VIEWPOINT

The Need to Improve the Clinical Utility of Direct-to-Consumer Genetic Tests

Either Too Narrow or Too Broad

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Direct-to-consumer (DTC) genetic testing for disease susceptibility is largely dominated by 2 extremes—narrow tests that only screen for a few variants and broad tests that include dozens of genes. These tests may lack clinical utility for consumers wanting to understand their disease risks. In the context of genetic testing, clinical utility refers to the ability of a test to generate results that can be used to reduce morbidity and mortality through the adoption of medical management strategies, including screening and surgery. Narrow and broad tests, however, lack clinical utility for different reasons. Narrow tests are often incomplete, and only include a limited number of relevant variants.[1] Broad tests, by contrast, are concerning because they often include genes for which well-established risk estimates, medical management guidelines, or both may be absent.

Narrow Tests

For some health conditions, there are hundreds, even thousands, of sequence variants (formerly called *mutations*) in different genes that could affect an individual's disease risk. Yet narrow tests only screen for a subset of the relevant variants. For example, the *BRCA1* and *BRCA2* test for breast and ovarian cancer susceptibility from 23andMe uses genotyping, a highly targeted method of analyzing DNA, to determine whether specific, prespecified variants of interest are present or absent in an individual. Although more than 1000 *BRCA1*/*BRCA2* variants are associated with an increased risk of breast and ovarian cancer, this test only screens for 3 variants, 2 in the *BRCA1* gene (185delAG and 5382insC) and 1 in the *BRCA2* gene (6174delT). This means that an individual who receives a negative test result could still carry a different *BRCA1/2* variant or variants in another cancer susceptibility gene. Importantly, because these 3 variants are found almost exclusively in individuals of Ashkenazi Jewish descent, the test is largely uninformative for individuals of other ethnic backgrounds.[1] Given the recent recommendation from the US Preventive Services Task Force that clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer for potential *BRCA1/2* testing regardless of their ancestry, the limited nature of narrow tests is especially concerning.[2]

In addition to its *BRCA* offering, the Health + Ancestry service available from 23andMe also includes a test for familial hypercholesterolemia. While more inclusive than it's *BRCA* test, the company's familial hypercholesterolemia test is by no means comprehensive; despite the existence of several thousand variants in 4 genes that are associated with familial hypercholesterolemia, the test by 23andMe only screens for 24 variants in 2 genes (LDLR and APOB) that are most prevalent in individuals of European, Lebanese, and Old Order Amish descent. Similar to the *BRCA* test from 23andMe, a negative result from the familial hypercholesterolemia test cannot rule out the possibility that an individual carries a pathogenic variant not included in the screen.

> Given the shortcomings of narrow and broad DTC genetic tests for disease susceptibility, there is a need to reevaluate the scope of current offerings.

Broad Tests

Whereas narrow tests lack clinical utility because they give an incomplete view of an individual's disease risk, broad tests are concerning because they include genes with uncertain risk estimates and strategies for medical management. Prominent examples of broad tests include a 60-gene cancer and cardiac disease susceptibility panel from Color Genomics and a 147-gene panel from Invitae that includes genes related to cancer, cardiac disease, and other inherited conditions (eg, malignant hyperthermia susceptibility). Both panels use next-generation sequencing, a method of analyzing DNA that aims to detect any clinically relevant variants in the genes being analyzed. Additionally, both panels sequence an array of genes that encompass a wide range of risk estimates. Germline *TP53* variants, for example, are at the high end of the risk spectrum and confer a 93% lifetime risk of cancer for women and a 68% lifetime risk of cancer for men.[3] Monoallelic *BARD1* sequence variants, by contrast, are thought to increase the risk of breast cancer, although more definitive risk estimates remain unknown.[4]

Besides varying risk estimates, many of the genes included in broad tests also vary in terms of whether and how their associated disease risks can be managed. Used appropriately, risk management strategies can be lifesaving. But used inappropriately, these interventions can harm patients by exposing them to unnecessary risks from screening, surgeries, and medications, along with psychological and emotional distress. Moreover, for many of the disease susceptibility genes included in large panels, medical management guidelines are uncertain and still evolving. Consequently, some individuals could

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learn that they have a pathogenic variant in a disease susceptibility gene, yet medical guidance would be lacking about how to manage their risk.

Moving Toward a Middle Ground

Revising the size and scope of DTC tests for disease susceptibility could substantially improve their clinical utility. For narrow tests, this would involve expanding their scope of analysis. Specifically, rather than screening for select variants in a particular gene, tests should, at a minimum, analyze entire genes for variants that could affect disease risk. Thus, instead of only screening for 3 *BRCA1/BRCA2* variants, a *BRCA* test would fully sequence the *BRCA1/BRCA2* genes for any variant that could negatively affect disease risk. A potential benefit of this approach is that individuals who receive a negative test result could be more confident that they do not carry a pathogenic variant in the genes being tested.

Conversely, improving the clinical utility of broad tests would involve limiting the scope of their analysis. That is, instead of analyzing dozens of genes, which can lead to uncertainty about disease risk and clinical care, tests should focus on genes that have well-established risk estimates and medical management guidelines. Professional recommendations could inform which genes are included in panels. For example, the American College of Medical Genetics and Genomics (ACMG) has generated a list of 59 genes for which results should be returned to patients in the event that a likely pathogenic or pathogenic variant is identified during the course of clinical sequencing. Inclusion in this list was largely based on medical actionability, which was evaluated according to 5 criteria: (1) the severity of the associated disease(s); (2) the likelihood that the disease will manifest; (3) the efficacy of risk-reducing medical intervention; (4) the overall strength of the association between a gene and a disease(s); and (5) the acceptability of the proposed medical interventions in terms of their risk-benefit profile.[5] Besides the ACMG recommendations, the Clinical Sequencing Evidence-Generating Research Consortium, a multisite research program focused on the application of genome sequencing in a range of clinical settings, has also developed lists of medically actionable genes.[6] However, lists from the ACMG and the Clinical Sequencing Evidence-Generating Research Consortium are based on clinical populations, with the ACMG stating that its list was not validated for general population screening and discouraging any reference to the term *ACMG 59* outside of reporting incidental findings from clinical sequencing.[7] These lists could nevertheless provide insight into which genes might be appropriate candidates for DTC services that report on serious disease risks. In developing evidence-based tests, it is also critical that laboratories include genomic data from underrepresented minority groups and otherwise underrepresented individuals. Doing so will help ensure that disease susceptibility genetic tests have the potential to benefit diverse populations.[8]

Conclusions

Given the shortcomings of narrow and broad DTC genetic tests for disease susceptibility, there is a need to reevaluate the scope of current offerings. Moving toward a middle ground—away from tests that are either too narrow or too broad—has the potential to improve the clinical utility of DTC genetic testing for consumers. To that end, narrow tests could expand their analysis to encompass entire genes and broad tests could limit their analysis to include only those genes for which there are both well-established risk estimates and medical management guidelines. As the DTC market continues to evolve and expand, focusing on the clinical utility of DTC tests is an important step toward ensuring that tests provide consumers with valuable insight into their disease risk.

ARTICLE INFORMATION

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