientific validity of genomic profiling needs to be based on well designed epidemiologic studies on genotype-disease associations and gene-gene and gene-environment interactions. To make sense of genotype-disease associations, epidemiologic methods and principles need to be applied to the design of such studies. These include a large sampling

base for cases, representativeness of controls, adequate sample sizes and proper adjustments for population stratification and other forms of confounding, including assessment of gene-gene and gene-environment interaction<sup>30,31</sup>. Replication of studies is also important: a gene-disease association should be validated across studies and should not be considered proven until it has been adequately replicated<sup>3,4</sup>.

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As we investigate the genetic etiology of complex diseases, the vastness of the genome and high degree of individual variability will create substantial challenges to identifying which gene or set of genes combines with non-genetic factors to produce a disease phenotype. Short of resequencing or genotyping the entire genome, which is not technically feasible or affordable at this time, one common approach is to analyze a set of candidate genes to identify gene variants associated with complex disease. But once a gene or set of genes has been identified, a second, more focused study based on the design approaches briefly discussed here is needed to confirm the initial positive association.

Association between a gene variant and disease does not automatically imply causation. The case for causality is strengthened if the association is strong, biologically plausible and replicated across multiple studies. Additional research is needed to prove that the gene variant is responsible for (or, for complex diseases, contributory to) the development of a disease. Even for simple mendelian disorders, the correlations between genotype and phenotype are not as direct and straightforward as previously thought. 'Phenotypic modifiers', such as variants in other genes and cofactors, lifestyle, diet and environmental factors, contribute in some part to a phenotype<sup>32,33</sup>. For common, multi-factorial diseases, a genetic risk factor may have no or minimal effect on its own but, in combination with a change in environment, may result in greater risk for disease. Functional tests of candidate disease genes in animal models, expression and cellular distribution data, protein expression, functional

and structural analysis of the variant allele and knowledge of how complicating factors may alter phenotype would substantially support the case for causation<sup>34</sup>. Until causation has been proven, any recommended treatment strategies based on genotype data may be ineffective.

To confirm the utility of a test, carefully controlled trials need to be designed with definitive and measurable clinical endpoints<sup>28</sup>. Ideally, the endpoints measured in such trials would include subjective factors, such as sense of well-being, as well as conventional medical outcomes. These types of studies would be longitudinal by nature and probably costly. Because some of the products of recommended preventive strategies, such as greater intake of vitamins or supplements, are not subject to regulatory review in the US, the commercial incentive to conduct such studies may be low.

### Consensus development and practice guidelines

Even as more evidence accumulates, few genomic profiles are likely to be assessed in well designed randomized clinical trials. Thus, careful thought needs to be given to the level of evidence that justifies clinical use of genomic profiling, taking into account the strength of the observational data, the plausibility of clinical benefit and the potential for harm. Experts may disagree in the evaluation of a particular body of evidence. For this reason, the public and the clinical community will be best served by a consensus process that incorporates well defined procedures for evaluating evidence and reaching conclusions and includes the participation of clinicians, health care payers and consumers<sup>35</sup>. Examples of consensus procedures used for evaluating preventive care are available (see <http://www.ahcpr.gov/clinic/cps3dix.htm> and <http://www.hta.nhsweb.nhs.uk/> for more information) and could be readily adapted to the evaluation of genomic profiling.

### Conclusion

It is unclear how successful companies have been in marketing genomic profiling to consumers and health professionals; thus, our concerns may be premature. But the predictive power and mystique associated with genetics, consumers' desire to take control of their health and be proactive, and the ease of advertising and ordering tests on the Internet combine to create a powerful incentive for companies to continue developing and promoting genomic profiling regardless of whether the tests have been validated and proven useful. The popularity of dietary

supplements and whole-body scans is proof that the public is willing to invest in products whose safety, validity or utility are unproven if the possibility exists of improving health or preventing disease.

Although genomic profiling may ultimately provide a sound basis for personalized lifestyle modification, and holds great promise for predicting an individual's future health risks, the science is still in the early stages of deciphering gene-gene and gene-environment interactions and their health implications. Even when associations are established, they will not be of clinical benefit unless they lead to effective interventions based on genotype, which need to be proven through observational studies and clinical trials with well defined endpoints. Furthermore, the integration of new medical tools requires an assessment of what criteria determine when a particular profile should be ordered (for example, family history, clinical symptoms), who can order tests (should it be restricted to health professionals?) and coverage and reimbursement by third party payers. Appropriate consensus procedures to address these questions should also be identified prospectively. The scientific, medical and public health communities, academic institutions, professional organizations, regulatory agencies and consumers are all involved in the successful translation and integration of genomic profiling to medical practice. The

premature use of such tests based on initial gene-disease associations and interventions of uncertain value could do more harm than good to both consumers and the field of genomic medicine. ■

**URL.** The Secretary's Advisory Committee on Genetic Testing report titled *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT* is available at [http://www4.od.nih.gov/oba/sacgt/reports/oversight\\_report.htm](http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.htm).

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