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ARTICLE

Shortcomings of ethnicity-based carrier screening for conditions associated with Ashkenazi Jewish ancestry

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ABSTRACT

Purpose: Carrier screening identifies reproductive risk for autosomal recessive and X-linked genetic conditions. Currently, some medical society guidelines continue to recommend ethnicity-based carrier screening for conditions associated with Ashkenazi Jewish (AJ) ancestry. We assessed the utility and limitations of these guidelines in a large, ethnically and genetically diverse cohort of genotyped individuals.

Methods: We characterized the self-reported ethnicity and genetic ancestry of over 110,000 consenting research participants identified as heterozygous for pathogenic variants associated with 15 autosomal recessive conditions recommended by the American College of Obstetricians and Gynecologists for screening in individuals of AJ descent.

Results: Out of 7.2 million research participants, 116,517 research participants were identified as heterozygous for pathogenic variants associated with 15 conditions evaluated. The majority (54.9%) of heterozygotes did not report qualifying ethnicity under American College of Obstetricians and Gynecologists ethnicity-based screening guidelines. Approximately half (51.3%) of all individuals heterozygous for pathogenic variants in genes associated with 1 or more conditions recommended to be screened exclusively in individuals of AJ descent had <20% computed AJ ancestry.

Conclusion: Ethnicity-based carrier screening leads to the under detection of heterozygotes and associated reproductive risk for conditions historically associated with AJ ancestry.

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Introduction

Carrier screening aims to identify reproductive partners who are at increased risk for pregnancies affected by autosomal recessive or X-linked genetic conditions. Carrier screening enables individuals and couples to make informed reproductive decisions. Identification of at-risk reproductive partners can lead to the utilization of preimplantation genetic testing for conception, prenatal diagnostic testing, changes to reproductive decision making, and medical management for the pregnant person and/or affected neonate. The criteria for which conditions should be considered for carrier

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screening, and for whom, continue to be the subject of debate.[1,2]

Self-reported ethnicity (SRE) has been utilized as 1 criterion for carrier screening because certain autosomal recessive disorders occur at a higher frequency in certain populations as a result of genetic drift and/or heterozygote advantage in combination with sociocultural and geographic factors. For example, the increased frequency of pathogenic variants in the Ashkenazi Jewish (AJ) population is a result of a population bottleneck that occurred over 600 years ago.[3,4]

There is a lack of consensus regarding the use of SRE in carrier screening eligibility. The American College of Medical Genetics and Genomics (ACMG) issued an updated practice resource in 2021 that recommends pan-ethnic carrier screening for a set number of conditions based on carrier frequency and perceived severity.[5] ACOG currently supports but has not officially endorsed ACMG's Practice Resource.[6] ACOG Committee Opinion 690 states that ethnicity-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening.[7] ACOG Committee Opinion 691 outlines ethnicity-specific carrier screening guidelines.[8] This Committee Opinion endorses pan-ethnic screening for cystic fibrosis and spinal muscular atrophy and ethnicity-based carrier screening for several other autosomal recessive conditions (Supplemental Table 1).[8] Specifically, recommendations state that carrier screening for Tay-Sachs disease be offered only to reproductive partners for which at least 1 individual is of Jewish, French Canadian, or Cajun descent and that carrier screening for a number of other conditions be offered only to reproductive partners for which at least 1 individual is of Jewish descent. Many payors cite these ACOG committee opinions and do not cover pan-ethnic or expanded carrier screening.[9]

Various challenges to ethnicity-based carrier screening have arisen. Incongruities between reported ethnicity on requisition forms, ethnicity gathered during clinical consultations, and genetic ancestry are frequent.[10,11] There is a lack of consensus on how to collect and use racial, ethnic, and ancestral information in clinical genetics practice.[12] In a study of over 93,000 individuals undergoing carrier screening, 9% had >50% genetic ancestry from a lineage inconsistent with their SRE.[11] Additionally, racial disparities in access to clinical genetics services or diagnostic efficacy of genetic testing may result in the underdiagnosis of monogenic conditions that would be considered for carrier screening.[13] This may reduce the reported incidence of certain autosomal recessive conditions in underserved ethnic groups and lead to incomplete information about the association of ethnicity with carrier frequency.[14] Furthermore, a lack of diversity in genomic databases may lead to poorer estimations for carrier frequency in groups that are historically underrepresented in genetics, especially historically isolated ancestral groups.[15]

The 23andMe database provides an ethnically and genetically diverse group of research-consented genotyped individuals. We sought to characterize a cohort of individuals heterozygous for pathogenic variants in genes associated with one or more conditions with ethnicity-based ACOG screening guidelines to assess the utility and limitations of current recommendations for ethnicity-based carrier screening.

Materials and Methods

All participants were drawn from the customer base of 23andMe, a consumer genetics company. 23andMe participants provided informed consent and volunteered to participate in the research online under a protocol approved by an external institutional review board, Ethical and Independent (E&I) Review Services, which is accredited by the Association for the Accreditation of Human Research Protection Programs. As of 2022, E&I Review Services is part of Salus institutional review board (https://www.versiticlinicaltrials.org/salusirb).

DNA extraction and genotyping were performed on saliva samples by CLIA-certified and CAP-accredited clinical laboratories of Laboratory Corporation of America. Samples were genotyped on 1 of 2 custom Illumina genotyping arrays.

We identified individuals heterozygous for pathogenic variants in genes associated with 15 autosomal recessive conditions recommended by ACOG to be screened in individuals of Jewish descent (hereafter: ACOG-AJ conditions) (Supplemental Table 1). Select analytically validated pathogenic variants were available in the following genes: *BLM* (Bloom syndrome, OMIM #210900), *ASPA* (Canavan disease; OMIM #271900), *ELP1* (also known as *IKBKAP*) (familial dysautonomia; #223900), *ABCC8* (familial hyperinsulinism; OMIM #256450), *FANCC* (Fanconi anemia group C; OMIM #227645), *GBA1* (Gaucher disease; OMIM #230800), *G6PC* (glycogen storage disease type Ia; OMIM #232200), *SLC37A4* (glycogen storage disease type Ib; OMIM #232220), *BCKDHB* (maple syrup urine disease type 1b; OMIM #248600), *MCOLN1* (mucolipidosis type IV; OMIM #252650), *SMPD1* (Niemann-Pick disease type A; OMIM #257200), *HEXA* (Tay-Sachs disease; OMIM #272800), *PCDH15* (Usher syndrome type 1f; OMIM #602083), and *CLRN1* (Usher syndrome type 3a; OMIM #276902) (Supplemental Table 2). All genes associated with ACOG-AJ conditions are also recommended by ACMG for pan-ethnic carrier screening.[5]

The analysis utilized SRE and genetically determined AJ ancestry. The survey question used to ascertain SRE asks, "Do any of the following cultural group labels describe your ancestry? Please check all that apply." Answer options for this question are: "Mennonite," "Amish," "Cajun," "French Canadian," "Turkish," "Jewish," "I'm not sure," and "None of the Above." Throughout this article, the "self-reported ethnicity" (and abbreviation [SRE]) of participants refers to the ethnic labels selected in response to this question.

To estimate the proportions of AJ genetic ancestry, we performed a local ancestry analysis as previously

described.[16] A reference group was comprising individuals who reported 4 Ashkenazi Jewish biological grandparents and their genetic similarity was validated by principal components analysis. Study participants' genomes were compared with this and other reference groups. Throughout this article, "AJ genetic ancestry proportion" refers to the proportion of an individual's genome determined to have high similarity to the AJ reference group.

Thirty variants in genes associated with conditions recommended for ethnicity-based carrier screening by Committee Opinion 691 were available for analysis (Supplemental Table 2).[8] Some variants identified as AJ founder variants were not available for analysis because of analytical limitations. No variants in genes associated with Joubert syndrome were available for analysis. Analysis of carrier status for Fanconi anemia was limited to 3 variants associated with Fanconi anemia complementation group C. Analysis of carrier status for maple syrup urine disease was limited to 2 variants in *BCKDHB* and did not include variants in *DBT* or *BCKDHA*. Literature-based carrier detection rate for individuals who self-report Jewish ethnicity was >90% for all conditions with the exception of mucolipidosis type IV (77% carrier detection rate) (Supplemental Table 3).

Table 1 Demographic characteristics of 116,517 heterozygotes included in the study

Sex, *N* (%)	
Female	65,062 (55.8%)
Male	51,455 (44.2%)
Age, median (range)	51.0 [18.0-100.0]
Carrier findings, mean (range)	1.0 [1.0-4.0]
Carrier status, *N* (%)[a,b]	
Bloom syndrome	2656 (2.3%)
Canavan disease	10,369 (8.9%)
Familial dysautonomia	8074 (6.9%)
Familial hyperinsulinism	4313 (3.7%)
Fanconi anemia group C	7814 (6.7%)
Gaucher disease	36,949 (31.7%)
Glycogen storage disease type Ia	8366 (7.2%)
Glycogen storage disease type Ib	4268 (3.7%)
Maple syrup urine disease type 1b	6446 (5.5%)
Mucolipidosis type IV	2066 (1.8%)
Niemann-Pick disease type A	2466 (2.1%)
Tay-Sachs disease	22,681 (19.5%)
Usher syndrome type 1F	2432 (2.1%)
Usher syndrome type 3A	2722 (2.3%)

[a]Some individuals were heterozygous of multiple conditions.
[b]Carrier status limited to identified variants on genotyping assay.

Results

Demographics

Out of 7,194,265 consented participants, 116,517 (1.6%) were heterozygous for pathogenic variants in genes associated with ACOG-AJ conditions (commonly referred to as "carriers" in the context of reproductive risk) (Table 1). The majority (55.8%, 65,062/116,517) of the cohort was female and the median age was 51 years (range 18-100 years). The most frequently identified carrier status was for Gaucher disease (31.7% of all heterozygotes) followed by Tay-Sachs disease (19.5% of all heterozygotes). The average number of carrier findings for all individuals with at least 1 heterozygous pathogenic variant was 1.0, and the range was 1 to 4.

Carrier frequency and SRE

In total, 95,330 participants were identified as heterozygous for at least 1 pathogenic variant associated with ACOG-AJ conditions excluding Tay-Sachs disease (Table 1). Tay-Sachs disease was analyzed separately because of distinct ethnicity-based carrier screening guidelines[8]; see next section. Less than half (46.8%) of these heterozygotes self-reported Jewish ethnicity, which would qualify them for carrier screening. Among those who reported Jewish ethnicity, 9.7% were heterozygotes of at least 1 of these conditions (Table 2). Among those who did not report Jewish ethnicity, 0.8% were heterozygotes of at least 1 of these conditions.

For 6 ACOG-AJ conditions, a larger number of heterozygotes were identified among individuals without qualifying SRE (ie, did not report Jewish ethnicity) than those with qualifying SRE (Figure 1). These conditions included glycogen storage disease type Ib (93.1% nonqualifying SRE) maple syrup urine disease type 1b (65.6%), Fanconi anemia group C (64.7%), glycogen storage disease type Ia (62.5%), Gaucher disease (59.6%), and Canavan disease (53.8%). For the remaining 7 ACOG-AJ conditions, more heterozygotes were identified among individuals with qualifying SRE.

Tay-Sachs disease carrier frequency and SRE

Tay-Sachs disease was analyzed separately because it fell under different ethnicity-based carrier screening guidelines than other conditions analyzed; specifically, ACOG recommendations state that carrier screening for Tay-Sachs disease be offered only to reproductive partners for which at least 1 individual is of Jewish, French Canadian, or Cajun descent. We identified 22,681 participants as heterozygous for pathogenic variants in *HEXA* associated with Tay-Sachs disease. Less than half (40.6%) of these heterozygotes self-reported Jewish, French Canadian, or Cajun ethnicity and would therefore qualify for Tay-Sachs carrier screening under ACOG guidelines (Table 3). Conversely, the majority (59.4%) of these heterozygotes did not self-report qualifying ethnicity (Figure 1). However, our assay did not include the 7.6 kb deletion in the *HEXA* gene, which is a French Canadian founder variant; therefore, our analysis may underestimate the number of individuals heterozygous for

Table 2 ACOG-AJ carrier frequency (excluding Tay-Sachs disease) among individuals with self-reported ethnicity (N = 7,194,265)

Carrier Status	Qualifying Self-Reported Ethnicity[a]	No Qualifying Self-Reported Ethnicity
Heterozygous for pathogenic variants associated with ACOG-AJ conditions	44,591 (9.7%)	50,739 (0.8%)
Not detected to be heterozygous for pathogenic variants associated with ACOG-AJ conditions	414,832 (90.3%)	6,684,103 (99.2%)
Total	459,423	6,734,842

[a]For individuals heterozygous for pathogenic variants associated with Bloom syndrome, Canavan disease, familial dysautonomia, familial hyperinsulinism, Fanconi anemia group C, Gaucher disease, glycogen storage disease type Ia, glycogen storage disease type Ib, maple syrup urine disease type 1b, mucolipidosis type IV, Niemann-Pick disease type A, Usher syndrome Type 1F and Usher syndrome type 3A, individuals with self-reported Jewish ethnicity were considered to have qualifying self-reported ethnicity. Individuals heterozygous for pathogenic variants associated with Tay-Sachs disease were excluded from this analysis.

pathogenic variants associated with Tay-Sachs disease who had qualifying ethnicity, particularly for those with French Canadian ancestry.

Of all individuals with qualifying SRE, the proportion of identified individuals heterozygous for pathogenic variants in *HEXA* associated with Tay-Sachs disease was 1.3% (Table 3). Among those who did not report qualifying ethnicity (N = 6,475,690), the proportion was 0.2%.

An additional analysis was conducted to capture the number of individuals heterozygous for pathogenic variants associated with ACOG-AJ conditions who would have been fully screened, ie, all of their carrier statuses would be captured under ethnicity-based carrier screening guidelines. For example, an individual heterozygous for pathogenic variants in *HEXA* and *BLM* and who self-reported Cajun ethnicity (but not Jewish ethnicity) was parsed as nonqualifying. Among 116,517 heterozygotes, the majority (54.9%, N = 64,025) had at least 1 carrier status that would have been missed by ethnicity-based carrier screening guidelines.

Genetic ancestry and self-reported Jewish ethnicity

The relationship between self-reported Jewish ethnicity and Ashkenazi Jewish genetic ancestry was explored among individuals heterozygous for pathogenic variants associated with ACOG-AJ conditions (N = 95,249). Heterozygotes with a greater proportion of estimated AJ genetic ancestry were more likely to report Jewish ethnicity ($\chi^2 < 0.001$) (Table 4). We compared individuals with and without at least 20% computed AJ ancestry because previous medical society guidelines and current payor guidelines utilize the criterion of at least "1 Jewish grandparent."[9,17] Approximately half of all heterozygotes (51.3%) had <20% computed AJ ancestry. Among heterozygotes with >20% computed AJ ancestry, 9.0% did not report Jewish ethnicity. Eighty-one individuals did not have computed AJ genetic ancestry information available and were excluded from this analysis.

Database comparison with US population

To understand the generalizability of our findings to the US population, we compared our database with publicly available data on ethnicity composition. Out of 7,194,265 consented participants in this study, 6.4% (459,423/7,194,265) self-reported Jewish ethnicity, 3.2% (228,524/7,194,265) self-reported French Canadian ethnicity, and 0.8% (58,897/7,194,265) self-reported Cajun ethnicity. In the US

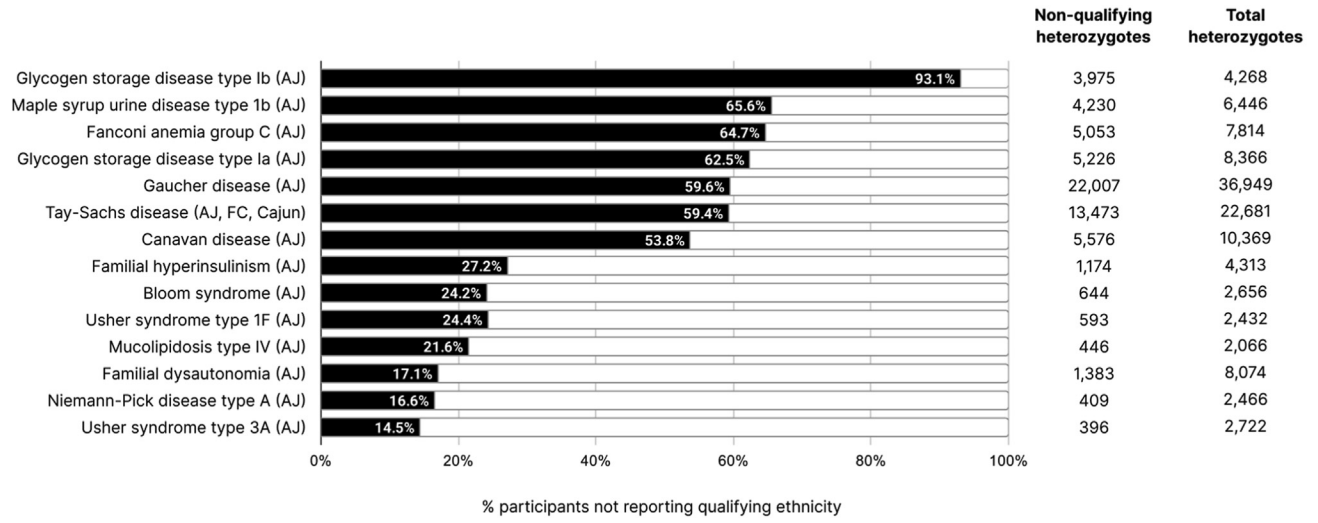

Figure 1 Percentage of individuals heterozygous for pathogenic variants associated with ACOG-AJ conditions who did not report a qualifying ethnicity. Qualifying ethnicities are listed in parentheses: AJ, Ashkenazi Jewish; FC, French Canadian.

Table 3 Tay-Sachs disease carrier frequency among individuals with self-reported ethnicity (N = 7,194,265)

Carrier Status	Qualifying Self-Reported Ethnicity[a]	No Qualifying Self-Reported Ethnicity
Heterozygous for pathogenic variants associated with Tay-Sachs disease	9208 (1.3%)	13,473 (0.2%)
Not detected to be heterozygous for pathogenic variant associated with Tay-Sachs disease	709,367 (98.7%)	6,462,217 (99.8%)
Total	718,575	6,475,690

[a]For individuals heterozygous for pathogenic variants associated with Tay-Sachs disease, self-reported Jewish, French Canadian, and/or Cajun ethnicity was considered qualifying self-reported ethnicity.

population, proportions of individuals with Jewish ethnicity have been estimated at approximately 7.5 million or 2.4% in 2020.[18,19] Data collected by the US Census suggests that the proportion of individuals in the US population with French Canadian ethnicity and Cajun ethnicity were approximately 0.5% and 0.03% in 2020, respectively.[20] Therefore, the 23andMe database may have a higher proportion of individuals with reported Jewish, French Canadian, and Cajun ethnicity based on these recent estimates for the general US population.

Discussion

We evaluated the efficacy of ethnicity-based carrier screening guidelines by analyzing SRE, genetic ancestry, and carrier status in a large, ethnically diverse cohort. We found that SRE may predict the likelihood of being a heterozygote; however, the majority of individuals heterozygous for pathogenic variants associated with ACOG-AJ conditions do not have qualifying SRE and would therefore not be identified under current ethnicity-based ACOG carrier screening guidelines.

Overall, the majority (54.9%) of our cohort had at least 1 carrier status that would have been missed by ethnicity-based carrier screening guidelines. The carrier frequency of ACOG-AJ conditions (excluding Tay-Sachs disease) among individuals with qualifying SRE was greater than that among individuals who would not have qualified (9.7% vs 0.8%). However, the majority of individuals heterozygous for a pathogenic variant associated with these conditions would not have qualified for ethnicity-based carrier screening based on ACOG guidelines (50,739 vs 44,591 individuals). The carrier frequency of Tay-Sachs disease among individuals with qualifying SRE was also predictably greater than among those without (1.3% vs 0.2%). However, the majority of individuals heterozygous for pathogenic variants in *HEXA* associated with Tay-Sachs disease would not have qualified for screening under these guidelines (13,473 vs 9208 individuals). The 23andMe database has a higher proportion of individuals with reported Jewish, French Canadian, and Cajun ethnicity than select recent estimates for the general US population, which suggests that the relative number of nonqualifying heterozygotes for these conditions in the US population would be even larger than that reported here. However, these estimates are likely sensitive to how SRE is ascertained.

Table 4 Self-reported Jewish ethnicity and computed Ashkenazi Jewish ancestry of individuals heterozygous for pathogenic variants associated with ACOG-AJ conditions (N = 95,249)

Computed Ashkenazi Jewish Ancestry	No Self-Reported Jewish Ethnicity	Self-Reported Jewish Ethnicity
<1%	40,285 (98.3%)	704 (1.7%)
1%-20%	6211 (78.5%)	1702 (21.5%)
20%-40%	1655 (35.4%)	3022 (64.6%)
40%-85%	1715 (11.9%)	12,692 (88.1%)
85%-100%	822 (3.0%)	26,441 (97.0%)
Total	50,688	44,561

Our findings are consistent with previous studies demonstrating that a considerable proportion of individuals heterozygous for pathogenic variants associated with an autosomal recessive condition do not self-report qualifying ethnicity. In 1 study examining the carrier frequency for 8 conditions associated with Jewish descent in patients undergoing carrier screening, 81.6% of heterozygotes identified either did not have any ethnicity noted on their laboratory requisition form by the clinician or did not note Jewish ethnicity.[21] Another study found that the majority of identified individuals heterozygous for pathogenic variants associated with 6 of 14 conditions recommended by ACOG for individuals of AJ descent did not have Jewish ethnicity noted on their laboratory requisition form.[11] This study additionally noted that 53% of individuals heterozygous for pathogenic variants associated with alpha thalassemia and 36% of individuals heterozygous for pathogenic variants associated with *HBB*-related hemoglobinopathy did not have qualifying ethnicity noted by their clinicians as defined by ACOG guidelines[11,22] (since this study, ACOG has pivoted to recommend universal screening for these hemoglobinopathies[23]). One distinction between our study and these previous studies is that participants' SRE in our study was ascertained directly and not by clinician report. Discrepancies between information obtained via medical interview and clinical documentation have been previously reported,[24,25] and there is a lack of standardization in how information on race, ethnicity, and ancestry are collected from patients by genetics professionals.[12]

Principles guiding population screening decisions include the analytical performance of the screening test, the cost-effectiveness of case finding, and the availability of interventions and treatment, among others.[26] Historically,

the cost of genetic testing has contributed to the cost of case finding and necessitated a high *a priori* likelihood of identifying a heterozygote to justify eligibility for carrier screening. However, advances in genetic testing technology, including next-generation sequencing, have decreased the overall cost of carrier screening, as well as the marginal cost of screening for additional conditions.[5,26] Our data provide evidence that, although ethnicity-based carrier screening guidelines may reliably capture those who are at higher likelihood to be heterozygous for pathogenic variants associated with certain autosomal recessive conditions, more than half of all heterozygotes are missed by ethnicity-based carrier screening guidelines. Evidence suggests that the incidence of some of these conditions may be greater outside of the high-risk population designated for carrier screening. For example, the incidence of Tay-Sachs disease is now higher in non-Jewish populations than in the Jewish population, likely because of the widespread adoption of carrier screening in the Jewish community.[11]

SRE is largely treated categorically by medical society guidelines, with little guidance on individuals of mixed ancestry, and is often inconsistent with genetic ancestry.[10] In one study of over 90,000 individuals undergoing carrier screening, approximately 20% of individuals self-reporting as AJ had less than 50% computed AJ genetic ancestry.[11] Approximately 40% of individuals self-reporting as Middle Eastern had less than 50% computed Middle Eastern ancestry. It is important to note that racial and ethnic identifiers are socially constructed; lack of ancestry concordance does not invalidate one's racial and ethnic identity. The present study in combination with other findings demonstrates that SRE is an imperfect proxy for genetic ancestry.

Importantly, genetic ancestry composition is also not a reliable decision-making criterion for carrier screening. One previous ACMG guideline regarding ethnicity-based carrier screening recommended that "one Jewish grandparent is sufficient to offer testing."[17] This threshold is also utilized by some payors.[9] This corresponds to individuals with approximately >20% ancestry when accounting for recombination. In our study, half of all individuals heterozygous for pathogenic variants associated with ACOG-AJ conditions (51.3%) had <20% computed Ashkenazi Jewish ancestry. Genetic ancestry was not a reliable indicator of carrier status, even when the analysis was enriched for Jewish founder variants. Genetic ancestry testing is also impractical for carrier screening decision making in the clinical setting given the added turnaround time and cost of additional testing.

Limitations

This study has several limitations. First, select causative variants in genes associated with the conditions of interest were reported. This set of variants was enriched for AJ founder variants (see Supplemental Tables 2 and 3). As a result, this study likely underestimates the number of true heterozygotes. In addition, the overrepresentation of AJ founder variants in our analysis would result in an overrepresentation of heterozygotes with qualifying ethnicity. Second, of the 14 conditions recommended by ACOG for carrier screening exclusively in individuals of AJ descent, our assay included analytically validated variants in genes associated with 13 conditions and did not include all subtypes. As a result, our analysis does not capture all heterozygotes that would be detected via sequencing. Third, some well-characterized founder variants in populations of interest were not included in our study (see Supplemental Table 4). As a result, our analysis may underestimate the number of individuals heterozygous for pathogenic variants associated with Tay-Sachs disease with qualifying ethnicity, particularly for those with French Canadian ancestry, as well as the number of individuals with qualifying SRE who are heterozygous for pathogenic variants associated with mucolipidosis type IV and pathogenic variants associated with Gaucher disease. Fourth, information about identification with Jewish subgroups, including AJ, Sephardic Jewish, or Mizrahi Jewish, was not collected for the majority of participants and was not used for analysis. For this study, self-identification as Jewish was considered to be a qualifying SRE. This may lead to an overestimation of the proportions of heterozygotes who qualified based on SRE. Lastly, ACOG guidelines state that individuals who have a first- or second-degree relative with a condition are eligible for carrier screening. Family history was not captured in our analysis and individuals who would have qualified for carrier screening due to family history could have been categorized as nonqualifying. We would expect this number to be nominal given the low frequency of these autosomal recessive conditions.

Conclusion

At the time of publishing, current guidelines are insufficient to drive payors to adopt medical policies supporting pan-ethnic carrier screening for conditions other than cystic fibrosis, spinal muscular atrophy, and hemoglobinopathies.[9,14] Utilization of ethnicity-based carrier screening based on SRE results in the under-identification of individuals heterozygous for pathogenic variants associated with autosomal recessive conditions. SRE is often discordant with genetic ancestry, and it is impractical and ineffective to utilize genetic ancestry in place of SRE.

All areas of clinical genetics intersect with questions of health equity. Clinical decision making based on a patient's racial, ethnic, or ancestral data should be particularly scrutinized for ways that current practice exacerbates existing health inequities. It has been suggested that the omission of guidance for individuals who have blended ancestry in ethnicity-based carrier screening is rooted in eugenic ideas about racial purity.[14] Lack of standardization of care may

result in racial, ethnic, and socioeconomic variations in how carrier screening is offered. Limited studies have shown that pregnant individuals of color and lower socioeconomic status are less likely to be offered and undergo aneuploidy testing[27,28]; however, sociodemographic differences in the offering and uptake of carrier screening have not been well studied.

Standardization of care is a recognized public health strategy for improving equity when clinical practice and access to certain medical interventions are inequitable. Access to carrier screening leads to the identification of at-risk couples and access to available reproductive options, which include (but are not limited to) preimplantation genetic testing for monogenic conditions, prenatal diagnosis, pregnancy termination, use of donor gametes, and adoption. Identification of at-risk couples can also shorten the diagnostic odyssey for affected fetuses with a prenatal phenotype or for affected neonates. The data presented in this study and others argue that medical societies should adopt strong stances in favor of pan-ethnic carrier screening and make clear recommendations against ethnicity-based carrier screening.

Data Availability

All data generated or analyzed during this study are included in this published article.

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Author Contributions

Conceptualization: H.L., N.S.A.-H.; Data Curation: S.L., J.Z.; Formal Analysis: S.L., J.Z.; Methodology: H.L., R.T., S.L., S.D., N.S.A.-H.; Supervision: R.T., S.D., N.S.A.-H.; Writing-original draft: H.L., R.T., N.S.A.-H.; Writing-review and editing: H.L., R.T., S.D., S.L., J.Z., N.S.A.-H.

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Ethics Declaration

23andMe Research participants provided informed consent and volunteered to participate in the research online under a protocol approved by an external AAHRPP-accredited institutional review board (IRB), Ethical and Independent (E&I) Review Services. As of 2022, E&I Review Services is part of Salus IRB (https://www.versiticlinicaltrials.org/salusirb).

Conflict of Interest

Hannah Llorin, Ruth Tennen, Sarah Laskey, Jianan Zhan, and Stacey Detweiler are current or recent employees of 23andMe, Inc and have stock, stock options, or both in 23andMe, Inc. Noura S. Abul-Husn is an employee and equity holder of 23andMe, Inc, a faculty member at the Icahn School of Medicine at Mount Sinai, and a scientific advisory board member for Allelica, Inc.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2024.101869) contains supplemental material, which is available to authorized users.

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