The audacity of interpretation: Protecting patients or piling on?

Misha Angrist

Science and Society, Social Science Research Institute, Duke University, Durham, NC, United States

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 uninterpreted genetic risk estimates for complex diseases derived from genome-wide association studies (Peikoff, 2013; Ng et al., 2009; Janssens et al., 2011; Lee, 2014). I’m sure there are others. But in each case the crux of the debate—whether the 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 unintertpretable) 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).

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 unintertpretable) 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. CSRs 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).
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’être 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 regulatory agencies to regulate molecular-based laboratory-developed tests: a position statement of the Association for Molecular Pathology. J. Mol. Diagn. 16 (1), 3–6.

Green, R.C., Farahany, N.A., 2014. Regulation: the FDA is overcautious on consumer genomics. Nature 505 (7483), 286–287.

Greshake, R., Bayer, P.E., et al., 2014. openSNP—a crowdsourced web resource for personal genomics. PLoS ONE 9 (3), e89204.

Gutierrez, A., 2013. U.S. Food and Drug Administration Warning Letter to 23andMe, Inc. (November 22).

Hamburg, M.A., 2013. FDA supports development of innovative genetic tests. Wall Str. J. (3 December).

Hibbs, K., 20 June 2014. Update On The Regulatory Review Process With The FDA http://blog.23andme.com/news/update-on-the-regulatory-review-process-with-the-fda/ WEjxYSfOgSwX3XPq9.

Janssens, A.C., Wilde, A.A., et al., 2011. The sense and nonsense of direct-to-consumer genetic testing for cardiovascular disease. Neth. Heart J. 19 (2), 85–88.

Kall, R.K., Milhaesco, R., et al., 2014. Variations in predicted risks in personal genome testing for common complex diseases. Genet. Med. 16 (1), 85–91.

Karczewski, K.J., Tirrell, R.P., et al., 2012. Interpretome: a freely available, modular, and secure personal genome interpretation engine. Pac. Symp. Biocomput. 339–350.

Kido, T., Kawashima, M., et al., 2013. Systematic evaluation of personal genome services for Japanese individuals. J. Hum. Genet. 58 (11), 734–741.

Lee, S.M., 2014. Anne Wojcicki Discusses Future of 23andMe. San Francisco Chronicle (24 May).

Meric-Bernstam, F., Gutierrez-Barrera, A.M., et al., 2013. Genotype in BRCA-associated breast cancers. Breast J. 19 (1), 87–93.

Ng, P.C., Murray, S.S., et al., 2009. An agenda for personalized medicine. Nature 461 (7265), 724–726.

Pant, S., Weine, R., et al., 2014. Navigating the rapids: the development of regulated next-generation sequencing-based clinical trial assays and companion diagnostics. Front. Oncol. 4, 78.

Peikoff, K., 2013. I Had My DNA Picture Taken, With Varying Results. The New York Times (30 December).

Ray, T., 2013. Clearer final RUO/IDU guidance raises concern regarding FDA regulation of LDTs. Pharmacogenomics Rep. (4 December).

Scott, M.G., Ashwood, E.R., et al., 2013. FDA oversight of laboratory-developed tests: is it necessary, and how would it impact clinical laboratories? Clin. Chem. 59 (7), 1017–1022.

Vayena, E., 2014. Direct-to-consumer genomics on the scales of autonomy. J. Med. Ethics 0, 1–5.

Competing interests

None.

Acknowledgments

I am supported in part by NIH grants SP50-HG003391-07 and NIDDK 1P50DK096415-01. I thank Jen Wagner and Carol Isaacson Barash for helpful feedback.

References

Angrist, M., 2014. Open window: when easily identifiable genomes and traits are in the public domain. PLoS ONE 9 (3), e92060.

Anonymous, 2014. FDA-approved next-generation sequencing system could expand clinical genomic testing: experts predict MiSeqDx system will make genomic testing more affordable for smaller labs. Am. J. Med. Genet. A 164A (3), x–x.

Baudhuin, L.M., 2014. The FDA and 23andMe: violating the first amendment or protecting the rights of consumers? Clin. Chem. 60 (6), 835–837.

Brady, D., 2013. Do Genetic Tests Need Doctors? FDA Defends Its Challenge to 23andMe. Bloomberg Businessweek (27 November).

Brownstein, C.A., Margulies, D.M., et al., 2014. Misinterpretation of TPMT by a DTC Genetic Testing Company. Clin. Pharmacol. Ther. 95 (6), 598–600.

Cariani, M., Lennon, G., 2012. SNPedia: a wiki supporting personal genome annotation, interpretation and analysis. Nucleic Acids Res., 40, D1308–D1312 (Database issue).

Davis, J., Wentz, J., 2007. How will the FDA impact the laboratory developed test? Clin. Lab. Sci. 20 (3), 130–131.

Downing, N.S., Rosi, J.S., 2014. Innovation, risk, and patient empowerment: the FDA-mandated withdrawal of 23andMe’s Personal Genome Service. JAMA 311 (8), 793–794.

Ferreira-Gonzalez, A., Emmadi, R., et al., 2014. Revisiting oversight and regulation of molecular-based laboratory-developed tests: a position statement of the Association for Molecular Pathology. J. Mol. Diagn. 16 (1), 3–6.

Green, R.C., Farahany, N.A., 2014. Regulation: the FDA is overcautious on consumer genomics. Nature 505 (7483), 286–287.

Greshake, R., Bayer, P.E., et al., 2014. openSNP—a crowdsourced web resource for personal genomics. PLoS ONE 9 (3), e89204.

Gutierrez, A., 2013. U.S. Food and Drug Administration Warning Letter to 23andMe, Inc. (22 November).

Hamburg, M.A., 2013. FDA supports development of innovative genetic tests. Wall Str. J. (3 December).

Hibbs, K., 20 June 2014. Update On The Regulatory Review Process With The FDA http://blog.23andme.com/news/update-on-the-regulatory-review-process-with-the-fda/WEjxYSfOgSwX3XPq9.

Janssens, A.C., Wilde, A.A., et al., 2011. The sense and nonsense of direct-to-consumer genetic testing for cardiovascular disease. Neth. Heart J. 19 (2), 85–88.

Kall, R.K., Milhaesco, R., et al., 2014. Variations in predicted risks in personal genome testing for common complex diseases. Genet. Med. 16 (1), 85–91.

Karczewski, K.J., Tirrell, R.P., et al., 2012. Interpretome: a freely available, modular, and secure personal genome interpretation engine. Pac. Symp. Biocomput. 339–350.

Kido, T., Kawashima, M., et al., 2013. Systematic evaluation of personal genome services for Japanese individuals. J. Hum. Genet. 58 (11), 734–741.

Lee, S.M., 2014. Anne Wojcicki Discusses Future of 23andMe. San Francisco Chronicle (24 May).

Meric-Bernstam, F., Gutierrez-Barrera, A.M., et al., 2013. Genotype in BRCA-associated breast cancers. Breast J. 19 (1), 87–93.

Ng, P.C., Murray, S.S., et al., 2009. An agenda for personalized medicine. Nature 461 (7265), 724–726.

Pant, S., Weine, R., et al., 2014. Navigating the rapids: the development of regulated next-generation sequencing-based clinical trial assays and companion diagnostics. Front. Oncol. 4, 78.

Peikoff, K., 2013. I Had My DNA Picture Taken, With Varying Results. The New York Times (30 December).

Ray, T., 2013. Clearer final RUO/IDU guidance raises concern regarding FDA regulation of LDTs. Pharmacogenomics Rep. (4 December).

Scott, M.G., Ashwood, E.R., et al., 2013. FDA oversight of laboratory-developed tests: is it necessary, and how would it impact clinical laboratories? Clin. Chem. 59 (7), 1017–1022.

Vayena, E., 2014. Direct-to-consumer genomics on the scales of autonomy. J. Med. Ethics 0, 1–5.