

# Genomic Profiles for Disease Risk

## Predictive or Premature?

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**T**HERE HAS BEEN A RECENT EXPLOSION OF COMMERCIAL availability of genomic “tests” for diseases, conditions, traits, and ancestry. Dozens of companies advertise their services directly to consumers who, if they are willing to provide a DNA sample (usually from saliva) and are also willing to pay the charges, can obtain genetic information about various health conditions. These “conditions” range from the tendency to form wet vs dry earwax to risk for significant adult-onset diseases (TABLE).<sup>1</sup>

Unlike a decade ago, when DNA tests for cancer risk were carefully introduced to health care professionals in advance of widespread marketing,<sup>2</sup> in 2008 the commercialization of genomic profiling started as a for-profit direct-to-consumer marketing campaign largely intended to bypass health care professionals. Now, most physicians learn through the media of the availability of “genome scans” that can be ordered for about \$1000 by their patients.<sup>3</sup> These tests are touted to predict medical conditions from risk of obesity to risk of cancer, diabetes, and blindness. Health professionals are now faced with the prospect of their patients coming to the office, DNA profile in hand, asking for preventive management tailored to their specific disease risks.

Although some concern remains about the direct-to-consumer marketing of *BRCA* tests for hereditary breast cancer,<sup>4</sup> direct-to-consumer marketing of genomic disease profiles seems to have escaped the careful vetting that accompanies the introduction of new biomedical technologies. Unlike the new harvest of genomic panels, *BRCA* testing and other cancer predisposition tests have been subject to a decade of prospective study and validation, physician education, and monitoring of laboratory quality by academic and regulatory groups. However, failure to provide similar protection to patients seeking their genomic information may have undesired consequences. The unregulated and unvalidated introduction of genomic self-testing may undermine physicians’ efforts to secure public confidence and acceptance of this vital component in the emerging field of “personalized” medicine.

More than a decade ago, professional groups such as the American Society of Clinical Oncology called for certain requirements before genetic testing could be introduced into general practice.<sup>2</sup> They outlined a broad set of problems to

be addressed before routine use of presymptomatic testing for hereditary risk for cancer. These requirements included addressing risk of insurance-based discrimination, validation of research data by prospective trials, and regulatory assurance of accuracy of testing. In each of these areas progress ensued. Genetic testing is now part of preventive practice, and guidelines have been established to inform the targeted use of costly but effective screening technologies.<sup>5</sup> Instead of discriminating, most insurance companies now pay for cancer genetic testing, preventive measures, and screening. Recent reviews have documented the disease risks and efficacy of management strategies after genetic testing for the most common syndrome of hereditary breast and ovarian cancer.<sup>6</sup> Many states passed laws on privacy of genetic information, and some states put into place standards for certification of laboratories providing predictive genetic testing.<sup>7</sup>

Academic organizations such as the American College of Medical Genetics have warned about the risks of genetic testing without professional counseling and oversight.<sup>8</sup> For adult-onset conditions such as macular degeneration, other debilitating neurologic conditions, or common malignancies, the potential emotional turmoil and need for support and guidance before and after genetic risk testing is evident. Some commercial laboratories that offer genetic testing directly to consumers recommend professional consultation. Some will even offer telephone access to a trained genetic counselor with a master’s degree. In-person genetic counseling by a physician trained in the relevant disease subspecialty is not required by most direct-to-consumer laboratories. However, even if referrals to experts are made, there remains a fundamental concern about the validity of many of the tests.

Assessing and comparing genetic testing quality between laboratories is not straightforward. The panels of disease-specific genetic markers used by some laboratories are proprietary and may vary between laboratories. The companies often state that the services offered are not medical tests because they are provided “for informational purposes only.” In some scenarios, the consequences of an incorrect genotype may be modest. For instance, in a widely reported example, one of the pioneers of genetic research

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underwent full sequencing and learned he had a genotype conferring lactose intolerance when, in fact, he did not have this condition.<sup>9</sup>

Some of the marketed genetic “tests” (eg, the earwax example or use of “antiaging” creams according to DNA profiles) may cause little harm if misinterpreted. However, the consequences of imprecise genotyping for adult-onset disorders may be much greater. Analytic genotyping error may result from different methods used by laboratories not monitored by proficiency testing.<sup>10</sup> Even if technically accurate, a genotype may lack clinical utility. For example, 2 of the discoverers of single nucleotide polymorphisms (SNPs) associated with macular degeneration do not consider these tests ready for clinical use until prospectively validated (Robert I. Klein, PhD, Sloan-Kettering Institute, New York, New York, and Burt Gold, PhD, National Cancer Institute, Frederick, Maryland; oral communication, December 2007).

Commercial companies have proceeded to market panels of genetic markers, as well as whole genome “health scans,” which have largely been derived from retrospective studies. However, there is an emerging consensus that extensive replication across diverse population subsets is needed to discern true disease associations from the “blizzard of false positives” that is inevitable when hundreds of thousands of genetic markers are probed at the same time.<sup>11</sup> Despite these concerns, some academic institutions may be influenced by commercial pressures to market as-yet-unvalidated tests based on recent discoveries. The field is already replete with such initially promising but ultimately false-positive associations between genetic markers and schizophrenia, obesity, stroke, and Parkinson disease, for example.<sup>11</sup> The reasons for the failure to replicate such studies include population heterogeneity, lack of statistical power, interactive effects, and technical issues related to genotyping.

The commercial companies are not unaware of the standards set by academic bodies; these standards are even cited in various “white papers” listed on some of the company Web sites.<sup>12</sup> Nonetheless, the implicit marketing strategy of these companies is to involve the consumer in a “voyage of genetic self-discovery,” even if some of the initial paths charted lead nowhere. In the worse-case scenario, the paths may lead to unnecessary medical interventions or false reassurances and missed diagnoses. The incentive for financial profit in such a journey is at fundamental odds with the skeptical nature of scientific inquiry and the conservative nature of clinical translation of new biomedical technologies.

The recent examples of whole-genome studies of breast and prostate cancer risk illustrate some of the problems in clinical translation of such research. A recent large study tested hundreds of thousands of SNPs in thousands of families and patients with breast cancers not linked to known genes.<sup>13</sup> SNPs in one gene, *FGFR2*, were found to be associated with increased risk of breast cancer. However, this particular marker was associated with a risk for disease of only 1.2-fold more than population risk, raising questions about clinical utility. By comparison, delaying age of first pregnancy to after 35 years confers a similarly modest elevation in risk for breast cancer. How is a patient or a physician to act on this type of small increase in risk? These questions are of more than academic concern because testing for SNPs in *FGFR2* is now offered by at least 1 direct-to-consumer laboratory. Similarly, there is controversy regarding the predictive sensitivity, specificity, and clinical utility of a panel of SNP markers for prostate cancer soon to be marketed in collaboration with an academic center.<sup>14</sup> The extent to which academic institutions will enforce existing “protective patents” or will license newly discovered “risk SNPs” for commercial use remains unclear.

**Table.** Examples of Commercial Direct-to-Consumer Genomic and Genetic Testing Laboratories<sup>a</sup>

Type of Testing	Examples of Commercial Laboratories	Description of Tests Offered
“Whole genome” testing	23 and Me, DeCode Me, Navigenics <sup>b</sup> Knome	Complex-trait (eg, cancer, diabetes) risk screening based on SNPs discovered through ongoing research Individualized full-genome sequencing
Single- or multiple-trait testing	Consumer Genetics, <sup>c</sup> Cygene Direct, DNAdirect, Genelex, <sup>c</sup> Genovations, Health Tests Direct, Mygenome.com, Proactive Genetics, <sup>c</sup> Pro DNA, <sup>c</sup> Smart Genetics	Testing for conditions (eg, “athletic performance,” “detoxification impairments”) or specific diseases (eg, breast or prostate cancer risk) by using proprietary SNP panels, SNPs discovered through ongoing research, or other genotyping methods
Ancestry testing	DNA Diagnostics Center, DNA Test Today, DNA Tribes, Family Tree DNA, Genetic Testing Laboratories, Graceful Earth, Identigene, Orchid Cellmark, Sorenson Genomics, Test Point DNA	Paternity and family relationship testing using mitochondrial or Y-chromosome genotyping or ancestry testing with SNP panels or STRs
Other	Dermatogenetics, Salugen, Sciona, Suracell	Provide products or recommendations for skin, nutritional, or body weight concerns according to analysis of proprietary SNP panels or SNPs discovered through ongoing research

Abbreviations: SNP, single nucleotide polymorphism; STR, short tandem repeat (markers used to identify DNA sequence).

<sup>a</sup>Table assembled using a previous review<sup>1</sup> and by a Google search with the following terms: *consumer, direct-to-consumer, and DNA testing.*

<sup>b</sup>Planned for 2008.

<sup>c</sup>Also offers paternity/familial relatedness or ancestry testing.

As disease association tests have appeared, another industry has emerged: genomic testing of maternal (mitochondrial) and paternal (Y chromosomal) DNA to learn of geographic ancestry.<sup>15</sup> Such tests, however, provide a snapshot of only a tiny percentage of an individual's genomic complement. Not surprisingly, the accuracy of these genealogic predictions is variable. It is difficult to critically analyze this approach because many of these companies use proprietary databases and differing "filters" for the data.<sup>15</sup> Because ancestry and risk for specific diseases are often intertwined, the policies and professional attention focused on direct-to-consumer genetic testing for disease should also be applied to testing for ancestry.

Groups such as the Institute of Medicine and the Genetics and Public Policy Center warned of the dangers of introduction of genomic tests on a population-wide basis before regulatory and scientific requirements were met.<sup>16,17</sup> Some states have the statutory authority to regulate genetic testing for disease risk of individuals residing within the state. Although not emphasized in the local press coverage,<sup>3</sup> commercial laboratories must obtain New York State Department of Health permits before providing predictive genetic tests to New York residents. By law, predictive genetic tests for New York residents must be ordered by a licensed health care professional. Other states have differing policies. All told, 25 states and the District of Columbia permit direct-to-consumer laboratory testing without restriction, whereas 13 categorically prohibit it. In 12 states, such testing is allowed for some types of tests, most likely not including genetic tests.<sup>16,17</sup>

For states with no regulations regarding direct-to-consumer genetic tests, there are few federal protections. In the final draft of its recent report, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) states that "there is currently no requirement that test providers disclose information to support claims about the accuracy and validity of testing," and warned that "the Food and Drug Administration [FDA] is not currently assessing the clinical validity of most genetic tests."<sup>18</sup> In contrast, the FDA does oversee claims made as part of direct-to-consumer marketing of prescription drugs. In response to a 2006 SACGHS recommendation, Secretary Leavitt requested that the FDA, Federal Trade Commission, and Centers for Disease Control and Prevention issue a joint warning to consumers titled "At Home Genetic Tests: A Healthy Dose of Skepticism May Be the Best Prescription."<sup>19</sup> Although this was a useful first step, it seems sensible and vital for the FDA and Federal Trade Commission to directly safeguard the scientific accuracy and safety of products marketed as predictive genetic tests.<sup>20</sup>

In the midst of the debate about breast cancer gene testing a decade ago, the National Human Genome Research Institute and other agencies called for and supported prospective clinical trials to assess the psychosocial and medical effects of genetic testing for cancer risk. Physicians and other health professionals in the field of genetic testing for cancer risk proceeded cautiously and, most would generally agree, respon-

sibly. The same approach should be followed for genomic testing for other disease risks. Such studies can provide clinical validation and proof of the reliability, utility, and safety of these tests. Not doing so runs the risk of dangerously reassuring some and needlessly worrying the already worried. Both groups, those at increased risk and those at average risk for disease, are depending on physicians to responsibly reap the harvest of progress in human genetics.

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