

## Prevalence and Type of *BRCA* Mutations in Hispanics Undergoing Genetic Cancer Risk Assessment in the Southwestern United States: A Report From the Clinical Cancer Genetics Community Research Network

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### A B S T R A C T

#### Purpose

To determine the prevalence and type of *BRCA1* and *BRCA2* (*BRCA*) mutations among Hispanics in the Southwestern United States and their potential impact on genetic cancer risk assessment (GCRA).

#### Patients and Methods

Hispanics (n = 746) with a personal or family history of breast and/or ovarian cancer were enrolled in an institutional review board–approved registry and received GCRA and *BRCA* testing within a consortium of 14 clinics. Population-based Hispanic breast cancer cases (n = 492) enrolled in the Northern California Breast Cancer Family Registry, negative by sequencing for *BRCA* mutations, were analyzed for the presence of the *BRCA1* ex9-12del large rearrangement.

#### Results

Deleterious *BRCA* mutations were detected in 189 (25%) of 746 familial clinic patients (124 *BRCA1*, 65 *BRCA2*); 21 (11%) of 189 were large rearrangement mutations, of which 62% (13 of 21) were *BRCA1* ex9-12del. Nine recurrent mutations accounted for 53% of the total. Among these, *BRCA1* ex9-12del seems to be a Mexican founder mutation and represents 10% to 12% of all *BRCA1* mutations in clinic- and population-based cohorts in the United States.

#### Conclusion

*BRCA* mutations were prevalent in the largest study of Hispanic breast and/or ovarian cancer families in the United States to date, and a significant proportion were large rearrangement mutations. The high frequency of large rearrangement mutations warrants screening in every case. We document the first Mexican founder mutation (*BRCA1* ex9-12del), which, along with other recurrent mutations, suggests the potential for a cost-effective panel approach to ancestry-informed GCRA.

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### INTRODUCTION

Hispanics, the fastest growing group in the United States, comprise 15.1% of the population. (Although we use the term “Hispanic” in this article, the more common census term for individuals of Spanish, Mexican, and Central and South American descent, referring to “ethnicity,” is “Latino.” Latino is generally considered a more ethnically/culturally based term for individuals of the aforementioned groups.) Breast cancer (BC) is the most commonly diagnosed cancer in Hispanic women and leading cause of cancer death. Although the incidence of BC in Hispanics is less than in non-Hispanic whites, our

initial studies on the prevalence of deleterious mutations in *BRCA1* and *BRCA2* (*BRCA*) suggested they may account for a higher proportion of BC in Hispanics than other non–Ashkenazi Jewish populations.<sup>1,2</sup> We and others have documented that *BRCA1* 185delAG is a recurrent mutation in Hispanics,<sup>1,3,4</sup> occurring on the Jewish haplotype.<sup>1,5</sup> Deleterious large rearrangement *BRCA* mutations are not detectable by standard sequencing.<sup>6-8</sup> The prevalence of *BRCA1* ex9-12del, a recurrent large rearrangement mutation initially identified in a small Mexican-American high-risk clinic cohort, is unknown.<sup>2</sup>

The risk for *BRCA* mutation carriers to develop BC varies from 57% by age 70 years<sup>9</sup> to 85% lifetime

risk among high-risk clinic patients, with lower risks reported from population-based studies.<sup>10</sup> They also have a 20% to 50% risk for ovarian cancer (OC).<sup>11</sup> The availability of effective screening, treatment, and risk reduction interventions makes *BRCA* testing a standard of care for patients with a personal and/or family history suggestive of an inherited predisposition to breast and/or ovarian cancer.<sup>12-16</sup> However, low-income, underinsured, and racial/ethnic minority individuals have a significant burden of cancer and have limited access to genetic cancer risk assessment (GCRA). In addition, there is a dearth of Hispanic-specific research, particularly in the area of genetic predisposition to BC.

The Hispanic population in the Southwestern United States is primarily of Mexican ancestry, whereas individuals of Puerto Rican, Dominican, and Cuban ancestry predominate in the Eastern United States. Admixture studies indicate significantly different ancestral populations among US Hispanics.<sup>17,18</sup> Because of the design of their test requisition form, the exclusive *BRCA* testing vendor in the United States cannot distinguish between Hispanics of Caribbean ancestry and those of Mexican and/or Central American ancestry.<sup>19</sup> Therefore, we assembled two large cohorts of US Hispanics with a focus on the latter groups—a clinic-based cohort of patients referred for GCRA in the Southwestern United States and a cohort selected from a cancer registry population-based study—to determine the prevalence and type of *BRCA* mutations and explore the potential to translate the findings into ancestry-informed strategies for cost-effective GCRA.

## PATIENTS AND METHODS

### Study Populations

**Clinic based.** The City of Hope Clinical Cancer Genetics Community Research Network includes a cross-section of cancer center and community-based clinics, primarily in the Southwestern United States, that provide GCRA to individuals with a personal or family history of cancer.<sup>20</sup> All GCRA patients are invited to participate in an institutional review board–approved prospective Hereditary Cancer Registry at the time of consultation (> 90% participation). Between May 1998 and June 2010, 746 probands with self-reported Hispanic origin, mostly from Mexico and Central America (Table 1), were seen for GCRA, enrolled in the registry, and underwent clinical *BRCA* testing after informed consent. Only one individual from each family was included in the analyses. Participants with mixed ancestry were eligible only if pedigree analysis indicated that the Hispanic lineage was the likely origin of the familial cancer pattern. Blood samples, demographic data, and five-generation pedigrees were obtained, including reported ethnicity and country/state of origin for each grandparental lineage. Clinical details were obtained for relatives affected with BC and/or OC. A bilingual cancer risk counselor or translator conducted GCRA sessions for Spanish-speaking patients, with adapted counseling aides and consent forms.<sup>21,22</sup>

**Population based.** Tested solely for *BRCA1* ex9-12del were DNA samples from 492 patients with BC of Mexican ancestry, negative for sequence-detected *BRCA* mutations, age less than 65 years with a family history of cancer, identified through the population-based Greater San Francisco Bay Area Cancer Registry and enrolled in the Northern California Breast Cancer Family Registry (NC-BCFR).<sup>3,23</sup>

### *BRCA* Gene Analyses

Genetic testing was offered to women in the clinic-based cohort who met National Comprehensive Cancer Network criteria.<sup>12</sup> *BRCA* testing was performed at Myriad Genetic Laboratories (Salt Lake City, UT) and included full sequencing of exons and flanking intronic segments,<sup>24</sup> five specific *BRCA1* rearrangements for testing after August 12, 2002, and multiplex quantitative differential polymerase chain reaction (PCR; *BRCA* Analysis Rearrangement Testing [BART])<sup>2</sup> after August 1, 2006, for large rearrangement mutation

**Table 1.** Mutation Status and Cancer History of Probands (N = 746)

Characteristic	Carriers (positive)	Noncarriers	
		Negative	Variant
Total no.	189	523	34
%	25	70	5
Sex			
Female	187	520	34
Male	2	3	0
Affected	169	449	31
No. with breast cancer	144	419	27
No. with ovarian cancer*	17	21	1
No. with breast and ovarian cancer*	8	9	3
Average age at first breast cancer diagnosis, years	40.0	40.8	39.5
Unaffected	20	74	3
Country of origin			
Mexico	148	412	22
El Salvador	14	18	3
Guatemala	8	18	1
Spain	7	26	2
Colombia	3	8	0
Peru	3	5	1
Honduras	2	4	0
Argentina	1	6	0
Ecuador	1	2	0
Cuba	1	3	0
Nicaragua	1	3	2
Panama	0	2	0
Costa Rica	0	1	1
Puerto Rico	0	7	1
Brazil	0	2	1
Belize	0	2	0
Dominican Republic	0	1	0
Chile	0	3	0

\*Includes fallopian tube and primary peritoneal cancer.

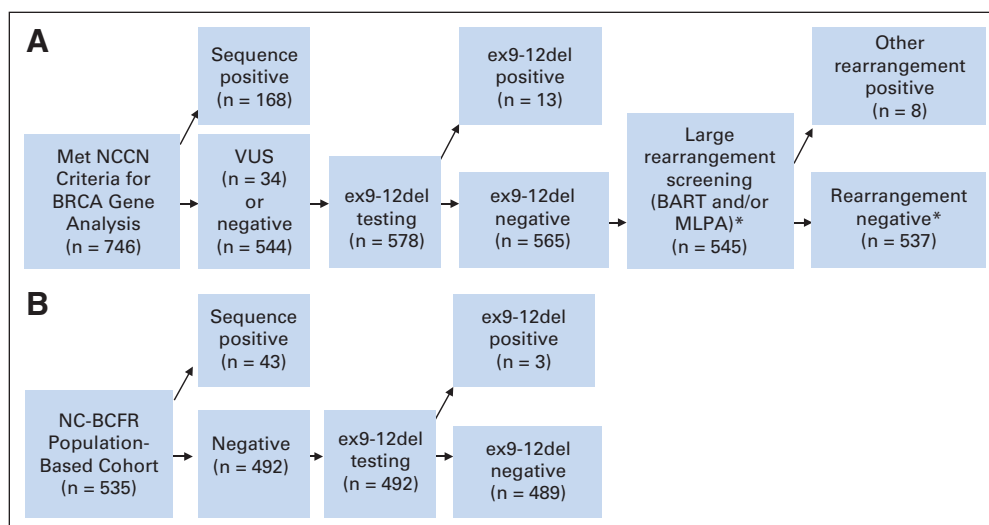
testing for cases that met the vendor's automatic criteria (~*BRCA* mutation probability  $\geq$  30%). Because of the frequency of the *BRCA1* ex9-12del mutation, as a triage step, a separate PCR analysis was performed for all cases in the clinic-based cohort that did not receive automatic BART. It was cost effective to test for that mutation specifically on a research basis (less than \$5 per sample) and then obtain a "single site" rate for clinical grade testing from Myriad for the known mutation. For all remaining cases not meeting the vendor's criteria, BART was conducted electively when covered by private insurance or patient payment; *BRCA1* was screened in the remaining uninformative cases by multiplex ligation-dependent probe amplification assay (MRC-Holland, Amsterdam, the Netherlands).<sup>25</sup>

### *BRCA1* ex9-12del Assay

To screen for the *BRCA1* ex9-12del large rearrangement, a three-primer PCR assay was used.<sup>2</sup> It resulted in coamplification of the mutant allele 742-bp breakpoint fusion product and a 1,145-bp wild-type allele product. As indicated in Figure 1, all *BRCA*-negative clinic-based cases and NC-BCFR<sup>3</sup> population-based samples were tested.

### Mutation Probability Models

Probabilities of carrying a *BRCA* mutation were estimated using the Myriad Tables (February 2010), BOADICEA (v2), and BRCAPRO (v2.0-5) models.<sup>24,26-28</sup> Pedigrees were created electronically using Progeny 8 (Progeny Software, Delray Beach, FL) and uploaded to the BOADICEA Web Application<sup>29</sup> and to Hughes riskApps<sup>30</sup> for BRCAPRO probabilities.



**Fig 1.** Mutation screening outcomes (A) among the high-risk clinic study population; (B) among the Northern California site of the Breast Cancer Family Registry (NC-BCFR). BART, *BRCA* Analysis Rearrangement Testing; NCCN, National Comprehensive Cancer Network; VUS, variant of uncertain significance. (\*) BART (Myriad Genetics Laboratory, Salt Lake City, UT) performed on 200 cases (34 automatic/166 elective); multiplex ligation-dependent probe amplification of *BRCA1* performed on 345 cases; no DNA available for 20 cases.

### Chromosome 17q Genotypes and Mutational Age

DNA samples from 18 *BRCA1* R1443X carriers and 20 *BRCA1* ex9-12del carriers were genotyped at 12 microsatellite markers spanning 4.1 Mb of chromosome 17q encompassing the *BRCA* locus. When possible, haplotypes associated with each mutation were inferred by determining phase from related individuals within each kindred with the same mutation. Primer sequence design and PCR amplifications were previously described,<sup>1,2,31,32</sup> with additional microsatellite markers (D17S649, D17S1787, D17S1801, D17S750, D17S951, D17S1860, D17S1861) from the University of California, Santa Cruz, genome database.<sup>33</sup> Mutation age estimation was performed using the statistical model used in Neuhausen et al.<sup>31</sup>

## RESULTS

### Demographics and Cancer History

Among the 746 clinic-based probands, there were 590 with BC, 39 with OC, 20 with both BC and OC, and 97 unaffected (Table 1). The average age at first BC diagnosis was 40 years. The majority of probands reported Mexico as their grandparents' country of origin (n = 582). Central America (n = 80), South America (n = 36), the Caribbean (n = 13), and Spain (n = 35) were also reported.

### BRCA Mutation Probability and Status

Overall, 189 (25%) had deleterious mutations (124 in *BRCA1*, 65 in *BRCA2*) in the clinic-based cohort; of these, 21 (11%) were large rearrangements (13 *BRCA1* ex9-12del, seven unique rearrangements in *BRCA1*, and one in *BRCA2*). Fewer than half of the large rearrangement mutation carriers in the present study met Myriad Genetic Laboratories criteria (~30% prior probability) for automatic large rearrangement testing. Thirty-four (5%) had one or more unclassified variants, and 523 (70%) had negative/uninformative results (Table 1).

For 745 cases with complete pedigree data, the mean probability of a mutation across the clinic-based cohort, a cross-section of cancer center and community-based clinics, was calculated at 18.7% by BOADICEA, 12.8% by BRCAPRO, and 9.2% by Myriad.

In Table 2, nine recurrent *BRCA* mutations (seen in four or more unrelated families) along with grandparental country of origin (Mexican state specified when known) are shown. This subset accounted for 53% of all detected *BRCA* mutations. Eighteen had a *BRCA1* 185de-

LAG mutation (15% of *BRCA1* mutation carriers) and 13 had an ex9-12del mutation (10% of *BRCA1* carriers). This subset also included R71G (n = 9), a Spanish founder mutation.<sup>34</sup> The six unrelated Hispanic *BRCA1* R1443X mutation carriers shared four distinct haplotypes: two independent haplotypes of Mexican ancestry, one of Columbian, and one of Peruvian ancestry. These were distinct from the haplotype seen in French-Canadian samples (samples courtesy of Dr. W. Foulkes).<sup>35,36</sup> The *BRCA2* 3492insT mutation (n = 10) accounted for 15% of the *BRCA2* mutations. Two recurrent *BRCA1* mutations, 917delTT (n = 5) and IVS5+1 G more than A (n = 4), were observed exclusively in probands with family origins in El Salvador and Guatemala; they were reported previously in Italy<sup>37</sup> and Spain,<sup>38</sup> respectively. Probands with the *BRCA2* 9254del5 mutation (n = 5), reported previously in Spain,<sup>39</sup> were exclusively of El Salvadoran origin.

In addition, the *BRCA1* ex9-12del mutation was detected in three of 492 *BRCA* sequence negative families of Mexican ancestry identified through the population-based Greater San Francisco Bay Area Cancer Registry and enrolled in the NC-BCFR; this represents 12% (three of 25) of the *BRCA1* mutations in the cohort (22 *BRCA1* mutations were previously reported in the overall cohort).<sup>3</sup>

### Mutational Age

*BRCA1*ex9-12del mutation carriers (n = 13) were genotyped, and mutational age analyses estimated the *BRCA1* ex9-12del mutation to have arisen 74 generations, or 1,480 years ago (95% CI, 920 to 2,260 years).

## DISCUSSION

To date, this is the largest study of Hispanic breast/ovarian cancer families in the United States, confirming a high prevalence of *BRCA* mutations (25%), as well as a pattern of multiple recurrent mutations in this mostly Mexican-American population. Large rearrangement mutations, not detectable on standard sequencing, represented a significant proportion of the carriers. Nine recurrent mutations accounted for 53% of the total, suggesting the potential

Genetic Screening and Hispanic *BRCA* Mutations

**Table 2.** Recurrent\* Mutations and Geographic Origins

Gene	BIC Variant	HGVS Variant	No. of Observations	Country (No.)	States in Mexico (No.)	
<i>BRCA1</i>	185delAG	c.68_69delAG	18	Mexico (16)	Chiapas	
				Spain (2)	Durango	
	Exon9-12del	c.548-?-4185+?del	13	Mexico (13)	Distrito Federal	
					Jalisco	
					Michoacán	
					Chihuahua (2)	
					Durango	
					Jalisco	
					Puebla	
					Tamaulipas	
					Veracruz	
					R71G	c.211A>G
R1443X	c.4327C>T	6	Spain (2)	Sonora		
Q1200X	c.3598C>T	5	Mexico (4)	Mexico (1)		
				Colombia (1)		
917delTT	c.798_799delTT	5	Mexico (5)	Peru (1)		
				Mexico (4)		
2552delC	c.2433delC	4	Mexico (4)	Mexico (5)		
				Mexico (4)		
S955X	c.2864C>A	4	Mexico (4)	El Salvador (4)		
				Guatemala (1)		
IVS5 + 1G>A	c.212 + 1G>A	4	Guatemala	Guatemala (1)		
				Guatemala		
A1708E	c.5123C>A	4	Mexico (3)	Coahuila		
				Mexico (3)		
C1787S & G1788D	c.5359T>A & c.5363G>A	4	Mexico (4)	Guajuato		
				Mexico (4)		
<i>BRCA2</i>	3492insT	c.3264dupT	10	Mexico (10)	Zacatecas (2)	
					Mexico (10)	
	E49X	c.145G>T	5	Mexico (5)	Durango	
					Mexico (5)	
	9254del5	c.9026_9030del5	5	El Salvador	Guerrero	
					El Salvador	
	G2793R	c.8377G>A	4	Mexico (4)	Jalisco	
					Mexico (4)	
						Sinaloa
						Sonora
					Zacatecas (2)	
					Chihuahua	
					Nuevo Leon	
					Durango	
					San Luis Potosí	
					Zacatecas	

Abbreviations: BIC, Breast Cancer Information Core Database (<http://research.nhgri.nih.gov/projects/bic/Member/index.shtml>); HBVS, Human Genome Variation Society mutation nomenclature (<http://www.hgvs.org/mutnomen/>).

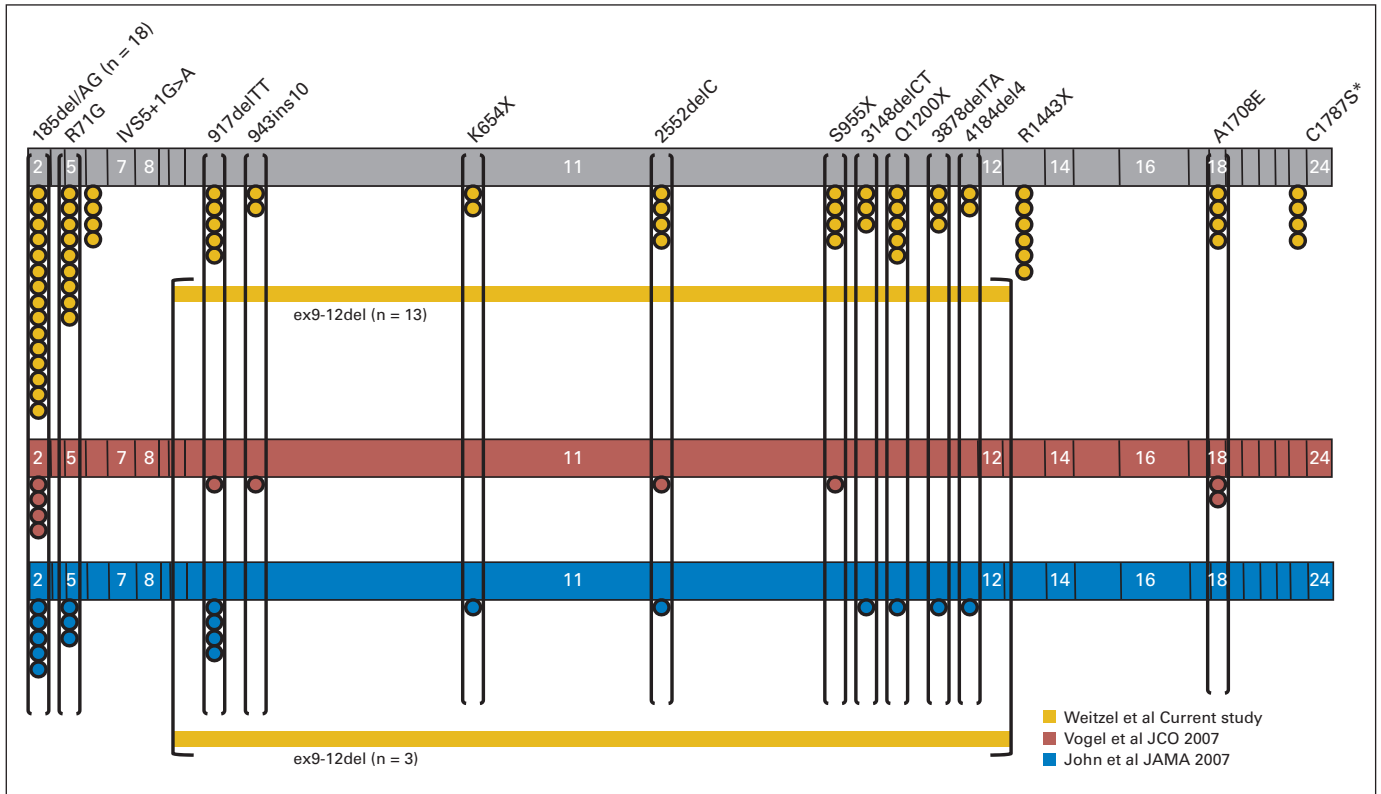
\*Recurrent mutations include four or more observations.

for more cost-effective, ancestry-informed genetic screening. Currently, the sensitivity of a Hispanic-specific *BRCA* panel is being evaluated prospectively.

As highlighted in Figure 2, the spectrum of mutations in Hispanic cohorts is similar in Texas, New Mexico, Arizona, and California,<sup>3,40</sup> and the relative proportions of specific recurrent mutations such as *BRCA1* 185delAG and ex9-12del are the same as those in the population-based series of patients with BC enrolled in the NC-BCFR,<sup>3</sup> suggesting that the pattern is generalizable and not due to referral bias. The persistence of village life and low rates of relocation among the Mexican population may account in part for persistent ancestral patterns of recurrent mutations.<sup>41</sup> Although the ancestry-driven pattern is evident in the immigrant Mexican-American population, acculturation and further admixture with majority populations

likely would ultimately diffuse the predictive value of a panel approach to testing. We would suggest that the patterns we observed in the immigrant Mexican-American population may be a relatively unbiased representation of the Mexican population, wherein there is currently little access to GCRA and *BRCA* testing. This hypothesis should be tested prospectively in Mexico.

Although most of the recurrent mutations are likely Spanish in origin, the *BRCA1* ex9-12del mutation has never been observed in Spain or South America.<sup>42,43</sup> Representing 10% to 12% of *BRCA1* mutations in clinic- and population-based cohorts, all ex9-12del carriers reported Mexican ancestry, and the mutation was estimated to have arisen 1,480 years ago, predating Spanish colonization. Thus *BRCA1* ex9-12del is clinically significant and one of the most frequent population-specific large rearrangement



**Fig 2.** Graphical comparison of recurrent mutations across three Hispanic cohorts: (1) Current study population, Weitzel et al, (2) Texas population, Vogel et al,<sup>40</sup> and (3) California population, John et al<sup>3</sup> \*The C1787S mutation is actually two adjacent missense mutations: C1787S and G1788D.

mutations in the world, as well as the first reported Mexican founder mutation.

Commercial *BRCA* rearrangement testing using the multiplex quantitative differential polymerase chain reaction method became available in 2006. Less than half of the large rearrangement carriers in the present study met Myriad's criteria (~30% prior probability) for large rearrangement testing. Furthermore, recent data from Myriad indicated that *BRCA* large rearrangement mutations are frequent (21%) in patients of Latin American/Caribbean ancestry who were tested for *BRCA* mutations and that *BRCA1* ex9-12del represented a significant proportion of these.<sup>44</sup>

Eighteen probands had a *BRCA1* 185delAG, a known Jewish founder mutation, in our Hispanic population (9.5% of *BRCA* carriers). The term *Hispanos* has been applied to the Colonial-Hispanic population<sup>45</sup> in the San Luis Valley, encompassing parts of Colorado and New Mexico, and it is suggested that their ancestral origins stem from the immigration of Spanish *Conversos* and *Crypto-Jews*.<sup>46</sup> Although five 185delAG carriers in our study were from New Mexico, and thus likely *Hispanos*, they reported grandparental ancestry as Mexican or Spanish. Given that the majority of 185delAG carriers in our cohorts were recruited from areas of the United States outside of known Colonial-Hispanic settlements, the high prevalence is clinically relevant and may represent a greater than appreciated diaspora of people with *Converso* and *Crypto-Jewish* ancestry. In other words, the *BRCA1* 185delAG mutation is of Jewish origin and prevalent across the Mexican-American Hispanic population.

Previously reported as a French-Canadian founder mutation with highly conserved haplotypes,<sup>35,36</sup> *BRCA1* R1443X was observed

six times in our study population, with ancestry reported from Mexico (n = 4), Colombia (n = 1), and Peru (n = 1). Our demonstration of distinct haplotypes, none in common with the French-Canadian samples, supports the hypothesis that there are multiple independent origins, possibly due to hypermutability of the CG dinucleotide to TG.<sup>35</sup>

The *BRCA* mutation prevalence of 25% in our high-risk population was higher than expected compared with the output of all three mutation probability models (BOADICEA, BRCAPRO, Myriad) that were applied. Reports of the predictive accuracy of the BRCAPRO, BOADICEA, and Myriad *BRCA* mutation probability models in Hispanic populations are conflicting.<sup>15,40,47,48</sup> Our data support the possibility that the underlying prevalence of *BRCA* mutations in the Mexican-American population may be higher than the reference populations used to validate the models. We also observed a higher prevalence than previous reports. One small clinic-based study of Hispanics reported a sequencing-detected *BRCA* mutation prevalence of 17.9%,<sup>40</sup> and a prevalence of 14.8% was reported among 1,936 cases with reported Latin American/Caribbean ancestry who received commercial *BRCA* sequencing, including the five-site large rearrangement panel.<sup>19</sup> The latter study was not able to segregate ancestry data according to Hispanic subsets (eg, Caribbean Islanders v Mexican or South American) because it was based on limited categorical information volunteered on a commercial test requisition form. Neither of these studies screened for other rearrangements such as *BRCA1* ex9-12del, which accounted for 10% of all *BRCA1* mutations in our cohort. With the exception of Ashkenazi-Jewish subjects, Hispanics had the highest rate of *BRCA1* mutations (10.8%) among women younger than 65 years with BC and with a family history of cancer, selected

from a population-based cancer registry (NC-BCFR).<sup>3</sup> This was likely an underestimate given that only *BRCA1* was screened,<sup>3</sup> and the testing would have missed genomic rearrangements, some of which were captured in our studies of this cohort. Thus the mutation prevalence observed in our study may be the closest approximation of the mutation prevalence in Hispanics who meet the criteria for *BRCA* testing and suggests that *BRCA* mutations may account for a higher percentage of familial BC in those of Mexican descent than other ethnic groups. This observation would be strengthened by future studies of the prevalence of *BRCA* mutations in other ethnic groups, both within the Clinical Cancer Genetics Community Research Network consortium of cancer center and community-based clinics and in other clinic- and population-based studies. Once validated, it may be appropriate to consider adjusting the threshold for recommending *BRCA* testing among Mexican-American Hispanics, similar to the situation in the Ashkenazi Jewish population. In addition, given the relatively higher proportion of *BRCA* mutations, future BC epidemiology studies among Hispanics with Mexican ancestry may need to consider analysis and stratification by *BRCA* status.

GCRA is a medical standard-of-care option for high-risk families and may identify persons at increased risk for cancer before the onset of disease, when early detection or prevention strategies are most effective.<sup>12,14,15</sup> For example, salpingo-oophorectomy substantially lowers BC risk and all-cause mortality in premenopausal *BRCA1* carriers.<sup>13,49</sup> We previously demonstrated that there is interest in genetics and cancer prevention among underserved Hispanic patients in Los Angeles<sup>50</sup> and that high-risk Hispanic women in an indigent care setting will attend their clinic visits.<sup>21</sup> Furthermore, culturally adapted GCRA protocols seem to be effective in promoting risk-appropriate follow-up behaviors.<sup>22,51</sup> Consequently, population-specific GCRA protocols and ancestry-informed genetic testing may have significant potential to be cost effective by superior allocation of health care resources to prevention and early detection of cancer in high-risk individuals, especially in a population in which families tend to be larger.

In this study of Hispanic breast/ovarian cancer families in the United States, the largest to date, we report a high prevalence of *BRCA* mutations, many of which were recurrent, and a significant proportion of which were large rearrangements. Many of these women and their family members would potentially be left unaware of extraordinary risk, as half of those with large rearrangement mutations did not meet the commercial vendor's criteria for automatic inclusion of comprehensive large rearrangement screening. From our professional education programs,<sup>52</sup> we are aware of a significant gap in clinicians' knowledge about large rearrangement mutations, ultimately resulting

in inadequate patient care and potential liability. In addition to the possibility of a relatively higher prevalence of *BRCA* mutations in Mexican-Americans, incomplete family cancer history reporting can influence the performance of probability models. The reasons for lack of apparent family cancer history may be a combination of limited family structure<sup>53</sup> and limited family knowledge. Although formal assessment of multigenerational pedigrees was employed in this study, the depth of information about the extended family was sometimes limited in part because of separation from their ancestors as an immigrant population or cultural influences regarding health communication, with implications for ancestry-informed genetic screening.

Regardless of the factors influencing the prevalence and type of *BRCA* mutations, our study affirms the need for access to *BRCA* testing for Hispanics, with inclusion of full large rearrangement screening (ie, BART) for all patients. The latter recommendation was included in the 2012 National Comprehensive Cancer Network guidelines, wherein *BRCA* gene analysis was defined as the combination of sequencing and large rearrangement analyses.<sup>54</sup>

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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