Is there a way to reduce the inequity in variant interpretation on the basis of ancestry?

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Summary

The underrepresentation of non-European ancestry groups in current genomic databases complicates interpretation of their genetic test results, yielding a much higher prevalence of variants of uncertain significance (VUSs). Such VUS findings can frustrate the goals of genetic testing, create anxiety in patients, and lead to unnecessary medical interventions. Approaches to addressing underrepresentation of people with genetic ancestries other than European are being undertaken by broad-based recruitment efforts. However, some underrepresented groups have concerns that might preclude participation in such efforts. We describe here two initiatives aimed at meeting the needs of underrepresented ancestry groups in genomic datasets. The two communities, the Sephardi Jewish community in New York and First Peoples of Canada, have very different concerns about contributing to genomic research and datasets. Sephardi concerns focus on the possible negative effects of genetic findings on the marriage prospects of family members. Canadian Indigenous populations seek control over the research uses to which their genetic data would be put. Both cases involve targeted efforts to respond to the groups' concerns; these efforts include governance models aimed at ensuring that the data are used primarily to inform clinical test analyses and at achieving successful engagement and participation of community members. We suggest that these initiatives could provide models for other ancestral groups seeking to improve the accuracy and utility of clinical genetic testing while respecting the underlying preferences and values of community members with regard to the use of their genetic data.

Current approaches to genetic testing—including use of multi-gene panels and exome sequencing—produce large amounts of data regarding genetic variation among persons being tested. Although most variants can be identified as benign/likely benign and a small number as pathogenic/likely pathogenic, insufficient data for some variants prevents distinguishing between those options. These variants are designated as variants of uncertain significance (VUSs), a term reflecting their ambiguous status. VUSs are common in clinical genetic testing. In the context of testing for hereditary cancer syndromes, perhaps the most common context for clinical sequencing of multi-gene panels, three large clinical laboratories reported an overall VUS frequency of 21.9%–33.3% for cancer panels.[1–3] Moreover, their prevalence increases dramatically as multi-gene panels replace tests involving one or a small number of genes. A study of genetic testing in women with breast cancer found a ten-fold increase in VUSs for patients having multi-gene panel testing compared with *BRCA1/2* sequencing.[4]

The underrepresentation of non-European ancestry groups in current genomic databases complicates interpretation of their genetic test results, yielding a much higher prevalence of variants of uncertain significance (VUSs). Such VUS findings can frustrate the goals of genetic testing, create anxiety in patients, and lead to unnecessary medical interventions. Approaches to addressing underrepresentation of people with genetic ancestries other than European are being undertaken by broad-based recruitment efforts. However, some underrepresented groups have concerns that might preclude participation in such efforts. We describe here two initiatives aimed at meeting the needs of underrepresented ancestry groups in genomic datasets. The two communities, the Sephardi Jewish community in New York and First Peoples of Canada, have very different concerns about contributing to genomic research and datasets. Sephardi concerns focus on the possible negative effects of genetic findings on the marriage prospects of family members. Canadian Indigenous populations seek control over the research uses to which their genetic data would be put. Both cases involve targeted efforts to respond to the groups' concerns; these efforts include governance models aimed at ensuring that the data are used primarily to inform clinical test analyses and at achieving

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successful engagement and participation of community members. We suggest that these initiatives could provide models for other ancestral groups seeking to improve the accuracy and utility of clinical genetic testing while respecting the underlying preferences and values of community members with regard to the use of their genetic data.

However, the likelihood that a genetic test will generate a VUS is not distributed equally across ancestral groups. (We acknowledge the difference between *genetic ancestry* groups and *ethnic* or *racial* groups—and that some of the studies we refer to conflate the two.) In the study of women with breast cancer noted above, VUSs were identified in 23.7% of White patients tested with multigene panels but in 44.5% of Black patients and 50.9% of Asian patients.[4] The discrepancy is markedly higher in multi-gene panels than in single-gene tests; the VUS frequencies for *BRCA1/2* testing only were 2.2% in White patients, 5.6% in Black patients, and 0% in Asian patients.[4] The higher rate of VUSs in populations not of European ancestry might be attributed to their relative underrepresentation in the genetic databases on which variant interpretations are based.[5]

VUSs are problematic in a number of ways. At the simplest level, a test that yields only a VUS has failed to generate information that can be of immediate clinical utility. Current guidelines discourage clinicians from making treatment decisions on the basis of VUSs.[6] However, clinicians and patients might feel compelled to act anyway. Reports of women having prophylactic mastectomies because of a VUS in a gene related to breast cancer can be found in both the medical literature and popular media,[7,8] including cases in which the VUSs were later reinterpreted as benign.[7,9] Even when drastic interventions are not undertaken on the basis of a VUS, patients might respond with anxiety and distress or express increased distrust of their physician or the medical system.[10] Misunderstanding of the meaning of a VUS appears not to be uncommon[10] and might be a particular problem in prenatal testing[11] and for populations with less education.[12]

Recognizing these issues, genetic researchers and funding agencies have made efforts to reach out to underrepresented groups—including Black, Latino, and Indigenous populations—to encourage their contributions to biobanks and their enrollment in genetic studies.[13] Such efforts have had only modest success. Lack of ancestral diversity across research projects derives from multiple factors, including mistrust of the medical and research enterprise, lack of representation of scientists from involved communities among those conducting the research, and general failure to engage members of diverse communities.[14] As a result, non-European ancestry groups remain strongly underrepresented in genetic databases, resulting in high rates of VUSs and complicating attempts to apply approaches such as polygenic risk scores to improve risk prediction and facilitate prophylactic interventions for these groups.[15]

The limited success of previous efforts has stimulated additional initiatives aimed at rectifying the underrepresentation of many groups. Although federal-government-funded initiatives such as *All of Us*[16] and NIH-funded consortia such as eMERGE and CSER will help to fill some of the gaps in current genetic datasets, there are recruitment goals that such broad-based efforts are not likely to accomplish. On the basis of historical, political, social, religious, or various other concerns, some population groups have hesitations about contributing to large-scale biobanking programs. Many Indigenous tribes, for example, are concerned that their genomes may be used to contribute to scientific progress that does not benefit their communities and, indeed, could be turned to purposes antithetical to their beliefs or well-being.[17-21] Without a greater degree of control over their data than is compatible with the goals of broad-based biobanking programs, many tribal members may be reluctant to join large-scale research efforts.[22] In addition, to the extent that smaller population groups carry distinct genetic variants, their needs for accurate interpretation will require focused efforts to recruit members of those groups, beyond what any broadly targeted efforts are able to accomplish. There is considerable genetic diversity among Native American groups[23], and they and a number of other ethnic groups in the US are small enough to require deliberate oversampling for adequate assessment.

In response, several efforts have been undertaken to more narrowly target discrete populations with the goal of improving the ability of clinical geneticists to interpret their test results. We briefly describe two of those initiatives, motivated by very different concerns, and consider their implications for reducing inequity in variant interpretation.

More targeted approaches to reducing inequity in variant interpretation

Jews of Sephardi origin, whose ancestors lived for centuries in North Africa and the Middle East, have some distinct genetic characteristics compared with those of their Ashkenazi co-religionists, whose presence in Europe can be traced back more than a millennium. Whereas many segments of the Ashkenazi Jewish community have engaged in concerted campaigns to encourage genetic testing, among many traditional Sephardi groups the stigma of being a carrier of a genetic condition created obstacles to testing.[24] A particular concern is that results indicating a propensity for a genetic disorder in one family member, including carrier status for a recessive condition, might need to be disclosed during the matchmaking process and thus might impair the marriage prospects of all siblings in the family. As a result, Sephardim have been under-represented in genetic databases, leading to difficulties in the recognition of many recessive conditions that are

more common in the Sephardi community and the provision of appropriate carrier screening tests. An effort to address this problem, however, has yielded impressive results.

The effort began in New York, which has a substantial population of Sephardi families, especially of Syrian descent. Concerned about the inaccuracy of genetic testing results, families of children with inherited conditions, physician leaders, and rabbis in the Sephardi community had multiple discussions with geneticists and physicians about the need for Sephardi-specific carrier-screening panels. Also involved were leaders of Dor Yeshorim, a non-profit, community-based carrier-screening program that began with a focus on Tay-Sachs testing and later expanded to include other recessive disorders found disproportionately among Jews, especially in the Ashkenazi community (see web resources). Dor Yeshorim is funded by a mix of philanthropy, subsidized fees for screening services, and Israeli government support for citizens of that country. As a result of these discussions, an innovative plan was developed in 2015 (Table 1).

Members of the Sephardi community in New York and in other communities in Europe, Israel, and the Americas were encouraged to donate anonymized samples and data to avoid the concerns about stigma that had stymied previous testing efforts. Samples from 1,000 participants were collected and used to determine carrier frequencies in the Sephardi community of variants included in the Ashkenazi carrier-screening panels. Conversely, pathogenic variants identified in Sephardi families were genotyped in anonymized Ashkenazi Jewish samples. Comparison of the results across the groups demonstrated that some pathogenic variants are shared by Ashkenazim and Sephardim, whereas others are exclusive to one group.[25] Based on these data, Dor Yeshorim now offers a Sephardi-specific screening panel (see web resources). Additionally, the approach was extended to the Ashkenazi community, segments of which share the concern about stigma and its impact on marriageability. More than 1,000 Ashkenazi adults have donated anonymized samples for genome sequencing through the Jewish Genome Project, the aggregate results of which are available through gnomAD, to facilitate interpretation of genetic information for individuals of Ashkenazi ancestry.

A second example of a more targeted effort to improve variant interpretation involves Indigenous groups, which as noted above have expressed concerns about the use of genetic data for research that might have stigmatizing consequences for tribes, failure to benefit the group, and exploitation of donors for benefits to other populations.[17,18,26,27] These concerns have led to reluctance among tribes to cooperate with genetic researchers and, in the case of the Navajo Nation, establishment of a moratorium on all genetic research on lands under tribal control.[28,29] Although a guarantee that data generated from donated samples would only be used to improve variant interpretation in clinical testing might assuage some of these concerns, tribal control over governance of the samples and the resulting data might also be essential.[30] Indeed, such a model already exists in the Silent Genomes Project, a collaboration involving a University of British Columbia research team, the BC Children's Hospital Research Institute, and the First Nations Health Authority (see web resources) with several Canadian First Nations, which launched in 2018 (Table 1) (see web resources).[31] The project is funded by a grant from Genome Canada and other funders as part of a national effort to advance precision health by contributing to more evidence-based approaches to improve health outcomes (see web resources). It has a goal of developing a library of genetic variation from First Nations and other Indigenous (Inuit and Metis) Canadians to support improved diagnoses for referred children (see web resources).

Consultations have been underway since the inception of the project with First Nations communities across Canada who are part of a large cohort study with stored samples available for future research. The Silent Genomes project team is working with these and other Indigenous partners to make decisions about security of the genomic information, conditions (level of restriction) for variant release for clinical diagnosis, and clinical research that might be acceptable. Active discussions are proceeding with Indigenous partners to determine to what extent Indigenous Nation or community identity will be revealed within the database. Clear conditions of use and governance of genomic information will be agreed upon prior to transfer of about 1000 samples and sequencing to achieve the goal of a sustainable resource responsive to community concerns.

Silent Genomes has already put multiple structures in place to prevent diversion of data for purposes incompatible with its goals. The database will include only population frequencies of variants, without individual-level data. Access will only be permitted for specific variant enquiry for clinical diagnostic purposes and, to preclude unauthorized research uses, the dataset as a whole, or in part, cannot be downloaded. Discussion, however, is underway to determine if limited clinical research will be acceptable. An International Indigenous Genomics Advisory Committee, comprising Indigenous scholars from Canada, the United States, Australia, and New Zealand, was established to provide guidance, along with a steering committee of Indigenous members to provide cultural oversight, strategic guidance, and input on decision-making (web resources). Given that Silent Genomes is at an earlier stage of development than the Sephardi initiative, how successful these steps will be in facilitating both collaboration of the Indigenous nations as the library is built and effective subsequent use remains to be seen.

Challenges to implementation and alternative approaches

Could these models of targeted engagement and recruitment to

Table 1. Characteristics of the silent genomes and Sephardi initiatives

Initiative	Target community	Anticipated use	Community concerns	Strategies to mitigate concerns	Governance	Controls on data access	Funding
Silent Genomes	Indigenous people in Canada	clinical genetic testing	data would be used for undesirable research purposes	data only available for comparison with clinical testing results and perhaps limited clinical research	steering committee of Indigenous members; input from international Indigenous advisory board	accessible data limited to variant population frequencies; dataset cannot be downloaded	Genome Canada, in collaboration with the Canadian Institutes for Health Research, Genome BC and others
Dor Yeshorim Sephardi initiative	Sephardi Jews	premarital carrier screening	results returned to participants would lead to stigmatization	samples for reference set donated anonymously; return of results not possible	trusted community-based organization; guided by a rabbinical council and a medical advisory board	data not available to the public, but variant frequency available on request	philanthropic, Israeli government support for citizens, subsidized fees for screening services

improve genetic variant interpretation be more widely applicable to other communities now underserved by genetic testing, even if the reasons for underrepresentation vary? Specifically, for groups that have been reluctant to participate in biobanks and other genetic research because of concerns about exploitation, stigma, privacy, lack of benefit, and other issues, could a campaign soliciting contribution of anonymous DNA samples to improve clinical testing be successful? The diverse concerns underlying the two examples discussed above suggest promise for this approach in a variety of circumstances. Contributed samples need not come with phenotypic data (although they would be more useful if such data were included), and their use would be limited to creating an improved reference set for "people like me." To protect against non-authorized uses, as with the plans for Silent Genomes, the reference set could be restricted from download and only allow visualization of aggregate allele frequencies.

Success of an effort of this type, as the examples discussed above suggest, would rely heavily on community engagement and collaboration. Although there is no single roadmap to success—defined as a sufficient reference dataset for adequate clinical validity and reduction of VUSs in interpreting genetic tests—understanding the concerns of the relevant community is key. Different communities might have different reasons for shunning both genetic testing and participation in genetic research. Meaningful inclusion of community members in the design and oversight of the project, and in long-term governance of the resulting datasets, might be the best way of appreciating and responding appropriately to community concerns.[32] This will most likely require training for community members in basic concepts of genetics and the relevant ethical, legal, and social issues; some highly motivated participants might elect further training. Silent Genomes, for example, is supporting 36 participants in yearly week-long workshops focused on next-generation genomic and bioinformatics analyses integrated with Indigenous perspectives on genetics and genomics (SING Canada; see web resources). Reciprocal training and support from researchers and community leaders, including religious leaders, physicians, and scientists in the community, will also be essential.

Ongoing governance of the project is another critical dimension. As more participants are recruited for datasets, the data will grow in value to researchers, pharmaceutical companies, and others. Projects focused on improving variant interpretation in clinical contexts are likely to be asked to contribute their data for other purposes. For example, the Silent Genomes variant library ultimately could be a source of reference data for genomic studies on transplantation success or on COVID-19 severity and treatment with Indigenous research participants. The steering committee is considering how such requests will be handled (see "genomics and COVID" in the web resources). Withholding data from research use cuts against current trends toward data sharing and open access and comes with a cost in limiting the size, diversity, and utility of research datasets; however, in some circumstances such limitations might be essential for gaining buy-in from the relevant communities and building trust.[33] As with the ongoing discussions in Silent Genomes, similar opportunities for research participation will present themselves to other databanks that contain group-specific data, suggesting the importance of building this possibility into the governance structure through consent procedures that allow re-contact or permission for governing bodies to authorize research uses.

Ensuring appropriate measures to determine how the data are used and in particular who, if anyone, should have access to the data for research purposes is important for maintaining the confidence and support of the community. Accordingly, the governance structure—i.e., the constitution and decision-making authority of executive and advisory personnel or

Box 1. Examples of issues to be addressed by governance mechanism

Defining scope and use of data:

- Should data be limited to genetic samples, or should phenotypic data also be included?
- Who should have access to the data, and what data should be available to them? E.g., only aggregate variant frequencies? Also linked phenotypic data?
- What protections should be created to prevent identification of contributors?

Procedures for soliciting community perspectives:

- What is the definition of the relevant community?
- How should community input be sought, e.g., membership on governing bodies, participation in advisory groups, community-based surveys or focus groups?
- When differences of opinion arise in the community, how should those differences be taken into account in decision making?

Criteria and procedures for responding to requests for uses of data beyond original intended uses (e.g., research):

- Should use be limited to improved interpretation of clinical genetic tests? Are there research uses to which the data should be put?
- What criteria should be used to determine when the dataset will be made available to researchers?
- To what extent should the governance body retain control over the use or interpretation of data that have been made available for research?

Methods for reporting to the community:

- By what means can the community be kept informed about the operation and use of the database?
- Are there key thought leaders in the community who should be the primary channels for dissemination of information?

committees charged with managing the database—is a key element in designing a repository of group-specific data.[34] A sample of the kinds of issues that might be considered by a governance board is given in Box 1. Participation of the community is essential but might take various forms, ranging from full ownership and management of the resource—as in the Native Biodata Consortium, a non-profit research institute led by Indigenous scientists and tribal members that aims to establish a biorepository of samples from tribal members used exclusively for research likely to benefit that group (see web resources)—to models in which the community advises an executive group or shares management with science experts who are not community members. Although the governance structure might vary, accountability to the community is crucial to ensure that decisions about data use accord with community expectations and requirements.

Whether approaches such as the ones used for the Sephardi community or Indigenous peoples in Canada would be successful elsewhere will depend in part on the concerns that different communities have about providing genetic samples and how well they can be addressed. Communities other than the two described here might present different challenges, and these might need to be addressed in other ways. African American communities, for example, are another markedly underrepresented population in genetic datasets and, as noted above, one consequence is a much higher frequency of VUS findings than in White patients. African American concerns about the use of genetic samples have focused less on group stigma and more on a history of exploitation of the Black community by American medicine and a failure to deliver benefits from research.[35,36] Moreover, unlike Indigenous communities or Sephardi Jews, groups that are often geographically concentrated, African Americans are dispersed throughout the U.S. Successful efforts to increase Black representation in genetic datasets might require a local focus, with cooperation and pooling of data across localities. Discrete subgroups, such as communities relatively recently arrived from Africa (e.g., the Senegalese community in New York, the Ethiopian community in the Washington, DC area), could be mobilized by targeted campaigns and will require measures to ensure adequate community representation in governance.

The field of genetics needs both large-scale research programs and targeted collection of genetic samples to enhance clinical testing. It is important for large-scale government programs to focus on underrepresented groups to reduce the inequities that exist in genomic medicine because of gaps in existing data sets. However, such an effort leaves little scope for local participation in data governance, which might limit the success of this effort with both larger (e.g., African American) and smaller (e.g., Native American and recent immigrant) communities. In the end, there is likely to be a role for both population-based and community-oriented datasets, with the latter filling the gaps that larger-scale efforts have been unable to address. Of course, targeted recruitment initiatives will involve costs related to efforts to develop partnerships, community training, collection of samples, and management of datasets, and these will need to be defrayed. Although clearly not a solution to the broader problem of inequities in healthcare, to the extent that local, community-accountable data sources could reduce the disproportionate burden of VUSs on underrepresented communities, efforts of this sort are worth funding as part of a multi-faceted strategy to reduce inequities in what is likely to be an increasingly important part of patient care.

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Declaration of interests

Laura Arbour is the Project Lead for the Silent Genomes Project. Nanibaa Garrison is a member of the International Indigenous Genomics Advisory Committee for the Silent Genomes Project. Wendy Chung is on the Scientific Advisory Board for All of Us. David Zeevi is Director of Research and Development for Dor Yeshorim. The opinions expressed in this article are those of the authors. No statement in this article should be construed as an official position of the National Human Genome Research Institute, National Institutes of Health, or Department of Health and Human Services.

Web Resources

CSER, https://www.genome.gov/Funded-Programs-Projects/Clinical-Sequencing-Evidence-Generating-Research-CSER2.

Dor Yeshorim, https://doryeshorim.org/.

eMERGE, https://www.genome.gov/news/news-release/NIH-funds-centers-to-improve-role-of-genomics-in-assessing-and-managing-disease-risk.

First Nations Health Authority, https://www.fnha.ca/about

Genome Canada. Request for Applications, 2017 Large-Scale Applied Research Project Competition: Genomics and Precision Health, https://www.genomecanada.ca/sites/default/files/2017_lsarp_rfa_final-en.pdf

Genomics and COVID, Silent Genomes Project, https://www.bcchr.ca/silent-genomes-project/genomics-and-covid.

GnomAD, https://gnomad.broadinstitute.org/about

Native BioData Consortium, https://nativebio.org/.

Research Capacity Building, Silent Genomes Project, https://www.bcchr.ca/silent-genomes-project/education/research-capacity-building.

Sefardi/Mizrachi Panel, Dor Yeshorim, https://doryeshorim.org/sefardi-non-askenazi-panel/

Silent Genomes Project, https://www.bcchr.ca/silent-genomes-project

SING Canada. https://indigenoussts.com/sing-canada/

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