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Improving genome understanding

The cost and accuracy of genome sequencing have improved dramatically. **George Church** *asks why so few people are opting to inspect their genome.*

Readers of *Nature*, we can assume, are bright and insatiably curious. So why have so few obtained and interpreted their own genome sequence? We should avoid being judgemental of people who practise genomic modesty or who choose not to act on genome information, but we should also ask if we are providing adequate and equal access to education about the benefits and risks of genome information.

For 7 years I led one of the teams registered to compete for the US$10-million Archon Genomics X Prize, and I was naturally disappointed by the abrupt cancellation of the competition in August. However, the confusion surrounding the X Prize does provide an occasion to reflect on the problems and misunderstandings in genomics. The first is that genomics is seen as expensive. In fact, sequencing costs have plummeted — from $2.7 billion for the first human genome in 2003 down to $1,000 today. That's not much more than the cost of a decent laptop, and much less than a car. However, people are reluctant to pay to have their genome sequenced — many feel that health care should be provided for free by insurance or the government and, indeed, this is our not-that-distant goal, as there are many in our community who would not benefit from genome information if it were not free. However, for those today who can afford a genome sequence, we would argue that, overall, the cost of sequencing is expected to be recovered over a lifetime through the avoidance of unnecessary diagnostics and therapeutics and time spent in waiting rooms and hospitals.

Perhaps too many think that genomics is inaccurate. When it announced the cancellation, the X Prize Foundation claimed that "no company is sequencing whole genomes to the accuracy the contest required". Aside from the pre-judgemental weirdness, is this statement true? Haplotype phasing quality — a measure of accuracy — has improved from 350 kilobases in 2007 to 2,463 kilobases in 2013, and point errors have improved from 1 in 100,000 to 1 in 10 million — both well beyond the X Prize goals. Genetic analyses of tough tandem repeats are now common diagnostically.

Are the results uninterpretable? Even if we place the As, Cs, Gs and Ts in the right order, how does this help? Genome-wide association studies (GWAS) and studies of twins can give the impression that predicting traits from genomic sequence is a haphazard science. But since 1991 the number of highly predictive gene tests has risen from two to 3,000. Even 'complex' traits include components that can be identified and applied clinically to individuals who are not classed to be directly at risk. For example, height and diabetes GWAS have shown that a vast number of common variants have small effects, but the alternative of seeking rare variants reveals large effects by altering levels of growth hormone for height and insulin for diabetes. These hormones are effective therapies even for individuals who are not mutant in them. Too often the messy results of GWAS and twin studies are down to poor selection of subjects and neglect of confounding environmental factors.

Even if they are interpretable, are the results useful? Yes! Even if there is no cure for the genetic conditions identified, there are effective preconception and prenatal options that could have an impact on the family. For example, Ashkenazi communities already use genetic screening to make lists of suitable marital partners early in life to avoid their offspring developing painful Tay–Sachs disease and more than 20 similarly devastating diseases (which are not restricted to their community, by the way). Although we are tempted to restrict genomics to those with ethnic or family risks, the fact is that we are all at risk. Even the possibility of finding markers for one treatable disease (such as a cancer or cardiomyopathy) could, for some, be a sufficient reason to check one's genome.

Perhaps most provocatively, some critics assert that genomics could be harmful. The US Genetic Information Nondiscrimination Act (GINA) prevents discrimination based on health insurance and employment; however, there is not a GINA in every country, and it doesn't cover the military, life insurance or person-to-person discrimination. But the question is: do the overall benefits of genomics exceed the risks? Do the benefits of driving trump the one-and-a-quarter million traffic-related deaths per year? A growing number of bioethicists and researchers are worried that typical consenting practices do not inform patients of the likelihood of data escape and re-identification. Certainly, conventional consents served to protect the researchers, not the volunteers. However, the huge numbers of volunteers who are willing to share their genetic data make this a moot point. Why insist on recruiting those — and setting policy around those — who would be upset if their data escapes?

It is important for those of us at the sharp end of work on genomics to work equally hard at conversations with the public. We already share our (very revealing) faces, voices and opinions. And, as we share more of our genetics and as we develop genomic progress into precision medicine, researchers and the public alike need frank assessments of all of these tests and treatments. We need the Genomics X Prize more than ever. ■

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