



Letting the Genome out of the Bottle — Will We Get Our Wish?

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It may happen soon. A patient, perhaps one you have known for years, who is overweight and does not exercise regularly, shows up in your office with an analysis of his whole genome at multiple

single-nucleotide polymorphisms (SNPs). His children, who were concerned about his health, spent \$1,000 to give him the analysis as a holiday gift. The test report states that his genomic profile is consistent with an increased risk of both heart disease and diabetes, and because the company that performed the analysis stated that the test was “not a clinical service to be used as the basis for making medical decisions,” he is in the office for some “medical direction.” What should you do?

This year has seen a dizzying number of genomewide association studies demonstrating associations between novel gene variants or chromosomal loci and common diseases and pheno-

types. These studies rely on microarrays that can assess 300,000 or more SNPs in each DNA sample; researchers use these microarrays to examine interpersonal differences in inherited genetic variability and to compare the prevalence of gene variants among patients who have a given disease with that among controls. Such studies have identified associations with many gene variants that were not previously suspected to be related to the phenotypes under consideration. The new technologies involved have been a boon to researchers who needed unbiased clues as to the causation of diseases that may be used to develop new therapeutic and preventive interventions.

The test undergone by the patient described above is one of the products of this new knowledge.

As of November 2007, two companies have made available direct-to-consumer “personal genome services” (www.23andme.com) or “gene profiles” (www.decode.me.com) that rely on the same arrays of 500,000 to 1 million SNPs used in genomewide association studies. A third company (www.navigenics.com) has announced that it will offer similar services later this year. Essentially, a client sends a DNA sample to one of these firms, which analyzes the sample by means of SNP array; the data are stored in an online private account, the results are compared with allele-phenotype databases maintained and updated by the company, and the customer receives a readout of his or her levels of risk for specific conditions.

But such premature attempts

at popularizing genetic testing seem to neglect key aspects of the established multifaceted evaluation of genetic tests for clinical applications. First, there is the question of a test's analytic validity, "its ability to accurately and reliably measure the genotype of interest."¹ Although appropriate monitoring and oversight of the analytic validity of genetic tests remain largely unaddressed,² most researchers report that the analytic validity of these platforms is very high. It is likely that sample-handling errors are a greater threat to the validity of results than are genotypic misclassification errors. Yet even very small error rates per SNP, magnified across the genome, can result in hundreds of misclassified variants for any individual patient. Without transparent quality-control monitoring and proficiency testing, the real-world performance of these platforms is uncertain.

Second, one must consider clinical validity, or the ability of the test to detect or predict the associated disorder.¹ Components of clinical validity include the test's sensitivity, specificity, and positive and negative predictive value. This is the area in which the data are in the greatest flux, and even the ardent proponents of genomic susceptibility testing would agree that for most diseases, we are still at the early stages of identifying the full list of susceptibility-associated variants. Most of the diseases listed by the direct-to-consumer testing companies (e.g., diabetes, various cancers, and heart disease) are so-called complex diseases thought to be caused by multiple gene variants, interactions among these

variants, and interactions between variants and environmental factors. Thus, a full accounting of disease susceptibility awaits the identification of these multiple variants and their interactions in



well-designed studies. What we have now is recognition of a limited number of variants associated with relative risks of diseases on the order of 1.5 or lower. Risk factors with this level of relative risk clearly do a poor job of distinguishing people who will develop these diseases from those who will not.^{3,4}

Finally, there is the issue of the test's clinical utility, or the balance of its associated risks and benefits if it were to be introduced into clinical practice.¹ Measures of utility address the question at the heart of the clinical application of a test: If a patient is found to be at risk for a disease, what can be done about it? This is the arena in which there are virtually no data available on the health impact of genome-wide analysis. There are very few observational studies and almost no clinical trials that demonstrate the risks and benefits associated

with screening for individual gene variants — let alone testing for many hundreds of thousands of variants. Thus, any claim to clinical utility currently rests on the assumption that interventions that have proven successful in the general population will behave the same way in a genetically at-risk population. Many of these interventions — such as smoking cessation, weight loss, increased physical activity, and control of blood pressure — are likely to be broadly beneficial in relation to many diseases, regardless of a person's genetic susceptibility to a specific disease.

It may be argued that knowledge of increased susceptibility to a disease, such as type 2 diabetes, for which protective lifestyle interventions exist, will motivate patients to follow relevant recommendations. Yet as intuitively appealing as this contention may be, evidence to support it, particularly in the case of low-penetrance alleles, is scanty. The flip side, of course, is that patients who test negative may be falsely reassured and thus less motivated to comply with preventive recommendations. In the absence of evidence of efficacy, this rationale for susceptibility testing should be regarded with skepticism.

So what advice should a physician offer patients? For the patient who appears with a genome map and printouts of risk estimates in hand, a general statement about the poor sensitivity and positive predictive value of such results is appropriate, but a detailed consumer report may be beyond most physicians' skill sets. For the patient asking whether these services provide information that is

useful for disease avoidance, the prudent answer is “Not now — ask again in a few years.” More information is needed on the clinical utility of this information in the light of existing disease-specific opportunities for prevention or early detection and the potential value that genomic profiles can add to that of simpler tools, such as the family health history. Finally, given the risk of commercial exploitation, if patients are determined to proceed, perhaps because they are simply curious, are genetic hobbyists, or are “early adopters” of new technology, it would make sense to encourage them to enroll in formal scientific studies.

Now that the genome is out of the bottle, how will our wish for better health be granted? Just as the emergence of a commercial entity (Celera) with ambitions

to sequence the human genome spurred public projects to accelerate their efforts, perhaps the emergence of commercial personalized genomic services will galvanize efforts to plan and conduct the necessary translational research⁵ for the rational integration of genomic information into medical training and practice. Until the genome can be put to useful work, the children of the man described above would have been better off spending their money on a gym membership or a personal trainer so that their father could follow a diet and exercise regimen that we know will decrease his risk of heart disease and diabetes.

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HIV in India — A Downsized Epidemic

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In 2006, the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimated that 5.7 million people in India were infected with the human immunodeficiency virus (HIV), a figure that captured wide attention and raised the possibility that India had more infected people than any other country.¹ In 2007, however, the estimate was revised downward to 2.5 million (range, 2.0 million to 3.1 million) — a revision so large that it reduced by nearly 10% the estimated number of people living with HIV globally and reinforced ongoing concerns about the validity of methods for producing such epidemiologic estimates.

Using revised methods that also resulted in reduced estimates for Kenya, Mozambique, Nigeria, and some other sub-Saharan African countries, UNAIDS and WHO now calculate that 33.2 million people worldwide (range, 30.6 million to 36.1 million) are living with HIV (see bar graphs), a 16% reduction from their 2006 estimate.² Global HIV incidence is now thought to have peaked about a decade ago at more than 3 million new infections per year; for 2007, new infections were estimated at 2.5 million (range, 1.8 million to 4.1 million). Sub-Saharan Africa continues to dominate the statistics, remaining the region most affected by AIDS. The estimated prevalence of HIV

among adults in sub-Saharan Africa is 5.0%, as compared with 0.36% in India; two thirds of all infected adults and nearly 9 in 10 infected children live in sub-Saharan Africa. In 2007, 76% of AIDS deaths occurred in this region — a fact that reflects the continuing unmet requirement for antiretroviral treatment.² Although the number of people receiving treatment in sub-Saharan Africa has increased substantially — from 100,000 in 2004 to 1.3 million in the spring of 2007 — many more still require it.

The revised numbers for India, which were announced in July 2007 by the National AIDS Control Organization, mean that the HIV epidemic in India is less gen-