Association of Racial/Ethnic Categories With the Ability of Genetic Tests to Detect a Cause of Cardiomyopathy

Latrice G. Landry, PhD; Heidi L. Rehm, PhD

**IMPORTANCE** Individuals of all races/ethnicities have a fundamental right to access health care and benefit from advances in science and medicine, including genetic testing.

**OBJECTIVE** To determine whether detection rates for cardiomyopathy genetic testing differed between white people, Asian people, and underrepresented minorities (individuals of black, Hispanic, Native American, Alaskan Native, or Pacific Islander descent).

**DESIGN, SETTING, AND PARTICIPANTS** We conducted a cross-sectional analysis of the genetic panel test results of 5729 probands who had a suspected diagnosis or family history of cardiomyopathy and who had been referred for testing between October 2003 and December 2017. Testing was performed at the Laboratory for Molecular Medicine at Partners Personalized Medicine in Cambridge, Massachusetts. Results were stratified into 3 categories of self-reported race/ethnicity: white, Asian, and underrepresented minorities.

**MAIN OUTCOMES AND MEASURES** The primary outcome was whether a pathogenic or likely pathogenic variant was identified that explained the features or family history of cardiomyopathy. A secondary outcome was the number of test results that were inconclusive because of the presence of 1 or more variants of uncertain significance in the absence of an explanation for cardiomyopathy features or family history.

**RESULTS** A total of 5729 probands were studied (of whom 3523 [61.5%] were male). Of these, 4539 (79.2%) were white, 348 (6.1%) were Asian individuals, and 842 (14.7%) were underrepresented minorities. Positive detection occurred in 1314 white individuals (29.0%) compared with 155 underrepresented minorities (18.4%; $\chi^2 = 39.8; P < .001$) and 87 Asian individuals (25.0%; $\chi^2 = 2.5; P = .12$). Inconclusive results were found in 1115 white individuals (24.6%) compared with 335 underrepresented minorities (39.8%; $\chi^2 = 83.6; P < .001$) and 136 Asian individuals (39.2%; $\chi^2 = 35.8; P < .001$).

**CONCLUSIONS AND RELEVANCE** These results show a significantly higher positive detection rate and a significantly lower rate of inconclusive results in white individuals in comparison with underrepresented minorities. This suggests greater clinical usefulness of genetic testing for cardiomyopathy in white persons in comparison with people of other racial/ethnic groups. This clear disparity warrants further study to understand the gaps in usefulness, which may derive from a lack of clinical testing and research in underrepresented minority populations, in the hopes of improving genetic testing outcomes for cardiomyopathy in nonwhite groups.

Author Affiliations: US Food and Drug Administration, Silver Spring, Maryland (Landry); Laboratory for Molecular Medicine, Partners Healthcare Personalized Medicine, Cambridge, Massachusetts (Landry, Rehm); Brigham and Women’s Hospital, Boston, Massachusetts (Landry, Rehm); Harvard Medical School, Boston, Massachusetts (Landry, Rehm); The Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Rehm).

**Corresponding Author:** Heidi L. Rehm, PhD, Laboratory for Molecular Medicine, Partners Personalized Medicine, 65 Landsdowne St, Cambridge, MA 02139 (hrehm@bwh.harvard.edu).

Published online February 28, 2018.
Over the past 10 years, genetic testing has become commonplace in the diagnosis of monogenic diseases for many patients. However, the application of genetic testing has not been equal in all sectors of the population. Racial/ethnic disparities in research study enrollment and the delivery of health care, favoring white individuals and racial/ethnic minorities of higher socioeconomic status, have led to differences in the development and application of the evidence base that underlies the usefulness of genetic testing.

The Laboratory for Molecular Medicine at the Partners Healthcare Personalized Medicine launched the first clinical genetic test for hypertrophic cardiomyopathy in 2003 and expanded testing over the subsequent 15 years to encompass 62 genes that have been implicated in cardiomyopathy. Here we present data from 15 years of genetic testing for cardiomyopathy. With a prevalence of 1 in every 500 individuals, cardiomyopathy is one of the most common monogenic cardiac diseases in the US population. We document the association between racial/ethnic disparities and genetic testing intended to inform the care of patients.

Methods

We conducted a cross-sectional analysis of 7409 probands referred for genetic testing. For analyses, we grouped black, Hispanic, Native American, Alaska Native, Hawaiian, and other South Pacific Islander individuals in a single category termed underrepresented minorities (URM) and did not consider those of mixed, unspecified, or other races/ethnicities. We analyzed probands for the detection rate for cardiomyopathy, which we defined as the percentage of probands with a positive report because of 1 or more pathogenic or likely pathogenic variants identified to be causative for the proband's clinical presentation or family history of cardiomyopathy. This study was approved by Partners Healthcare institutional review board and conducted under a protocol for which consent procedures were waived.

For comparison, we analyzed the detection rates of other diseases, including hearing loss and RASopathies (ie, Noonan syndrome and related disorders). Additionally, we analyzed the rate of inconclusive findings, which resulted largely from the presence of 1 or more variants of uncertain significance in the absence of a pathogenic or likely pathogenic variant. Categorical variables were assessed using a χ² analysis or Fisher exact test. We used SAS version 9.4 (SAS Institute) and regarded a 2-tailed P value of less than .05 as significant.

Results

Of the 7409 probands identified, 5729 were described as white, Asian, or URM. Of these, 4539 were white (of whom 2753, or 61.1%, were male), 348 were Asian (of whom 210, or 61.0%, were male), 565 were black, 237 were Hispanic, and 40 were Native American, Alaskan, Hawaiian, and other South Pacific Islander. Collectively, the URM group included 472 males (61.1%), were male), 348 were Asian (of whom 210, or 61.0%), and RASopathies (URM: 22/382; 5.8%; vs white individuals: 842; 18.4%), compared with the detection rate for white individuals (314/4539; 29.0%; χ² = 39.8; P < .001). Asian individuals also had a lower detection rate compared with white individuals (87/348; 25.0%), but these findings were not statistically significant (χ² = 2.5; P = .12).

We compared this reduction with other diseases, including hearing loss and RASopathies (ie, Noonan syndrome and related disorders). Similar differences were seen in hearing loss, although in this case, Asian individuals (62/164; 37.8%) had a higher detection rate than white individuals (360/1579; 22.8%; χ² = 18.2; P < .001). For RASopathies, detection rates were higher in both the URM group (128/382; 33.5%) and the Asian group (40/105; 38.1%) than in the white group (502/1887; 26.6%; χ² = 7.6 and P = .01 for comparisons of the URM and white groups; χ² = 6.6 and P = .01 for comparisons of the Asian and white groups). These results are shown in the Table.

Additionally, the rate of inconclusive results was higher for the URM group in comparison with the white group for cardiomyopathy (URM: 335/842; 39.8%; vs white: 1115/4539; 24.6%), hearing loss (URM: 169/465; 36.3%; vs white: 500/1579; 31.7%), and RASopathies (URM: 22/382; 5.8%; vs white: 81/1887; 4.3%) testing. However, the difference was not statistically significant for cardiomyopathy (χ² = 83.6; P < .001). Inconclusive results for cardiomyopathy testing in Asian individuals was also higher than in white individuals (Asian: 136/348; 39.2%; vs white individuals: 1115/4539; 24.6%; χ² = 35.8; P < .001). Results are shown in the Table.

Discussion

We posit the following explanation for the reduction in positive test rates in URM individuals for cardiomyopathy and hearing loss but not RASopathies. Given dominant inheritance and

Key Points

Question: Do racial/ethnic disparities reduce the usefulness of genetic testing for cardiomyopathy and other diseases?

Findings: In this cross-sectional study, molecular diagnostic testing data from 5729 probands over a 15-year period were analyzed. A statistically significant reduction in the detection rate of pathogenic and likely pathogenic variants for cardiomyopathy was seen in patients from underrepresented minority racial/ethnic groups compared with white patient populations.

Meaning: Disparities in access to genetic testing have already reduced the rate of detection of disease via genetic testing in underrepresented minorities; improvements in access to testing will be needed to overcome these disparities.
reduced reproductive fitness of affected individuals, most children born with a RASopathy disorder have unaffected parents, and therefore most causative variants occur de novo. This type of variant typically does not require a prior evidence base to implicate the variant as likely pathogenic in a diagnostic setting (the tested patient is affected with a disease). As such, one would expect that prior efforts in research and clinical testing would not affect detection rates. This is consistent with the observation that the positive RASopathy detection rate in white people is not higher than the rate in URM individuals.

In contrast, for hearing loss and cardiomyopathy, reproductive fitness is not substantially reduced by the disorder, which leads to much rarer observations of de novo occurrence that can be used as evidence for pathogenicity. Furthermore, a large percentage of variants that are pathogenic for hearing loss and cardiomyopathy are missense variants, which are difficult to distinguish from benign variants that are not disease-causing and which require multiple case observations and/or functional studies to implicate the variants in disease. Thus, these disorders are likely to suffer more significantly from a poor evidence base as observed in the URM populations tested for cardiomyopathy and hearing loss. Interestingly, RASopathy detection rates in the URM and Asian groups were actually statistically significantly higher than in the white group, which may be because the small number of patients of these races/ethnicities sent for testing have a more convincing phenotype and are therefore more likely to have positive test results.

Also, we found that the detection rate in Asian individuals was higher than white individuals for hearing loss, yet similar to URM individuals for cardiomyopathy. We believe this difference is because the Asian population has been well-studied for the genetic basis of hearing loss, with several founder mutations identified. \(^2,3\) \((\text{GJB2} \ p.\text{Val37Ile} \text{ is the most common cause of genetic hearing loss in the Asian population.})\) In contrast, to our knowledge, Asian individuals have not been as well studied for cardiomyopathy, especially given that basic testing requires a large expensive sequencing panel; this is unlike hearing loss, for which many positive individuals can be identified through simple genetic tests. \(^5,6\)

A second challenge encountered in genetic testing is the receipt of an inconclusive test result because of the identification of 1 or more variants of uncertain significance (VUSs) in the absence of an explanation for disease; inconclusive reflects the identification of a variant of uncertain significance in the absence of an explanation for disease; negative reflects the absence of pathogenic, likely pathogenic, or uncertain significance variants.
cardiomyopathy had a statistically significant increased rate of inconclusive test results in both the URM subgroup and the Asian subgroup compared with the white subgroup (Figure). Cardiomyopathy and hearing loss genes encode many large structural proteins that are highly susceptible to benign variation, whereas the RASopathies are largely caused by variants in the small, highly conserved signaling proteins of the Ras-MAP kinase pathway, which are largely devoid of benign variants. The main reason for the inability to interpret the variants of uncertain significance seen in URM individuals compared with white individuals is that limitations exist in the databases of normal genetic variation that aid in ruling out pathogenicity when allele frequencies are too high to be consistent with pathogenicity. The negative impact of the slower development of databases of allele frequencies in diverse populations has been previously published.

To our knowledge, this represents the first empirical analysis of differences in detection rate and inconclusive result rates for cardiomyopathy between different racial/ethnic groups. Our data suggest that cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals. To counter these challenges, we encourage recruitment of members of URM groups into both research and clinical practice to enable these populations to equally contribute to and benefit from genetic testing in the care and treatment of cardiomyopathy and other genetic disorders.

Conclusions

There are several limitations to this study. One limitation is the difference in sample size between white, Asian, and URM populations. Because the study was conducted at a clinical molecular laboratory, the population evaluated was not randomly sampled. For this reason, the proportion of individuals from each racial/ethnic group is reflective of differences in referrals for genetic testing. Also, race/ethnicity was self-reported in this study and may not fully reflect biologic genetic ancestry. Lastly, there was a significant difference in the age of URM individuals referred for testing compared with the ages of the white and Asian subgroups, which leaves age as a potential confounder. This should be adjusted for in future studies with sufficient sample sizes.

Limitations

There are several limitations to this study. One limitation is the difference in sample size between white, Asian, and URM populations. Because the study was conducted at a clinical molecular laboratory, the population evaluated was not randomly sampled. For this reason, the proportion of individuals from each racial/ethnic group is reflective of differences in referrals for genetic testing. Also, race/ethnicity was self-reported in this study and may not fully reflect biologic genetic ancestry. Lastly, there was a significant difference in the age of URM individuals referred for testing compared with the ages of the white and Asian subgroups, which leaves age as a potential confounder. This should be adjusted for in future studies with sufficient sample sizes.

Conclusions

To our knowledge, this represents the first empirical analysis of differences in detection rate and inconclusive result rates for cardiomyopathy between different racial/ethnic groups. Our data suggest that cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals. To counter these challenges, we encourage recruitment of members of URM groups into both research and clinical practice to enable these populations to equally contribute to and benefit from genetic testing in the care and treatment of cardiomyopathy and other genetic disorders.

Conclusions

To our knowledge, this represents the first empirical analysis of differences in detection rate and inconclusive result rates for cardiomyopathy between different racial/ethnic groups. Our data suggest that cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals. To counter these challenges, we encourage recruitment of members of URM groups into both research and clinical practice to enable these populations to equally contribute to and benefit from genetic testing in the care and treatment of cardiomyopathy and other genetic disorders.

Conclusions

To our knowledge, this represents the first empirical analysis of differences in detection rate and inconclusive result rates for cardiomyopathy between different racial/ethnic groups. Our data suggest that cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals. To counter these challenges, we encourage recruitment of members of URM groups into both research and clinical practice to enable these populations to equally contribute to and benefit from genetic testing in the care and treatment of cardiomyopathy and other genetic disorders.

Conclusions

To our knowledge, this represents the first empirical analysis of differences in detection rate and inconclusive result rates for cardiomyopathy between different racial/ethnic groups. Our data suggest that cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals. To counter these challenges, we encourage recruitment of members of URM groups into both research and clinical practice to enable these populations to equally contribute to and benefit from genetic testing in the care and treatment of cardiomyopathy and other genetic disorders.

Conclusions

To our knowledge, this represents the first empirical analysis of differences in detection rate and inconclusive result rates for cardiomyopathy between different racial/ethnic groups. Our data suggest that cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals. To counter these challenges, we encourage recruitment of members of URM groups into both research and clinical practice to enable these populations to equally contribute to and benefit from genetic testing in the care and treatment of cardiomyopathy and other genetic disorders.
Obtained funding: Both authors.
Administrative, technical, or material support: Both authors.
Study supervision: Rehm.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Rehm is employed by Brigham and Women’s Hospital, which offers fee-based clinical sequencing. No other disclosures are reported.

Funding/Support: This study was sponsored by a fellowship appointment through the US Food and Drug Administration Office of Minority Health (Dr Landry), administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US Food and Drug Administration.

Role of the Funder/Sponsor: The US Food and Drug Administration had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The opinions expressed are the authors' own and do not reflect the policies or positions of the FDA.

REFERENCES