

Angrist GTR Comments, Washington DC, 2 Nov 2010

My name is Misha Angrist and I am an Assistant Professor at the Duke University Institute for Genome Sciences & Policy. I want to make two points that come out of my experience preparing a case study in 2008-2009 on the effects of gene patents on diagnostic testing. The case I prepared was on Long QT Syndrome, a rare but significant cause of sudden cardiac death, susceptibility to which can be inherited in either autosomal dominant or autosomal recessive fashion. This work was done for the late, great Secretary's Advisory Committee on Genetics, Health & Society, may it rest in peace.

The first point concerns variants of unknown significance. Perhaps my antennae are poorly calibrated or perhaps I am hanging around with the wrong crowd, but I hear a lot of talk about direct-to-consumer genetic testing and how the tests being offered by this renegade band of evil startups lack clinical validity, that is to say, some (most?) of these companies' tests are not strongly predictive of the presence or absence of disease. We can argue about the significance of this, but it is undeniably true. That said, it makes one wonder: Is this issue peculiar to DTC genetic testing for complex traits or does it also affect testing for Mendelian disorders?

In the course of preparing the Long QT study, I interviewed a prominent cardiologist (not for attribution). When I asked him about his use of commercial Long QT testing, this is what he said: "Here's the dirty little secret: I tend *not* to order genetic tests for Long QT because it opens up a can of worms. More than half of people with mutations never have a cardiac event. Ten percent of probands have two mutations. Genetic testing [in these cases] doesn't tell you a lot about phenotype. When you take people with nonspecific symptoms and do genetic testing—what you end up with is a person who has a variant of uncertain significance." Without question LQTS testing benefited thousands of patients. But my point is this: the clinical genetics community must be clear about the limitations of *every* test it offers, whether marketed directly to consumers or not. It should go out of its way *not* to give the impression that testing for Mendelian disorders is simple, definitive and always yields unequivocal answers. When we surveyed Long QT patients and family members online, several expressed shock and/or dismay that the suite of presumptive gold-standard genetic tests for their condition had added little or nothing to their risk profile for sudden cardiac death. Of course this phenomenon is not unique to LQTS. The BRCA genes that confer susceptibility to hereditary breast cancer are littered with variants of unknown significance: more than 1400 had been reported through 2007 and 1 in 14 women who receive BRCA testing are found to carry such a variant. I therefore believe that every test listed in the GTR should include information about yield, about clinical validity, and about what sorts of probabilistic expectations patients and clinicians should have for getting meaningful results.

The second point is a broad call for transparency and a plea for test providers to view the GTR not as a threat, not as a burden, *but as an opportunity*. Again, I take you back to 2008 when the Duke Center for Public Genomics was gathering information from and exchanging views with Long QT test providers at the behest of the SACGHS. At the time, PGxHealth, a subsidiary of Clinical Data, basically had a monopoly on LQTS-related intellectual property: the company had exclusively licensed patents on the major LQTS susceptibility genes from the University of Utah. PGxHealth had not shared its Long QT mutation data openly, had published few peer-reviewed papers on the subject, and had declined to disclose any specifics regarding its patent estate. We let it be known that we thought that this was unfortunate: it seemed to us that it was neither good business practice nor in the interests of LQTS patients and their at-risk family members.

So what happened? In 2008 PGxHealth announced it would make its mutation data public. In 2009-2010 PGxHealth and Mayo Clinic scientists published three peer-reviewed cardiac

channelopathy mutation compendium papers based on large numbers of patients; more than in the previous five years since the test was launched. And a few months ago, in its 2010 10-K form, Clinical Data included an extensive, three-page list of its IP holdings. When I saw this my jaw hit the floor. This is not to flatter ourselves and say that Duke played a significant role in bringing about these remarkable gestures of openness by Clinical Data. I imagine emerging competition had something to do with it. In the final analysis it doesn't matter. The point is that the company took these brave steps and the sky didn't fall. Not only that, the entire Long QT community can now benefit from having unfettered access to this information. I would argue that if Clinical Data can do it, then so can every other genetic test provider. If done right, the GTR offers the perfect avenue to make these sorts of disclosures regarding mutation data and intellectual property holdings the norm rather than happy anomalies.

Thank you for your attention.