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We Are the Genes We've Been Waiting For: Rational Responses to the Gathering Storm of Personal Genomics

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If knowledge can create problems, it is not through ignorance that we can solve them.

— Isaac Asimov

In 2008, the medical establishment told us that learning genomic information about ourselves without—and sometimes even with—professional handholding is a bad idea, because the information is either 1) not worth much or 2) dangerous (Anonymous 2008; Hunter et al. 2008). Critics seemed to reserve special indignation for the upstart genome-scanning companies, perhaps because of their high public profiles and high-end marketing (celebrity spit parties, anyone?).

But when the history of personal genomics gets written, we would do well to remember that one genome interpretation website, SNPedia (available at: <http://www.snpedia.com>), actually began stealing Zeus's fire and giving it away for free way back in 2005. In light of McGuire and colleagues' (McGuire et al. 2009) report of social networkers' largely positive views of personal genome testing (PGT) companies, SNPedia's four-year growth curve from zero to almost 5,000 annotated single nucleotide polymorphisms (SNPs) and 10,000 visitors per month (M. Cariso personal communication 2009) makes perfect sense. The number one reason respondents gave McGuire and colleagues (2009) for their past or possible future use of PGT services was "general curiosity about my genetic make-up" (3), which is probably what most interests the early adopters who frequent SNPedia. This is obviously a far cry from 'so I can abort my unborn child' or 'so I can have my prostate removed' or 'so I can commit suicide'.

But will survey respondents' general curiosity be satisfied? Maybe not. In a funny and cutting indictment of the "DNA R Us" generation (Evans 2008), geneticist Jim Evans observed that consumers who purchase direct-to-consumer genetic tests may come away with a few "things that are fun to know" (e.g., ancestry), but most current SNP-based tests are more apt to yield "things that aren't true" (709) (bogus or weak associations), "things that we already know" (710) (e.g., eye and hair color) or "things we don't really want to know" (e.g., an apolipoprotein E (APOE) genotype indicating increased risk for Alzheimer's disease [AD]).

Fair enough, although I would take issue with the last point. Green and colleagues have shown that 1) people—especially relatives of AD patients—are interested in their AD risks to make plans for the future or otherwise negotiate how they will live their own lives (Gooding et al. 2006); 2) those who do receive bad news are remarkably resilient (Cassidy et

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al. 2008); and 3) many of those who discover that they are at increased risk are inclined to make positive and lasting health and lifestyle changes (Chao et al. 2008).

But even if we concede that such changes are futile and will do little to stem the awful, inexorable course of AD (time will tell), to say that the PGT services McGuire and colleagues' (2009) subjects want are worthless is simply not true anymore (if it ever was). In February 2009, 23andMe (Mountain View, CA) began offering to inform customers, on an opt-in basis, of their carrier status for the three most common high-penetrance susceptibility mutations for hereditary breast cancer in Ashkenazi Jews (23andMe 2009). Carrying one of these variants raises a woman's lifetime risk of developing breast cancer from 13% to more than 80% (King et al. 2003).

We can argue about an appropriate out-of-pocket price for PGT and about whether a woman who opts in for BRCA testing needs immediate access to a credentialed and knowledgeable human being with whom she can discuss her results (I would say she absolutely does). But however the parameters evolve, it is clear we are 'not in Kansas any-more': this is not 'recreational genomics' *à la* finding out whether one has the allele for wet earwax or nine variants that raise one's lifetime risk of Crohn's disease from four in 1000 to six in 1000. Hereditary breast cancer testing is clinically useful, clinically valid and clinically actionable. We cannot count it among 'things that aren't true', nor can we neatly assign it to 'things we'd rather not know'.

When I spoke to a representative of a PGT company in late 2007 and asked what happens in the event of a customer learning bad news, I was told, "There will be no bad news—this is not deterministic information. These are complex traits mediated by many genes and the environment" (personal communication 2007). But if customers are being given BRCA1 and BRCA2 results, then clearly that no longer applies. And as we move ineluctably toward inexpensive whole-genome sequencing on demand, it will apply less and less. The few thousand genes strongly associated with serious human phenotypes and catalogued so meticulously by Online Mendelian Inheritance in Man (2009) will assume a much higher profile in direct-to-consumer genomics, and rightfully so: after all, do we not finally want our money's worth? Thus, assuming PGT providers can escape further regulatory crackdowns and/or gene patent enforcement actions (a big assumption, perhaps), it will be incumbent upon them to manage the disclosure of substantial risk for relatively rare, highly penetrant Mendelian disorders mediated by one or a few genes. Typing two million anonymous SNPs per person will soon seem quaint (if it does not already).

And while it is easy for me to say, these companies will also have to make their disclaimers consonant with their actions. When you tell someone she has an 80% chance of developing breast cancer based on your product, it is hard to then turn around and, with a straight face, say that this same product "is not designed to ascertain the state of [her] health" or "is not a medical test." Not only are these statements disingenuous, they keep the debate about access to one's own medical information mired in semantics and legalese: "What *is* a 'medical test' anyway?" I am more than a little sympathetic to the 'it's only information and therefore nontoxic' argument, but in this case I think it is trumped by the 'if it quacks like a duck' argument. A woman's BRCA1 or BRCA2 mutation carrier status can have a direct and serious bearing on her health that implies critical medical surveillance and treatment options.

So, if we are to venture further down this road, who will handle the onslaught? A cohort of geneticists whose numbers are roughly the same as the number of astronauts in the United States? (Bohe 2009). Is it realistic to think that other patients will be able to ignore the emerging power of these tests and say to their genome-savvy patients, 'Come back in five years' and then go on about their business? Elsewhere I have argued that it is not (Angrist

2008). For their part, McGuire and colleagues (2009) report that, in addition to general curiosity, most potential PGT users are interested in their disease susceptibilities. Moreover, they *expect* their physicians to help them navigate their genomic data. We can and should bemoan the state of genetics education in medical school and figure out how to fix it (Guttmacher et al. 2007). But when sequencing a human genome costs less than cosmetic surgery and disease-centric social networking is all the rage, the current ranks of general practitioners and indeed, all manner of health professionals, are certain to be put on the spot.

We are all geneticists now.

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