Debate

Its screen for selected variants of some disease-linked genes gives customers an incomplete picture of their risk—do they know?

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When MyHeritage's chief scientific officer Yaniv Erlich announced the launch of the company's new Health+Ancestry test on Twitter earlier this summer, the feedback wasn't entirely positive.

ABOVE: The new MyHeritage Health+Ancestry test uses a DNA microarray to detect single-nucleotide polymorphisms.
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The array-based screen offering insights into a customer's genealogical and health background from a cheek swab is a rival to 23andMe's service of the same name. It promises risk reports for genetic variants associated with conditions including breast cancer and heart disease, and, unlike 23andMe, provides conversations with a genetic counselor, should the test turn up anything concerning—all for the price of $199 plus shipping.

But, as some Twitter users were quick to point out, the company's 5,000-word blog post on the product was thin on medical specifics. "Your blog brags that it tests for, 'hereditary BRCA cancers (for which we support more variants than our major competitor),'" tweeted Kyla Dunn, a genetic counselor at the Stanford Center for Inherited Cardiovascular Disease, on May 21. "Can you please provide a LIST OF THE VARIANTS . . . so the biomedical community can better understand the limitations of this new, inadequate test marketed directly to consumers."

We know that our test isn't comprehensive.

—Yaniv Erlich, MyHeritage

As for many disease-related genes, there are thousands of variants of *BRCA1* and *BRCA2*, most of which are rare in any given population, and many of which are caused by the sort of mutations—large deletions or insertions, for instance—that are undetectable with an array-based test. Some variants are pathogenic, meaning they're associated with an increased risk of disease—typically cancers such as breast or ovarian cancer—although many other genetic and environmental factors interact to influence the outcome. A

Feedback

negative test result for one variant, particularly if that variant is rare in the population being tested, offers negligible information about the overall risk of developing cancer.

When 23andMe received market authorization last year for its "BRCA (selected variants)" test, which it added to a list of tests for variants associated with other medical conditions, it kicked up a storm in the medical community. Physicians and genetic counselors reported cases in which patients had misunderstood their test results—overestimating the seriousness of a positive result, for example, or underestimating their risk of disease after a negative result. 23andMe's *BRCA* test covered just three single-nucleotide polymorphisms (SNPs) that principally affect women of Ashkenazi Jewish descent, rendering the results uninformative about disease risk to the vast majority of the population.

See "Opinion: No, FDA Didn't Really Approve 23andMe's *BRCA* Test"

On May 22, following some back-and-forth over Twitter, Erlich tweeted a list of 13 *BRCA* variants that MyHeritage offers testing for—still just a fraction of the variants associated with disease risk. Erlich tells *The Scientist* that the company's test should currently be able to identify almost half of people carrying potentially deleterious mutations in *BRCA1*, and a third of those with mutations in *BRCA2*—almost double 23andMe's statistics, he notes.

At the time of this article's publication, the variant information isn't listed on the company's website—an omission that Erlich notes is due to a delay in website design rather than a lack of transparency. "There is no secret—it's just that we didn't have time to put it on the webpage, basically," he says. "When people get the results, they'll see all the variants that were tested, all the technical information, and so on."

The omission of variant information, which also applies to the other conditions the company tests for, isn't the only detail to raise medical professionals' eyebrows. Researchers who spoke to *The Scientist* highlighted other aspects of MyHeritage's move into health-related genetic testing—from the company's approach to regulatory oversight, to the language in its marketing materials—that heighten their concerns about this minimally regulated marketplace, and the risks it presents to consumers.

Hank Greely
@HankGreelyLSJU

Replying to @erlichya @MyHeritage

Can't say I'm "excited," but I am interested, & nervous. "11

Genetic Risk Reports, including a hereditary breast cancer (BRCA) report that tests 10 pathogenic variants; 3 Polygenic Risk Reports; and 15 Carrier Status Reports." They're positioning this as an LDT so no FDA review

7 5:13 PM - May 20, 2019

See Hank Greely's other Tweets

A regulatory blind spot?

Founded in 2003, MyHeritage now has more than 110 million registered users, who can use the company's platform to create family trees, share photos, and explore their ancestry via online historical records. The company began offering ancestry-related DNA testing in 2016 to customers interested in learning more about their past, and currently holds DNA data for more than 3 million users. According to a recent report by *MIT Technology Review*, it now has the third largest repository of customer DNA, after Ancestry.com's 14 million customers (who can only access ancestry-related tests) and 23andMe's 9 million or so (for whom ancestry and health analyses are available).

Although MyHeritage's latest product bears many similarities to that of its rival, there are some key distinctions in how the company offers access to particular variant tests—several of which have implications for its relationship with regulators.

While 23andMe's service is a true direct-to-consumer test, as customers order the product themselves, MyHeritage involves an intermediary step as part of what the company refers to as "physician oversight." In practice, this means that, after purchasing a Health+Ancestry kit but before receiving the results, a customer fills in a questionnaire about his medical history for review by a physician at telemedicine firm PWNHealth.

The physician uses the answers to identify any conditions for which a customer has a particularly high risk, and MyHeritage then withholds reports on variants related to that particular condition. For example, Erlich explains, "if you indicate that you [or your family] have a history of breast cancer . . . which means that you are high risk to carry a *BRCA* mutation, you are not eligible to get this report." Such a person would then be encouraged to speak to her health care provider to see whether she should get more thoroughly tested.

This extra step allows MyHeritage (and a handful of smaller companies taking a similar approach) to

address a key concern about direct-to-consumer genetic testing, Erlich says—that people with a known high risk for a certain condition might mistakenly view selected-variants tests as a substitute for getting properly screened. "We know that our test isn't comprehensive," he explains. Customers will still be able to get reports on variants related to conditions for which they haven't reported risk factors, he adds.

I think if it's done well, thoughtfully, carefully, then that is perfectly appropriate.

—Robert Green, Brigham and Women's Hospital

There's another consequence of physician involvement, though: it has allowed MyHeritage to avoid the sort of regulatory oversight associated with traditional direct-to-consumer products such as 23andMe's. As US Food and Drug Administration (FDA) press officer Megan McSeveney explains in an email to *The Scientist*, the FDA historically hasn't required companies to seek regulatory authorization for genetic tests "if they are offered to patients only when prescribed or ordered by a health care provider"—a policy "premised on the presence of physician assistance and oversight."

Steven Woloshin, a codirector of the Center for Medicine and Media at The Dartmouth Institute, notes that the agency originally adopted this discretionary approach to physician-mediated tests so that it wouldn't interfere in one-off, laboratory-developed tests (LDTs) that doctors order for individual patients to answer specific questions in a medical setting. Those tests "weren't meant to be marketed on a large scale," he says, so premarket review wasn't a priority.

But some mass-marketing companies may now be exploiting this "loophole" to sidestep regulation, he says. He highlights the story of Kailos Genetics, a small, Alabama-based company that received a violation letter in 2015 from the FDA for marketing unapproved, health-related genetic tests directly to consumers. Soon after, the company added a physician-oversight step to its procedure. "Now, they're able to sell exactly the same unapproved test," Woloshin says, "because a physician order is required."

Erlich did not directly respond to a question about whether the regulatory situation played a role in MyHeritage's decision to include physician oversight, but writes in an email to *The Scientist* that he disagrees with the idea that getting physicians involved amounts to "exploiting a loophole." Oversight of LDTs via telemedicine "is a rapidly growing segment in health care," he says. Noting that 23andMe's test doesn't offer such oversight, he says that "all in all, I feel much better with our approach."

There are signs that regulators are paying attention to the medical community's concerns about how health-

related genetic testing is presented to customers. FDA's McSeveney, for example, notes that "Congress is considering possible legislation regarding regulation of in vitro clinical tests," including the sort of tests used by MyHeritage and other personal genetic testing companies—a move that researchers who spoke to *The Scientist* suggest is partly a result of the way some companies have employed physician oversight.

Robert Green, a medical geneticist at Brigham and Women's Hospital and Harvard Medical School, as well as a consultant for a number of genetic testing companies, notes there's a spectrum of behavior in how companies make use of physician involvement. "I do have a problem with companies that are simply using physicians as a workaround so they don't have to get FDA approval," says Green, who cofounded Genome Medical, a telemedicine company focusing on genetic health information, in 2016.

But, he says, if a physician's input is used for "prescreening, not necessarily in person, [to] flag people for whom this is not the appropriate test," then it allows companies to provide a better service. "I think if it's done well, thoughtfully, carefully, then that is perfectly appropriate."

Mixed messaging

Physician oversight may help companies mediate what information is provided to people with particularly elevated health risks. But it can't identify everyone who will go on to test positive for disease-related risk variants, nor does it guarantee that people will be able to interpret the results of selected-variants tests when they receive them. (MyHeritage offers genetic counseling to customers only in certain circumstances—for example, when a report indicates that they have an elevated disease risk.) As a result, some researchers are concerned that this extra safeguard does little to reduce customer confusion.

The situation might not be helped by the products' presentation on company websites. For instance, language near the bottom of the product page for MyHeritage's Health+Ancestry test explains that "the new health product is not intended . . . for making medical decisions," and that "users may need to obtain further services from their physician, a genetic counselor, or other healthcare provider, in order to obtain diagnostic results regarding the conditions or diseases indicated within the MyHeritage DNA health reports."

At the top of the same page, however, MyHeritage says that its Health+Ancestry test "offers new dimensions of genetic insight to enrich your life, enlighten you about your health, and help you make informed lifestyle choices." The 23andMe website describes its product

This isn't just a patient confusion issue; providers are really confused by it too

in similar terms, and CEOs from both companies have referred to their work as part of a movement to "democratize health care."

> "This isn't just a patient confusion issue; providers are really confused by it too."
> —Susan Domchek, Perelman School of Medicine University of Pennsylvania

"This language is ridiculously confusing," says Susan Domchek, a medical oncologist at the University of Pennsylvania's Perelman School of Medicine who wrote in *STAT* last year about her experiences with patients who'd received results from selected-variants tests. Doctors don't usually consider selective, array-based tests—as opposed to a full scan of a person's gene sequences—to be enlightening about a patient's risk of complex health conditions such as breast cancer, she adds, so it's not clear what people should do with the results they receive. "This isn't just a patient confusion issue; providers are really confused by it too."

Woloshin also finds some of the product descriptions "pretty fishy," he says, adding that regulators typically pay less attention to the marketing claims of companies that haven't been required to pursue premarket review. "The question is: What do consumers understand? What's the impression that a consumer gets when they see this sort of language?"

There's little research on how consumers perceive companies' marketing materials for health-related selected-variants tests, but advocates of such testing dispute the idea that consumers misinterpret what's on offer. A comprehension survey that Erlich's team carried out on a "representative sample of 100 people," for example, found that each question was answered correctly by at least 90 percent of respondents, demonstrating that most people have a good understanding of the principles behind the company's product, he tells *The Scientist*.

And research carried out a few years ago by Green and colleagues found that, of more than 1,500 people who had already taken a health-related, array-based test such as 23andMe's, just 2 percent expressed regret about their decision to take the test, while 1 percent reported that the decision had "done them harm." (That study also found that nearly 40 percent of respondents had given no thought before purchasing the test to whether they might receive unwanted results.)

Green notes that there's now a huge amount of available information about health-related genetic tests, both on company websites and in the press, so people are alerted to the implications of taking such a test before they buy. He adds that "it's tough for a business to market its own limitations to its customers," but that most responsible businesses do state their products' caveats, albeit "in a way that doesn't debase the whole product."

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