

Direct to Consumer Testing (DTC)

Power and Pitfalls

What is DTC Testing?

- ▶ Direct to Consumer (DTC) genetic tests are advertised and sold directly to the public.
- ▶ Offers information that many include ancestry, risks of developing certain conditions, carrier status for some autosomal recessive diseases, predicted drug response, and non-disease phenotypic traits such as eye color.
- ▶ DTC tests are not diagnostic and offers risk information for only a limited set of conditions.

Who offers DTC Testing?

- ▶ Family Tree DNA
- ▶ My Heritage
- ▶ 23andMe
- ▶ Ancestry
- ▶ Mayo Clinic GeneGuide
- ▶ Color

DTC Power

- ▶ DTC testing may promote awareness of genetic diseases.
- ▶ It may provide you with personalized information about your health, disease risk, and other traits.
- ▶ This testing may allow consumers to take a more proactive role in their health care.
- ▶ Offers a means for people to learn about their ancestral origins.
- ▶ It does not require approval from an insurance company or a healthcare provider.
- ▶ Results are available relatively quickly.
- ▶ Your data is added to a large database that may be used to further medical research. Depending on the company, the database may represent up to several million participants.

DTC Limitations

- ▶ Unexpected information that you receive about your health, family relationships, or ancestry may be stressful or upsetting. For example, one may learn of non-paternity or that they are adopted.
- ▶ People may make important decisions about disease treatment or prevention based on inaccurate, incomplete or misunderstood information from their tests results.
- ▶ There is currently little oversight or regulation of testing companies.
- ▶ Unproven or invalid tests can be misleading. There may not be enough scientific evidence to link a particular genetic variation with a given disease or trait.
- ▶ Genetic privacy may be compromised if testing companies use your genetic information in an unauthorized way or if your data is stolen. For example, the company may sell your data to corporations, research groups or may work with law enforcement.
- ▶ The results of genetic testing may impact your ability to obtain life, disability or long-term care insurance.

DTC Limitations cont...

- ▶ In the US, the FDA restricts DTC testing companies from offering products that function as diagnostic tests.
- ▶ In April 2017 FDA authorized 23andMe to market genetic HEALTH RISK tests for 10 specific multifactorial conditions (Parkinson disease, Alzheimer disease, celiac disease, alpha-1-antitrypsin, early-onset primary dystonia, factor XI deficiency, Gaucher type I, glucose-6-phosphate dehydrogenase def'y, hereditary hemochromatosis, hereditary thrombophilia).
- ▶ The risk assessment of these 10 diseases is based on the presence or absence of a limited list of genetic variants in the sample, which are statistically higher in affected vs healthy cohorts but not necessarily causal of the conditions because additional environmental and lifestyle factors affect risk.
- ▶ None of the genes associated with these conditions are comprehensively sequenced or analyzed in DTC tests NOR do the tests include all of the genes that have been associated with these conditions.

Example of DTC Gene Risk Analysis

- ▶ 23andMe's genetic health risk test for Parkinson disease reports on just ONE variant in each of two genes, LRRK2 and GBA, linked to this disorder.
- ▶ There are additional known pathogenic variants in these two genes
- ▶ They do not report out on other genes known to be linked to Parkinson disease such as SNCA and PARK2/PARKIN.
- ▶ The consumer is not provided with a comprehensive genetic risk assessment.
- ▶ In contrast, diagnostic tests are comprehensive with analysis of the full coding sequences of all genes associated with that disease and the results are used by the provider to guide disease management or surveillance.

Raw Data Analysis

- ▶ Although the FDA prohibits most DTC companies from offering diagnostic genetic tests, some companies provide their raw genotyping data if requested.
- ▶ Patients can access interpretation services for their raw genotyping data through fee-for-service third party companies.
- ▶ A study in 2017 reviewing third party companies found they operate by querying publicly available databases, despite reports that the majority of classifications in some of these databases is incorrect resulting in, for example, the interpretation of single nucleotide polymorphisms as pathogenic when they may be VUS, likely benign variants, and benign polymorphisms. In addition, these companies are providing information to the consumer with the assumption that these variants in the raw data they are interpreting are actually true abnormalities in the first place and not false positives. Badalato et al. *Eur J Hum Genet* 2017;25:1189-1194

23andme Statement on Testing Clinical Utility

They made the following statement regarding the clinical utility of their DTC testing:

“The test is not intended to tell you anything about your current state of health, or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take, or determine any treatment... These carrier reports are not intended to tell you anything about your risk for developing a disease in the future, the health of your fetus, or your newborn child’s risk of developing a particular disease later in life.”

Ambry Genetics DTC Testing Study - Tandy-

Connor, et al; *Genetics in Medicine*;2018;20(12):1515-1521

- ▶ Analyzed variants previously identified by DTC testing and raw data analysis in 49 patients between January 2014 and December 2016.
- ▶ 91.8% of patients were female; 73.5% unaffected by disease; 53.1% aged 30-49 years.
- ▶ In 44.9% of cases, single-site analysis was ordered to confirm DTC raw data findings; 87.8% was testing of cancer genes, 8.2% in CF genes, and 2% each in connective tissue disorders and Familial Mediterranean Fever genes.
- ▶ Overall, 60% of the variants were confirmed while 40% were false positives, the latter most commonly found in the breast cancer BRCA1/2 genes.
- ▶ Misclassification of variants by the third party interpretation service, some of which were variants found in the general population at frequencies too high to be associated with disease (one BRCA2 gene variant is found in about 25% of the general population).

Lessons Learned

- ▶ Alarming high false positive rate
- ▶ High incidence of discrepant classification/misinterpretation of variants coming from DTC companies and/or third-party interpretation services.
- ▶ It is critical that clinical confirmatory testing be performed on any variants reported in the raw data provided by a DTC company prior to any changes in medical management to confirm the presence of that variant in the individual as well as an accurate classification.
- ▶ Many DTC genetic tests do not include comprehensive gene analysis.
- ▶ Genetic testing needs to be interpreted by a qualified health-care professional in the context of several other factors to include personal and family medical history.

My Biggest Concern

The Ambry study data was generated on 49 patients whose providers knew enough to refer for additional testing. How many people are out there with false positive data making poor decisions for themselves and their families based on inaccurate information?

American Society of Human Genetics Statement on DTC Testing

“Because of the fragmented regulatory environment for genetic testing in general, there is concern that the quality of the tests offered DTC may be inadequate. For a test to be of good quality, the laboratory performing it must be able to obtain the correct answer reliably, meaning that it detects a particular genetic variant when it is present and does not detect the variant when it is absent. A test’s accuracy is referred to as “analytic validity”. Further, there must be adequate scientific evidence to support the correlation between the genetic variant and a particular health condition or risk - the so-called clinical validity.”

“Claims made regarding DTC genetic tests may in some cases be exaggerated or unsupported by scientific evidence. Exaggerated or unsupported claims may lead consumers to get tested inappropriately or to have false expectations regarding the benefits of testing. Further, consumers may make unwarranted, and even irrevocable, decisions on the basis of test results and associated information, such as the decision to terminate a pregnancy, to forgo needed treatment, or to pursue unproven therapies.”

American College of Medical Genetics Comment on DTC Testing

“Due to the complexities of genetic testing and counseling, the self-ordering of genetic tests by patients over the telephone or the Internet, and their use of genetic “home testing” kits, is potentially harmful. Potential harms include inappropriate test utilization, misinterpretation of test results, lack of necessary follow-up, and other adverse consequences.”

NIH Concerns for DTC Testing

Statement from the National Institutes of Health (NIH):

“DTC genetic testing may promote awareness of genetic diseases, allow consumers to take a more proactive role in their health care, and offer a means for people to learn about their ancestral origins.” However, “consumers are vulnerable to being misled by the results of unproven or invalid tests” and “may make important decisions about treatment or prevention based on inaccurate, incomplete or misunderstood information about their health.”

Federal Concerns for DTC Testing

- On November 28, 2017, Senator Chuck Schumer called on the Federal Trade Commission (FTC) to regulate consumer DNA testing
- Schumer cautions that these test kits put consumer privacy at risk because DNA firms could potentially sell personal and genetic information. Now Schumer is calling on the Federal Trade Commission to investigate and ensure that the privacy policies are clear, transparent, and fair to consumers, according to a statement released by Schumer's office.
- "When it comes to protecting consumers' privacy from at-home DNA test kit services, the federal government is behind," Schumer said. "Besides, putting your most personal genetic information in the hands of third parties for their exclusive use raises a lot of concerns, from the potential for discrimination by employers all the way to health insurance. That's why I am asking the Federal Trade Commission to take a serious look at this relatively new kind of service and ensure that these companies have clear, fair privacy policies and standards for all kinds of at-home DNA test kits. We don't want to impede research but we also don't want to empower those looking to make a fast buck or an unfair judgement off your genetic information. We can find the right balance here, and we must." Ref Mobihealth News

