Science 25 September 2015:
Vol. 349 no. 6255 pp. 1472-1477
DOI: 10.1126/science.349.6255.1472

- News

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Can 23andMe have it all?

1. **Kelly Servick**[*]

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23andMe analyzes its customers' DNA with a customized “SNP chip,” which uses fluorescent tags to identify 650,000 potential genetic variants.

PHOTO: SPENCER LOWELL

How much do your eyes water when cutting onions? Does fresh cilantro taste like soap to you? Do you have stretch marks on your hips, thighs, or the backs of your arms? Have you ever been diagnosed with brain cancer?

Mail off your spit for a $99 genetic analysis from 23andMe, and you will get information about your ancestry, served up on a web account. You will also encounter a list of optional survey questions. A *lot* of survey questions. Some are quirky queries about your tastes and habits. Others are intimate probes into your experiences with disease and medicine.

For the team of more than 30 geneticists and statisticians behind one of the world's largest genetic biobanks, the surveys are bread and butter, allowing them to pin down links between DNA markers and people's health, appearance, and bodily idiosyncrasies. New medical and physiological connections have been incorporated into the $99 analysis, adding value for customers. The formula has enabled the Silicon Valley firm to outlast most of its competitors and become a poster child for the fledgling field of direct-to-consumer genetic testing.

23andMe suffered a major setback in 2013 when the U.S. Food and Drug Administration (FDA) warned the firm it was illegally returning health information using tests that the agency hadn't vetted. But even though the growth of its customer base slowed after the company pulled the health data from its personal genome service for new customers, 23andMe's research team pushed ahead. Today, the company has collected DNA from more than a million people. (That amounts to more than 2000 liters of saliva.) And its self-curious customers

seem almost addicted to participating in research; they collectively answer about 2 million new survey questions every week as the company searches for new health-related DNA sequences.

Gradually, a research group that started out analyzing the genetics of freckles and the sneeze reflex has moved into deeper scientific waters: the hunt for disease-related genes that could make good drug targets. “It's really been an evolution from, ‘Tell us whether you're a morning person or not,’ to ‘Let's solve disease,’” says Joyce Tung, 23andMe's director of research.

The company says it has made roughly 30 deals with pharmaceutical and biotech companies seeking access to its database—14 of them last year, most of them undisclosed. “There's no other group that has as many samples,” Tim Behrens, Genentech's senior director of human genetics in San Francisco, says of 23andMe's database of Parkinson's disease patients, which Genentech paid an initial $10 million to explore, with the promise of up to $50 million more.

23andMe went even further in March, when it announced that it would hire a therapeutics team and begin drug discovery efforts of its own. That's a move even some of its champions see as audacious. “Their main contribution, to me, has been democratization of genomics,” says Eric Topol, a physician and geneticist at the Scripps Research Institute in San Diego, California, who studies digital health technologies. “This is a very different look, and a pivot. Maybe they'll accomplish it, but there are a lot of entities out there that are trying to develop drugs.”

23ANDME SITS ALONG THE CALTRAIN tracks in downtown Mountain View, in a four-story glass cube that doesn't quite feel lived in yet. The company logo, a whimsical doodle of pink and green crisscrossed chromosomes, is still taped above the entrance, printed across four sheets of letter-sized white paper. On this summer morning, Anne Wojcicki is breezing around the deserted staff cafeteria in flip flops, preparing a hard-boiled egg. A row of treadmills outfitted with standing desks sits idle on the other side of the room.

This is a building that Wojcicki, 23andMe's co-founder and CEO, intends to grow into. In May, the company abandoned its previous nest on the campus of Google, Mountain View's most famous corporate resident. Google was both an early investor in 23andMe and an influence on Wojcicki's vision. A biologist and health care investment analyst, she launched the company in 2006 with biologist Linda Avey and financial executive Paul Cusenza based on what she calls a social mission to “integrate genetic information into the world,” and on the theory that collecting DNA and health information from every person could turn disease research into “a data problem.”

Tung, lured away from academia after a postdoc at Stanford University in Palo Alto, in which she studied the genetics of pigmentation in mice and people, was among the company's first recruits. At the time, skepticism abounded about the firm's vision of gleaning valuable data from a relatively cheap genetic test and an online survey. “My postdoc adviser was like ‘Well, it's nice that you guys want to do research, but you're never going to find anything real—like medical, or anything like that,’” she recalls.

In a glass-walled meeting room upstairs from the cafeteria, Tung's thunderous laugh rings out at unpredictable moments. When asked what makes the database valuable for researchers now, she stretches her arms dramatically and exclaims: “It's big!”

23andMe has extracted genetic information from its growing stockpile of samples by testing them for single nucleotide polymorphisms (SNPs, pronounced “snips”), relatively common variations in a single DNA base pair. DNA from each customer's saliva is broken into fragments and washed over a “SNP chip”—a credit card–sized plate of microscopic silica beads covered in DNA probes. Each single-stranded probe grabs the DNA fragment with a complementary sequence, leaving exposed the DNA letter at a location of interest. Then, free-floating nucleotides with fluorescent tags bind to and reveal the identity of that SNP.

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23andMe's scientific leadership (left to right): research director Joyce Tung, principal scientist David Hinds, senior research director Joanna Mountain, Chief Executive Officer Anne Wojcicki, platform architect Arnab Chowdry, and head of therapeutics Richard Scheller.

PHOTO: DEANNE FITZMAURICE

Biophysicist Arnab Chowdry, responsible for 23andMe's technology platforms, is always trying to squeeze more information from the limited chip real estate. The current model detects 650,000 SNPs, but using publicly available reference genomes, the team can also predict more than 14 million other variants that are likely to be inherited alongside those tested directly.

For its customers, 23andMe uses the SNPs to predict ancestry and other traits. The analysis can say what percentage of a customer's DNA originates from a population in Northern Europe, for example. And until 2013, it could warn about potentially elevated risk of conditions including Parkinson's disease, breast cancer, and cardiomy-opathy. (One of the company's initial analyses famously informed Sergey Brin, Google's co-founder and Wojcicki's ex-husband, that he has a gene that substantially increases his risk of Parkinson's; Brin, who publicly disclosed that finding, has since become a major funder of research into the disease.)

Using survey responses from more than 800,000 customers who have agreed to take part in the research, 23andMe's scientists look for new links between SNPs and physical traits, or phenotypes. Their stock-intrade is the genomewide association study (GWAS): They group customers who share a phenotype—haters of cilantro, or those with type 2 diabetes—and identify SNPs that occur more frequently in that group than a control.

Since 2009, 23andMe has also provided its personal genome service for free to certain patient populations in exchange for their participation in more focused, disease-specific surveys. Its Parkinson's disease “community” now includes 12,000 people; smaller projects have targeted sarcoma, myeloproliferative neoplasms—a group of rare bone marrow diseases—inflammatory bowel disease, and lupus.

All of the survey responses and genotypes are stripped of identifying information to protect privacy. And the participants readily volunteer more data. When the team sends out a new survey question, Tung says, it's not unusual to get millions of fresh data points within 24 hours. That responsiveness sets the 23andMe cohort apart from the average subjects recruited into a research study, who are often “ready to quit at the drop of a hat,” says George Church, a geneticist at Harvard University and a member of 23andMe's scientific advisory board. “The 23andMe cohort—for whatever reason, they're highly engaged.”

23andMe has cultivated this community carefully. Its researchers devote part of their time to studies that will pique customer interest, but that are unlikely to win grants from the National Institutes of Health. They've found four SNPs associated with a tendency to develop stretch marks, for example, and observed that a variant nestled among olfactory receptor genes turns cilantro soapy for certain tasters.

Yet the online surveys that have helped 23andMe's database flourish have also made it a questionable source of information in the eyes of some disease researchers. “It was met with incredible skepticism,” says Mark

Cookson, a cell biologist studying Parkinson's disease at the National Institute on Aging's laboratory of neurogenetics in Bethesda, Maryland. Casual questionnaires seemed to many to be a poor substitute for a medical exam or a patient's health records. “The clinical guys were saying, ‘Well hang on, if you don't know that someone has Parkinson's, how will you get clean data sets?’”

A cohort of customersCREDITS: (DIAGRAM) G. GRULLÓN/*SCIENCE*; (DATA) 23ANDME

Cookson says that skepticism has faded somewhat. For one thing, the search for statistically significant associations between a trait and a DNA sequence “is a numbers game,” he says, and with enough responses, concerns about reliability “melt a little bit.” And 23andMe has shown in several studies that the associations its researchers turn up match results from other groups.

By 2012, 23andMe had more than 180,000 customers, and had contributed to studies identifying new genetic associations for freckles, curly hair, alopecia, Parkinson's disease, and hypothyroidism. At that year's annual gathering of the American Society of Human Genetics (ASHG), 23andMe's principal scientist, statistical geneticist David Hinds, noticed that his status had changed. “Between one ASHG meeting and the next, it went from largely disinterest in what we were doing—thinking it was not very relevant—to being approached by lots of people who were interested in collaborating with us, getting access to our data.” As of this summer, the 23andMe team had put out more than 30 papers, many of them in collaboration with academic labs.

The 23andMe team has also demonstrated—retrospectively—that its database can help guide drug discovery. At the 2014 ASHG meeting, they presented an analysis of 2751 candidate drugs showing that 23andMe data could predict which ones succeeded in clinical trials. They observed a nearly twofold increase in the odds that a drug would ultimately be approved by FDA if the 23andMe database revealed an association between the disease trait and a SNP somewhere on or around the gene whose product the drug targeted, compared with a drug without a genetic association.

But association studies alone are feeble drug discovery tools. The SNPs linked to a disease are often just markers for a nearby region of the genome where the real disease-influencing mutation lies. Association studies also fail to lay out how illness might arise from a mutation, or how targeting a gene product might affect the body. Until recently, a completed GWAS was “sort of the end of the road” for the 23andMe team, Hinds says. “We were pretty limited, because we could find associations, but we're not set up to do biology.”

INDEED, THE COMPANY'S WIDE-OPEN office space is more suggestive of a generic Silicon Valley internet startup than a biotech lab. Headset-clad customer service representatives field calls at their standing desks. “Welcome to our gene pool” balloons flag the workstations of new hires.

But Richard Scheller, the most conspicuous new hire, is here to do biology. Last December, on the same day the 61-year-old drug discovery veteran announced his retirement from a 15-year career at Genentech, he got an email from Wojcicki. “I knew he had not retired,” she says. “I grew up on Stanford's campus. I know his phenotype. That man is never going to stop.” Wojcicki says she had long been debating whether the company should do its own drug discovery, and Scheller's enthusiasm for the idea pushed her over the edge.

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“It's really been an evolution from, ‘Tell us whether you're a morning person or not,’ to ‘Let's solve disease.’”

Joyce Tung, 23andMe's director of research

PHOTO: DEANNE FITZMAURICE

At 23andMe, Scheller is on foreign ground. The informatics experts on Tung's team are not his scientific ilk. “They use algorithms with famous statisticians' names behind them, and I have absolutely no idea what they're talking about,” he says.

Drug discovery is new territory for 23andMe's core research team, too. The group has long aspired to influence how drugs are developed, says Chowdry, but “I don't think most of us really imagined that we would ever bring it in-house.” Still, he quickly got on board. “If we actually believe that there's value in the database—which all of us do—having it in-house means that we get a bigger chunk of the value.”

As head of the new therapeutics group, Scheller plans to hire about 25 scientists by sometime next year, and to double the team again in another year. He is checking out potential lab space in South San Francisco and talking to contract labs. Slowly, 23andMe may start to look more like a typical biotech firm, doing the dicey work of drug development: finding candidate genes, screening compounds that might interact with them or their proteins, testing the compounds in animals and then in people.

The company has revealed almost nothing about what its new group will pursue. The only area definitively ruled out is neuropsychiatric disease—because of its “particular complexities,” says Scheller, who headed a Stanford neuroscience lab before joining Genentech. He also says that 23andMe's first drug candidates will likely be antibodies that target disease-related molecules, because they are easier to make than small molecule drugs.

Running a drug discovery program will mean going beyond 23andMe's old standby, the SNP chip, to partial- or full-genome sequencing. SNP chips are generally geared toward flagging common mutations—occurring in roughly 3% to 5% of the population—and these have so far failed to explain a large percentage of a person's genetic risk for common diseases. 23andMe's chip has been tweaked to include many rarer SNPs, but it can't physically accommodate hundreds of uncommon variants for every given gene. And it can only probe for known mutations—not reveal new ones.

Newer efforts to scan huge collections of DNA for disease-causing mutations—including geneticist J. Craig Venter's San Diego–based Human Longevity, Inc. and the 1-million-person cohort launched in January as part of President Obama's precision medicine initiative—are betting on large-scale genome sequencing instead (see sidebar, p. 1475). As DNA sequencing gets cheaper, “a whole realm of genetic variation that we've just not had access to is possible,” says Genentech's Behrens, who is heading an effort to sequence the genomes of 3000 Parkinson's patients in the 23andMe database. He says the company decided to ramp up its sequencing projects when the cost dipped to about $1600 last year.

23andMe has preserved many other saliva samples, with the customers' permission, and they are ripe for fuller sequencing. But $1600 is still astronomical in the context of 23andMe's model of $99 genotyping for the masses. “Some people ask me, ‘Wouldn't it be much better if you just did sequences?’” Scheller says. “That would be $2 billion, and most of that sequence would be completely uninteresting to us.” Instead, he intends to use SNPs to identify interesting regions of the genome, and then use sequencing to zoom in on those regions in certain patients. (Wojcicki says the company will eventually integrate sequencing into the personal analysis it provides to consumers.)

The bigger hurdle facing 23andMe is the one confronting any group with ambitions of genome-based drug development, Cookson says: the challenge of moving from a DNA region suspected of having a disease connection to a druggable target. “Can they get smart enough to really make contributions to the next stage? … I don't know,” he says, “But not that many people have really done that, so it would be churlish of me to say, ‘Oh, those guys will never do it.’ I haven't done it either.”

FOR ALL THE BUZZ around 23andMe's new foray into therapeutics, much of Wojcicki's energy is focused on a more immediate business goal: relaunching its consumer health service. That service was shut down after FDA warned that the company hadn't demonstrated that its health-related tests were properly validated, or responsibly communicated to customers, who might be confused or alarmed by the estimates of disease risk.

Wojcicki says the run-in with the agency arose from a poor understanding of government regulation and what was expected. 23andMe is now working with FDA to bring its health reports for customers back by the end of the year. In February, the agency approved 23andMe's test for whether a person carries a recessive mutation that could give offspring Bloom syndrome, a rare disease that affects the stability of DNA structure and elevates the risk of cancer. FDA also exempted other such carrier tests from its premarket review process, meaning the company won't have to seek approval before providing those results to customers. But it's not clear whether or when 23andMe will resume providing other kinds of health information, such as drug responses and disease risks. “There's going to be a path forward,” Wojcicki says, but “we might have to make certain kinds of compromises.”

Meanwhile, the company is quick to dismiss the idea that it's shifting focus away from spit kits—and the customers whose willingness to expound on their experiences with cilantro and cancer built the drug discovery platform in the first place. “We make a consumer product,” Tung says. Part of her responsibility, she says, is to figure out “what is the next coolest thing that we can provide back to our customers?”

In that light, there's a certain “inevitable logic” in a consumer genetics company turning to drug discovery, says Michael Eisen, a biologist at the University of California, Berkeley, and a member of 23andMe's scientific advisory board. “If there's really a long-term future in this, if it's anything more than just a curiosity for people, we've got to be able to use people's genetic information to provide them with actual treatment.”

↵* in Mountain View, California