BRCA1/2 Variant Data-Sharing Practices

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The breast cancer susceptibility genes *BRCA1* and *BRCA2* were identified and sequenced in 1994 and 1995, respectively. Individuals identified as harboring a pathogenic variant in *BRCA1* or *BRCA2* are at a significantly elevated lifetime risk of developing breast and ovarian cancer and face treatment choices ranging from prophylactic surgery to increased surveillance.[1] After two decades of *BRCA1/2* testing, however, new variants continue to be discovered. Interpreting the significance of new variants relies upon data sharing among the generators and holders of *BRCA1/2* data.

BRCA1/2 variant data sharing originated in the research context in the mid 1990's, even as the *BRCA* genes were being identified. Early efforts included the Breast Information Core (BIC), part of the U.S. National Human Genome Research Institute (NHGRI; then named the National Center for Human Genome Research), and the International Agency for Research on Cancer, part of the World Health Organization (WHO).[2] The advent of commercial testing for *BRCA1* and *BRCA2* in 1996 shifted the bulk of *BRCA1/2* variant generation out of research laboratories and into the clinical context. Early commercial testing for *BRCA1/2* was limited to a few laboratories in the U.S., Australia, and Europe. Myriad Genetics' patent on *BRCA1/2* testing, and subsequent fear of patent liability following the 1997 patent enforcement against Oncormed and the University of Pennsylvania resulted in Myriad becoming, for all intents and purposes, the exclusive provider of commercial *BRCA1/2* testing in the United States until June 2013. Despite strong patent rights in many countries, the Myriad

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patent was largely ignored in most countries outside the U.S.[3] In addition, despite its participation in early, public data-sharing efforts, Myriad, the single largest contributor of variant data to BIC, ceased sharing its *BRCA1/2* variant data with BIC in late 2004.[4] This move, coupled with its patent-based U.S. service monopoly on *BRCA1/2* testing, allowed Myriad to accumulate the largest proprietary database of *BRCA1/2* variants anywhere in the world.

In 2013, the U.S. Supreme Court overturned the patent-eligibility of patents on DNA molecules whose sequence is found in nature.[5] In the immediate aftermath of the Supreme Court decision, several U.S. laboratories began offering *BRCA1/2* testing or announced plans to do so. Furthermore, advances in high-throughput sequencing technologies, plummeting sequencing costs, and rapid adoption of clinical sequencing into clinical care led to an increased number of laboratories offering large, multi-gene panels for inherited risks of cancer, panels that included testing for *BRCA1/2* variants. Beginning in 2013, a growing number of clinical laboratories began generating large amounts of *BRCA1/2* genomic variant data. In parallel, ClinVar, an open-access database of the National Library of Medicine in the United States, was established in 2013 as an open variant database for all genes.[6] And that same year, the newly formed Global Alliance for Genomics and Health (GA4GH) declared the BRCA Challenge a flagship project to enable sharing of data about *BRCA1/2* variants, leading to establishment of the BRCA Exchange, an open-access data resource with clinically-vetted information on over 20,000 *BRCA1/2* variants.[7]

Despite strong patent rights in many countries, the Myriad patent was largely ignored in most countries outside the U.S. In addition, despite its participation in early, public data-sharing efforts, Myriad, the single largest contributor of variant data to BIC, ceased sharing its *BRCA1/2* variant data with BIC in late 2004. This move, coupled with its patent-based U.S. service monopoly on *BRCA1/2* testing, allowed Myriad to accumulate the largest proprietary database of *BRCA1/2* variants anywhere in the world.

Many laboratories and databases that generate and house *BRCA1/2* variant data are located outside of the United States. Data from populations outside North America and Europe are likely sources of new variants, as founder mutations have been well documented in many different populations that are not common in Europe and North America, where genetic testing is most common. Variants common in countries where testing is more prevalent are likely to have been discovered and would be found in current databases, but testing is limited in many world populations and hence these populations may well harbor variants that have eluded detection.[8] Furthermore, studies have shown the prevalence of *BRCA1/2* variants, including variants of unknown significance, differ by race/ethnicity.[9] Today, *BRCA1/2* clinical testing can be interpreted approximately 95% of the time (i.e., 5% VUS rate) in individuals of North European ancestry with lower interpretation rates for other groups.[10] In other parts of the world, however, the fraction of variants whose clinical significance is not yet known is significantly higher in non-whites. Ensuring the bi-directional flow of data between world regions with established and emerging clinical sequencing will be critical to accumulate the volume of data necessary to determine the statistical and clinical significance of new variants.

Here we describe current *BRCA1/2* data-sharing practices in the U.S. and globally, as described in interviews with academic and commercial clinical laboratories (8 U.S., 10 non-U.S.) and databases (2 U.S. and 8 non-U.S.). We address the data-sharing practices among laboratories and databases, identify incentives and barriers to *BRCA1/2* data sharing, and highlight the resources clinical laboratories reported using to interpret the clinical significance of *BRCA1/2* variants.

Methods

The data presented here were collected under two separate, but parallel efforts: one focused on *BRCA1/2* data sharing in the U.S., the other focused on *BRCA1/2* data sharing from laboratories and databases outside the United States. The U.S. analysis was led by researchers at Arizona State University and Baylor College of Medicine, while the analysis of non-U.S. efforts was led by collaborators at GA4GH at the Broad Institute in Cambridge, MA. While the two research "sub-teams" (i.e., the "U.S. team" and the "non-U.S. team") collected data independently, they

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met weekly throughout the project to develop project materials and discuss findings. The U.S. interviews were conducted under a protocol for semi-structured interviews approved by and IRB at the Baylor College of Medicine and exempted by the IRB at Arizona State University. The non-U.S. survey was done as a work product, leveraging the existing contacts of the GA4GH, BRCA Challenge, and BRCA Exchange.

Semi-structured interviews were conducted with representatives of U.S. clinical laboratories (both academic and commercial) generating *BRCA1/2* variant data and databases that house such variant data. Interviews with representatives of U.S. laboratories and databases occurred between August and December 2017. Phone and email-based interviews were conducted with key personnel from laboratories and databases from 15 countries across North America, South America, Europe, Africa, the Middle East, and Asia. These interviews were conducted between November 2017 and February 2018.

Sample Selection

U.S. laboratories and databases were identified by searching for laboratories offering *BRCA1/2* testing using the Genetic Testing Registry, reviewing the list of *BRCA1/2* variant data submitters listed on the ClinVar Website, and through Google and PubMed searches.[11] Non-U.S. laboratories and databases were identified through Genetic Test Registry, as well as by our colleagues at GA4GH (including suggestions from leadership of the BRCA Challenge project) as many of the representatives of these entities are currently working with, or have plans to work with, GA4GH. The list of potential interviewees collected was not exhaustive. By design, invitations were preferentially directed to the laboratories and databases generating and storing the larger volumes of *BRCA1/2* variant data. More specifically, invitations were extended to commercial laboratories known to provide the bulk of *BRCA1/2* testing in the United States, including those known to share *BRCA1/2* variant data and those known to not share data.

Potential interviewees were sent an emailed invitation to participate in a project interview or were already known contacts in non-U.S. databases and labs. U.S. interviewees opted to participate via telephone or videoconference. Non-U.S. interviewees agreed to a telephone interview or returned answers to the interview questions via email.

Data Collection

U.S. interviewees expressed verbal consent to participate in an audio-recorded interview. Each interview was conducted by two project team members: an interviewer and a dedicated note-taker. Non-U.S. interviewees expressed verbal consent to participate in an interview or responded to email inquiries. Each interview was conducted by a project team member. To facilitate a more nuanced discussion and systematic exploration of major themes, four semi-structured interview guides were developed: a U.S. laboratory interview guide, a non-U.S. laboratory interview guide, a U.S. database interview guide, and a non-U.S. database guide. All four guides included a core set of questions regarding *BRCA1/2* variant data-sharing practices, resources used when interpreting new variants, and incentives and barriers to *BRCA1/2* data sharing.

In order to increase willingness to participate in an interview and to foster an open discussion, interviewees were assured that (1) their name and the name of the institution they represented would remain confidential and (2) their answers to our questions would be considered not for attribution, unless they provided explicit permission for public attribution.

Data Analysis

U.S. Interviews

Responses from the data collection forms were entered into an Excel spreadsheet in order to analyze responses across all interviews. Two members of the U.S. research team reviewed the data collection forms and Excel data and independently developed a list of themes that emerged through the interviews. The research team met as a group to discuss the themes identified and resolve any discrepancies.

Non-U.S. Interviews

Responses from the data collection forms were entered into an Excel spreadsheet in order to analyze responses across all interviews. Two members of the U.S. research team and both members of the non-U.S. team reviewed their respective data to discuss the themes identified and resolve any discrepancies in interview interpretation. Non-U.S. interviewees were also provided with a written summary of the interview and provided the opportunity to clarify answers or correct inaccuracies (which was particularly helpful for those individuals whose first language was not English). A detailed report summarizing the results from the non-U.S. laboratory and database interviews was provided to the U.S. project team [Online Supplementary Material: public version of the GA4GH report].

Results

Twenty-two invitations for an interview were extended to 19 clinical laboratories (academic and commercial) offering *BRCA1/2* testing and three databases collecting *BRC1/2A* variant information based in the U.S.

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Representatives from eight laboratories and two databases agreed to participate in an interview (response rate 47.6%). Four interviews included more than one interviewee for total of 17 participants.

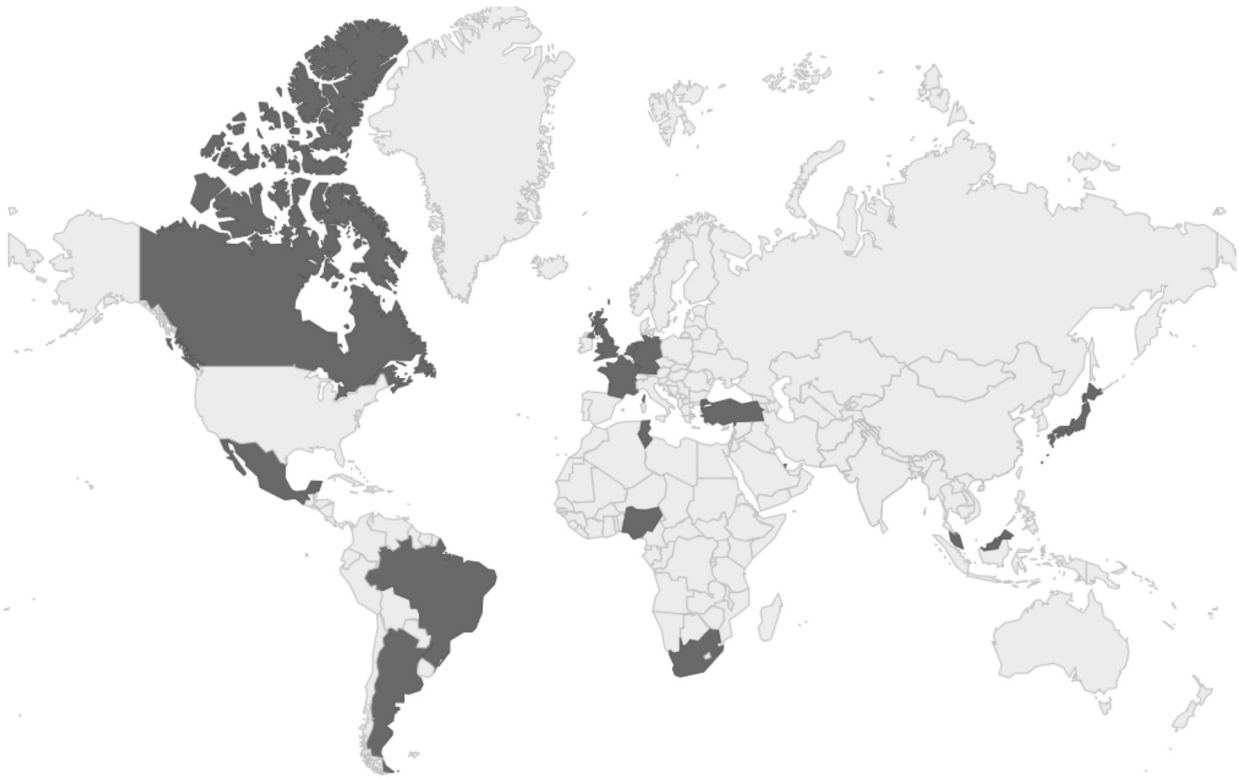
The report on non-U.S. *BRCA1/2* data sharing was based on responses from 10 clinical laboratories (academic and commercial) and 8 databases, representing fifteen countries in North-America, South America, Europe, Africa, the Middle East and Asia (Figure 1). Five interviews included more than one interviewee, for a total of 23 participants.

Summary of BRCA1/2 Testing and Sharing Practices

U.S. clinical laboratories reported an average of six years of experience with *BRCA1/2* testing. Of the eight laboratories interviewed, all but one laboratory began offering *BRCA1/2* testing after the Myriad patent was overturned in 2013. One laboratory reported 15 years of experience with *BRCA1/2* testing, having paid a royalty to Myriad for approximately 10 years prior to the patent being invalidated. In contrast, the non-U.S. laboratories reported an average length of experience with testing for *BRCA1/2* of 10 years (range 1- 22 years).

Figure 1

Map Displaying 15 Non-U.S. Countries Represented



- Argentina
- Brazil
- Canada
- France
- Germany
- Japan
- Malaysia
- Mexico
- Netherlands
- Nigeria
- Qatar
- South Africa
- Tunisia
- Turkey
- United Kingdom

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Resources Used to Interpret New Variants

All 18 laboratories interviewed were asked to specify which resources they routinely access during the process of *BRCA1/2* variant interpretation. Both U.S. and non-U.S. laboratories reported using a number of resources when interpreting *BRCA1/2* variants. Resources cited included in-house databases, genomic variant databases (ClinVar, LOVD, ARUP, etc.), population databases (ExAC, gnomAD, 1000 Genomes, etc.), commercial or paid access databases (ThermoFisher's BRCA Oncomine™ database, UMD/BRCAShare™, HGMD, SOPHiA Genetics, etc.), as well as literature (PubMed, OMIM) and Google searches (Table 1).

Overwhelmingly, both U.S. and non-U.S. laboratories favored the use of publicly available resources. In both groups, ClinVar was the most commonly used genomic variant database and was considered by many as the "go-to" resource. Four factors appeared to drive ClinVar's favorability: (1) ClinVar represented a centralization of multiple data sources. Many of the disease- and locus-specific databases that were historically consulted when interpreting a variant now contribute their data to ClinVar (e.g. BIC, ARUP, LOVD, etc.); (2) The amount of variant data housed in ClinVar and the number of laboratories and databases submitting data to ClinVar continues to grow; (3) ClinVar displays the basis of evidence for clinical interpretation, and is linked to the ClinGen network of experts; (4) ClinVar uses the standard reporting categories for genomic variants. These categories have been recommended by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology and the European Society for Human Genetics.[12] A few U.S. interviewees expected that the amount of *BRCA1/2* variant data in ClinVar would soon rival, if not surpass, Myriad's proprietary database. Finally, (5) ClinVar is free and publicly available and allows unfettered use of its data. One U.S. interviewee commented that they no longer consult the pay-for-access resource, BRCAShare™, because "[we] can get the same data from ClinVar."

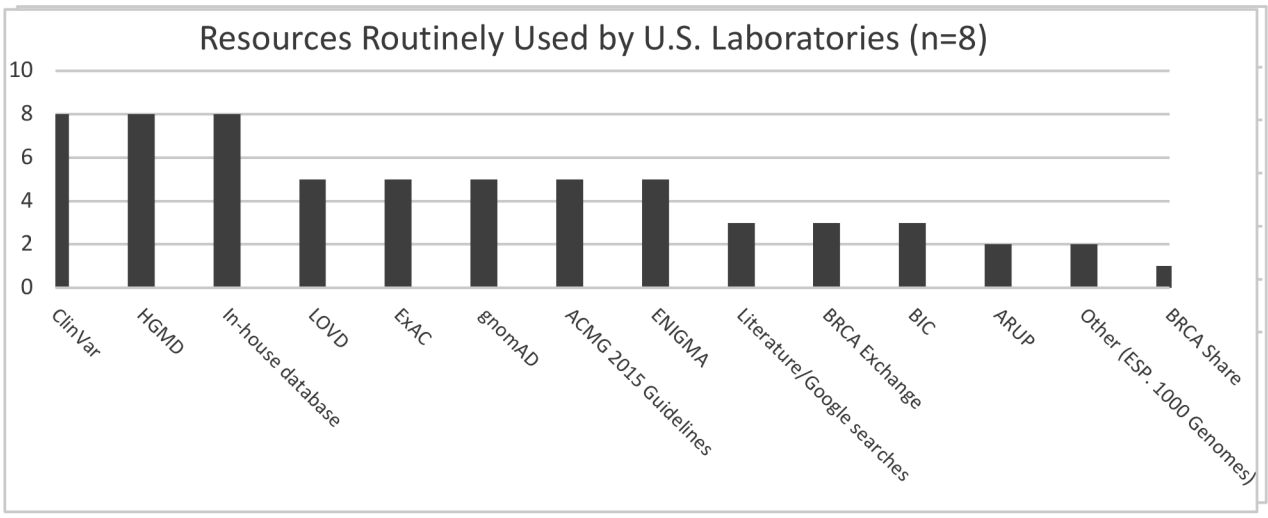
Both U.S. and non-U.S. laboratories consistently relied upon publicly-accessible population databases when interpreting new *BRCA1/2* variants. While ExAC, gnomAD, and 1000 Genomes were commonly cited resources, gnomAD was gaining favor as the preferred population database. These databases were largely used to assess allele frequency, and were preferred because of their size, the quality of curation, and their open science ethos, with free availability and unfettered use. Only a few laboratories reported using the BRCA Exchange database (3 U.S., 1 non-U.S.).

While laboratory personnel both in the U.S. and abroad are utilizing a growing number of online database resources when interpreting *BRCA1/2* variants, our interviews reveal that they also continue to employ more traditional methods including: reviewing their own in-house data collections, reaching out to colleagues, and conducting literature searches using PubMed, Google Scholar, or other tools for surveying the medical and scientific literature.

Interviews with both U.S. and non-U.S. laboratory personnel revealed several common themes:

Table 1

Resources Routinely Used by Laboratories



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- Preference for publicly available databases.
- Aversion to pay-for-access or proprietary databases.
- A preference for resources that are easy to access and navigate, and comprehensive resources (i.e. avoidance of having to query numerous datasets).
- Preference for databases that compile information from other resources.
- Preference for ability to determine how variants were classified and aversion to databases that lack clarity on data quality, data submitters, and how interpretations were made.
- Preferred datasets that are updated regularly.
- Preferences for databases that draw from large, ethnically diverse populations.

BRCA Data-Sharing Practices

All eight U.S. clinical laboratories reported sharing *BRCA1/2* variant data with ClinVar. Five of the laboratories shared the variant data with ClinVar exclusively, three shared data with ENIGMA, and two reported sharing some data directly with BRCA Exchange (but note that ClinVar and ENIGMA both share data with BRCA Exchange). The majority of laboratories reported sharing *BRCA1/2* data shortly after the inception of ClinVar in 2013.

While all of the U.S. laboratories interviewed reported sharing variant data with ClinVar, the type of information and level of detail varied. Descriptions of the *BRCA1/2* variant information shared included: (1) "everything seen"; (2) "formally classified" variants; (3) Sanger-confirmed variants; (4) variants observed at least once before; and (5) only variants with interpretation.

The fact that ClinVar is a publicly-available resource was the key factor in its emergence as the primary vehicle for sharing *BRCA1/2* variant data in the U.S. Interviewees explained that putting variant data into the public domain not only honored their belief in the importance of sharing data freely and broadly, it also minimized the logistical burdens associated with contributing variant data to multiple places. By depositing variant data into a public database, one interviewee explained, they can direct all inquiries for data to the ClinVar database. All eight U.S. laboratories reported having multiple personnel involved in the data-sharing process including database managers, curators, bioinformaticians, engineers, clinical variant specialists, laboratory personnel, and genetic counselors.

In contrast, six of the ten non-U.S. laboratories interviewed reported sharing *BRCA1/2* data. Four non-U.S. laboratories are currently not sharing data: three of these laboratories planned to begin sharing in the future and one did not have plans to share data but was open to the idea of sharing in the future. Among the six laboratories currently sharing data, three contribute to CIMBA, two share their data with ClinVar, two with LOVD, and two with ENIGMA. One laboratory reported sharing with the Breast Cancer Association Consortium (BCAC), Asian BRCA Consortium (ABRCA), and BIC. Laboratories sharing *BRCA1/2* data reported having done so for different durations, ranging from 1 to 20 years.

The most frequently shared data were variants alongside their interpretations or associated evidence (i.e., publications). One laboratory shared pedigrees and penetrance data, and another shared case-level (i.e., with information about individual cases) and clinical or epidemiological research data. None of the non-U.S. laboratories reported having dedicated staff devoted exclusively to data sharing; the task was typically shared among team members and/or laboratory leadership.

Incentives for Sharing

The majority of U.S- based laboratories described a strong sense of duty to share *BRCA1/2* variant data. Interviewees described a belief that data sharing was "the right thing to do," part of their "clinical duty," and demonstrated their "commitment to patient healthcare." Many stated that data sharing was critical to advancing scientific progress, improving patient care, and ultimately benefiting the quality of their field overall. Interviewees expressed a strong aversion to data hoarding ("I have no patience for that") and keeping data sequestered in silos. Furthermore, interviewees from U.S. laboratories described a growing expectation, or as one interviewee put it, a "pressure," to share data within the genetics/genomics community. One interviewee observed that laboratories did not want to be seen as not sharing.

Non-U.S. laboratories had less to report when asked about incentives and motivations for sharing *BRCA1/2* data. The most commonly cited incentive for sharing was the existence of supportive collaborators/peers/community with which to share. Other incentives mentioned more than once included the existence of tools to initiate sharing/make the process easier, and a sense that sharing improves the quality of work for all involved (e.g., stronger variant interpretations and emergence of community-supported best practices). Finally, data sharing was seen as meeting patient expectations, supporting patient autonomy (e.g., in the case of returning results directly to patients), and helping the community.

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Barriers to Sharing

When asked about barriers to *BRCA1/2* data sharing, all interviewees (both U.S. and non-U.S.) cited personnel-related burdens, most commonly the lack of dedicated staff. Interviewees commonly described the process of sharing/submitting data as a time-consuming, burdensome task that was distributed among a variety of laboratory personnel (and in addition to their regular job responsibilities). Other barriers cited by more than half of all interviewees included a lack of time for data-sharing activities and the associated financial/budget/cost burdens (e.g., an inability to recoup costs, uncompensated personnel time/effort). Two U.S-based-laboratories mentioned receiving some financial relief through ClinVar/ClinGen grants.

Given that all of the U.S. laboratories interviewed are submitting data to ClinVar, the technical challenges mentioned were specific to the ClinVar submission process: the lack of an API interface, a cumbersome and time-consuming submission process, and the need to extract and format data prior to submission because ClinVar currently takes data only in Excel spreadsheet format, requiring submitters to reformat their data. Several laboratory representatives recounted acute technical challenges when beginning/implementing sharing data with ClinVar, but they reported that many of these challenges have been ameliorated over time.

Among the non-U.S. laboratories sharing *BRCA1/2*-variant data, five additional barriers were mentioned: technical constraints, liability concerns, lack of education/awareness about available databases for sharing, competitive incentives to keep data, and a lack of sharing culture. Among the four non-U.S. laboratories *not* currently sharing *BRCA1/2* variant data, additional barriers were mentioned: institutional barriers (needing permission from multiple levels of the institution), logistical concerns over maintaining data sovereignty (e.g., to avoid potential misappropriation or exploitation of local patient data by other world regions), national laws and procedures requiring approval for data export, and potential inability to get patient consent (due to lack of available counselling services, low regional patient literacy rates, and patient fears regarding insurance discrimination).

Experience Hosting BRCA1/2 Data in a Shareable/Accessible Context

The ten interviewed databases (2 U.S., 8 non-U.S.) are each hosted in a way that enables sharing in an online context, at least among consortium members and many allowing open access. The databases interviewed varied with respect to age, size, access, and level of curation. The oldest databases interviewed were established in the mid-1990s, before the advent of commercial *BRCA1/2* testing, while other resources started as recently as the past 1-2 years. Databases that launched in the 1990s reported more total variants than those that launched more recently. Databases cited collections of unique *BRCA1/2* variants ranging from a few hundred to several thousands. Access constraints varied among the databases, with some allowing full access, some requiring registration, and others being closed except to participating national consortium members. In addition, databases provided variable levels of curation, including none at all, submitter-based, formal vetting and clinical interpretation by ENIGMA, or relying on specific contexts.

Our examination of the *BRCA1/2* data-sharing landscape demonstrates strong support for and robust sharing of *BRCA1/2* data around the world, increasing global accesses to diverse data sets. All U.S. laboratories and databases and the majority of the non-U.S. laboratories interviewed reported sharing at least a subset of their *BRCA1/2* variant data with public databases, though the amount and type of information varied. There was general consensus about the value of sharing to support both variant classification and well-informed clinical decision-making.

Discussion

Our examination of the *BRCA1/2* data-sharing landscape demonstrates strong support for and robust sharing of *BRCA1/2* data around the world, increasing global accesses to diverse data sets. All U.S. laboratories and databases and the majority of the non-U.S. laboratories interviewed reported sharing at least a

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While the value of sharing data was reported in both the U.S. and non-U.S. interviews, it was most strongly expressed in the interviews with U.S. laboratories and databases. U.S. interviewees reported being motivated to share data by an ethical obligation, clinical duty, and service to the greater good. Many explicitly expressed strong anti-data-hoarding sentiments. Likely this asymmetry can be attributed to the impact of the Myriad patents and resulting service monopoly on *BRCA1/2* testing in the U.S. Myriad's decision to cease contributing *BRCA1/2* variant data to the public database BIC in 2004, and instead sequester its data in a proprietary database, has likely further fueled a strong anti-data-hoarding sentiment among other U.S. laboratories and databases. In contrast, most countries outside the U.S. largely ignored Myriad's patents and testing was not impeded.

Despite strong support for data sharing worldwide, our interviews also revealed the fragility of a sharing norm. Both U.S. and non-U.S. laboratories and databases reported significant financial, technical, and logistical barriers and unreimbursed costs of preparing data to be shared, personnel time and effort required to share data, and associated technical infrastructure costs. In addition, interviewees with non-U.S. laboratories and databases reported other substantive barriers to data sharing including issues of data sovereignty, legal and liability issues (one country reported sharing data across borders is illegal), and a lack of a supportive, sharing culture.

In general, interviewees expressed a preference for publicly-accessible, freely-available, comprehensive databases as well as those that are easy to access and navigate. The databases ClinVar, ExAc, and gnomAD were the most commonly cited publicly-available resources. Our interviews show a consolidation of data-sharing efforts, with ClinVar emerging as the leading resource used for interpreting and sharing *BRCA1/2* variant data. ClinVar appears to be becoming a "one-stop-shop" for clinical interpretation and deposit of genomic variant data. Interviewees repeatedly attributed ClinVar's appeal to its public and open-access status. ClinVar's role as central resource minimized the burdens of consulting with and submitting data to multiple resources, while ensuring data are in the public domain. Many of the databases historically consulted when interpreting *BRCA1/2* variants (e.g., BIC, LOVD, etc.) prior to the creation of ClinVar in 2014 now submit their data to ClinVar. However, it is important to note that in light of some the substantive, and in some cases intractable, barriers to the flow of data (particularly) internationally, it is likely that there will not be a single, central location for depositing *BRCA1/2* variant data. Rather, data will need to remain in place and methods and tools for accessing data developed.[13] GA4GH is actively working on development of such standards and tools.[14]

It is noteworthy that all eight of the U.S. laboratories interviewed reported sharing *BRCA1/2* variant data compared to slightly more than half of the laboratories (6/10) outside the U.S. This finding likely reflects a selection bias in the U.S. sample. Laboratories currently sharing *BRCA1/2* data were more willing to agree to participate in an interview about *BRCA1/2* data sharing. However, this finding may also reflect the fact that in the U.S., data sharing has been strongly promoted in the National Institutes of Health (NIH) and many scientific and medical journals have implemented policies that ensure publications rest on evidence that can be verified. In addition, in the United States, small grants from ClinVar/ClinGen are available to assist small laboratories off-set costs associated with submitting data to ClinVar.

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Note

Additionally, Dr. Liao reports other from GA4GH and personal fees from UCSC, outside the submitted work.

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