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# Promises and Pitfalls of Direct-to-Consumer Genetic Testing



The dawn of the 21st century has brought a radical shift in patient-driven ownership of healthcare. The emergence of search engines, social media, wearables, and digital health have transformed the traditional access barriers to health information. The dominance of search engines has lifted the veil of obscurity between healthcare providers and patients, abruptly closing the information gap that once left the decision making solely to physicians. While this provides a novel system of checks and balances on physicians, it undoubtedly has led to a false sense of medical expertise and clinical judgment among patients.

Tom Nichols, author of *The Death of Expertise: The Campaign Against Established Knowledge and Why It Matters*, describes this phenomenon as part of a broader societal issue where laymen, now empowered by a plethora of sources in the digital age, have cast aside expertise in favor of self-reliant evaluation:

“The Google-fueled, Wikipedia-based, blog-sodden mirage of knowledge, with an exhaustible supply of ‘facts’ to feed any confirmation bias...encourages not only the illusion that we are all equally competent, but that we are all peers. And we’re not.”

While Nichols is lamenting a wider experience not limited to healthcare, his analysis is particularly apt as we look at healthcare in the post-digital age.

**Undoubtedly, the democratization of health information has granted tremendous freedom to those seeking medical data, and has empowered the public to be an informed partner for better health. However, it has also placed an undue amount of power and responsibility on patients to make informed decisions in the absence of medical training.**

The sheer breadth of medical information available on the Internet, both reliable and unreliable, is challenging to manage even for physicians and scientists, and is certainly a far greater challenge to those lacking the expertise to parse fact from fiction.

Genetic testing technologies are a prime example of tools that were once limited to experts and are now accessible by the general public. With a few clicks, anyone can order a testing kit to their home, send a sample to a lab, and receive results. In the past few years, millions of people around the world have undergone these tests, requiring a serious discussion regarding the merits of their use for the general public without expert guidance.

# DTC Genetic Testing: An Introduction

While most genetic tests are used by healthcare providers in clinical settings, genetic data is now available in non-clinical, direct-to-consumer (DTC) environments. These tests do not require a physician middleman to reach the customer, and yet provide consumers with highly personalized data. From a marketing perspective, utilizing genetic information in commercial products is an attractive way to make consumers feel empowered – with results that are custom-tailored, reliable and potentially actionable.

DTC genetic testing is capitalizing on the concept that many of our traits can be explained by our genetics. Do you sweat heavily? Take a genetic test. Does cilantro taste like soap to you? Take a genetic test. There are even tests that provide guidance based on your genetics to change your diet, recommend vitamin supplementation, alter your skincare regimen, among many other types. While there is little evidence that supports the relationship between some of these genomic regions and the claimed associations, this aspect of genetic testing in many instances is fairly harmless. These non-clinical tests are under little regulatory scrutiny, and are generally given free reign within certain parameters.

A more well-established, yet still controversial type of non-clinical test, ancestry genetic testing, has exploded in popularity in the last few years. These tests analyze genomic regions that are associated with different populations and provide ethnicity estimations. Commercial tests from companies like 23andMe and Ancestry.com have dominated the market in recent years, offering tests from about \$99 to \$150 that can now even be purchased in the supermarket. When using these tests, it is not uncommon to discover hidden ethnicities previously unknown to you.

To the untrained eye, these claims seem rather innocuous, and in many ways they are.

**While there are established methodologies for evaluating the genetics of certain ethnicities, much of the companies' algorithms and data are proprietary, preventing most of their techniques and claims from being validated by the research community. However, since no clinical action is generally taken from this testing, the results are usually of little consequence, and are not considered actionable.**

It is this distinction of actionable vs. non-actionable results that is a major concern for the clinical genetics community.

# 23andMe's Personal Genome Service

After years of deliberations, warning letters from the U.S. FDA, a brief marketing discontinuation, and discussions among policymakers, researchers, and experts, the FDA granted marketing authorization to 23andMe for the first DTC genetic test with clinical implications. The "Health + Ancestry" test combined the standard ancestry test with select variants associated with a small number of genetic conditions. Some conditions, like Alpha-1-Antitrypsin Deficiency and Gaucher Disease Type I, are each linked to a single gene, and typically require both parents to be asymptomatic carriers of the disease. The current version of the test reports select mutations in 40+ diseases that are more commonly found on carrier tests for family planning.

The report also included variants for more complex diseases, such as Parkinson's disease and late-onset Alzheimer's disease. However, these are complex diseases with both environmental and polygenic risk factors; and no one genetic variant can determine or diagnose a patient with these progressive neurodegenerative conditions. From a clinical perspective, inclusion of these complex diseases is concerning due to the dearth of useful medical interventions a physician can recommend to screen, prevent or even mitigate future disease risk. While the presence of one of the variants increases relative risk, or the risk of having the disease compared to the relative population, the absolute risk, or total overall risk of being diagnosed with the disease, is still fairly low. Second, it is simple to imagine a patient receiving a result linked to one of these diseases who misunderstands the information provided and believes they have been diagnosed with the condition.

While genetic counselors are excellent resources for proper interpretation of this data, most patients who receive DTC testing will not have access to them, as a visit with a genetic counselor can be expensive for patients with little-to-no healthcare coverage. Even for clinical genetic tests, many patients do not receive proper counseling from a genetics professional due to cost barriers.

In June 2019, a bill was introduced in Congress to recognize genetic counselors as Medicare practitioners, allowing CMS to reimburse genetic counselors through Medicare's Part B program for counseling. The bill, entitled "Access to Genetic Counselor Services Act of 2019," is expected to lower costs, provide better care, and eliminate disparities for low-income and elderly patients with no previous access to counseling.

**As the DTC industry moves to continuously add more clinical results to their test, access to appropriate genetic counseling is more important than ever.**

# New Frontiers – Identifying Cancer Risks

In March 2018, another major innovation was announced: FDA marketing authorization of a genetic testing report from 23andMe with implications for cancer risk. This report allows 23andMe to tell patients about whether they have one of three select mutations in the BRCA1 or BRCA2 genes that are especially common to those of Ashkenazi Jewish descent. BRCA1/2 mutations are notoriously high risk for breast and ovarian cancer, but also increase risk for prostate and pancreatic cancers, among others. As the first DTC test allowed by the FDA to report on DNA variants linked to cancer, 23andMe opened a door previously shut to the industry. Historically, cancer-risk testing has been a testing modality solely performed by healthcare providers since they are most knowledgeable regarding decisions for cancer monitoring and treatment. These changes allow a new host of challenges to surface.

# Genetics Community Raises Concerns

In a critique from one of the premier institutions of clinical genetic testing, the American College of Medical Genetics (ACMG) lambasted the decision to approve the use of DTC BRCA testing, as well as clinical DTC testing more broadly, due to its limited scope and potential for misuse. Their concerns are serious and warranted. The first, in the case of BRCA1/2 gene testing, is the sheer number of mutations that are possible. DTC reports only give information on the three major variants, yet there are well over 1,000 mutations in these genes that are linked to increased cancer risk.

Second, the variants tested are intended for individuals of Ashkenazi Jewish descent, but the test is available to the general public. For the general population, the chance of receiving a true positive result, what is termed the positive predictive value, is quite low. Furthermore, a patient who receives a negative result cannot be confident in their BRCA-negative status, as there are many untested mutations that may have gone undetected. The strength of a clinical test stems from either the positive or negative predictive values, and often has strong utility on both ends. It is unusual for the FDA to authorize a test that performs poorly on both fronts.

# FDA approval vs. FDA marketing authorization

The distinction between marketing authorization and FDA-approval is significant.

**Under normal circumstances, FDA approval is considered a formal endorsement that the intervention is proven to be safe and effective. On the other hand, marketing authorization is granted after a favorable risk-benefit analysis, but is not considered an endorsement of its use.**

The 23andMe BRCA report received marketing authorization, and not FDA approval, permitting the use of this report for appropriate patients with the added caveat that the significant associated risks are mitigated. These mitigation strategies, what the FDA deems general and special controls, ensure that the scope of the claims is limited and that the sample collection device is FDA-approved, among other requirements.

Following the authorization of the BRCA report, the FDA authorized a second report from 23andMe, testing mutations in the MUTYH gene. Biallelic mutations in the MUTYH gene are associated with MUTYH-Associated Polyposis (MAP), a high-penetrance cancer syndrome with a lifetime risk of colorectal cancer up to 100% in the absence of timely surveillance. This report provides information for the two most common MUTYH mutations, which are common among certain ethnicities.

In their authorizations, the FDA made clear their viewpoint on the limitations of these reports, and yet decided to authorize them. These decisions were met with intense scrutiny and criticism from the genetics community, supported by a growing list of a literature that is documenting some of the drawbacks of this approach.

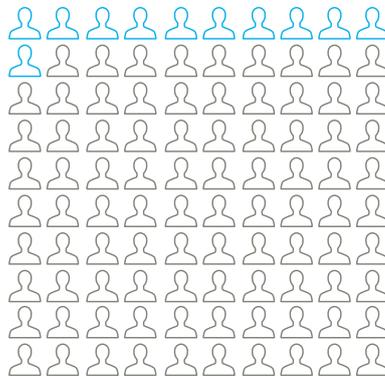
# Questionable Clinical Utility

A recent study presented at the 2019 annual meeting of the American College of Medical Genetics illustrates the questionable clinical utility of DTC testing for hereditary cancers. Esplin et al. presented a cohort of roughly 120,000 patients referred for comprehensive BRCA testing due to a clinical suspicion of hereditary breast and ovarian cancer, where 11% of patients were found to have pathogenic BRCA mutations that are considered to elevate cancer risk.

Of those, only 12% were found to harbor one of the three mutations reported in DTC BRCA tests, equivalent to approximately 1.3% of all patients in the cohort. Shockingly, this would translate into an 88% false-negative rate for patients that are truly positive for cancer-linked BRCA mutations had they received DTC BRCA testing, leading Dr. Esplin to conclude that “many patients’ high cancer-risk would have gone undetected” if they did not receive comprehensive, clinical BRCA testing.

## BRCA Positive Patients

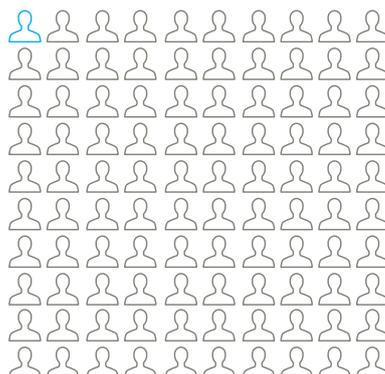
BRCA Positive  
11%



BRCA Negative  
89%

## BRCA Positive Patients with DTC Testing

BRCA Positive  
1.3%



BRCA Negative  
98.7%

Seven months later at the American Society of Human Genetics (ASHG) 2019 annual meeting, Esplin et al. presented follow-on data on the same topic, including data from both BRCA1/2 and MUTYH genes, and came to the same critical conclusions, with 40% of patients with biallelic MUTYH mutations anticipated to be missed by DTC MUTYH testing available in the marketplace.

**While the approach presented by Esplin et al. was sound, it unfairly characterized the BRCA and MUTYH reports as failed attempts to evaluate comprehensive mutation status, when that is far from the intent of the test.**

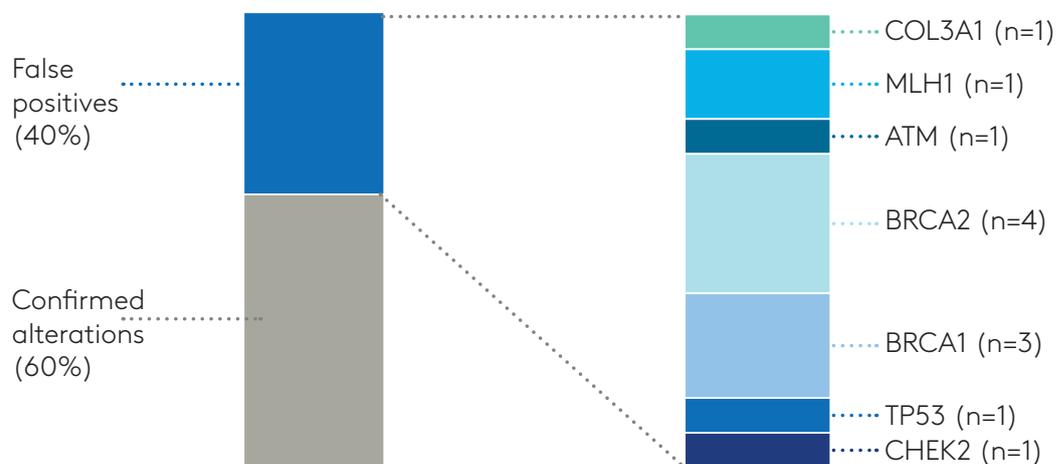
These tests are not attempting to create a full risk assessment of cancer-related mutations, but rather they are working to increase access to testing for some of the most common mutations by offering an inexpensive test to the public.

In many ways, 23andMe's attempt to increase access is addressing an unmet clinical need, as numerous papers, most notably Yang et al. (2018) and Beitsch et al. (2019), have demonstrated that strict following of the National Comprehensive Cancer Network (NCCN) guidelines for which patients to recommend BRCA testing may miss up to half of patients with these mutations. On this note, several studies are evaluating population and ethnicity-based BRCA screening in healthy patients that would otherwise not meet NCCN's screening guidelines for genetic risk assessment, including the BRCA Founder Outreach (BFOR) study that is providing comprehensive BRCA testing for patients of Ashkenazi Jewish descent, regardless of personal or family history of cancer.

# Raw Genetic Data Files

Aside from the actual results reported by DTC companies, consumers also reserve the right to receive the unredacted genotyping data that companies use to interpret their results. Given the overlap between genes related to ancestry and genes linked to disease, many patients request this raw data to send to third-party interpretation vendors that will, for a fee, interpret the data provided and provide insight into disease risk.

A study reported on this topic by Ambry Genetics published in the journal *Genetics in Medicine* caused significant concern. Tandy-Connor et al (2017) reported that 40% of variants reported in the raw data files from 49 DTC tests sent to Ambry for confirmatory testing were false positives, in which almost all were in cancer-related genes.



Adapted from Tandy-Connor et al

The study caused immediate uproar among clinical geneticists, genetic counselors and the major genetics associations, and raised legitimate concerns about the unintended consequences that could occur with the growing use of DTC testing. Importantly, it validated many of the fears that have been bubbling under the surface since the commercialization of these products.

As the Ambry study depicted, these raw data files are riddled with errors, which may lead not only to false positives but also confirmatory genetic testing, familial cascade testing and any other diagnostics or screening procedures to confirm the presence or absence of these conditions, all of which are an increasingly heavy financial burden on the healthcare industry.

To illustrate the possible ramifications of false-positive results stemming from third-party interpretation of DTC raw data, Moscarello et. al (2018) presented vignettes from four cases of patients that received positive results related to rare cardiovascular conditions.

	Patient description	Disease of Concern (Gene)	Possible Symptoms
<b>Case 1</b>	Age 12, Female	Ehlers-Danlos Syndrome Type III (COL3A1)	Life-threatening rupturing of blood vessels, intestines, and other organs
<b>Case 2</b>	Age 36, Male	Hypertrophic Cardiomyopathy (MYBPC3)	Increased risk of heart failure and sudden death
<b>Case 3</b>	Age 22, Male	Hypertrophic Cardiomyopathy (MYBPC3)	Increased risk of heart failure and sudden death
<b>Case 4</b>	Age 18, Female, died suddenly while running, received testing before death	Arrhythmogenic right ventricular cardiomyopathy (PKP2)	Abnormal heartbeat and sudden death

**In each case, third-party vendor analysis of the patients' raw data files reported positive results related to high risk cardiovascular conditions. Upon confirmatory testing, however, these were subsequently found to be false-positives.**

The patient in Case 3, a young graduate student and avid cyclist, had tremendous anxiety due his result and decided to take medical leave from his PhD "to focus on [his hypertrophic cardiomyopathy] and risk of sudden death." Many of these patient's family members also received evaluations from disease-experts and geneticists, highlighting the financial effect of false-positives could have on patients and the healthcare system. These case studies illustrate very serious ramifications that could occur with using the raw data files and third-party interpretation vendors to learn about genetic risk outside the intent of the original test.

# Final Thoughts

A careful analysis of the advantages and disadvantages of DTC clinical genetic testing paints a complicated portrait. In many cases, DTC testing can provide helpful information in the case of a true-positive for patients who would have otherwise not undergone testing. However, when used incorrectly or without proper guidance, testing can lead to false positives and negatives, unnecessary familial testing, extra costs, and anxiety when more comprehensive options are available in consult with trained healthcare professionals.

**In its current iteration, DTC genetic testing relies heavily on an informed consumer base, which is a major challenge due to the rapidly developing genetic science that undergirds it.**

Before undergoing DTC genetic testing, it is critical to be fully informed of all the possible outcomes to ensure that appropriate conclusions are made from testing, especially as clinical results continue to be embedded into the design of these tests.

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