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# 23andMe Health Report Concerns Linger Amid Incremental Acceptance of DTC Testing Model

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NEW YORK (GenomeWeb) – 23andMe is one of the most recognized brands in consumer genetics and the only company in the space to have submitted its health risk tests for US Food and Drug Administration scrutiny. Yet, the public health concerns that have trailed the company since its inception aren't going away.

In 2017, 23andMe received FDA authorization for the first crop of 10 genetic health risk tests. Last year, the agency authorized a test that gauges three BRCA1/2 variants that tend to show up in the Ashkenazi Jewish population and are associated with increased risk for breast, ovarian, and prostate cancers.

23andMe now seems poised to introduce new health risk reports at a faster clip. Earlier this year the company announced it would soon launch a new FDA-cleared report for two MUTYH variants associated with high risk of a colorectal cancer syndrome, and last week it unveiled a new report for familial hypercholesterolemia that gauges 24 variants in the LDLR and APOB genes.

These tests aren't intended to be used for medical decision making and aren't as comprehensive as clinical tests are. But recognizing people's increasing interest in mining their DNA for insights, the FDA gave 23andMe permission to market its reports directly to consumers (DTC), without a doctor's prescription, after evaluating the way it presents test results in reports and surveys showing consumers understand this information, among other things. But the FDA's scrutiny hasn't reassured healthcare providers, genetic counselors, and patient advocates who say they are encountering people who do not fully grasp the limitations of 23andMe's offerings.

Part of the problem is that there isn't an established framework for ensuring that customers of DTC genetic testing firms, who initiate testing on their own, are brought into the healthcare system when appropriate for follow-up care. 23andMe's critics argue that as a loud proponent of empowering people with their genetic information, the company has a responsibility to help ensure its customers aren't missing opportunities to use their genetic information to prevent disease.

Some have called on 23andMe to incorporate genetic counseling into its services at a minimum. 23andMe has said that it has no plans to provide genetic counseling at this time, which some industry observers believe is part of the company's plan to disrupt the healthcare system and force it to adapt to

a future where unfettered consumer access to health-related information is the new normal.

In response to a recent piece published by the *New York Times* editorial board highlighting some of the limitations of 23andMe's BRCA test, CEO Anne Wojcicki defended the company, highlighting the FDA's authorization of its tests and studies that show a high customer comprehension rate of concepts in reports, including negative results. "More equitable health care will come only if we can provide direct access — access without a medical professional barrier — in affordable ways," she wrote.

In the meantime, for healthcare professionals on the ground it feels a bit chaotic. "It's a little bit the Wild Wild West right now, because we really don't know the implications of a lot of these home test kits," said Carol Mangione, chief of general internal medicine and a primary care physician at the University of California, Los Angeles. She and her UCLA colleagues are seeing patients who have gotten DTC genetic testing, some of whom are "very alarmed" by their results.

Individuals with positive results indicating they're at high genetic risk for a serious illness like breast cancer may be more motivated to follow up with medical professionals and genetic counselors and get confirmatory testing. However, Mangione is more uncertain about what patients do after getting negative DTC test results. "There probably are some people who are very high risk [based on personal and family history of cancer] … who maybe shouldn't be so happy when they get a negative result," she said.

At Fox Chase Cancer Center in Philadelphia, a couple of patients come in for confirmatory testing each month after learning they are positive for one of the BRCA mutations reported by 23andMe. However, Andrea Forman, senior genetic counselor at the cancer center, also worries more about the mutation-negative patients, whether they'll understand the test gauges three variants and not being a carrier for any of them doesn't necessarily change their risk.

23andMe hasn't yet launched the MUTYH-associated polyposis (MAP) test, but she harbors similar concerns that a negative result will give people false reassurance. For people who test positive for one of the common MUTYH mutations, guidelines now recommend full gene analysis to check for a possible second mutation that would not be detected by 23andMe's test. Individuals with two mutations are at significantly higher risk for colorectal cancer than those with one mutation and should start screening earlier. Forman is eager to see how 23andMe will communicate this and ensure that customers with one mutation know to get additional testing.

"Some patients are going to say I don't have this [cancer-risk variant] so I'm in the clear," Forman said. "Patients are already not great about doing colonoscopies. I don't like that someone may use these test results to say, 'I don't have this genetic risk factor and it's not in my family, so I don't need a colonoscopy,' because most people who get colon cancer don't have a family history and don't have a genetic risk."

Forman has yet to see any patients with a family history of cancer who sought out more comprehensive testing after getting a negative BRCA test via 23andMe. It could be that some people are coming in for more comprehensive evaluations based on their personal or family history of cancer, and just not mentioning they bought a 23andMe test first. It is also a legitimate concern, according to healthcare professionals and patient advocates GenomeWeb spoke to, that there are some high-risk individuals with negative 23andMe BRCA1/2 reports who are candidates for further screening but are not seeking it out, thus missing the chance to take preventive action.

It's not clear at the moment just how often this is happening. "I'm sure that there is some degree of misunderstanding and some degree of false reassurance. I'm sure that's going on," said Robert Green, a physician-scientist at Brigham and Women's Hospital who has been studying the impact of DTC genetic testing. "But we have not been able to measure evidence of it in any widespread way."

**'We are confident'**

23andMe's FDA-authorized genetic health risk reports come with a lot of caveats, the main one being that these tests aren't intended for medical use. In its BRCA test reports, for example, the company tells customers this and also highlights in bold letters that there are more than 1,000 variants known to increase risk. The reports state that variants in different genes, as well as environmental factors could impact cancer risk, and that individuals with a family history of cancer should consider other tests.

23andMe tells customers that test results need to be confirmed in a clinical setting if they are positive or negative for one of the three BRCA1/2 variants. Negative reports make a specific point of telling individuals to speak to a doctor if there is a family history of cancer.

Amy Byer Shainman, a patient advocate, said that 23andme is presenting accurate information in its reports and noting caveats and limitations as needed, yet something is still getting lost in translation. She talks with people at least twice a week who say they got tested through 23andMe and were relieved to learn they didn't "have the gene."

"The people who find out they're [BRCA1/2 mutation]-positive always feel very thankful," said Shainman, whose paternal grandmother and great-grandmother died of breast cancer, and who learned of her own BRCA1 mutation status after her sister got ovarian cancer. "Where I'm picking up the pieces are with those who have a negative result."

In those instances, Shainman asks questions and tries to reinforce the basics in her answers. What gene are they talking about? If it is BRCA1 or BRCA2, do they know that 23andMe tests for only three variants in these genes when there are more than 1,000 variants associated with breast and ovarian cancer risk? Do they understand that the FDA may have authorized 23andMe's test but that the agency also tells people not to make medical decisions based on the results, but instead to talk to a doctor and to get confirmatory testing?

"If someone gets a 23andMe result telling them they have a BRCA1 mutation, I think that's extraordinarily powerful," said Amy Sturm, president of the National Society of Genetic Counselor's (NSGC), but she has yet to see data that gives her a good sense of what is happening to the individuals with negative results.

"Anecdotally, I think there are concerns about that because I've seen patients myself with results who might not fully understand or might put more weight on that negative," said Sturm, who also directs a genomic screening and counseling program at Pennsylvania-based Geisinger Health System. "They might not fully understand that this is not a clinical test, this is not a thorough test, and if they have a personal or family history [of a disease] that they need a much different test."

The company provides educational videos within its online reports and a link to the NSGC website for those who want to speak to a genetic counselor. 23andMe doesn't offer pre-test or post-test genetic counseling as part of its service, however, which has brought criticism, but 23andMe hasn't capitulated.

"For the time being we are confident," said Jamaica Perry, senior product scientist at 23andMe. "We

have gone through the FDA. We have shown through our user comprehension testing that people are able to understand these reports … all written at a ninth grade or below reading level … [T]hat is the position of 23andMe to date."

Perry highlighted that 23andMe does employ trained customer service representatives to answer questions and discuss appropriate next steps. The company also hosts webinars for medical professionals to help them understand the reports.

Several years ago, before getting FDA authorization, the company published a survey of around 60 customers, half of whom were positive for one of the three BRCA1/2 mutations 23andMe tests for and the other half of whom were negative. Most of the mutation-positive customers discussed the results with their healthcare providers, as well as their families, and said they planned to have preventive surgeries.

Of the 31 individuals who had negative results, 12 had a family history of breast cancer, nine had a history of prostate cancer, and several reported other cancers in their families at lower rates. Only one woman with a negative result said she felt "extremely relieved" because she had a family history of cancer and 15 said they were "relieved." The majority of those who felt relieved not to be in the mutation carrier group still understood that other genetic or environmental factors could impact their cancer risk, the authors reported, and no one thought that a negative result meant they had no cancer risk or lower-than-average risk.

However, mutation-negative customers were less likely to share their reports with healthcare providers compared to mutation-positive customers, 26 percent versus 60 percent. Moreover, doctors were more willing to refer mutation-positive patients for genetic counseling and for confirmatory testing but tended to be unhelpful when patients brought in negative reports.

It's not clear if these results from this small 2013 study still hold true today, particularly since 23andMe's new FDA-authorized reports include specific language around confirmatory testing and the need for counseling and additional testing for negative patients. 23andMe spokesperson Christine Pai said the company is interested in updating this research but doesn't have any data to share at the moment. She did highlight however that customers are very interested in learning their genetic risks for diseases because when prompted on the website to decide if they want to open their reports on BRCA1/2, late-onset Alzheimer's disease, and Parkinson's disease variants, most do.

**A new normal?**

When the first consumer genetics companies launched more than a decade ago, they branded themselves as disruptors in a cumbersome, broken, and paternalistic healthcare system, where consumers would be empowered to direct their own healthcare. When the FDA cracked down on these companies for making unproven health-related claims, they accused the government of getting in the way of people's ability to access knowledge about their own DNA.

In response, healthcare providers said that by providing genetic testing that lacked clinical utility, DTC services like 23andMe's would end up needlessly worrying customers and drive up unnecessary medical procedures that could result in more harm than good. And when patients brought in test reports, they'd pay little attention.

These battle lines have softened in recent years as new consumer-facing genetic testing firms have evolved, separating recreational genetics from medically useful testing by offering the latter with genetic

counseling support, and moving to next-generation sequencing to keep up with advancing technology. In kind, more healthcare providers have stopped treating consumer genetics as a passing fad.

23andMe is unique in the consumer genetics space as the only firm to seek FDA authorization for its tests, while others have largely avoided the agency's oversight by relying on physicians or third-party physician networks to order tests. While 23andMe is one of the leading consumer genetics firms, it's not clear the extent to which FDA authorization has helped its market position and mainstream reception. While the agency's nod allows it to stick to its DTC ethos when it comes to health risk tests, the company is still relying on older microarray-based SNP testing at a time when competitors are offering more comprehensive, clinical grade next-generation sequencing tests at a comparable price. (A shift to NGS would be a significant enough change to likely require new FDA filings.)

The *New York Times* editorial board last month published an editorial, entitled "Why you should be careful about 23andMe's health test," and highlighted this point to its readers. "There are more comprehensive BRCA tests on the market," they wrote in reference to 23andMe's BRCA test. "They require a doctor's prescription, but they are much more useful, because they look at the entire gene."

Sturm was surprised that an institution like the *Times* would take a stance on this and try to clarify to its readership what 23andMe's tests can and can't tell them. To her it felt like a shift in the public discourse about DTC testing. If the *Times* felt this topic was important enough to address, she reflected, then they must also have a level of concern that consumers aren't sufficiently understanding the limits of this testing.

Brigham and Women's Green  also read the *Times* piece with fascination but saw it as a reflection of the public's increasing appetite for preventive genomics. He has also heard concerning anecdotes of people not fully grasping the information they're learning through consumer genetic testing, but he also pointed out that there isn't data to suggest that the risks of providing this testing directly to consumers is outweighing the benefits.

In 2012, Green and his colleagues surveyed customers of 23andMe and Pathway Genomics (which previously offered DTC tests but now requires a physician's order), and reported a high degree of comprehension of concepts and hypothetical testing scenarios presented to them. However, the study also showed comprehension levels differed between subgroups, for example by age and education level, and these differences might be more pronounced as a greater swathe of the general population gets tested.

Green didn't disagree with the cautionary points in the *Times* piece, but he thought the editorial board focused too much on the limited utility of 23andMe's tests and failed to recognize that DTC access has also helped some people. The company has highlighted the stories of customers who learned they had Ashkenazi Jewish ancestry through 23andMe, and then opted to learn their BRCA mutation status, only to find they carried a mutation.

"Direct-to-consumer companies have done a great service by popularizing and interpreting the genomic information they provide," Green said. "But ultimately this is important medical information that should be part of our everyday medicine."

Anticipating a future where genomic information is increasingly integrated into medicine, Green cofounded Genome Medical, a company that provides genetics expertise, including telegenetic counseling services. "We started Genome Medical in part because there is so much interest and there is

a certain amount of potential confusion," he said. "It's hard to measure and I'm not convinced if it's a public health hazard, but surely we all agree there is some. I do think genetics expertise should be readily available, not necessarily required, for everyone."

The dropping price and rapid growth of genetic testing has kept the company busy. In recent years, there's been a steady stream of customers who have sought out telegenetic counseling through Genome Medical after getting tested through 23andMe, buying one of the genomics apps sold by Helix, or having their raw 23andMe data analyzed by a third-party analysis company like Promethease.

The genetic counselors, providers, and patient advocates who continue to express concerns about 23andMe's health risk tests aren't trying to be obstructionist or hinder people's access to their own genetic information, many noted. "I genuinely do believe that they're coming from a good place when they raise those concerns," said Erynn Gordon, Genome Medical's VP of clinical operations. She predicted that in time consumer genomics will become "the new normal," with the companies in this space and healthcare providers working together to find the best path forward.

To an extent this is already happening. Clinical diagnostics labs have launched low-cost confirmatory testing programs for DTC testing customers. Community healthcare providers, such as NorthShore University HealthSystem in Illinois and Renown Health in Nevada have recognized consumers' growing appetite for genetic testing, and are now offering their patients the chance to learn their genetic health risks as part of population health studies. In this way, researchers are starting to gather the critically missing data on DTC genetic testing: how giving people direct information about their genetic health risks impacts their outcomes, medical utilization, and costs.

Meanwhile, as more and more patients continue to show up to their doctors' offices with DTC genetic test reports in hand, it will force some providers to get up to speed but also create some angst because doctors still lack genetic knowhow, reflected Genome Medical CEO Lisa Alderson. "That's probably deliberate on the part of 23andMe because it's trying to serve as that catalyst," she said.

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