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Direct-to-consumer genetic testing hits a speed bump

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Abstract
Richman explores the costs and benefits associated with "retail genomics"

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In 2006, researchers at Vrije Universiteit in Amsterdam announced that they had found a connection between genes and intelligence. Their study of hundreds of Dutch families focused on close analysis of the SNAP-25 gene, one that has long been thought to have a relationship with the brain's ability to learn and memorize.[1]

Specifically, one small part of the gene was realized to have a strong affiliation with performance IQ. Any individual with one version of the gene—a variant scientists call the "A" allele—were likely to average at least three points higher on a non-verbal IQ test, the Dutch scientists claim.

Solid evidence that genes have a direct effect on intelligence is not easy to come by. Some scientists argue that such a connection may never be proven. A claim of a discovery of this sort is, to say the least, to be treated cautiously.

Yet today, you yourself might be the subject of such a claim. You need only a credit card and $99 at your disposal to receive an analysis of your genes from a company called 23&me. After logging onto the secure results webpage, your report might include a section entitled "Measures of Intelligence." Beneath this heading, a tiny portion of your genome is transcribed, and with luck, you would see the letters "AA." Beside this, an explanation would read "Subject's non-verbal IQ performance averaged three points higher." Whatever you make of the news, you should know that claims of your intellectual superiority as posited by the Dutch researchers may be looked upon with trepidation by other members of the scientific community.

If you are that consumer of 23&me's product with the "AA" readout under "Measures of

1 Gosso MF et al. (2006) . "The SNAP-25 gene is associated with cognitive ability: evidence from a family-based study in two independent Dutch cohorts." *Mol Psychiatry* 11(9):878-86.

Intelligence," do you take comfort in this result? Ignore it? Understand that your actual intelligence is a function of a complex web of factors, only some of them genetic? Is intelligence even quantifiable? Would you invest more faith in the result if, instead of measuring your intelligence, it articulated your elevated risk for Alzheimer's disease?

"It's a nice marketing ploy," states Jonathan D. Moreno, Professor of Medical Ethics and Health Policy at the University of Pennsylvania. The services offered by 23&me—the "23" referring to the total number of human chromosomes that we inherit from each of our parents— and other genetic testing companies such as Navigenics are "entertaining," he adds, but some scientists are skeptical of the verisimilitude of these companies' analyses of genes.

23&me "has pioneered consumer-oriented genetic testing," notes Dr. Gholson Lyon, a human genetics researcher at Cold Spring Harbor Laboratory in New York. However, "people might argue that they started too early."

Genetic testing became the norm amongst medically-minded individuals almost half a century ago. It began with testing newborns for PKU, or phenylketonuria, a metabolism disorder, and grew to include testing for the so-called "Jewish" disorders such as Tay-Sachs. Soon, fetuses could be tested for Down Syndrome and for rare single-gene diseases known to run in families.

It was a type of self-inflicted population control. The more people knew about their own genetic makeup, or that of their parents or children, the better they could prevent the births of family members that would live a life of suffering, or shape their healthcare to prepare for illness in later life. As the century turned and the scientific community sunk its teeth into the information cornucopia that is human genetics, the retail industry has slowly found a way to carve its own profit from this DNA age.

Founded in 2006 by Anne Wokcicji and Linda Avey, 23&me is among a collection of genetic testing companies considered to be the founders of retail genomics. The organization's colorful website boasts its dedication to improving the health of individuals, and the incredible power that genetic

testing can have in helping people take control of their lives. For a modest fee, each DNA sample the company receives from curious consumers is analyzed for over 100 traits and markers that may offer clues into the consumer's health and ancestry.

To map each consumer's entire genome would cost thousands more than 23&me's reasonable $99 dollar fee, and take far longer to sequence than the company's speedy six-week processing time.

23&me says its motives stretch beyond simple human interest; they seek to answer some of medicine's most pressing questions about diseases by compiling genetic information and using it to expand the field of knowledge about the ways in which these diseases operate. The company recently announced that they have discovered two new genetic associations with Parkinson's disease, which is the subject of their largest research initiative.

Dropping subscription prices combined with generous investments by Google, whose co-founder is Wojcicji's husband Sergey Brin, place 23& me on the precipice of reaching a far wider audience than the science-geeks and geneticists that were its initial customers. However, this new pool of potential clients likely possess only basic, if any, knowledge of genetics, leading some to question whether or not it is right to sell a product to consumers that are ignorant of its level of scientific integrity.

23&me's technology for processing customers' saliva samples is advanced and effective. Each DNA sample is cut into small, manageable pieces that can be inspected in the most cost-effective manner possible. Single-nucleotide polymorphisms, or SNPs, are sequences of DNA within which a single nucleotide, or variant "letter" of genetic information, differs between members of the same biological species. SNPs are an important source of variation among members of any species. If enough individuals in a population possess the varying sequence, that particular section of the human genome can be called a SNP. 23&me scours scientific literature on gene sequencing and picks out SNPs that are thought to have certain effects on human health, or that are known markers for members

of the same ancestral lines.

These small insights into our genetic makeup are products of the current period of scientific discovery intent on untangling the human genome. The Human Genome Project, an international scientific endeavor beginning in the 1990s whose ultimate goal, reached in the early 2000s, to map the entire human genome, was "partly sold to Congress with a certain amount of hyperbole," claims Moreno. "We didn't really know what the hell we were talking about." Genetics is "generational," he explains, and we have not figured it all out yet.

"We live in an uncertain world," adds Misha Angrist, Assistant Professor of Genetics at Duke University and one of the first ten people to have his entire genome mapped by Harvard's Personal Genome Project. "Science is based on the idea that hypotheses are disprovable," so genetic knowledge is absorbed and accepted as it is discovered, but with the understanding that this knowledge "may very well change tomorrow or next week or next year."

23&me attempts to stay afloat this wave of genetic discoveries by charging customers a yearlong subscription service so buyers can periodically be updated with new results and possible changes to old results if information has changed.

One problem with these young genetic testing companies, claims Lyon, is that they "decided to focus on complex diseases" which are still not greatly understood by scientists. Thus, results have "fluctuating" accuracy.

Yet some results offered by 23&me are indeed "highly predictive," explains Barbara A. Bernhardt, a genetic counselor and Professor of Medicine at the University of Pennsylvania, such as certain indicators for breast cancer and macular degeneration. "Some tests are better than others," but in general it should be understood that most indicators only "capture a very tiny proportion of the genetic component to disease risk."

"Common diseases that we are all susceptible to," says Angrist, such as diabetes, heart disease,

and cancer, "are generally determined by a combination of genes and environmental factors," which "interact in complicated ways that we don't understand."

23&me's decision to provide results to consumers about complex, common diseases about which comparatively little is known is an attempt to increase the cost-effectiveness of their product, suggests Lyon. It would be too expensive to test all consumers for a rare disorder when only a miniscule percentage would receive a positive result. Instead, 23&me tests for indicators of diseases that most people would have a chance of developing. Yet in this effort to give consumers results that are "actionable" in this way, 23&me provides indicators that often have questionable ability to predict disease very well, says Lyon. Indicators for common disease are often so erroneous that their perceived value "ends up dying and descending into the noise" of genetic discovery, Lyon claims.

How, then, does 23&me filter though the abundance of scientific studies claiming to find relationships between certain genes and disease risk, or traits, or ancestry and relay these findings to customers? The company has adopted a system whereby each indicator provided on a consumer's results page is marked by one, two, or three stars.

Three stars means the result is based on clinical research that 23&me considers "established." To be deemed "established" research, a study must have been completed on a sample size of at least 750 cases and replicated and proven statistically significant at least once by an alternative group of researchers.

These standards might not be adequate, says Lyon. The truth-value of any study's results does not rest simply on its design methodology. "It depends entirely on the disease," he explains. Any sort of "defacto threshold" that legitimizes a study's findings "that is independent of what disease you're studying is certainly not perfect."

"Preliminary" research, a category that includes the Dutch study on intelligence, is marked with one or two stars, and is based on knowledge obtained through research that did not pass 23&me's

guidelines. However, the company claims, these indicators are included on a customer's results page to account for diseases that may be rare, thus limiting available sample sizes. 23&me says this allows them to report on new and interesting findings that may not be replicated as of yet.

In a recent move thought to soon be copied by other states, New York has banned its residents from purchasing 23&me's services precisely due to the company's insistence on providing consumers with so-called "preliminary" health indicators that have not been thoroughly proven.

One problem lies in 23&me's advertizing strategy that presents its product not solely for those simply curious about their genetic makeup, but also as a means to potentially change the way consumers approach their own healthcare.

"In an ideal world," Bernhardt explains, "it would be terrific if the risk information actually resulted in people making some meaningful changes in their behaviors to improve their health." Perhaps those with an increased probability of developing type II diabetes would eat healthier, and frequent the gym.

However, counters Moreno, most of the indicators provided by 23&me are "coming too early to be useful other than for diet and exercise." He suggests that catalysts such as the increased tax on cigarettes are more likely to cause appreciable changes in people's behavior than a number on 23&me's results page with little scientific meaning.

Genetic testing at this point in time remains "very peripheral in the healthcare industry," says Lyon. The results offered by 23&me are not "linked into anyone's medical record, nor are they going through any physician." As a result, any potential that direct-to-consumer genetic testing holds for individualizing buyers' healthcare lies in their hands alone.

"I think one of the things we need to do is lower the expectations of those people," suggests Angrist, and "disabuse them of the idea that genetics is likely to radically change their health."

Consumers' ability to absorb the results they are given, some of which are neither medically

actionable nor grounded in firm scientific proof, is a major concern among critics of 23&me's product.

On the one hand, Angrist argues, people will never be able to understand the results they are given as long as the "gatekeepers" of genetic information continue to assume that laypeople are "neither smart enough nor emotionally stable enough to learn how to contextualize" their results. Indicators that are not definitively proven should not necessarily be hidden from public view, he says. "We have this obsession with utility that unless the information is useful, unless it can tell us something that we can act upon, then we are playing with fire if we choose to know it. And that's extremely unfortunate."

Others maintain that direct-to-consumer genetic testing only fuels the "idea that the genome is the 'blueprint' of the human body," explains Moreno. 23&me's services "can be abused through lack of understanding about how little it tells you."

At the moment, Lyon suggests, direct-to-consumer genetic testing has "unfortunately been kind of recreational genomics."

"Culture is going to have to absorb this trend," says Moreno, "and people are going to have to get gradually better and better at understanding it. But it could take 60 years for that to happen."