Personalized investigation

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Despite continued doubts about the clinical utility of direct-to-consumer genetic tests, tens of thousands of people have sent away tubes full of their saliva to learn more about their genetic profiles. Armed with such DNA data, a number of early adopters are showing how empowering—and beneficial to science—personal genetic information can be. **Elie Dolgin** reports on one company's plans to make medical genetics more participatory.

Three years ago, the DNA technology provider Illumina teamed up with the company 23andMe to develop genotyping chips for the latter's direct-to-consumer gene test kits. To celebrate the partnership, Illumina employees had the rare opportunity to order discounted gene tests for just $249—a low cost compared to the $999 price tag at the time.

Raymond McCauley, a senior bioinformaticist at Illumina's Northern California office in Hayward, jumped on the opportunity to learn about his family's DNA, ordering kits for himself, his partner, his twin sons and seven other members of his family. "It's what we did instead of Christmas sweaters," McCauley says.

The three generations of genetic data obtained through the tests refuted the family legend that McCauley's grandmother was half Cherokee. It also helped the family find distant cousins who had posted their details online. But, more importantly, says McCauley, learning about his genetic predispositions to diabetes, obesity and cardiovascular problems prompted him to lose 90 pounds over the next six months.

Even after shedding close to a third of his body weight, McCauley still wanted to do more with the gene profile data—a collection of around 600,000 single nucleotide polymorphisms (SNPs) associated with various ancestries and disease risks. Yet, beyond the obvious lifestyle changes such as improved diet and exercise, the numerous published genome-wide association studies (GWASs) contained few clues for how McCauley could actively improve his health. To probe his genome a bit deeper, McCauley decided to take matters into his own hands.

McCauley's self-starter attitude has a rich history in biology. For example, so-called 'citizen scientists' have helped track bird migration patterns for decades. More recently, the Internet has fueled crowd-sourced 'games' such as FoldIt, in which participants help determine three-dimensional protein structures. And the plummeting cost of technology has created a do-it-yourself culture of biological engineering epitomized by the International Genetically Engineered Machine competition and groups such as DIYBio (*Nat. Med.* **15**, 230–231, 2009).

Now, with an explosion of companies offering personalized genetic tests, the intersection between genetics and medicine is starting to be tapped by amateur biologists-at-large as well, and their contributions could ultimately be a boon to biomedical research. In June, for instance, scientists at Mountain View, California–based 23andMe showed that an analysis of genetic information from their clients combined with surveys identified previously unknown links between certain DNA variations and traits such as freckles (*PLoS Genet.* **6**, e1000993, 2010). The study demonstrated for the first time that self-reported phenotypic data can be gathered over the Web from involved participants who also receive interpretations of their genetic data to reveal previously unknown genetic associations.

Although that study has bolstered the notion of decentralized, participant-driven research, all the contributors remained relatively passive, doing little more than responding to a questionnaire and signing an informed consent form to share their data. For McCauley, such studies provide little of what he calls "actionable personal information"—the type of inferences that could instruct him how to nonintuitively improve his health. So he has taken the next step.

Taking action

When McCauley learned through his 23andMe readout that he was at a 30% lifetime risk of age-related macular degeneration, he became particularly curious about vitamin B, which is thought to help maintain proper vision.

Earlier this year, he teamed up with four early adopters of the 23andMe tests—a human resources consultant, a commercial strategist for a major biotech company, a recent bioinformatics PhD graduate and the founder of the citizen science organization DIYGenomics—to investigate whether a pair of SNPs within a gene coding for the enzyme methylenetetrahydrofolate reductase (*MTHFR*), which is involved in vitamin B metabolism, could inform whether they would respond to vitamin supplements.

"We kind of said, 'let's be empirical,'" McCauley recalls. "Let's figure out if this works for us or not based on our genome profiles." (He emphasizes that his self-experimentation was done outside of his day job and does not reflect his role at Illumina.)

McCauley's team embarked on a series of two-week miniexperiments. In the first two-week phase, they all refrained from taking any supplements whatsoever. In the next part they took Centrum multivitamins, followed by a period when they received a more active form of vitamin B called L-methylfolate, then a combination of both vitamin sources and, finally, a washout phase with no vitamin supplements. In between each treatment, the group tested their own blood to measure concentrations of homocysteine, an undesirable amino acid that serves as a suitable biomarker for vitamin B activity.

For four of the study participants, all of whom paid out of pocket to participate in the research, either type of vitamin supplement decreased homocysteine levels by almost a third, indicating that the vitamins were having the desired effect and leading to homocysteine getting converted into more benign amino acids. But for McCauley—the only person in the study who was homozygous at both SNPs tested—run-of-the-mill pills raised his homocysteine concentrations, and only the more active L-methylfolate seemed to aid his vitamin metabolism. After completing the experiment last month, McCauley changed his source of supplementary vitamin B to L-methylfolate.

"I look at this as a proof of concept trial," says study participant Chris Hogg, director of commercial strategy for Gilead Siences, a Foster City, California–based biotech company. "We proved basically that it is possible to ask a question, do an intervention and measure an outcome."

Along the way, the self-experimenters posted all of their study data to the Wikipedia-style website called DIYGenomics.org, which facilitates sharing of genetic information and data tracking. Although the website serves as a starting point, its founder Melanie Swan (also one of the vitamin study participants) cautions that the site will not be enough to handle the larger sample sizes needed to provide statistically significant—and clinically relevant—findings.

"To really go to the scale of larger cohorts, we need some sort of automated platform where it's very easy for individuals to share their genome and where anybody can post up a study," she says. Without the resources and expertise to develop that platform herself, Swan decided to partner with a fledgling tech company called Genomera.

Scaling up

The story of Genomera begins two years ago, when Greg Biggers, a longtime technology entrepreneur, went looking for a new problem to solve. He'd been working for Chordiant Software, a developer of customer relationship management applications then based in Cupertino, California. But, he says, "I got the itch to do something new and innovative again." For about a year, Biggers kept a ranked list of around a dozen ideas in his pocket that he gradually whittled down to a handful of top contenders, including something to do with personalized genomics.

He was still undecided where to devote his attention until he attended the 2008 O'Reilly Emerging Technology Conference in San Diego. There, he heard Hugh Rienhoff, the medical geneticist behind the community website MyDaughtersDNA.org, speak about his efforts to deduce his own daughter's undiagnosed disease from his home office using secondhand laboratory equipment. "That event was the final thing that made 'do something in personal genetics' move to the top of my list," Biggers says, "because it made concrete for me how intensely personal it can be, and in a beneficial way."

Last year, Biggers left Chordiant to focus full time on incubating his new company. He raised a modest amount of seed money, hired a staff of seven software developers and enlisted an advisory board, which counts Rienhoff, Swan, Harvard Medical School geneticist George Church, and ex-Google and former LinkedIn executive Lloyd Taylor.

Citizen scientist: Raymond McCauley.

The result was Genomera (pronounced GEE-no-MEH-ra), a Mountain View, California–based company that helps people share genomic and phenotypic information and provides an intuitive platform for conducting sophisticated research analyses. The service will be free, with revenue expected to come from test referrals, sponsorship and advanced analytic services. Ultimately, Biggers, Genomera's 'chief instigator' and CEO, hopes that projects stemming from the company's platform will yield clinically useful studies, conducted with sufficient rigor to be published in major scientific journals.

"Genomera is helping develop tools that make it easier for people to contribute to research," says Daniel Vorhaus, editor of the Genomics Law Report and an attorney at the law firm Robinson Bradshaw & Hinson (which consulted for Genomera earlier this year to help craft the legal language in the company's user agreement). "You have a desire, an opportunity and a need for something that will allow people who have an interest to find like-minded people and to do it in a way that will generate useful and publishable research. You can't rely on

the model of running everything through the historic, traditional research channels."

That's personal

Genomera may be the only current start-up pushing to make money from participatory genomic research, but the company will face some competition from more established academic and commercial groups along the way.

The Personal Genome Project (PGP), an initiative launched by Harvard's Church in 2007, now boasts some 16,000 people who have voiced an interest in sharing their full genome sequences along with information about certain traits, although only ten participants have been enrolled to date. Interested parties must first pass an entrance exam that gauges comprehension of the risks of publically disclosing genetic data, after which they will have their genomes sequenced and share details about a number of phenotypic characteristics including allergies, immunizations, diet and ethnicity.

Linking thousands of full-genome scans to various human traits promises to improve the ability to diagnose, treat and prevent illness, says Church. But, he adds, Genomera's proposal to create opportunities for prospective, longitudinal experimentation "is more aggressive and maybe even more creative" than the PGP's current plans.

The Wiki-style website SNPedia, meanwhile, helps people extract more information from their gene scans than is routinely provided in the interpretations supplied by the testing companies themselves. The website contains more than 40 public genomes from people who have chosen to share their data, including several from PGP participants. But you don't have to divulge any information to take advantage of the site, notes SNPedia cofounder Mike Cariaso, a bioinformatician at the Dutch biotech company KeyGene. With the associated program Promethease, people can compare their personal genetic results against others within the SNPedia database, and all from the comfort of their home computers. As such, SNPedia "has stronger privacy than is possible with a purely centralized solution," Cariaaroso says, although he recognizes that the platform is not intended for collective data pooling and more active experimentation.

Since releasing its landmark proof-of-principle paper demonstrating the power of self-reported, Internet-based data, 23andMe is continuing to call on its clients to participate in research. According to the study's lead author Nicholas Eriksson, a statistical geneticist with the company, 23andMe currently has around 40 research surveys in progress in an attempt to link genes to a variety of ailments ranging from migraines to psoriasis. "Every week we run several hundred GWASs based on different phenotypes," he says.

Although industry-based projects have taken off, Daniel MacArthur, a geneticist at the Wellcome Trust Sanger Institute in Hinxton, UK and author of the personal genomics–focused blog Genetic Future, argues that Genomera's model is ultimately more democratic. 23andMe's model "is definitely to some extent top down—the company is still the one that makes the decisions about which projects are worth pursuing," he says. Other test providers, such as Foster City, California–based Navigenics, which is partnering with academic centers to explore using personal genomic testing as a primary research discovery tool, tend to be even less participatory. "With Genomera," MacArthur says, "the situation should be different, and individuals will decide what's worth pursuing."


Greg Biggers

"The locus of control is different and distributed."
– Greg Biggers

Biggers echoes this point. With Genomera, he says, "the locus of control is different and distributed. There are no principal investigators and subjects. Instead, there are organizers and participants, and both of those are collaborators."

Regulatory uncertainty

Genomera's entire business plan could be derailed, however, should federal regulators decide to restrict the range of consumer gene testing. In July, both the US Food and Drug Administration (FDA) and the US Government Accountability Office held hearings about the direct-to-consumer gene-testing industry, and it remains to be seen whether more oversight will be enacted. (The UK Human Genetics Commission also issued voluntary guidelines last month, but the agency does not plan to mandate additional rules for the industry in the immediate term.)

Vorhaus notes that this level of uncertainty makes Genomera's venture risky. But Biggers maintains that the regulatory deliberations are a short-term distraction, and more industry oversight could be beneficial in the long run. "The discussion and sometimes fear people express about what regulation might come we'll see in hindsight was overdone, and, actually, it'll help the industry to have some standards and consistency," says Biggers, who spoke at the FDA's public hearings in July to challenge plans for overly restrictive government scrutiny.

Through Biggers' discussions with McCauley and Swan, Genomera now plans to roll out the vitamin study as the first open participatory project under its platform. Anyone can contribute—all you need is a 23andMe-type gene test (similar products from Navigenics, Pathway Genomics, deCODE and a number of other companies also work if they also tested the same SNPs around the *MTHFR* locus) and a willingness to repeat the study protocol. Swan estimates that, all told, taking part in the study will cost each experimenter around $500.

As *Nature Medicine* went to press, Genomera's website was still more of a placeholder than the so-called "Facebook of genomics," as Swan describes the company. However, Biggers says that several of the members of the initial vitamin study are actively piloting the website to help work out all the kinks, and he expects to unveil the site to the public in the next month or two.

Future participatory projects in the works at Genomera range from the more obvious, including linking genes to athletic performance, mood and intelligence, to the outright wacky, such as testing the link between genetics, breakfast butter consumption and afternoon cognitive aptitude. And more user-friendly analytic tools are in development. Whereas McCauley relied on his bioinformatics know-how to analyze the five-person pilot project using open-access tools, such as a program called simply 'R', Biggers expects to develop specific software to automate the statistical analysis for a series of experimental protocols.

Once the site goes live, McCauley, who presented some of his early data at the Open Science Summit in Berkeley, California in July, anticipates an overwhelming response. "I thought this was the geekiest, narrowest thing that I could be doing, and I thought no one would be interested in this," he says. "But what's amazing is that anytime we have talked to anybody, somebody's like, 'I would really like to know what you guys find. Can I participate in this?'" And, once they do, perhaps McCauley's decision to switch his vitamin regime will be reaffirmed by a statistically significant—and publishable—finding.

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