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The audacity of interpretation: Protecting patients or piling on?

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1. Wait a minute, Mr. Postman

In November 2013, the United States Food and Drug Administration set off a media firestorm (or what passes for one in our world) when it sent a warning letter to the highest-profile direct-to-consumer genetic testing company, Silicon Valley-based 23andMe (Gutierrez, 2013). The company, the agency alleged, had committed a litany of transgressions during its six years in business, most notably violation of the Federal Food, Drug and Cosmetic Act by marketing its spit kit and Personal Genome Service (PGS) as a medical device without proper FDA clearance. By doing so, the FDA averred, 23andMe had put its customers at risk because they might "self-manage their treatments through dose changes or even abandon certain therapies depending on the outcome" of the company's PGS test. Or, in the case of hereditary breast and ovarian cancer caused by mutations in the BRCA1 and BRCA2 genes, "if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist" (Gutierrez, 2013).

Setting aside all of the other complaints in the FDA's missive (e.g., the company launching a high-profile ad campaign while ignoring the agency's communiqués for months on end), the implications were clear: as far as the FDA was concerned, 23andMe could not be trusted to dispense information on genetic risks for actionable traits with fairly high penetrance like drug response and Mendelian forms of cancer. This aspect of *l'affaire 23andMe* was a surprise: recent criticism of the company's assessment of a single pharmacogenetic locus notwithstanding (Brownstein et al., 2014), it seems to me that most—and arguably the most robust—criticisms of the substance of DTC genetics companies' offerings have been directed at their speculative and often contradictory lifetime risk estimates for complex diseases derived from genome-wide association studies (Peikoff, 2013; Ng et al., 2009; Janssens et al., 2011; Kido et al., 2013; Kalf et al., 2014). Thus, for the FDA to attack the company's assessment of the genetic basis of warfarin metabolism or BRCA alleles seemed less convincing: would any self-respecting surgical oncologist subject a woman to a radical mastectomy and/or oophorectomy based on nothing more than a $99 direct-to-consumer test that examined three known pathogenic alleles out of many hundreds (Meric-Bernstam et al., 2013)? This would be akin to an ob-gyn forgoing both a blood hCG pregnancy test and a pelvic exam because her patient had already reported a positive home pregnancy test.

2. The remainder of the proof is left as an exercise for the reader

Perhaps more surprising still was the FDA's insistence that it supports the development of a direct-to-consumer model (Hamburg, 2013) and does not wish to stand between Americans and their genomes. "People have every right to get their data," the agency's Alberto Gutierrez told *Bloomberg Businessweek* a few days after the warning letter to 23andMe he authored became public (Brady, 2013). And indeed, even though 23andMe customers can no longer get access to the company's interpretations of their health-related alleles while they wait for 23andMe to satisfy the FDA's demands, they can still download their raw genotype data from 23andMe.com and upload those hundreds of thousands of alleles to any number of freely available genome interpretation sites (Cariaso and Lennon, 2012; Karczewski et al., 2012; Angrist, 2014; Greshake et al., 2014). The message, then, seems to be that the FDA is comfortable with the idea of American citizens having access to their own *uninterpreted* (and, at the moment, mostly *uninterpretable*) genomic data and making of those data what they (and/or others) will. The agency is not comfortable with people relying on a company's interpretations about alleles related to health information as extrapolated from the literature.

For its part, the company appears to have accepted this constraint (and I suppose, other than moving the entirety of its operations offshore, what else could it do?). As of mid-2014 it was reportedly working toward FDA compliance while remaining committed to the direct-to-consumer model and recently reported FDA's agreement to review the company's health report on genetic risk of Bloom Syndrome (Hibbs, 2014; Lee, 2014).

3. CSERs must render unto Caesar?

The kerfuffle surrounding 23andMe's tête-à-tête-gone-public with the FDA can be (and has been) seen as a proxy for any number of competing values: autonomy versus beneficence (Vayena, 2014); free speech versus consumer protection (Baudhuin, 2014); risk mitigation versus patient empowerment (Downing and Ross, 2014; Green and Farahany, 2014); and perhaps investigational-use-only versus research-use-only devices (Ray, 2013). I'm sure there are others. But in each case the crux of the debate—is PGS subject to FDA oversight?—has hinged upon 1) *what 23andMe is* (a commercial enterprise); and 2) *what it is doing* (marketing and selling parsed genetic information to consumers without the involvement of medical professionals).

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That is, until now.

The FDA, it seems, is interested not only in direct-to-consumer genomics, but in "indirect-to-patient" genomics as well. The Clinical Sequencing Exploratory Research Program, an initiative funded by the National Human Genome Research Institute and the National Cancer Institute since 2011, is a network of research projects aimed at assessing the impact of large-scale sequencing in a range of clinical settings (https://cser-consortium.org/projects). In recent months three independent sources from different CSER projects (none of which I am affiliated with) have told me that the FDA has had discussions with them on whether the CSERs might need Investigational Device Exemptions (IDEs) and/or other regulatory submissions related to their clinical sequencing research programs. While the agency approved a sequencing machine and associated reagents for clinical genomics in 2013 as well as particular assays related to cystic fibrosis variant detection (Anonymous, 2014), it has yet to publicly signal any broad regulatory plans with respect to large-scale sequencing protocols in clinical settings per se.

That said, the FDA has long since made it known that it believes that regulation of so-called molecular-based laboratory-developed tests is within its purview (Davis and Wentz, 2007), despite resistance from the clinical pathology community (Scott et al., 2013; Ferreira-Gonzalez et al., 2014). So maybe this is neither a surprise nor a big deal. Certainly many legitimate questions remain about next-generation clinical sequencing, among them: how many mutations must one clinically validate? What are acceptable false positive and false negative rates? And what is the appropriate comparator technology (Pant et al., 2014)?

But those are more about assays than they are about research participation. As constituted, the CSERs are research studies already subject to both institutional review board and NIH/NCI oversight, neither of which is trivial (ask any principal investigator doing human subjects research or any IRB member). The CSERs carry out sequencing in clinically certified laboratories regulated by the Centers for Medicare and Medicaid Services; they are not in it to make money nor are they returning results to patients without physician involvement (not that there's anything a priori wrong with either of those things). On the contrary: one might argue that the *raison d'etre* of the CSERs is to explicitly involve physicians and clinical genetics researchers in the non-commercial clinical sequencing enterprise.

4. Department of redundancy department?

It is clear that 23andMe has work to do rebuilding its image and reconciling its promises with its product, to say nothing of finding its way into the good graces of the FDA. Each of those will take time. So be it.

But federally funded clinical sequencing experiments can hardly be accused of "going rogue." If the FDA is sincere in its wish to "promote innovation" in personalized medicine and thereby "improve the care and treatment of patients" (http://www.fda.gov/newsevents/speeches/ucm387755.htm), it ought to tread carefully in its overtures to regulating medical genomics in its bold but iterative instantiations in the clinic. To impose additional oversight on something that is already being overseen by academic medical institutions as well as individual clinicians and researchers might be simple prudence: no one who's involved in almost any aspect of a clinical sequencing pipeline would argue that it is not hard to build and execute well, whether in healthy people or in patients. It is critical that we get this right.

But more regulation is not always better regulation. For those involved in clinical sequencing at an academic medical center, satisfying one's local IRB can feel like a full-time job. It would be a shame if one more agency's good intentions ended up as an exercise in "piling on" and fanning the flames of genetic exceptionalism.

Competing interests

None.

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