Businesses ready whole-genome analysis services for researchers

The cost of sequencing an individual's entire genome has fallen precipitously over the past five years, from around $100 million for the first personal genome to under $5,000 today when sequencing services are purchased in bulk. In response, a handful companies have started developing whole-genome annotation services that give clinical researchers lacking expertise in bioinformatics the ability to use genomic data for disease-discovery and drug-response testing.

One company, Knome, based in Cambridge, Massachusetts, already offers a package deal. For about $5,000 it will sequence and annotate a genome—with a minimum order of ten genomes. Meanwhile, two California companies, Emeryville-based Omicia and Personalis in Palo Alto, are beta-testing annotation services in academic settings, with future plans to roll out their services in the clinic. Although neither of the two has set its pricing yet, Omicia is expected to release an annotation service for academics and clinicians in early 2012.

Notably, the whole-genome approach to DNA analysis stands in stark contrast to the single nucleotide polymorphism (SNP) method. Whereas the former involves sequencing the full three billion base pairs of DNA in the human genome, the latter typically looks only at around a million single-letter variants at disparate points along chromosomes.

In the past five years, companies such as 23andMe, based in Mountain View, California, and deCODE Genetics in Iceland have kicked off services that enable consumers to mail them saliva samples and receive their SNP-based genomic profiles in return. In contrast, the newer whole-genome–focused companies are not opting for the direct-to-consumer route. Nonetheless, their genome-wide analyses, which are focused on pharmacogenetic annotation and disease gene discovery, are gaining ground on the SNP-based approach.

On 15 September, for example, scientists at California's Stanford University School of Medicine, many of whom are scientific founders of Personalis, published a proof-of-principle paper detailing the whole genome of the company's chief executive, John West, his wife and their two teenage children (*PLoS Genet.* **7**, e1002280, 2011). This paper improved upon the analysis used in an earlier report from the same authors that probed the health-related information contained in another personal genome, that belonging to Stanford bioengineer Stephen Quake (*Lancet* **375**, 1525–1535, 2010)

Linking the clues

By comparing West's sequence against a reference genome, the study confirmed that he should maintain his current dosage of Nexium (esomeprazole), a proton pump inhibitor drug marketed by London-based AstraZeneca that West takes for his acid reflux. West's version of the gene *CYP2C19*, which encodes the cytochrome P450 proton pump, had two sequence variations—one thought to speed up metabolism of the drug and the other thought to slow it down. "Each one of these interpretations alone might lead to a different conclusion," says West, whose company just became operational in August. Since the two variants are believed to balance each other out, he hasn't changed his dosage.

In another study, researchers at the University of Utah in Salt Lake City collected a trove of genomic data from a boy with a fatal X-linked disorder that makes infant males resemble old men, tentatively dubbed Ogden syndrome in honor of the Utah city where his family lived. They pored over the information for a month before they outsourced the data crunching. "They knew the variants, but they couldn't figure out which change was the cause" of the disease, says Martin Reese, chief executive of Omicia. Thanks to the algorithm designed by Omicia and a University of Utah colleague, he says, "within a day, they had the answer."

The whole-genome annotation, verified by biochemical activity tests by an international team of scientists, found the disease is caused by a dysfunctional gene important in protein 'acetylation' modifications, the research team reported in June (*Am. J. Hum. Genet.* **89**, 28–43, 2011).

Quintin Lai, senior research analyst at Baird, an assets management firm out of Milwaukee, Wisconsin, says that these companies' annotation services allow basic and clinical researchers to bypass the cumbersome and complicated step of bioinformatic analysis. "It really doesn't make sense to have specialized people on your payroll to do a handful of [whole-genome] tests," he says. "The more complex the diagnosis, the more it is better-suited for a services-based approach."

And it should be a lucrative market, analysts say. These personalized genomics products represent part of the growing biomarker industry, which is expected to reach $34 billion by 2017, according to a report released this year by the San Jose–based market research firm Global Industry Analysts.

But, for now, these companies plan to keep the services strictly in the academic arena. "This is a first step," says Russ Altman, a Stanford bioinformatics expert and Personalis cofounder. "We don't have any clinical development goals anytime soon. But if we figure out how to do [genome annotation] for a research market, then we can have discussions with the regulatory agencies to see if it's anywhere close to clinically usable. That's exciting, but that's far away."

Trevor Stokes

Going forward, HHMI will continue to sponsor seminars for students enrolled in NIH training programs. But the loss of major financial support made it impossible for the NIH to keep the program going in its current form. So, agency officials decided to combine the Cloister Program with the 30-student Clinical Research Training Program (CRTP), a more applied research apprenticeship established in 1997 at the NIH Clinical Center. The combination results in what's known as the Medical Research Scholars Program, which spans both clinical and more basic research and will begin in the 2012–2013 year.

"It will really be a melding of the two [programs]," says Fred Ognibene, Clinical Center deputy director for educational affairs and strategic partnerships who currently directs the CTRP and will oversee the transition. "By realizing the strengths of both, we're hoping that somehow the sum will be a little bit better" than each individually.

As finances currently stand, however, the combined program will only be able to support 40 students instead of the 72 funded between the two programs in past years. The NIH is looking for public and private funding to boost the number of students, but raising the necessary cash will prove challenging, especially as the NIH faces tough budget lines.

"In the late 1990s, there was a huge enthusiasm about the problem of attracting clinical investigators with MDs into translational research," says David Nathan, former president of the Dana-Farber Cancer Institute in Boston who chaired the NIH Director's Panel on Clinical Research in 1996 that evaluated the Cloister Program. The idea of training students at the NIH "came through in the era of expansion," he adds, "and I would hate to see it go."

Hannah Waters

Correction

In the October 2011 issue of *Nature Medicine*, the article entitled "Businesses ready whole-genome analysis services for researchers" (*Nat. Med.* **17**, 1161, 2011) stated that the researchers spent nine months analyzing the data when, in fact, they spent only one month doing so. Additionally, the data were sent to Mark Yandell of the University of Utah, who applied the VAAST algorithm, rather than to Omicia directly. The error has been corrected in the HTML and PDF versions of the article.