original reports

Germline Pathogenic Variant Prevalence Among Latin American and US Hispanic Individuals Undergoing Testing for Hereditary Breast and Ovarian Cancer: A Cross-Sectional Study

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abstract

PURPOSE To report on pathogenic germline variants detected among individuals undergoing genetic testing for hereditary breast and/or ovarian cancer (HBOC) from Latin America and compare them with self-reported Hispanic individuals from the United States.

METHODS In this cross-sectional study, unrelated individuals with a personal/family history suggestive of HBOC who received clinician-ordered germline multigene sequencing were grouped according to the location of the ordering physician: group A, Mexico, Central America, and the Caribbean; group B, South America; and group C, United States with individuals who self-reported Hispanic ethnicity. Relatives who underwent cascade testing were analyzed separately.

RESULTS Among 24,075 unrelated probands across all regions, most were female (94.9%) and reported a personal history suggestive of HBOC (range, 65.0%-80.6%); the mean age at testing was 49.1 ± 13.1 years. The average number of genes analyzed per patient was highest in group A (A 63 ± 28, B 56 ± 29, and C 40 ± 28). Between 9.1% and 18.7% of patients had pathogenic germline variants in HBOC genes (highest yield in group A), with the majority associated with high HBOC risk. Compared with US Hispanics individuals the overall yield was significantly higher in both Latin American regions (A *v* C $P = 1.64\times10^{-9}$, B *v* C $P < 2.2\times10^{-16}$). Rates of variants of uncertain significance were similar across all three regions (33.7%-42.6%). Cascade testing uptake was low in all regions (A 6.6%, B 4.5%, and C 1.9%).

CONCLUSION This study highlights the importance of multigene panel testing in Latin American individuals with newly diagnosed or history of HBOC, who can benefit from medical management changes including targeted therapies, eligibility to clinical trials, risk-reducing surgeries, surveillance and prevention of secondary malignancy, and genetic counseling and subsequent cascade testing of at-risk relatives.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Most studies that have assessed pathogenic/likely pathogenic germline variants (PGVs) in patients undergoing genetic testing for hereditary breast and ovarian cancer (HBOC) predisposition genes have focused on patients of Northern European descent,[1-5] leaving PGV prevalence and clinical presentations from under-represented, and often underserved, populations less well known. Reasons for this may be attributed to the lack of access to genetics providers and genetic testing,[6] differences in testing practices in other countries,[7-9] and the relatively new emergence of mainstream testing for HBOC-related cancers. However, it is clear that PGV rates, at least for *BRCA1* and *BRCA2*, are similar across geographic regions although the particular PGVs vary greatly by region or ancestry.[10]

Among Latin American countries, the distribution of PGVs is likely due to the diversity of population structures and unique admixture of several European, African, Asian, and indigenous American populations.[11-18] Most Latin American–based studies reporting on prevalence among patients with a personal or family history of breast and ovarian cancer have focused on

CONTEXT

Key Objective

What is the prevalence of pathogenic germline variants (PGVs) in individuals with breast and ovarian cancer in Latin America?

Knowledge Generated

PGVs in genes that increase the risk for breast and ovarian cancer were identified in 18.7% of individuals tested in Mexico, Central America, and the Caribbean and in 13.8% of individuals tested in South America. PGVs in *BRCA1* and *BRCA2* were most common, but PGVs in many other genes account for the remaining findings. Rates of variants of uncertain significance were similar across all regions, and when additional evidence was available, > 90% of variants of uncertain significance were reclassified into benign or likely benign.

Relevance

These data highlight the importance of multigene panel testing in Latin American patients with newly diagnosed or history of breast or ovarian cancer.

BRCA1 and *BRCA2*,[19-36] with several founder variants commonly observed.[19,30,37-40] *TP53*, associated with Li-Fraumeni Syndrome, has also been studied because of the Brazilian founder variant c.1010G>A (p.Arg337His, also referred to as R337H).[23,41-43] A limited number of small studies using multigene panels have demonstrated that expanded testing provides clinical utility.[33,44-47] Other genes of interest, such as *PALB2*, *CHEK2*, and *ATM*, have not been extensively investigated in large Latin American cohorts, and thus, the PGV incidence and penetrance in these genes remain unknown in this population. Furthermore, the proportion of patients with variants of uncertain significance (VUSs) are generally higher in studies with non-European individuals compared with those in study populations of European descent.[48,49]

In this study, we measured the prevalence of PGVs and VUSs among individuals undergoing germline testing for HBOC from Mexico, Central America, the Caribbean, South America, as well as individuals from the US self-reporting Hispanic ancestry.

METHODS

Study Population

Unrelated individuals and their relatives were included in this retrospective study if they met the following criteria: clinician-ordered germline testing for HBOC performed at Invitae between December 2014 and June 2019 by a clinician based in Mexico, Central America, the Caribbean, or South America or by a US-based clinician for an individual with self-reported Hispanic ethnicity (including individuals from Puerto Rico) and reported a personal and/or family history of breast and/or ovarian cancer (including primary peritoneal and fallopian cancers). Review and analysis of fully deidentified data were approved by the WCG Institutional Review Board (1167406).

Genetic Testing

Genomic DNA extracted from blood or saliva samples was sequenced using a next-generation sequencing (NGS) assay.[50] Requisitioned genes (Data Supplement) were targeted using oligonucleotide baits designed to capture exons, the 10-20 bases flanking intronic sequences, and certain noncoding regions of interest (Agilent Technologies, Santa Clara, CA; Roche, Pleasanton, CA; Integrated DNA Technologies, Coralville, IA). Targeted gene regions were sequenced at an average of 350× coverage (50× minimum).

A customized bioinformatics pipeline aligned NGS reads to GRCh37 and reported single-nucleotide variants, small and large insertions/deletions (indels), structural variants, and intragenic copy number variants.[50,51] Clinically significant variants that did not meet stringent NGS quality metrics were confirmed by an orthogonal method.[52] Detected variants were interpreted using Sherloc,[53] a point-based system that incorporates the joint consensus statement guidelines from the American College of Medical Genetics and the Association of Molecular Pathology,[54] and classified as a PGV, VUS, benign, or likely benign.

Data Analysis

Individuals were divided into three groups on the basis of the ordering clinician's region. Group A included tests ordered in Mexico, Central America, or the Caribbean. Although genetically diverse, these regions were grouped because of small sample size. Group B included tests ordered in South America. Group C included individuals with a self-reported Hispanic ethnicity who received testing in the United States. Unrelated probands, defined as the first individual tested in a family or an individual without relatives tested by Invitae, were analyzed separately from relatives.

Diagnostic yield (proportion of probands with a PGV) was calculated for each region and stratified by HBOC cancer gene risk (probands with more than one PGV were categorized according to the highest HBOC risk group). Categories of increased HBOC risk included high (> 4× lifetime risk compared with the general population), moderate (2-4× lifetime risk compared with the general population), and low/preliminary (< 2× lifetime risk and/or uncertain risk; Data Supplement). PGVs in genes unrelated to HBOC were further categorized according to the risk associated

with the other hereditary cancer syndrome (HCS; high risk, moderate risk, low risk, or carrier [of an autosomal recessive HCS]). Variants categorized as possibly mosaic (when a variant is not present at an allelic fraction that is consistent with or expected in diploid or heterozygous situations) were excluded from this analysis (n = 21 patients).

PGV frequency per gene was calculated. The distribution of variants was assessed by country. The clinical impact of a PGV was measured based on potential management changes based on current clinical guidelines,[55] approved therapies (in the United States), or clinical trials (group C only; Data Supplement). Furthermore, the VUS rate among probands with no PGVs was calculated.

The proportion of probands with at least one relative who pursued no-charge cascade testing was calculated.

Where appropriate, significance testing was performed (differences in proportions, prop.test function; differences in means, tsum.test function; RStudio version 1.2.5033), with $P < .05$ as significant.

RESULTS

Study Population

Among 24,075 unrelated probands, the majority were female (94.9%) and the mean age at testing was 49.1 ± 13.1 years, with significant differences between all three groups (Table 1). In all regions, the majority of probands reported a personal history suggestive of HBOC (65.0%-80.6%).

Clinicians based in Central America, Mexico, and the Caribbean ordered the most number of genes, on average (group A, 63 ± 28 genes), followed by South America–based clinicians (group B, 56 ± 29) and US-based clinicians (group C, 40 ± 27; Table 1). The most common genes selected for testing included high-to-moderate HBOC-risk genes, such as *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *PALB2*, and *TP53* (Data Supplement), among others. When provided, the clinician-reported reasons for testing varied, but included personal or family history of cancer, clinical decision making, and patient concern.

TABLE 1. Demographic and Clinical Characteristics of Probands

Characteristic	Group A (Central America, Mexico, and the Caribbean)	Group B (South America)	Group C (US Hispanic)	*P*		
				A *v* B	A *v* C	B *v* C
No.	331	5,867	17,877	—	—	—
Sex, No. (%)				.810400	.37470	.02293
Female	311 (94.0)	5,531 (94.3)	16,998 (95.1)			
Male	20 (6.0)	336 (5.7)	879 (4.9)			
Age, years, mean (SD)	45.2 (13.2)	48.1 (12.7)	49.5 (13.1)	.000116	$1.012e^{-08}$	$3.875e^{-13}$
Age group, years, No. (%)				—	—	—
< 20	6 (1.8)	27 (0.5)	112 (0.6)			
20-29	22 (6.6)	265 (4.5)	909 (5.1)			
30-39	87 (26.3)	1,325 (22.6)	2,885 (16.1)			
40-49	102 (30.8)	1,784 (30.4)	5,565 (31.1)			
50-59	61 (18.4)	1,301 (22.2)	4,364 (24.4)			
60-69	44 (13.3)	831 (14.2)	2,739 (15.3)			
70-79	8 (2.4)	278 (4.7)	1,066 (6.0)			
≥ 80	1 (0.3)	56 (1.0)	237 (1.3)			
Cancer affected, No. (%)				$5.419e^{-06}$	.01531	$< 2.2e^{-16}$
Yes	231 (69.8)	4,730 (80.6)	11,627 (65.0)			
No	83 (25.1)	936 (16.0)	5,705 (31.9)			
Not provided	17 (5.1)	201 (3.4)	545 (3.0)			
Genes ordered, mean (SD)	63 (28.0)	56 (29.0)	40 (27.0)	$1.317e^{-05}$	$< 2.2e^{-16}$	$< 2.2e^{-16}$
Genes ordered, No. (%)				—	—	—
1-5	10 (3.0)	195 (3.3)	817 (4.6)			
6-15	18 (5.4)	444 (7.6)	2,894 (16.2)			
16-50	90 (27.2)	2,167 (36.9)	10,128 (56.7)			
> 50	213 (64.4)	3,061 (52.2)	4,038 (22.6)			

Abbreviation: SD, standard deviation.

Diagnostic Yield of Germline Testing Results Among Probands

The overall diagnostic yield ranged from 11.6% (group C: US Hispanic) to 20.8% (group A: Mexico, Central America, and the Caribbean). The PGV rate in genes associated with HBOC risk ranged from 9.1% to 18.7%, most of which were in genes with high HBOC risk (Fig 1A). Compared with US Hispanic individuals, the overall yield was significantly higher in both Latin American regions. Diagnostic yield was highest in individuals with a gene panel size ranging from 1 to 15 genes, decreasing as panel size increased (Appendix Fig A1). In groups B and C, the diagnostic yield was generally similar regardless of whether a personal history of cancer was reported (unaffected vs affected; group B, 13.0% *v* 13.9%; group C, 7.9% *v* 9.6%), whereas the yield among those without a personal history of cancer was lower compared with individuals with a reported personal cancer history in group A (10.8% *v* 20.9%; Appendix Fig A2). Among genes associated with other HCS risk, PGVs were observed in 3.3%-6.2% of individuals (Fig 1B). Less than 1% of individuals in each region were found to be heterozygous for genes with autosomal recessive inheritance (eg, *MUTYH*).

The distribution of HBOC-risk genes with PGVs was similar across regions (Data Supplement). As expected, PGVs were most commonly detected in *BRCA1* and *BRCA2* (Fig 2). The most common PGV observed in Brazil was the Ashkenazi Jewish founder variant c.5266dupC in *BRCA2* (also referred to as 5382insC). The most common variant in patients from Chile was the founder variant c.3331_3334delCAAG in *BRCA1*.[19] As reported elsewhere, the African founder variant c.4357+1G>A in *BRCA1* was the most common variant in patients from the Bahamas.[56-58] After *BRCA1* and *BRCA2*, the most common P/LP findings were in *CHEK2*, *ATM*, *PALB2*, and *TP53* (Fig 2, Fig 3, and Data Supplement).

The clinical utility of PGVs was determined from US-published management guidelines (National Comprehensive Cancer Network), available precision therapies such as poly (ADP-ribose) polymerase or checkpoint inhibitors, and clinical trials (group C only; Data Supplement). As expected, the majority of PGVs in genes with increased risk of HBOC were associated with clinically actionable management changes (group A, 100%; group B, 99.8%; and group C, 99.9%). Potential clinical implications were also found in PGVs associated with other HCS genes (group A, 71.4%; group B, 83.6%; and group C, 86.1%).

Rate of VUSs

At least one VUS was returned for 35.5% of all patients who did not receive any PGV (group A, 42.6%; group B, 40.6%; and group C, 33.7%; Fig 4A), the majority of whom had a single VUS and were tested for more than 15 genes (data not shown). VUS rates were significantly higher in the Latin American regions compared with US Hispanic individuals (A *v* C, $P = .000714$; B *v* C, $P < 2.2e^{-16}$). Overall, 10.0% of individuals with no PGVs had at least one VUS in *BRCA1* or *BRCA2* (group A, 15.6%; group B, 10.5%; and group C, 9.7%).

Approximately one third of patients with a variant originally classified as VUS (n = 2,575 of 8,514, n = 767 variants) have since been reclassified by observation in clinical cases, cosegregation with disease, an alternative molecular diagnosis, or incorporation of newly available experimental or *in silico* data. The majority of VUS (93.2%, n = 715 of 767) were reclassified into benign or likely benign, and the remaining 6.8% upgraded to a PGV (Fig 4B).

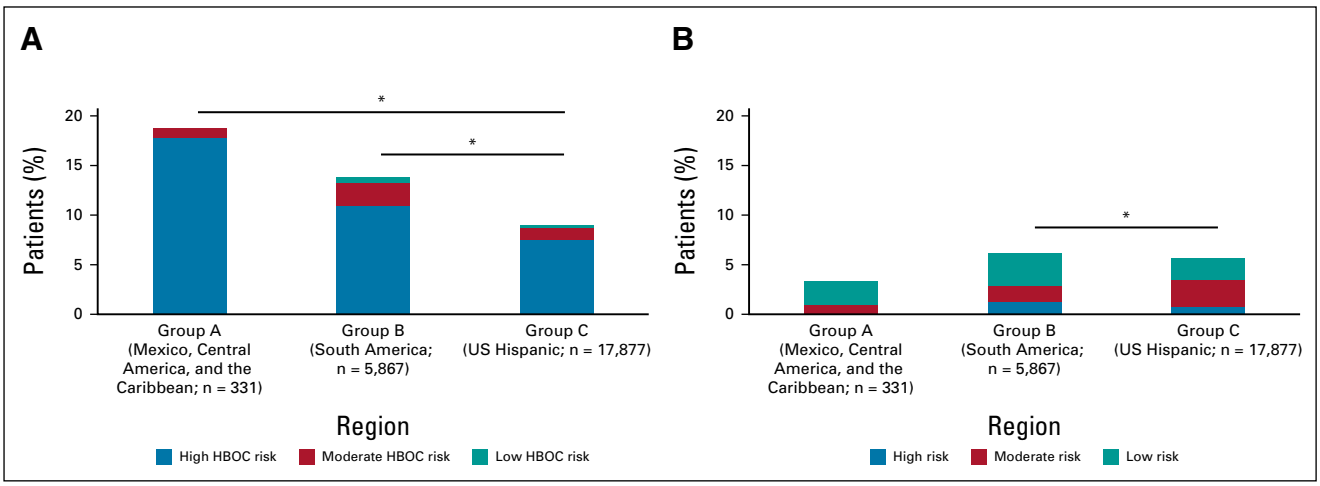

FIG 1. Diagnostic yield of unrelated individuals with PGVs in (A) HBOC-risk genes and (B) non–HBOC-risk genes, stratified by region. Individuals with a finding in more than one gene are classified according to the highest HBOC-specific risk. Individuals with PGVs in genes associated with cancer risk outside of HBOC were classified according to the highest risk for the other cancer type. *Indicates a significant difference ($P \leq .05$). BOC, breast and/or ovarian cancer; HBOC, hereditary breast and/or ovarian cancer; HCS, hereditary cancer syndrome; PGV, pathogenic germline variant.

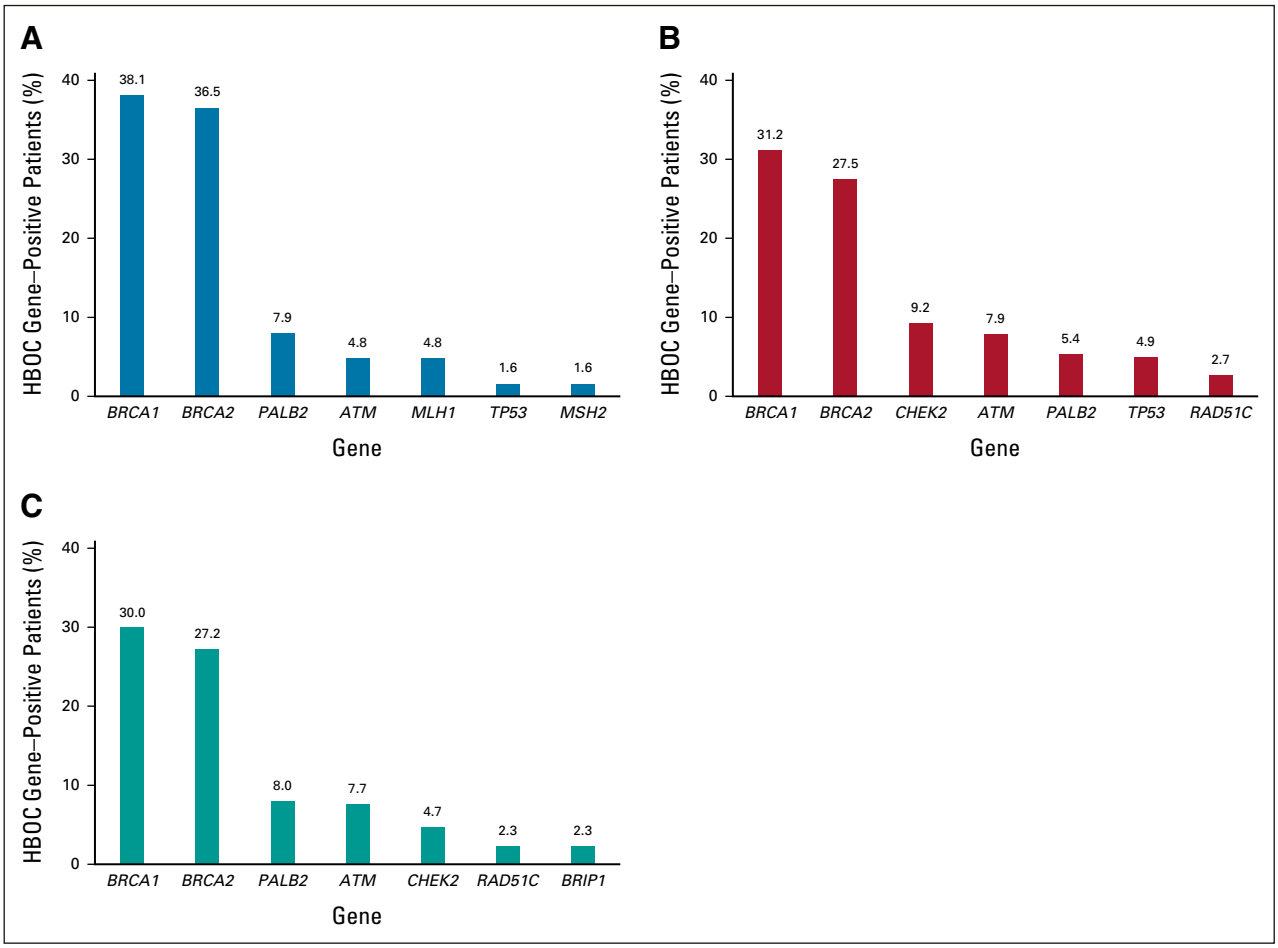

FIG 2. Most frequent PGVs in HBOC-risk genes in (A) Mexico, Central America, and the Caribbean; (B) South America; and (C) US Hispanic individuals. For each HBOC-risk gene, the number of individuals with a PGV was calculated and represented as a proportion of patients with a PGV. Individuals with more than one variant in a gene (either homozygous or compound heterozygote) were only counted once. The five genes with the highest yield for each region are shown. A list of all genes and the yield is reported in the Data Supplement. HBOC, hereditary breast and/or ovarian cancer; PGV, pathogenic germline variant.

Family Testing

Compared with US Hispanic indiviuals, a larger proportion of probands with PGVs in Latin America had cascade testing ordered for at least one relative (group A, 6.6%; group B, 4.5%; and group C, 1.9%; Table 2) although their exact relationship to the proband is unavailable. Most relatives were reported to have no personal history of cancer (group A, 93.7%; group B, 81.7%; and group C, 84.6%). Compared with South America (2.0 relatives/proband) and the United States (1.9 relatives/proband), more relatives were tested per proband in Mexico, Central America, and the Caribbean (3.6 relatives/proband). The majority of relatives were tested for between one and five genes. The overall diagnostic yield ranged from 40.0% to 43.1% (Table 2), with the majority of genes with PGVs considered to have high HBOC-specific risk.

DISCUSSION

To our knowledge, this is the largest study to date to report on the genetic test results in a cohort of Latin American individuals tested for HBOC. As seen in other studies, the PGVs most commonly found were in genes associated with high HBOC risk, with the overall diagnostic yield ranging from 11.1% (US Hispanic) to 20.8% (Mexico, Central America, and the Caribbean).[19-32,34,59] Although largely limited to reporting on the results from *BRCA1* and *BRCA2* testing, a large study demonstrated that the yield of *BRCA1* and *BRCA2* PGVs varies greatly by country.[36] Furthermore, the first results from the Latin American Consortium for HBOC (LACAM) have demonstrated the diversity of PGVs across many HCS genes in this population.[60] Most recently, similar to these previous reports, nearly two thirds of HBOC-associated PGVs were detected in *BRCA1* and *BRCA2*, whereas the remainder were identified across 28 other genes. Furthermore, genes with PGVs associated with HBOC all had potential clinical implications for the individual (precision therapy, clinical trials, and/or published management guidelines for risk-reducing surgical and/or cancer screening interventions) and at-risk relatives. This finding should be interpreted with caution as this analysis was based on management guidelines and treatments available in the United States and may not be relevant or accessible in Latin America. When assessing diagnostic

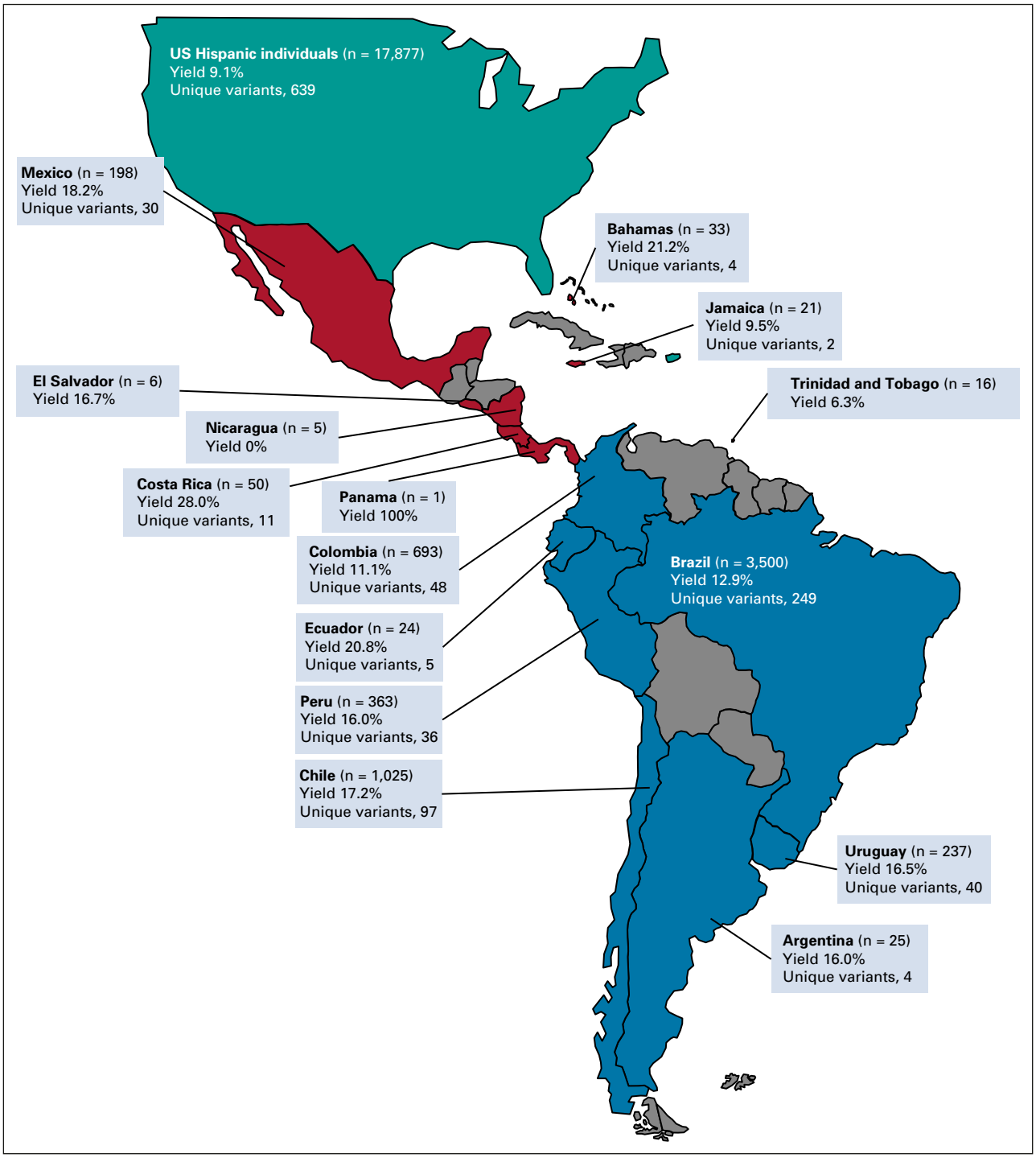

FIG 3. Distribution of pathogenic germline variants in genes associated with increased hereditary breast and/or ovarian cancer risk among countries.

yield by panel size, yield decreased as panel size increased, suggesting that individuals with a higher index of suspicion for HBOC had more targeted panels ordered compared with larger panels for individuals with a lower index of suspicion for HBOC. However, those with a high suspicion of HBOC with a negative result from limited testing might have PGVs in unrequisitioned genes. These series of observations, taken together, demonstrate the importance of HBOC genetic testing in genes beyond *BRCA1* and *BRCA2*. However, differences in national guidelines, access to genetic services, insurance coverage, and clinician ordering preferences likely contribute to whether genetic

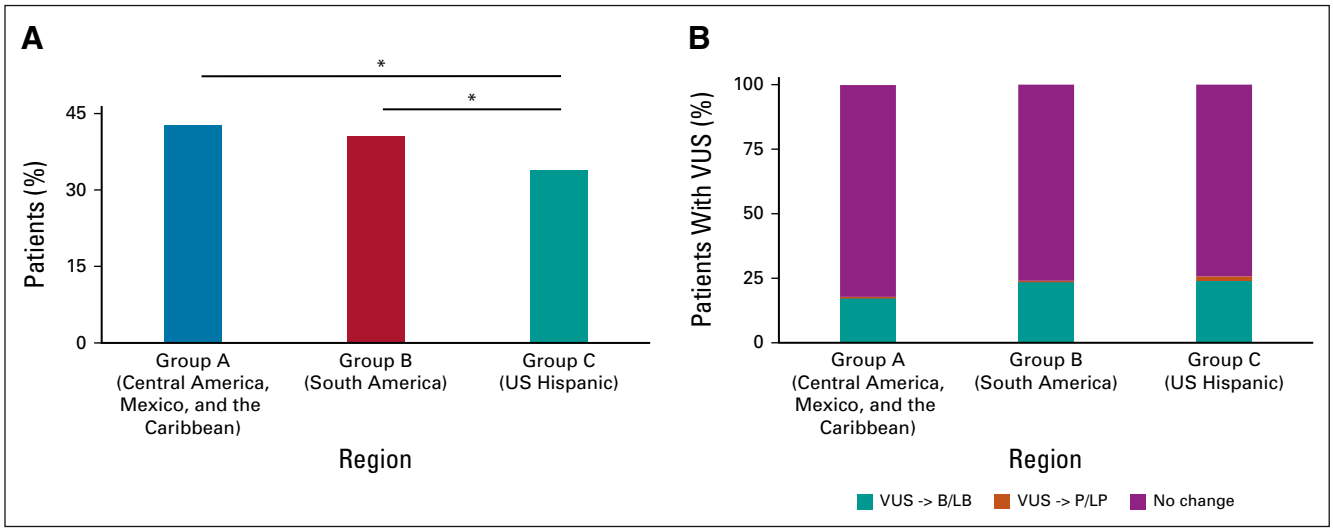

FIG 4. Proportion of individuals with (A) a VUS in the absence of a pathogenic germline variant and (B) rates of VUS reclassification. *Indicates a significant difference ($P \leq .05$). B/LB, benign/likely benign; P/LP, pathogenic/likely pathogenic; VUS, variants of uncertain significance.

testing is pursued and which testing approach (ie, single gene *v* targets panel *v* expanded panel) is performed in individuals with histories suggestive of HBOC.[7-9]

In addition to observing differences in overall diagnostic yield across these three regions, the distribution of variants varied as well. As expected, many of the observed PGVs in well-established HBOC-risk genes with a well-established risk of HBOC were also reported previously. For example, in Brazil, the two most common variants observed were an Ashkenazi Jewish founder variant in *BRCA1* (NM_007294.3:c.5266dupC, p.Gln1756Profs*74) and the Brazilian Li-Fraumeni syndrome founder variant in *TP53* (NM_000546.5:c.1010G>A, p.Arg337His). Of note, the third most common variant associated with increased HBOC risk was in *CHEK2* (NM_007194.3:c.349A>G, p.Arg117Gly), which has been reported to be observed in two different haplotypes in Europe, Australia, and the United States.[61] In US Hispanic individuals, one of the two most recurrent *BRCA2* variants (NM_000059.3:c.3922G>T, p.Glu1308*) may be explained by the inclusion of individuals from Puerto Rico in this group, as this variant has been reported to be a founder variant for this population.[35] Similarly, the most common variants observed in other Latin American countries, often in *BRCA1* and *BRCA2*, have been previously reported as recurrent or founder variants in these populations. Of the most common PGVs in other genes, most were associated with a high to moderate risk of cancer predisposition. Of interest, a recurrent PGV among patients from Colombia in *PALB2* (NM_024675.3:c.2288_2291del, p.His762_Leu763insTer) has been recently reported in the literature,[62] and further haplotype analysis will help to determine if these carriers shared a common ancestry. These findings demonstrate the importance of continually investigating the genetic landscape in populations that are less well studied. Among those genes not associated with HBOC, the most common variant was c.1187G>A (p.Gly396Asp) in *MUTYH*, generally associated with colorectal cancer, with a high penetrance of colorectal cancer/polyps in the homozygous state or in compound heterozygosity with another PGV in *MUTYH*.[63] This variant has been shown to be a European founder variant.[64] Whether this variant increases the risk of breast cancer is controversial although a subtle increase in risk has been reported.[65-68] The data reported here may help to inform future studies investigating the risk of HCS genes related to breast cancer, for both genes with well-established associations and those that are not yet fully documented.

A frequent concern with broader testing in populations of non-European ancestry, where testing is not common, is the high rate of VUS reported back to the ordering clinician.[69,70] Although VUS rates were higher in Latin America compared with US Hispanic individuals, this was not at the cost of diagnostic yield. Professional guidelines recommend that VUS do not provide a definitive molecular diagnosis and should not be used to inform clinical management. As demonstrated here and in previous studies,[71,72] 93.2% of VUSs that had sufficient additional information for reclassification were downgraded to benign or likely benign, reinforcing recommendations from professional guidelines. More expansive testing in Latin American populations will help to provide more accurate classifications of these VUS and may help to reduce VUS rates.

Cascade testing among relatives of a proband with a PGV is critical for implementing appropriate cancer risk–reducing interventions, including referrals to more intensive cancer screening protocols, risk-reducing surgeries, and/or chemoprevention. Furthermore, as therapies emerge that improve outcomes in patients with early-stage breast

TABLE 2. Cascade Testing

Characteristic	Group A (Mexico, Central America, and the Caribbean)	Group B (South America)	Group C (US Hispanic)	*P*		
				A *v* B	A *v* C	B *v* C
Probands with relatives tested, No. (% total probands)	22 (6.60)	265 (4.50)	340 (1.90)	.072830	$8.937e^{-10}$	$< 2.2e^{-16}$
Relatives tested, No.	80	531	636	—	—	—
Personal history of cancer, No. (%)				—	—	—
Affected	6 (6.30)	111 (17.60)	106 (12.20)			
Unaffected	74 (81.70)	402 (81.70)	506 (84.60)			
Unknown	0	18 (0.70)	24 (3.30)			
Relatives tested per proband, mean (SD)	3.6 (2.57)	2.0 (1.44)	1.9 (1.81)	.008613	.005745	.4495
Genes tested, mean (SD)	3 (13.00)	15 (29.00)	12 (24.00)	$< 2.2e^{-16}$	$< 2.2e^{-16}$	$8.737e^{-13}$
Genes tested, No. (%)				—	—	—
1-5	78 (97.50)	414 (77.80)	489 (76.90)			
6-15	0	6 (1.10)	14 (2.20)			
16-50	0	32 (6.00)	89 (14.00)			
> 50	2 (2.50)	79 (14.90)	44 (6.90)			
PGVs in HBOC-risk genes, No. (%)	32 (40.00)	229 (43.10)	268 (42.10)		$< 2.2e^{-16}$	$< 2.2e^{-16}$
High HBOC risk	31 (38.80)	202 (38.00)	243 (38.20)	—	—	—
Moderate HBOC risk	1 (1.30)	23 (4.20)	22 (3.50)	—	—	—
Low HBOC risk	0	4 (0.80)	3 (0.50)	—	—	—
PGVs in non–HBOC-risk genes, No. (%)	0	10 (1.90)	14 (2.20)			
High risk	0	0	3 (0.50)	—	.538200	.1130
Moderate risk	0	2 (0.40)	6 (0.90)	—	.426100	.3669
Low/uncertain risk or low penetrance	0	7 (1.30)	3 (0.50)	—	.476900	.2249
Carrier	0	1 (0.20)	2 (0.30)	—	.615500	.6717

Abbreviations: HBOC, hereditary breast and/or ovarian cancer; PGV, pathogenic germline variant; SD, standard deviation.

cancer (eg, poly (ADP-ribose) polymerase inhibitors[73]), it will be critical to have test results available at or shortly after diagnosis to determine eligibility for these precision therapies and aid in treatment decisions. Finally, cascade testing for HBOC-related cancers has been shown to be cost-effective,[74,75] and an effort should be made to address its importance whenever an individual with a PGV is identified. Of note, < 10% of probands in this cohort had relatives tested although no-charge cascade testing uptake was significantly higher in Latin American regions compared with US Hispanic individuals. In a US-based population with multiple solid tumor cancer types, who were of mostly White self-reported ancestry, nearly 20% of patients with a PGV had relatives pursue family testing.[5] Increased awareness of the importance of cascade testing among both clinicians and patients will lead to wider spread implementation of testing relatives. Initiatives in other countries have identified challenges and approaches to introducing cascade testing at scale, including telecounseling.[76-78] New technological advances aimed to streamline the genetic testing process, such as the use of chatbots and continuous improvements to telecounseling, may help to broaden the utilization of testing for patients and their families.[79]

This analysis grouped Latin American regions into two groups in an effort to achieve sample sizes that would overcome statistical biases. However, because of the significant admixture of populations across these regions, the interpretation is limited by this grouping. In particular, the sample sizes in Central America and the Caribbean were very small and thus combined with patients who received testing in Mexico although the ancestries of populations in these areas are very different. In addition, individuals residing in Puerto Rico were grouped with the United States (group C). Future studies with larger sample sizes in the Caribbean and Central America will allow for more granular investigation in the PGV rates among women testing for HBOC.

The findings presented here demonstrate the importance of testing for HBOC among individuals of Latin American descent. Although *BRCA1* and *BRCA2* account for the majority of PGVs identified, a long tail of PGVs in other genes that

confer an increased risk of cancer was also detected. Continuing to study these populations will lend to a fuller understanding of the genetic variation contributing to HBOC. Efforts should be undertaken to increase awareness and access to genetic testing and counseling in the region for cancer-affected patients and their at-risk relatives.

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APPENDIX

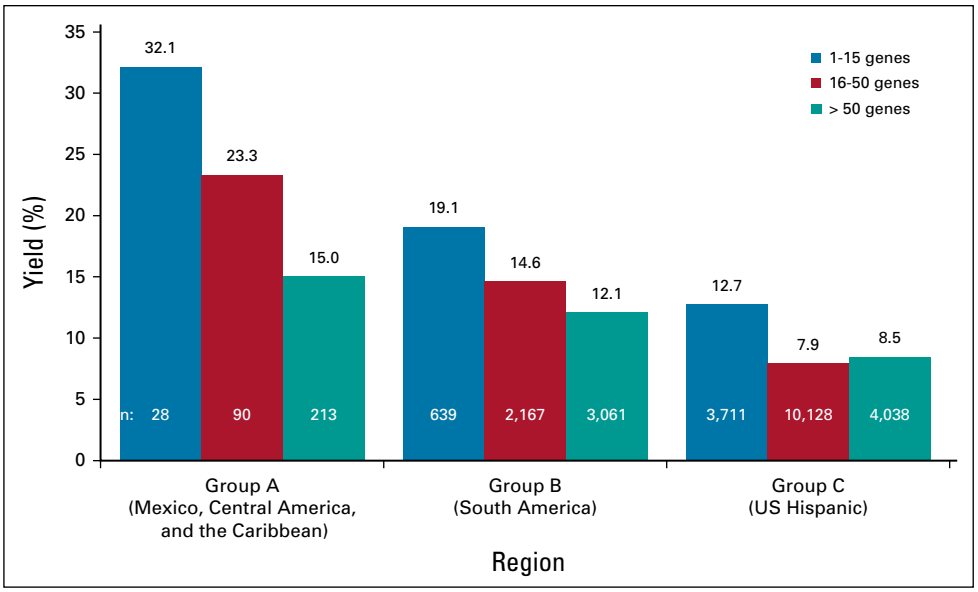

FIG A1. Diagnostic yield by panel size, by region.

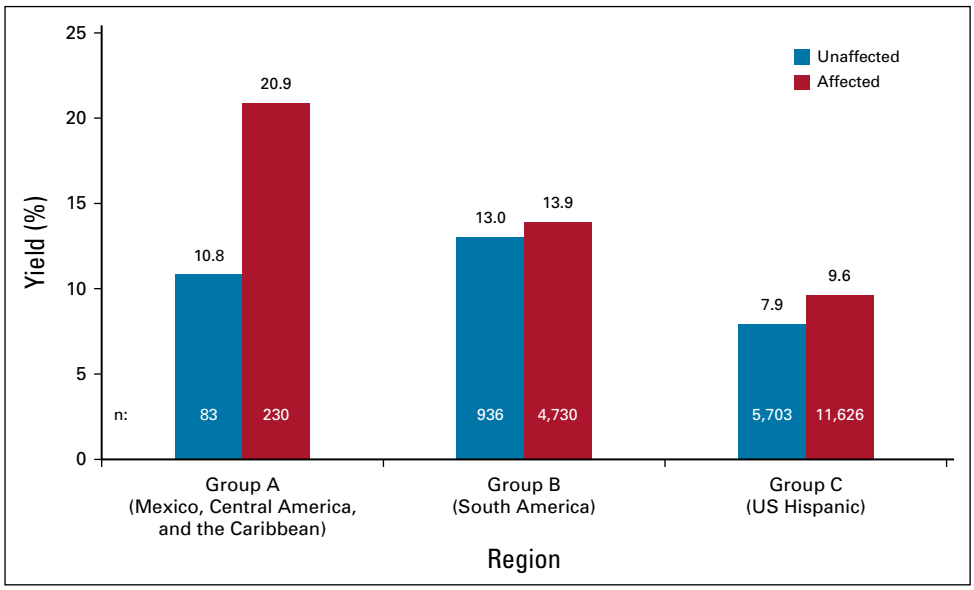

FIG A2. Diagnostic yield among individuals reported to have a personal history of cancer, by region.