Germline Pathogenic Variants and Genetic Counseling by Ancestry in Patients With Epithelial Ovarian Cancer

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ABSTRACT

PURPOSE To evaluate rates of germline pathogenic/likely pathogenic variants (PVs) and genetic counseling by ancestry in patients with epithelial ovarian cancer (EOC).

METHODS Patients with pathologically confirmed EOC who underwent clinical tumor-normal sequencing from January 1, 2015, to December 31, 2020, inclusive of germline analysis of ≥76 genes were included. Patients with newly identified PVs were referred for Clinical Genetics Service (CGS) counseling. Ancestry groups were defined using self-reported race/ethnicity and Ashkenazi Jewish (AJ) heritage. Genetic ancestry was inferred computationally using validated algorithms. Logistic regression models were built.

RESULTS Of 1,266 patients, self-reported ancestry (AJ, 17%; Asian, 10%; Black/African American, 5.4%; Hispanic, 6.2%; non-Hispanic White, 57%; other, 0.16%; unknown, 4.0%) correlated with genetic ancestry (AJ ancestry, 18%; admixed, 10%; African, 4%; East Asian [EAS], 6%; European, 56%; Native American, 0.2%; South Asian [SAS], 4%; unknown, 2%). Germline PVs were observed in 313 (25%) patients, including 195 (15%) with PVs in EOC-associated genes. Those with PVs were younger at diagnosis (59 *v* 62 years; $P < .001$) and more likely to have high-grade serous ovarian cancer (83% *v* 72%; $P = .009$). PV prevalence varied between ancestry groups ($P < .001$), with highest rates in the AJ (39.9%) and Asian (26.5%) groups and similar rates (>10%) across other ancestry groups. Use of genetic ancestry demonstrated similar findings and further characterized high rates of PV in EAS/SAS groups. Younger age, high-grade serous histology, and self-reported AJ or Asian ancestry were associated with PV in an EOC-associated gene. Rates of CGS counseling for newly identified PVs were high (80%) across ancestry groups.

CONCLUSION Rates of PV, particularly in EOC-associated genes, were high regardless of ancestry, with similar rates of counseling between groups, emphasizing the importance of universal genetic testing in all patients with EOC.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Ovarian cancer (OC) is the leading cause of gynecologic cancer–related death, and 15%-20% of women with epithelial ovarian cancer (EOC) harbor a germline pathogenic/likely pathogenic variant (PV) in a hereditary cancer predisposition gene.[1,2] The majority occur in *BRCA1* and *BRCA2*,[1,3] as well as other genes involved in homologous recombination (*RAD51C, RAD51D, BRIP1, PALB2,* and *ATM*) or DNA mismatch repair (*MLH1*, *MSH2*, *MSH6*, and *PMS2*).[4,5] Accordingly, universal germline testing for all women with newly diagnosed EOC is recommended[3,6-9]; however, there are disparities in genetic testing and counseling uptake on the basis of race, ethnicity, and insurance status, with potential implications for treatment, cancer prevention, and at-risk family members.[10,11]

CONTEXT

Key Objective

Although universal germline testing is recommended in epithelial ovarian cancer (EOC), much of the knowledge about rates of pathogenic/likely pathogenic variants (PV) and genetic counseling are derived from those of European ancestry, and less is known about those of other ancestries. This study evaluated rates of germline PV and subsequent genetic counseling by self-reported ancestry and genetic ancestry in a large and diverse cohort of patients with EOC.

Knowledge Generated

Rates of PV in EOC-associated genes were high across all self-reported and genetic ancestries (10%-24%) and were highest in the Ashkenazi Jewish and Asian cohorts. Integration of germline testing with clinical tumor-normal sequencing resulted in high levels of post-test genetic counseling across all ancestry groups.

Relevance

These findings validate the need for universal genetic testing in all patients with EOC, regardless of background, given the implications on both oncologic treatment and at-risk family members via cascade testing.

Most of the knowledge surrounding inherited predisposition to EOC is derived from non-Hispanic White and Ashkenazi Jewish (AJ) cohorts.[12-14] Consequently, less is known about the prevalence of EOC-associated PVs in more diverse cohorts, potentially contributing to disparities in genetic testing and counseling uptake.[15] Data from preliminary studies suggest high rates of germline PVs in *BRCA1/2*[16,17] and other EOC-associated genes[18] in minority groups in the United States and in other non-European (EUR) countries[19-21]; however, more studies are needed to evaluate rates of PV and subsequent counseling for EOC-associated genes in diverse populations.

We hypothesize that rates of germline PV in EOC-associated genes may vary between ancestry groups and influence subsequent genetic testing, counseling, and care. We sought to evaluate differences in PV rates and subsequent genetic counseling by self-reported and genetic ancestry in a diverse cohort of patients with EOC who underwent germline assessment as part of clinical care.

METHODS

Patient Selection

We included all patients with pathologically confirmed EOC at a single institution between January 1, 2015, and December 31, 2020, who underwent tumor-normal sequencing via a Food and Drug Administration-approved targeted next-generation sequencing (NGS) panel (Memorial Sloan Kettering Cancer Center-Integrated Mutation Profiling of Actionable Cancer Targets [MSK-IMPACT]) inclusive of germline analysis of ≥76 genes. The assay uses DNA from formalin-fixed, paraffin-embedded tumors and patient-matched blood samples to assess for PVs in coding exons.[22,23] Testing was ordered by the primary oncologist per standardized workflow (Data Supplement, Fig S1), as previously described.[24]

Germline Analysis and Protocol for Genetic Counseling

PVs were independently assessed and manually curated using standards for variant classification by the American College of Medical Genetics and Genomics/Association of Molecular Pathology at the time of data collection.[25] Variants of uncertain significance (VUS) were not reported in this study, given limited data. PVs were classified as high (relative risk [RR], >4), moderate (RR, 2-4), or low (RR, <2) penetrance, recessive, or of uncertain clinical actionability on the basis of previous modeling.[6,26,27] EOC-associated genes included *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[3,28,29]

All patients with newly identified PVs, defined as germline findings that were not previously known by the patient or their provider, received expedited referrals to our institutional Clinical Genetics Service (CGS) for additional counseling and identification of at-risk family members. Patients with known PVs who desired additional counseling were also referred to CGS. For patients who declined CGS appointments, failed to return at least three phone calls to schedule appointments, or did not have written documentation of a results discussion with their treating provider in the medical record, letters were sent to disclose the results. Patients who did not speak English received telephone calls via an interpreter or letters translated into their preferred language.[24] Nondisclosure rate was calculated as the percentage of patients with newly diagnosed PV who had no documentation of results disclosure. Data regarding CGS follow-up and counseling rates were available from clinical databases up until December 31, 2019; patients enrolled in 2020 were not included in these analyses because of conversion to a telemedicine format during the COVID-19 pandemic.[24,30]

Data Collection

Self-reported ancestry was defined using patient-reported race/ethnicity and AJ heritage from the electronic medical record, and patients were categorized into mutually exclusive ancestry groups: AJ, Asian, Black/African American (AA), Hispanic, non-Hispanic White, other, or unknown, with patients who self-identified as AJ or Hispanic classified as such, regardless of race. Patients who self-identified as American Indian, Alaskan Native, Native Hawaiian, or Other Pacific Islander were classified as other.[24]

Genetic ancestry was inferred from MSK-IMPACT as previously described.[31] Briefly, we ran ADMIXTURE v1.3[32] in supervised mode using the 1000 Genomes Project[33] cohort as reference to infer ancestral proportions of African (AFR), EUR, East Asian (EAS), Native American (NAM), and South Asian (SAS) populations; AJ genetic ancestry (ASJ) was added recently. Patients who had an ancestral fraction of >0.8 for any single population were assigned that population label, otherwise they were considered admixed (ADM). Patients with no sequencing data available for genetic ancestry were labeled unknown.

Statistical Analysis

Clinical characteristics, including age at diagnosis, stage, BMI, and histologic type (ie, high-grade serous, low-grade serous, endometrioid, clear cell, carcinosarcoma, mucinous, mixed, and poorly differentiated/undifferentiated), were collected. Descriptive statistics were provided for clinical characteristics by PV status. The association between the clinical features and PV status were tested using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Logistic regression was applied to examine the associations between clinical features and PV status. Variables shown to be statistically significant in univariate analyses were entered into the multivariable models. Two outcomes (PV in any gene and PV in EOC-associated genes) were examined. Analyses were performed using R 4.2.2 (The R Project for Statistical Computing[34]). All tests are two-sided and $P < .05$ was considered statistically significant. All patients were consented to MSK-IMPACT per protocol, and this study was approved under MSK institutional review board #12-245 (ClinicalTrials.gov identifier: NCT01775072).

RESULTS

Clinical Characteristics

Between January 1, 2015, and December 31, 2020, 1,266 patients with EOC underwent germline assessment and were included in this study (Fig 1). Median age at EOC diagnosis was 61 years (range, 16-94 years; Table 1). Most patients had stage III (42%) or IV (43%) EOC; 75% of tumors were high-grade serous ovarian cancers (HGSOCs), 6.2% were clear cell, 5.4% were endometrioid, and 5.1% were low-grade serous (Table 1).

PVs were identified in 313 (25%) patients, including 195 (15%) with PVs in an EOC-associated gene (Table 1; Data

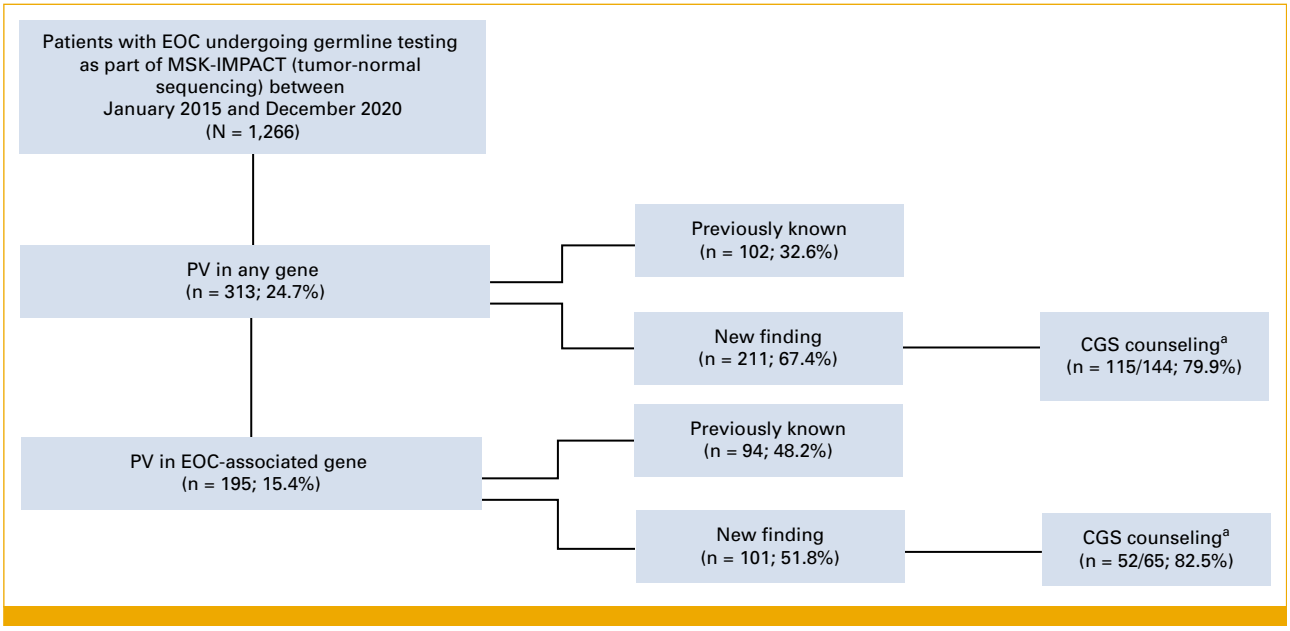

FIG 1. Patient flow diagram depicting patients with epithelial ovarian cancer undergoing MSK-IMPACT and the proportion with PV, new and previously known, as well as those undergoing subsequent genetic counseling. EOC-associated genes: *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2, ATM, MLH1, MSH2, MSH6, PMS2*. [a]Percentages are based upon 2015-2019 data only as CGS follow-up data are available only for this time period. CGS, Clinical Genetics Service; EOC, epithelial ovarian cancer; MSK-IMPACT, Memorial Sloan Kettering Cancer Center-Integrated Mutation Profiling of Actionable Cancer Targets; PV, germline pathogenic/likely pathogenic variant.

TABLE 1. Patient Demographics

Characteristic	Overall	Any PV	No PV	*P*[a]	EOC-Associated PV	No EOC-Associated PV	*P*[a]
No. of patients, (%)	1,266	313 (25)	953 (15)		195 (15)	1,071 (85)	
Age, years							
Median (range)	61 (16-94)	59 (27-87)	62 (16-94)	<.001	56 (34-82)	62 (16-94)	<.001
≤65 years, No. (%)	754 (64)	210 (70)	544 (61)	.005	142 (76)	612 (61)	<.001
>65 years, No. (%)	433 (36)	89 (30)	344 (39)		44 (24)	389 (39)	
BMI, kg/m^2, median (range)	25.4 (16.3-61.0)	25.1 (16.3-54.9)	25.5 (16.6-61.0)	.36	25.2 (16.3-47.4)	25.4 (16.6-61.0)	.81
Stage, No. (%)				.046			<.001
I	74 (8.8)	10 (4.7)	64 (10)		4 (4.4)	70 (9.8)	
II	50 (6.0)	11 (5.2)	39 (6.2)		6 (4.9)	44 (6.1)	
III	353 (42)	87 (41)	266 (42)		40 (33)	313 (44)	
IV	362 (43)	103 (49)	259 (41)		72 (59)	290 (40)	
Histology, No. (%)				.009			<.001
HGSOC	948 (75)	260 (83)	688 (72)		171 (88)	777 (73)	
LGSOC	65 (5.1)	11 (3.5)	54 (5.7)		0 (0)	65 (6.1)	
Endometrioid	68 (5.4)	14 (4.5)	54 (5.7)		5 (2.6)	63 (5.9)	
Clear cell	78 (6.2)	13 (4.2)	65 (6.8)		8 (4.1)	70 (6.5)	
Carcinosarcoma	45 (3.6)	8 (2.6)	37 (3.9)		6 (3.1)	39 (3.6)	
Mucinous	26 (2.1)	1 (0.3)	25 (2.6)		0 (0)	26 (2.4)	
Mixed	26 (2.1)	4 (1.3)	22 (2.3)		3 (1.5)	23 (2.1)	
Poorly differentiated or undifferentiated	10 (0.8)	2 (0.6)	8 (0.8)		2 (1.0)	8 (0.7)	

Abbreviations: EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; PV, germline pathogenic/likely pathogenic variant.
[a]Pearson's chi-square test.

Supplement, Tables S1 and S2). The most common PVs were in *BRCA1* (n = 94) and *BRCA2* (n = 54), representing 7.4% and 4.3% of the group, respectively (Data Supplement, Tables S1 and S3). The median age at diagnosis was 59 years for patients with PVs compared with 62 years for those with sporadic EOC ($P < .001$; Table 1). Patients with PVs compared with those without were more likely to have HGSOC (83% *v* 72%, respectively; $P = .009$). Compared with those without, patients with a PV in an EOC-associated gene were more likely to have stage III/IV disease at diagnosis (92% *v* 84%; $P < .001$).

Self-Reported Ancestry and Genetic Ancestry

Using self-reported ancestry, patients were classified as AJ (17%; n = 218), Asian (10%; n = 132), Black/AA (5%; n = 68), Hispanic (6%; n = 79), non-Hispanic White (57%; n = 716), other (0.2%; n = 2), or unknown (4%; n = 51; Fig 2; Data Supplement, Fig S2A). Using genetic ancestry, patients were classified as ADM (10%; n = 127), AFR (4%; n = 53), ASJ (18%; n = 223), EAS (6%; n = 72), EUR (56%; n = 713), SAS (4%; n = 46), NAM (0.2%; n = 2), or unknown (2%; n = 30; Fig 2; Data Supplement, Fig S2B). In patients self-identifying as unknown (n = 51), genetic ancestry was able to further classify these patients into ADM (25%), ASJ (8%), AFR (8%), EAS (6%), EUR (43%), or SAS (8%; Data Supplement, Table S4). In those of self-reported Asian ancestry (n = 132), genetic ancestry calculations further classified these patients as EAS (52%), SAS (30%), ADM (14%), or unknown (4%). Patients who were classified to have a genetic ancestry of ADM (n = 127), for which no one ancestry group met the prespecified 80% threshold, corresponded to self-reported ancestry groups of AJ (0.8%), Asian (15%), Black/AA (14%), Hispanic (43%), non-Hispanic White (15%), other (2%), or unknown (10%) (Data Supplement, Table S4).

Germline Findings by Ancestry

The prevalence of PVs differed by self-reported ancestry (AJ, 39.9%; Asian, 26.5%; Black/AA, 17.7%; Hispanic, 17.7%, non-Hispanic White 21.8%; and other/unknown, 17.7%; $P < .001$; Fig 3A; Data Supplement, Table S5). Most PVs occurred in either high- or moderate-penetrance genes. However, there was significant variation in rates of uncertain/low/recessive PVs among self-reported ancestry groups (AJ, 34%; Asian, 8.6%; Black/AA, 25%; Hispanic, 14%; non-Hispanic White, 37%; and unknown, 33%; $P = .019$; Data Supplement, Fig S3A), with the highest rates in the non-Hispanic White and AJ cohorts. Similar patterns were seen when using genetic ancestry, with high rates of PV in all groups, mostly in high-penetrance genes (Data Supplement, Table S6 and Fig S3B). This method also allowed further

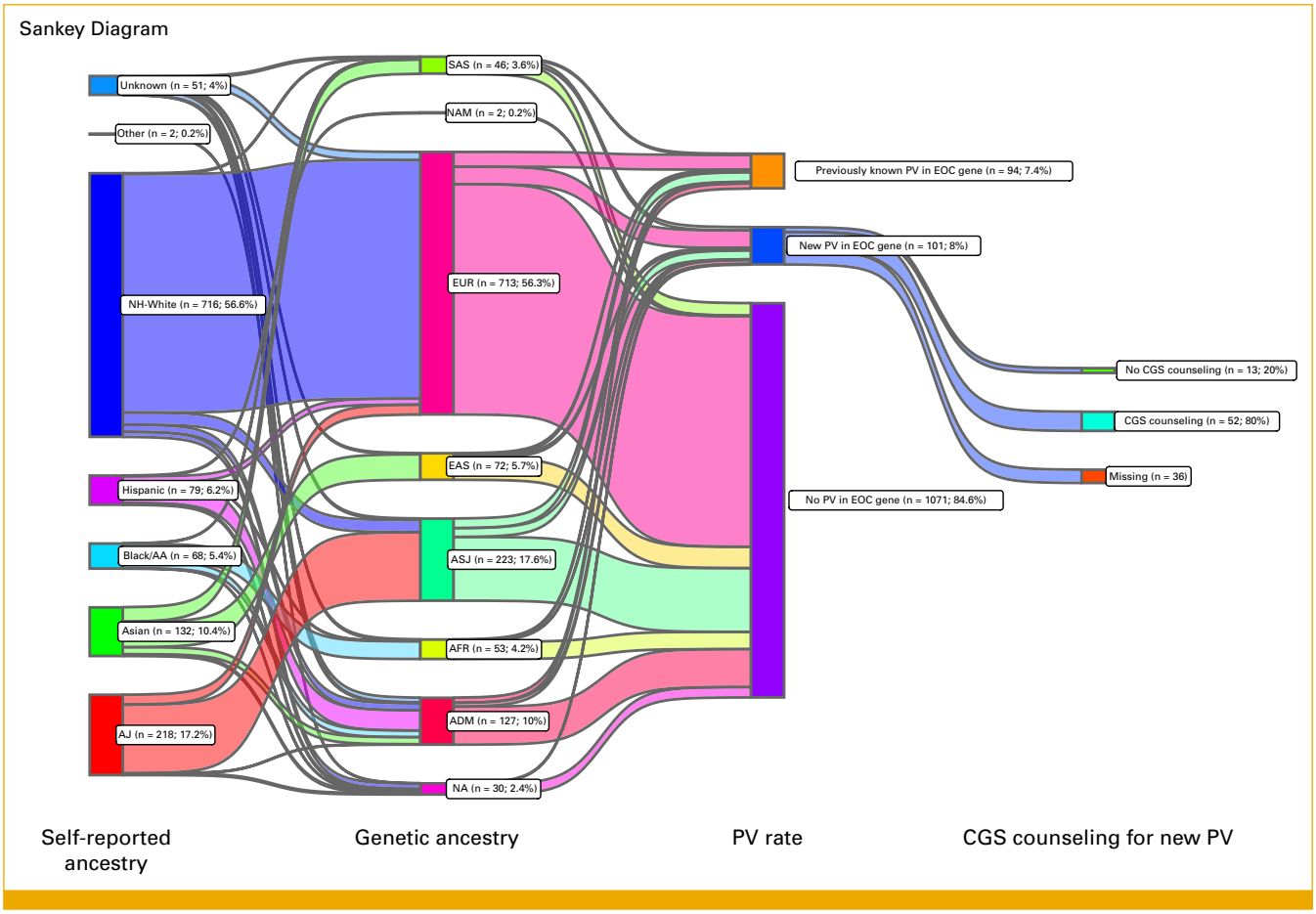

FIG 2. Sankey diagram depicting self-reported ancestry, genetic ancestry, presence of germline pathogenic variants, and clinical genetics counseling. Using self-reported ancestry, patients were classified into AJ, Asian, Black/AA, Hispanic, NH-White, other, and unknown groups. Use of genetic ancestry further classified patients into ADM, AFR, ASJ, EAS, EUR, NAM, and SAS groups. A small subset (2.4%) of patients were unable to be classified into a genetic ancestry category. The rate of newly diagnosed PV in an EOC-related gene was 8%, compared with 7.4% of patients who previously knew about their PV in an EOC-related gene. Of patients with a new PV finding in an EOC-related gene for whom we have CGS data available, 80% underwent CGS counseling. AA, African American; ADM, admixed; AFR, African; AJ, Ashkenazi Jewish; ASJ, AJ genetic ancestry; CGS, Clinical Genetics Service; EAS, East Asian; EOC, epithelial ovarian cancer; EUR, European; NA, not applicable; NAM, Native American; NH, non-Hispanic; PV, germline pathogenic/likely pathogenic variant; SAS, South Asian.

elucidation of high PV rates in both EAS and SAS groups (Data Supplement, Table S6).

When assessing specifically for EOC-associated genes, rates of PV were high in all self-reported ancestry groups (AJ, 24.3%; Asian, 24.2%; Hispanic, 15.2%; non-Hispanic White, 11.9%; Black/AA, 11.8%; and other/unknown, 9.8%; $P < .001$; Fig 3A; Data Supplement, Table S5). When evaluating rates of PV by genetic ancestry, similar patterns were identified (Fig 3B; Data Supplement, Table S6), with high rates of EOC-associated PV in both the SAS and EAS groups.

Within EOC-associated genes, *BRCA1* (n = 94; 48%) and *BRCA2* (n = 54; 28%) comprised most PVs (Figs 4A and 4B; Data Supplement, Table S3). This was particularly notable in the AJ group, in whom the prevalence of *BRCA2* almost equaled *BRCA1* because of AJ founder mutations (Data Supplement, Table S1). PVs in other genes related to homologous recombination deficiency (*RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, and *ATM*) comprised 18% of all PVs and were primarily found in the non-Hispanic White and Asian groups, although numbers were limited (Fig 4A; Data Supplement, Table S3). When using genetic ancestry, rates of PVs in other homologous recombination deficiency genes were highest in the EUR population (Fig 4B). PVs in Lynch syndrome–associated mismatch repair genes accounted for 6.7% of all PVs and were primarily found within the non-Hispanic White and EUR groups (Figs 4A and 4B).

Predictors of PVs

On univariate analyses, age of diagnosis, HGSOC histology, self-reported ancestry, and genetic ancestry were all predictors of presence of PV, overall and for EOC-associated genes. On multivariable models, self-reported ASJ (odds ratio [OR], 2.56; 95% CI, 1.82 to 3.59) was associated with increased odds of PV overall, even after adjustment for age at diagnosis and histology (Table 2). When examining PVs

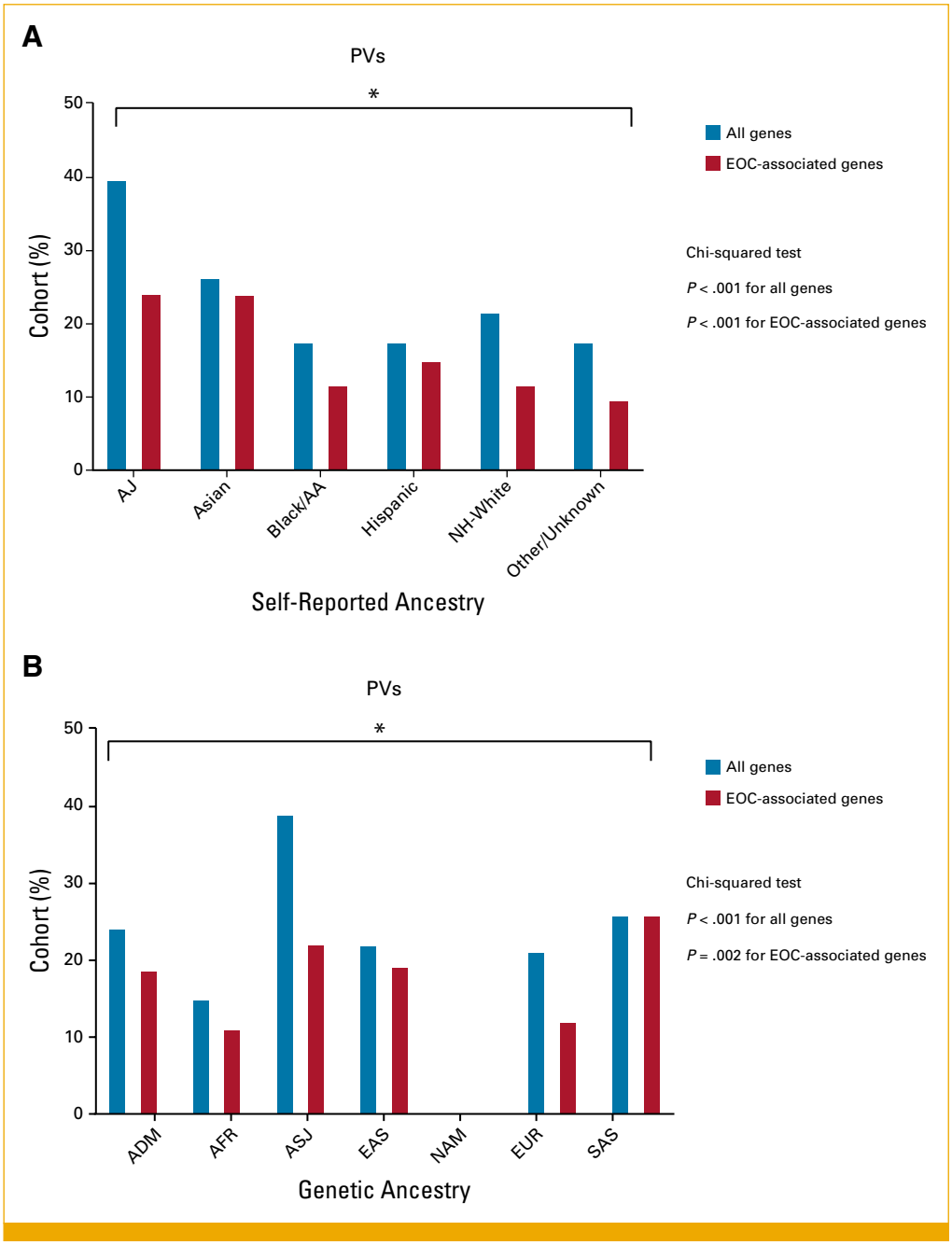

FIG 3. Germline pathogenic variant by (A) self-reported ancestry and (B) genetic ancestry. (A) Rates of PVs in all assessed genes were high across all self-reported ancestries but were highest in the AJ and Asian populations (blue). When assessing EOC-associated genes only (red), rates of PVs continued to be highest in the AJ and Asian populations (24% each), and lowest in the Black/AA and NH-White groups (11% each). Rates of pathogenic/likely pathogenic variants differed between all groups for all genes and EOC-associated genes ($P < .001$). Other includes patients who self-identified as American Indian, Alaskan Native, Native Hawaiian, or Other Pacific Islander. (B) When evaluating rates of PVs across genetic ancestry admixture, similar patterns were seen, with high rates of EOC-associated genes in the ASJ, East Asian, and South Asian groups, and lowest in the African and non-AJ EUR groups. Notably, no pathogenic/likely pathogenic variants were identified in the two patients classified as NAM. Rates of pathogenic/likely pathogenic variants differed between all groups for all genes ($P < .001$) and EOC-associated genes ($P = .002$). AA, African American; ADM, admixed; AFR, African; AJ, Ashkenazi Jewish; ASJ, AJ genetic ancestry; EAS, East Asian; EOC, epithelial ovarian cancer; EUR, European; NAM, Native American; NH, non-Hispanic; PV, germline pathogenic/likely pathogenic variant; SAS, South Asian.

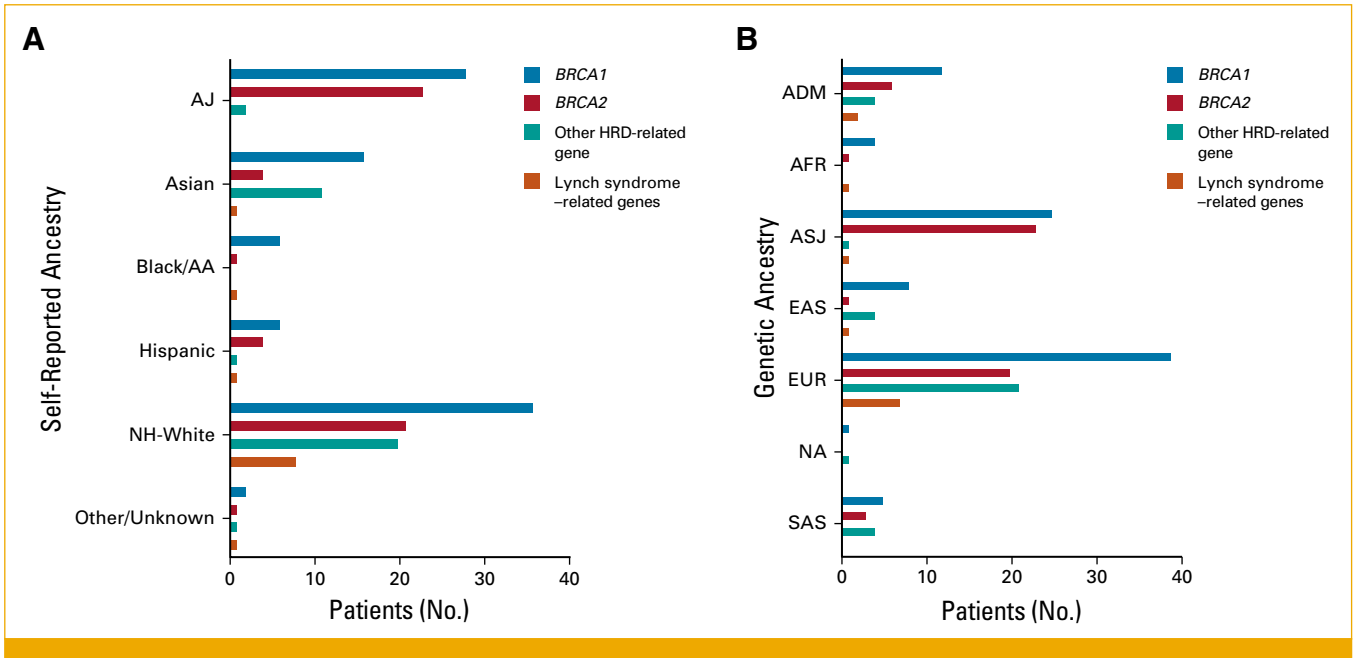

FIG 4. Distribution of the genes with germline pathogenic variants found in patients with epithelial ovarian cancer by (A) self-reported ancestry and (B) genetic ancestry. Other HRD-related gene includes the following genes: *ATM*, *BRIP1*, *PALB2*, *RAD51C*, and *RAD51D*. Lynch syndrome–related genes includes the following genes: *MLH1*, *MLH2*, *MSH6*, and *PMS2*. Other includes patients who self-identified as American Indian, Alaskan Native, Native Hawaiian, or Other Pacific Islander. As the number of patients in the other and unknown groups were low, these groups were combined. AA, African American; ADM, admixed; AFR, African; AJ, Ashkenazi Jewish; ASJ, AJ genetic ancestry; EAS, East Asian; EUR, European; HRD, homologous recombination deficiency; NA, genetic ancestry not available; NH, non-Hispanic; SAS, South Asian.

specifically in EOC-associated genes, self-reported ASJ (OR, 2.64; 95% CI, 1.76 to 3.96) and Asian ancestry (OR, 2.32; 95% CI, 1.40 to 3.77) were associated with increased odds of PV, even after adjustment for age at diagnosis and histology (Table 2). Similar findings were noted using genetic ancestry for PVs overall and EOC-associated PVs (Table 2).

Genetic Counseling

Of the 313 patients with PVs, 102 (32.6%) knew about this result before MSK-IMPACT germline assessment (Fig 1). Among the 144 patients with a newly identified PV and available CGS follow-up information, 115 (79.9%) completed CGS counseling, including 69 (47.9%) via in-person appointment and 46 (31.9%) via phone call. Close-out letters were sent to 29 patients (20.1%), and the nondisclosure rate was 5 patients (2.4%). Although limited in numbers, rates of CGS counseling for those with new PV were high across all self-reported ancestry groups (Data Supplement, Table S5).

Of the 195 patients with PVs in an EOC-associated genes, 94 (48.2%) previously knew about the result (Fig 1). Of the 65 patients for whom this was a new finding with available CGS follow-up information, 52 (80%) completed CGS counseling. Rates of CGS follow-up for EOC-associated genes were high across all self-reported ancestry groups (Fig 2; Data Supplement, Table S5).

DISCUSSION

We evaluated rates of germline PV and subsequent genetic counseling in a large cohort of patients with EOC to assess for potential differences across populations. Rates of PV in EOC-associated genes, mostly *BRCA1/2*, were high across all self-reported ancestries (10%-24%) and were highest in the AJ and Asian cohorts (24%), even in multivariable logistic regression models. Using a novel algorithm to infer genetic ancestry admixture from MSK-IMPACT, we found similar results, further strengthening our findings. For patients with newly identified PVs in EOC-associated genes, rates of follow-up counseling were high across all ancestry groups. This highlights the importance of universal genetic testing in OC, regardless of ancestry, and supports integration of germline assessment into routine oncologic care given implications for treatment, cancer prevention, and at-risk family members.

We found that 25% of patients with EOC within our diverse cohort had a PV and 15% of patients had a PV in an EOC-associated gene, which is consistent with other studies demonstrating rates between 14% and 22%.[1,12,35] Although rates of PV varied between ancestry groups, much of the variation was found within the low/uncertain/recessive gene penetrance group, and rates of PV in EOC-associated genes were high across all groups. A study of 6,000 diverse women with OC from California and Georgia

TABLE 2. Multivariable Logistic Regression Models for PVs, Using Self-Reported Ancestry and Genetic Ancestry

	Any PV		PV in EOC-Associated Gene	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Self-reported ancestry model				
Age at diagnosis, years	0.97 (0.96 to 0.98)	<.001	0.95 (0.94 to 0.97)	<.001
Histology		<.001		<.001
HGSOC	Ref		Ref	
Other	0.47 (0.32 to 0.67)		0.26 (0.15 to 0.42)	
Self-reported ancestry		<.001		<.001
AJ	2.56 (1.82 to 3.59)		2.64 (1.76 to 3.96)	
Asian	1.27 (0.80 to 1.98)		2.32 (1.40 to 3.77)	
Black/AA	0.79 (0.38 to 1.52)		0.99 (0.39 to 2.17)	
Hispanic	0.63 (0.31 to 1.17)		1.03 (0.47 to 2.06)	
Non-Hispanic White	Ref		Ref	
Other/unknown	0.82 (0.36 to 1.69)		0.86 (0.29 to 2.10)	
Genetic ancestry model				
Age at diagnosis, years	0.97 (0.96 to 0.98)	<.001	0.95 (0.94 to 0.97)	<.001
Histology		<.001		<.001
HGSOC	Ref		Ref	
Other	0.44 (0.30 to 0.64)		0.24 (0.14 to 0.39)	
Genetic ancestry		<.001		<.001
ADM	1.09 (0.67 to 1.72)		1.50 (0.86 to 2.54)	
AFR	0.76 (0.32 to 1.60)		1.10 (0.40 to 2.55)	
ASJ	2.71 (1.92 to 3.81)		2.52 (1.66 to 3.79)	
EAS	1.14 (0.60 to 2.07)		2.01 (0.99 to 3.87)	
EUR	Ref		Ref	
NAM/unknown	1.20 (0.43 to 2.91)		0.69 (0.11 to 2.46)	
SAS	1.07 (0.67 to 1.72)		1.94 (0.88 to 4.04)	

Abbreviations: AA, African American; ADM, admixed; AFR, African; AJ, Ashkenazi Jewish; ASJ, AJ genetic ancestry; EAS, East Asian; EOC, epithelial ovarian cancer; EUR, European; HGSOC, high-grade serous ovarian cancer; NAM, Native American; OR, odds ratio; PV, germline pathogenic/likely pathogenic variant; Ref, reference; SAS, South Asian.

found the highest PV rates among Hispanic patients (27.6%) compared with non-Hispanic White (12.3%), Black/AA (13.2%), and Asian (13.3%) patients.[17] Somasegar et al[35] studied rates of germline PV in EOC-associated genes in 51 self-reported Black/AA patients with OC and reported a PV rate of 25.5%, the majority of which were in *BRCA1* (13.7%) and *BRCA2* (7.8%). In a study of germline genetic testing results of patients from the Caribbean diagnosed with breast cancer and/or OC, the rate of germline PV was 14.2%.[36] In our study, we observed a high PV rate for all patients, particularly Asian patients (24%), whereas the PV rates in our Hispanic and Black/AA cohorts were lower at 18% each. These differences likely reflect ascertainment bias, size of multigene panels, and variations within specific populations and geographical locations; however, overall rates of PV were high across all groups. These findings further highlight the importance of testing in all women with OC and the need for continued studies in large, diverse OC cohorts.

Despite recommendations for universal germline testing in all patients with EOC since 2010, rates of actual testing in practice have remained low (10%-30%).[17] Our study found high rates of genetics follow-up across all ancestry groups (64%-100%), which may be influenced by our institutional practice to integrate germline and tumor assessment in oncology clinics, a form of mainstreaming that is becoming more common.[10] The testing is offered directly by oncologists to expand access and decrease barriers and is particularly important in EOC, given implications on treatment with PARP inhibitor therapies.[37-39] However, rates are not 100%, and reasons may be complex and involve various social determinants of health at multiple levels of care. Studies have observed that disparities in referrals to genetic counseling/testing persist, and vulnerable patients including racial/ethnic minorities, low-income patients, and non–English-speaking patients are at increased risk for not receiving either recommended genetics care[17,37,38,40] or guideline-concordant treatment.[41] Other reasons include lack of availability of genetic counselors, language and cultural discordance, fear of potential retribution from insurance carriers, and lack of awareness about genetic testing and prevalence of PVs across demographic groups

because many studies and educational campaigns focus on non-Hispanic White and AJ communities.[11,42,43] Additional work investigating the social determinants of health outside of ancestry that influence tumor-normal genetic testing in EOC are ongoing, and recent work has demonstrated progress with the use of NGS in historically underserved ethnic groups.[44]

Our study has several strengths. Our population contained a large and diverse cohort of patients with EOC, with >25% of patient self-reporting ancestries that were not non-Hispanic White or AJ, a group we separated out, given high rates of PV, to avoid bias. Additionally, patients underwent germline assessment of ≥76 cancer-associated genes, which encompassed *BRCA1/2* and other moderate-penetrance genes. Although the most common PVs across all groups were found in *BRCA1/2*, we observed that PVs in other homologous recombination deficiency genes (ie, *PALB2* and *RAD51D*) may be more prevalent within Asian compared with other ancestry groups. This is hypothesis-generating and should be further explored. We acknowledge the limitations of race/ethnicity measures, which are social constructs and closely tied to identity.[45,46] To address this, we used a second measure of ancestry inferred from sequencing of normal tissue, which correlated well with self-reported measures and added additional insights, particularly in patients of self-reported Asian and unknown ancestry. Importantly, high rates of PV were observed across all groups using both methods, further highlighting the need for universal genetic testing.

A limitation of our study was the lack of VUS data, which may occur more frequently in Black/AA, Asian, and Hispanic patients,[25] as genetic counseling and ongoing follow-up for these results are critical to equitable care. Reclassification of PV and VUS findings is ongoing, and our results published here reflect classification designations at the time of data analysis. Additionally, patients undergoing genetic testing through an outside laboratory were not included in our cohort, leading to potential underestimation of PV rates. We also acknowledge the possibility of ascertainment bias, given our tertiary cancer center with a large AJ population. However, our New York City patient cohort is racially/ethnically diverse, with >25% of patients identifying as non-White. Finally, our CGS follow-up data are limited for each ancestry group and should be interpreted with caution. Additional analyses of our telemedicine experience are ongoing as studies have demonstrated disparities in access to and use of telemedicine platforms for health care delivery, with lowest rates of uptake in Hispanic, Asian, and non–English-speaking groups.[47-49] Notably, disparities among Black/AA patients found on pan-cancer analysis were not observed in patients with EOC,[24] which may reflect smaller sample size or differences by tumor types.

In conclusion, we found that the prevalence of germline PVs in patients of diverse ancestries with EOC was high across all groups, particularly among AJ and Asian patients, using both self-reported and genetic ancestry to define populations. Integration of germline assessment with clinical tumor-normal sequencing resulted in high levels of post-test genetic counseling, with no differences between ancestry groups. These findings highlight the need for universal genetic testing in all patients with EOC, regardless of background. We hope these data increase public awareness and improve health equity in genetic testing and counseling of patients with EOC, particularly given the implications on oncologic treatment and family members via cascade testing.

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