



## Commentary

## Distributing the future: The weak justifications for keeping human genomic databases secret and the challenges and opportunities in reverse engineering them



Misha Angrist <sup>a,\*</sup>, Robert Cook-Deegan <sup>b,\*\*</sup>

<sup>a</sup> *Science and Society, Social Science Research Institute, Duke University, Durham, NC, United States*

<sup>b</sup> *Sanford School of Public Policy, Duke University, Durham, NC, United States*

“The future is already here – it’s just not very evenly distributed.”

[– William Gibson]

### 1. So sue me

Myriad Genetics, founded in 1991 as a spin-off from the cancer genetics epidemiology unit at the University of Utah and initially funded in part by public money, went on to build a multi-billion-dollar business by discovering and patenting two genes that, when mutated, predispose to hereditary breast and ovarian cancer (HBOC) (Williams-Jones, 2002; Allison, 2014). While Myriad’s reputation as a competent test provider was generally exemplary and there was no apparent price premium attributable to the patents, the company’s monopoly on the two genes kept patients from obtaining second opinions or confirmatory testing. Moreover, researchers were prevented from returning results on the two genes to research participants (Carbone et al., 2010; Cook-Deegan et al., 2010). In 2009 the American Civil Liberties Union sponsored litigation against Myriad on behalf of twenty plaintiffs (including HBOC patients), seeking to overturn Myriad’s US service monopoly on genetic testing for HBOC. In 2013 the United States Supreme Court ruled that genomic DNA was a product of nature and therefore not patentable (Association for Molecular Pathology et al., 2013), while engineered DNA molecules were eligible to patent. Almost immediately, a spate of other genetic testing firms announced that they would begin testing for the two genes, *BRCA1* and *BRCA2*, that were once the exclusive province of Myriad (Karow, 2013).

But, as Conley et al. describe in their review of the HBOC genetic testing landscape post-Myriad, whatever the legal precedent the Supreme Court established, in the immediate aftermath of the decision the HBOC marketplace only became messier and more confusing (Conley

et al., 2014). In the first of its two commercial strategies for HBOC testing post-SCOTUS, Myriad filed suit against most of its new would-be competitors, some of whom countersued while Gene by Gene acquiesced and settled out of court in February 2014 (Allison, 2014; Conley et al., 2014; Sherkow and Scott, 2014). Others have tried to be proactive before launching their own HBOC tests, seeking declaratory court judgments that would allow them to enter the market without fear of litigation (Conley et al., 2014). In all, thus far eight firms have been sued by Myriad, one settled, and several have countersued; the ongoing cases have been consolidated in the US Federal District Court for Utah, Judge Robert Shelby presiding. In all likelihood, the legal wrangling will outlive the first and broadest of Myriad’s surviving patent claims on *BRCA1* and *BRCA2*, which begin to expire in 2015.

Litigation and uncertainty ensure a contentious and turbulent HBOC genetic testing market in the near term. But while Myriad’s patent estate may be vulnerable, the company retains a two-decade head start on its competition and a war chest in excess of \$250 million (Gleason et al., 2014b). That is why, at least in part, it seems to us that it is not litigation but rather Myriad’s other major post-SCOTUS commercial strategy – to keep its data as a trade secret in the name of “accuracy” (Tucker, 2014) – that is more important and could set a worrisome precedent for the future of precision medicine, which relies on transparency as to how the work was done and broad access to data in order to replicate initial findings and draw robust conclusions about the use of genomics in clinical care (Angrist and Jamal, 2014).

### 2. The sagacity of opacity?

Myriad’s nearly two decades of control over the *BRCA1* and *BRCA2* genes allowed it to amass a large proprietary database of variants in these genes (Cook-Deegan et al., 2013). To its credit, company scientists have classified more than 25,000 mutations in cancer-related genes with respect to their pathogenicity (Gleason et al., 2014b). According to Myriad, its rate of variants of unknown significance (VUS), that is, *BRCA* variants whose pathogenicity (or lack thereof) cannot be determined with high certainty, was down to 2% in 2013–2014 versus 13%

\* Corresponding author.

\*\* Correspondence to: North Building Box 90222 Durham, NC 27708-0222.

E-mail addresses: [misha.angrist@duke.edu](mailto:misha.angrist@duke.edu) (M. Angrist), [bob.cd@duke.edu](mailto:bob.cd@duke.edu) (R. Cook-Deegan).

in 2002 (Eggington et al., 2014; Pruss et al., 2014). This is commendable indeed.

What Myriad has not done for ten years, however, is share those variant classifications with the broader scientific community (Tucker, 2014; Cook-Deegan et al., 2013), which means its VUS rate is unverifiable by anyone outside of the company. Why has Myriad declined to share its data? In recent months it has taken the opportunity to slam public databases time and again for their presumptive inaccuracy, lack of oversight/curation and the liability risks attached to using information contained within them to make clinical decisions (Gleason et al., 2014a; Bowles, 2014; Gleason et al., 2014b; Ray, 2014b). Public databases, according to Myriad's Chief Medical Officer, are not "sufficiently clinic-ready" and their VUS rate is unacceptably high (Tucker, 2014).

Fine. Let's concede that: 1) public databases harboring cancer-related variants like ClinVar and the Breast Cancer Information Core (BIC) along with the hundreds of locus-specific databases and handful of other genome-wide variant databases have inaccuracies in them – all databases do, of course, because as the science improves, variants will inevitably be re-classified; and 2) there is arguably a greater incentive for commercial laboratories returning results to patients and subject to liability concerns to ensure that variant classifications are accurate for clinical purposes.

But, as we and others have argued elsewhere, the only way these databases will improve, and the promise of personalized medicine will be realized, is through broad data-sharing, not construction of new silos and fortification of existing ones (Field et al., 2009; Angrist and Jamal, 2014; Quackenbush, 2014). Data quality – and by extension, patient care and liability mitigation – improves when the data have more eyes on them, not fewer. Myriad's withholding data impoverishes the public databases, while sharing data does not hinder Myriad's use of either its own data or public data. If other labs do as Myriad has, we will have – forgive us – a myriad of private, competitive databases to the detriment of all. Recently, in light of their discovery that family history of breast and ovarian cancer is an inadequate predictor of familial risk on its own (Gabai-Kapara et al., 2014), HBOC pioneer Mary-Claire King and colleagues called for universal screening of *BRCA1/2* in women after age 30 (King, et al., 2014). Whatever the merits and financial/logistical challenges of such an undertaking (and we should not underestimate the latter), in the near term how feasible would it be to expand HBOC genetic testing by many orders of magnitude while most of the allelic interpretation data remain inaccessible to anyone outside of Myriad?

### 3. Legerdemain and the public domain

Myriad's position is that if public databases are not "clinic-ready" then the company will simply take its ball and go home. And so it has.

But of course this is a non sequitur.

There is nothing preventing Myriad from publishing its own mutation data wherever it wants and curated however it wants to whatever exacting standards it wishes. Commercial laboratories certified in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) deposit their genetic disease-related variants in public databases all the time and the genomics community has developed professional standards and guidelines for assessing those variants, whatever their source (Duzkale et al., 2013; Rehm et al., 2013; MacArthur et al., 2014). Are CLIA-certified clinical variant data rendered suspect just because they sit alongside variants generated by research laboratories?

Myriad is not obligated to share its data (at least not yet); it is free to treat cancer-causing variants the way the Coca-Cola Company does its vaunted soft-drink formula (Kolata, 2013; Conley et al., 2014). But the company should at least do us the service of giving it to us straight. The "public databases aren't good enough for our data" argument is an eye-roller. The simplest way to improve public databases is to populate them with data and to play an active role in ensuring that the standards for interpretation are rigorous. Myriad would assume no more liability for depositing data than the dozens of other

laboratories that already do so for countless genetic diseases. Recently, Myriad's Chief Medical Officer told a reporter that the company would consider sharing its data *if it could do so without competing laboratories exploiting the information for their own HBOC testing efforts* (Tucker, 2014). This complaint strikes us as a far cry from concerns over inadequate databases.

Earlier this year, on a quarterly conference call with investment analysts (Gleason et al., 2014a), Myriad CEO Peter Meldrum discussed olaparib, a chemotherapeutic agent currently in Phase III clinical trials that is accompanied by *BRCA* testing for patient selection because data suggest that the drug is more effective in HBOC and prostate cancer patients with germline *BRCA1* or *BRCA2* mutations (Lee et al., 2014). Because Myriad's *BRCA* mutation database is deeper and more extensive than the public's (due in part to Myriad ceasing its variant contributions to public databases a decade ago), olaparib testing will allow the company to expand its franchise further into large-scale mutation detection in cancer. Meldrum:

... our competitors' reliance on public databases with high VUS and error rates will further restrict patient access to this life-saving medicine.

[Gleason et al. (2014a)]

Meldrum's clumsy assertion that ill people will suffer because other HBOC testing companies do not have access to Myriad's data is indeed a cruel reality, a claim of strategic business advantage rooted in a morally suspect choice. And let's be clear: it is a *business choice*, not a legal obligation. And yes, withholding data relevant to interpretation of genetic test results everywhere in the world outside of a single laboratory as a business strategy is a moral issue. Nothing personal, cancer patients ... it's just business.

For its part, Myriad is contributing variants to the Prospective Registry of Multiplex Testing (PROMPT), an academic-commercial partnership designed to create a registry of patients who have undergone multiplex genetic testing, curate their data, and characterize their genetic variants (Myriad, 2014). So, will this registry include *BRCA1/2* variants? Not many. "The genes of focus in this study are the less-studied genes that are now appearing on pan-cancer panels," according to a Myriad spokesman (Ray, 2014a). The academic principal investigator of the study confirmed to one of us (MA) that PROMPT will be "concentrating on non-*BRCA* predispositions" (M. Robson, personal communication, 18 August 2014).

PROMPT is a laudable effort to improve interpretation of many cancer variants, and Myriad's participation is welcome. It can also, perhaps, set a precedent for future efforts to pool data. But it does not obviate the abiding policy issue confronting the system: as things stand, incentives make data-hoarding a commercial advantage. Payers should beware: the precedents beginning to take hold now will set the pace for future costs of genetic testing. Without the principles of data-sharing and transparent analysis as prior conditions for coverage, reimbursement, and accreditation of genetic testing, proprietary data strategies may well proliferate, and costs will rise accordingly. If payers, accreditors and governing bodies choose to remain toothless, precision medicine will be less effective and more expensive. It really is that simple.

### 4. Reverse engineer agonistes

A couple of years ago, a consortium of advocates, academics and clinical diagnostic laboratories led by Robert Nussbaum at the University of California, San Francisco, launched Free the Data (<http://www.free-the-data.org/>) and Sharing Clinical Reports (<http://www.iccg.org/about-the-iccg/collaborations/sharing-clinical-reports-project/>). Meanwhile, the Evidence-based Network for Interpretation of Germline Mutant Alleles (ENIGMA) consortium received an NIH stimulus grant to systematically characterize *BRCA* mutations of unknown significance using a multitude of biological, computational, and other methods (Spurdle

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