genomeweb
A CRAIN FAMILY BRAND

Myriad Genetics to Submit Hereditary Cancer Risk Variants to ClinVar in 2023

Nov 01, 2022 | Turna Ray

Premium *Save for later*

iStock

NEW YORK – Myriad Genetics will begin submitting variants detected by its hereditary cancer risk test, including variants in BRCA1 and BRCA2 genes, to the public database ClinVar starting in the spring of 2023.

The Salt Lake City-based company is infamous, derided, and even boycotted in certain circles in the genetic testing community for using its patents on BRCA1/2 genes to establish what critics said was a testing monopoly that harmed patients and for refusing to share variant data to try to maintain market share even after the Supreme Court in 2013 deemed naturally occurring DNA fragments patent ineligible. Nearly a decade after the court's decision, in a much more crowded, competitive hereditary cancer testing market and undergoing a strategic shake-up, Myriad appears to have changed its stance on sharing data.

Since launching its first genetic test, BRACAnalysis, in 1996, Myriad has evaluated more than 2 million patients' inherited risks for cancer. All the variants in BRCA1/2 and other genes detected in patients over 26 years and the scientific rationale as to whether those variants are associated with cancer are housed in the company's proprietary database. "Data sharing with Myriad has been a big thorn in the side [of potential collaborators] and we've been hearing from customers and the broader community that this is something that's really desired," said Thomas Slavin, who became Myriad's chief medical officer just over a year ago. "We've finally come to the decision that this is something we should get behind."

The decision was spearheaded by Myriad CEO Paul Diaz, who was hired in 2020, following several quarters of lower-than-expected financial performance and at the end of Mark Capone's reign. During his two-year tenure, Diaz has tried to remake Myriad as a more fiscally responsible, patient-focused, equitable, and collaborative company.

Although the company has been submitting variant data to ClinVar from noninvasive prenatal tests it acquired through Counsyl a few years ago, by sharing information on hereditary cancer risk variants, the "new Myriad" is attempting to come out from under the shadow of the landmark Supreme Court case that took away its dominance over BRCA1/2 testing and its much criticized decision to maintain its variant data as a trade secret.

Ellen Matloff, a genetic counselor and CEO of the health technology company My Gene Counsel, was a plaintiff in *Association for Molecular Pathology v. Myriad*. In 2009, she joined numerous medical organizations, geneticists, women's health groups, and patients in challenging Myriad's ability to patent

BRCA1/2 gene sequences. They alleged that the lab's overly broad patent claims allowed it to limit patients' ability to get a second opinion on their test results and hinder research that would improve the field's understanding of BRCA1/2 variants and their links to breast and ovarian cancer.

For example, Matloff, who started the genetic counseling program at Yale Cancer Center, suspected in the late 1990s that Myriad's BRACAnalysis test wasn't detecting certain types of high-risk pathogenic variants in patients. Research had shown that large rearrangements in BRCA1/2 increased breast and ovarian cancer risk and weren't detected by the only commercially available test on the market. When Matloff asked if Yale's lab could start testing women who were negative via BRACAnalysis but had personal and family histories strongly indicative of a cancer predisposition syndrome, Myriad said no.

"It's fair to say that I have been one of Myriad's loudest and harshest critics for more than 25 years," said Matloff, recounting how she has taken the company to task publicly over its gene patents, advertising, and data hoarding. Myriad's decision to finally share data on cancer risk variants in ClinVar marks a "sea change," she said, in terms of the company's ethos and the attitudes of its leadership. "For me to say, 'It's time to give credit where credit is due,' is a big deal," Matloff said.

John Conley, a law professor at the University of North Carolina at Chapel Hill, who closely followed and has written extensively on *AMP v. Myriad*, reminded that even after the Supreme Court's decision, Myriad made no secret of the fact that it planned to hold the variant data it had amassed as a trade secret. "If they kept their variant data as proprietary, then others could still test, but Myriad would continue to have a virtual monopoly on the ability to interpret the variants because they have so much more data than anyone else," he said, adding that because of this, "Myriad emerged as a villain," especially among medical geneticists and genetic counselors at academic medical centers.

Reflecting on the company's history and its recent change of heart about sharing this data, Slavin said, "I can't think of anything bigger that says we're a different company."

Over recent months, Myriad has focused on lifting barriers that have hindered clinicians, health systems, and genetic counselors from working with the company previously. For example, the company rolled out a self-pay option for its tests and partnered with Intermountain Healthcare to add somatic variant testing capabilities to its germline analysis offerings — changes that clinicians wanted to see at the company, according to Slavin. As part of the Intermountain program, Myriad also launched a registry to share with researchers de-identified, aggregate genomic and clinical data from patients.

That was a step toward recognizing that Myriad's data-sharing policies needed to change if it wanted to collaborate with the broader precision medicine community. "It definitely hurt us," Slavin said, acknowledging that Myriad's historic position on data sharing made it a "non-favorable partner to a lot of people," particularly genetic counselors, who are accustomed to looking up variants detected in their patients in ClinVar to see how different labs have classified them.

"We can have a great [test], but things like cost or not being transparent about data sharing will drive some people away, and we don't want to be that [company] anymore," Slavin said. "We're making significant investments, and a lot of that is just making sure that we're great partners and people want to work with us."

Myriad is still figuring out its variant submission process. Generally, the company anticipates depositing thousands of variants that its scientists have recently vetted in BRCA1/2 and 46 other genes associated with 11 hereditary cancers and gauged by its MyRisk next-generation sequencing panel. Slavin couldn't specify the time frame within which a variant would be considered recently vetted, but he added that the company plans to submit "clinically impactful" variants each quarter as well as detailed annotation of the evidence used to classify them.

A 'big deal' for patients

In recent weeks, Slavin and other experts at Myriad reached out to key opinion leaders in the broader genetic testing community to share that the company would deposit data on cancer risk variants into ClinVar. "I will admit that I cried when I heard the news," said Matloff, who believes this decision is a "big deal" for patients.

Given the amount of BRCA1/2 variant data Myriad has, combined with the company's suite of variant classification tools and the expertise of its scientists, patients who received variants of uncertain significance (VUS) from another lab may get a more definitive result based on the data shared by Myriad.

"With all the things I've said about Myriad, I never said they weren't a good testing company or that they weren't a good scientific company," Matloff said, explaining that as the company starts depositing reclassified variants into ClinVar, some patients' VUS result may be upgraded to pathogenic based on that. But since a lot of VUS turn out benign, more people may find out that their variants are not disease causing because of Myriad's interpretations and that maybe they don't need prophylactic surgery or frequent, invasive surveillance.

The lower VUS rate for Myriad's BRACAnalysis test, helped by the lab's proprietary variant data, was a boasting point for the company in the chaotic months following the Supreme Court's decision, when other labs wasted no time introducing competing BRCA1/2 tests. Myriad sued those labs alleging infringement of patent claims it still held, but these competitors fought back. For example, in a countersuit accusing Myriad of antitrust violations, Ambry Genetics alleged that Myriad was falsely telling genetic counselors that between 10 percent and 30 percent of its BRCA1/2 test results were VUS; Ambry claimed the VUS rate was much lower, around 5 percent.

Whatever the VUS rate was back in 2013 for these newly launched BRCA1/2 tests, BRACAnalysis undoubtedly had the most experience on the market at that point, and Myriad claimed its test had a VUS rate of less than 3 percent. While the company is planning to deposit variant data across all the genes gauged by the MyRisk panel, the company's vast trove of BRCA1/2 variant data has always been what really interested other labs and researchers in the genetic testing industry, and over the years, the lab's detractors found creative ways to get their hands on these interpretations.

For example, a project started around a same time as ClinVar encouraged doctors to share de-identified BRCA1/2 test reports from Myriad so the detected variants and their classifications could be deposited in the database. In another attempt to shine a light on Myriad's variant classifications, in 2016, four patients represented by the American Civil Liberties Union asked the lab for information on all the variants the lab detected via hereditary cancer testing, not just the ones it reported as clinically significant. The patients asserted their rights under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and Myriad complied after conferring with the Office for Civil Rights.

Matloff, when she was still seeing patients as a genetic counselor, would use a little-known backdoor to peek at how Myriad had interpreted a variant. She would call up the lab's genetic counseling department and say that she had a patient whose family member harbored a variant of interest and that she was considering sending Myriad this patient's sample to see if it harbored the same variant. However, Myriad had an internal policy not to test a patient for a familial variant they had classified as benign, according to Matloff. Using this strategy, she was able to get Myriad to look up the classification of a variant and disclose what it thought about it.

Julie Eggington, who was a leading variant classification scientist at Myriad from 2009 to the fall of 2013, recalled a brief period when under the leadership of Mark Capone the lab tried to shut down genetic counselors' ability to access its variant interpretations in this way. But it was short-lived, lasting

only a few weeks, Eggington recalled, "because everyone internally at Myriad thought it really was not nice and profoundly sucked," and the company continued to allow some of its variant interpretations to trickle out to the community through this backdoor.

A change of heart for ClinVar

Even though Myriad for a time submitted information on BRCA1/2 variants to the Breast Cancer Information Core, it stopped doing so in 2006, and following the loss of its gene patents made clear that it had no plans to share data via public databases. The company's former leaders seemed to have a particular ax to grind with ClinVar, which was launched with National Institutes of Health funding in the fall of 2013, a few months after the Supreme Court's decision.

They published papers and spoke at conferences to warn that the resource was riddled with errors and that other labs would only invite liability by sharing data in it. Heidi Rehm, medical director of the Broad Institute Clinical Research Sequencing Platform and one of visionaries behind ClinVar, recalls this all too well, but said she wants to focus on the positive news going forward that Myriad is sharing this data.

Ultimately, the realization of the benefits of data sharing in ClinVar, as well as multiple market pressures, likely swayed Myriad to change its practices, Rehm suspects. Genetic testing is a highly competitive business, adding on average 22,000 new tests per year since 2015, and payors are becoming much more vigilant that the tests they're paying for are medically necessary and of high quality. Several payors now look to see if labs submit variant data to ClinVar when deciding whether to grant in-network status. The database, in turn, has grown to contain more than 2 million records with interpreted variants from around 2,300 submitters.

Back in 2013, when Myriad's leadership balked at data sharing, there were "very few people" among the company's rank-and-file employees who didn't support contributing to ClinVar, recalled Eggington. Even so, she was surprised to hear Myriad was sharing hereditary cancer risk variants in the repository. "This is something I thought I'd never see," said Eggington, who is now CEO of the Center for Genomic Interpretation, a nonprofit that uses in silico-based methods to help labs and payors validate NGS tests.

However, she said that the company had voiced some legitimate concerns about submitting to ClinVar in the early years of its launch. ClinVar is described as an archival database that records how a lab classifies a variant and any subsequent updates it makes to that classification over time. However, many labs submit to the database and don't necessarily update submissions in an iterative fashion as more evidence accumulates or variant classification guidelines change. This makes it more of a variant archive, and less a database fit for clinical use, in Eggington's view, and this distinction is "essentially what gave Myriad pause about contributing to ClinVar."

Eggington published papers with other Myriad scientists pointing out reasons why databases like ClinVar weren't robust enough for clinical use. For example, in a paper published in 2015, Eggington and colleagues compared some 2,000 BRCA1/2 variants classified by Myriad against the classifications in five public databases including ClinVar. They found significant disagreement in variant interpretations between databases and a proclivity for submitting labs to classify variants definitively when according to the latest guidelines the classification should have been uncertain. Other groups have now also shown that labs submitting to the repository are overcalling variants as pathogenic, but there is also data suggesting that as variants accumulate more data, they are reclassified as benign or uncertain.

While the inflated calls remain a problem in Eggington's view, she conceded that ClinVar today is a much cleaner database in terms of limiting "type-in" errors.

Meanwhile, even though more labs are now submitting to ClinVar and using data in it to inform their own variant classification efforts, this hasn't resulted in the lawsuits that Myriad's leaders had previously warned of. Other than a case in South Carolina challenging Quest and subsidiary Athena Diagnostics' 2006 classification of an SCN1A variant as having uncertain links to Dravet syndrome, UNC's Conley isn't aware of other lawsuits challenging a lab's variant interpretation. The judge in that case did not allow the lawsuit to move forward beyond the summary judgment stage and legal experts believe cases challenging labs' variant interpretations would be hard for plaintiffs to win.

Even if a lab's variant interpretation shared publicly via ClinVar turns out to be wrong, this is likely not sufficient to prove medical malpractice or ordinary negligence, in Conley's view. The plaintiff would have to prove that the lab failed to follow the standard processes for variant classification. "The question would be, did the people and companies that do that kind of work, given the difficulty of interpreting variants, meet the standard of care, which is really more about process," Conley said. "Did you follow the process correctly? If you did, even if you're wrong, you wouldn't have committed malpractice and under ordinary negligence you get to the same place."

Impact of Myriad's submissions

The Supreme Court's gene patenting decision not only impacted Myriad's business but also transformed the genetic testing landscape. As of 2020, there are nearly 167,000 genetic tests on the market, according to health IT firm Concert Genetics. Genetic tests for assessing cancer risk that cost patients several thousand dollars not too long ago can cost a few hundred dollars at some labs if they are paying out of pocket. And while Myriad's more than 15-year dominance over BRCA1/2 testing may still give it a leg up over other labs, newer entrants in the hereditary cancer space have also had a decade to build up their in-house data not just for BRCA1/2 variants but also for variants in a host of other cancer risk genes.

As such, it's not clear to Conley how the market will respond to Myriad's change in data-sharing policy. "The positive interpretation is that they've had a conversion, like Paul on the road to Damascus being hit by lightning … [and] they're going to disclose lots of useful heretofore proprietary variants. And that's going to make a big change in scientists' ability to interpret variants and other healthcare companies' ability to compete with them," he said. "The less generous interpretation is that they're just disclosing stuff that … might be of interest to the scientific community but won't make that much of a difference in the market." It'll be interesting, Conley said, to watch how Myriad's shareholders react to this news.

Myriad's embrace of a more permissive data-sharing policy comes as precision medicine-focused companies are struggling. Amid economic pressures, Invitae, one of Myriad's biggest competitors in hereditary cancer testing and the top submitter to ClinVar, announced in July it was restructuring its business, laying off 1,000 workers, and changing leadership, all in an attempt to reduce costs. "For Myriad to make a big move like this that will not necessarily benefit them financially in any way, that signals that their core values have changed," said Matloff.

In terms of the impact Myriad's data sharing will have, Eggington suspects that researchers and competing labs alike will pay attention to what the lab is putting into ClinVar. By focusing first on submitting recently vetted variants, Myriad is likely to start depositing information on reclassified variants based on new evidence as well as variants it has seen for the first time. As of 2017, the lab estimated that 60 percent of BRCA1/2 variants in its database had been seen in only one or two patients.

Rehm is expecting Myriad will contribute data on variants that haven't been seen by others, since around 75 percent of variants in ClinVar are rare alterations that have been submitted by only one lab.

"That just speaks to the fact that all disease has as its basis incredibly rare and often singleton variants," she said. "Any contribution from another lab, not just Myriad, will enrich our knowledgebase."

In Eggington's view, Myriad's reclassified variants will likely be what other labs are most interested in. Myriad has to accumulate a lot of data on a variant before it will reclassify it, she explained, and a key tool in the lab's arsenal is the Pheno algorithm, a personal and family cancer history-weighting algorithm that the lab developed after sequencing more than 400,000 patients. The algorithm has a positive and negative predictive value of more than 99 percent in determining the pathogenicity of a variant in BRCA1/2 and several other cancer risk genes.

Eggington is particularly interested in how Myriad's variant classifications will affect other labs' determinations, especially ones Myriad has reclassified using Pheno. "No laboratory can reproduce that because the methodology is based upon the entirety of the Myriad database and statistically leveraging that," noted Eggington, who was involved in validating the algorithm.

The most recent consensus variant classification guidelines from the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and the College of American Pathologists allow labs to use "reputable sources" as "supporting evidence of pathogenicity" for a variant even if they cannot independently verify the underlying evidence used to make that classification.

When these guidelines first came out in 2015, Eggington recalled this criterion created a stir among some experts who felt it was dangerous to suggest that labs could blindly trust the classifications of other labs, however "reputable," without evaluating the evidence . But one of the main drivers for including such a criterion back then, Eggington suspects, was to allow the field to use Myriad's BRCA1/2 variant interpretations as a reference point in their own classification work, if they could get their hands on the test reports.

Starting next year, when other labs will have regular access to a subset of Myriad's cancer risk variant interpretations through ClinVar, "is the industry going to blindly accept this Pheno method if Myriad reclassifies variants [using it] and submits them?" Eggington wondered.

She hopes that labs and researchers will take a very close look at the papers describing Pheno and challenge Myriad on it. "Nobody gets everything right. That's just not how science works," said Eggington. "It's time that people take a serious look at that methodology, question it, and push Myriad. This is what peer review is for."

Filed Under + Molecular Diagnostics + Cancer + Myriad + data sharing + ClinVar + BRCA Biomarkers + hereditary cancer + gene patents + Genomics: Clinical Implementation + Editor's Pick

Privacy Policy. Terms & Conditions. Copyright © 2025 GenomeWeb, a business unit of Crain Communications. All Rights Reserved.