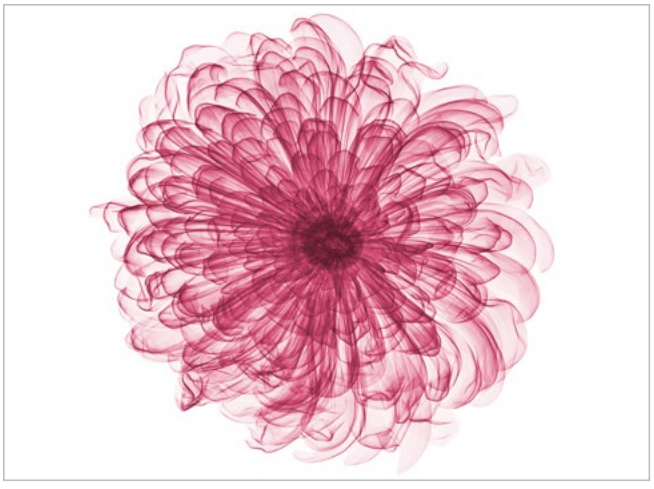

Chrysanthemum. X-Ray image courtesy of Bryan Whitney. www.x-rayphotography.com.

There is an urgent need to ensure that existing genomic research considers the unique needs of US Latinas with breast cancer.

Genomic Disparities in Breast Cancer Among Latinas

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Background: *Breast cancer is the most common cancer diagnosed among Latinas in the United States and the leading cause of cancer-related death among this population. Latinas tend to be diagnosed at a later stage and have worse prognostic features than their non-Hispanic white counterparts. Genetic and genomic factors may contribute to observed breast cancer health disparities in Latinas.*

Methods: *We provide a landscape of our current understanding and the existing gaps that need to be filled across the cancer prevention and control continuum.*

Results: *We summarize available data on mutations in high and moderate penetrance genes for inherited risk of breast cancer and the associated literature on disparities in awareness of and uptake of genetic counseling and testing in Latina populations. We also discuss common genetic polymorphisms and risk of breast cancer in Latinas. In the treatment setting, we examine tumor genomics and pharmacogenomics in Latina patients with breast cancer.*

Conclusions: *As the US population continues to diversify, extending genetic and genomic research into this underserved and understudied population is critical. By understanding the risk of breast cancer among ethnically diverse populations, we will be better positioned to make treatment advancements for earlier stages of cancer, identify more effective and ideally less toxic treatment regimens, and increase rates of survival.*

Introduction

An estimated 55 million individuals living in the United States identify as being Hispanic or Latino.[1] Latinos are a culturally and genetically diverse group with origins in Mexico, the Caribbean, Central America, and South America. In the United States, 64.0% of Latinos are of Mexican background, 9.6% of Puerto Rican background, 3.8% of Salvadoran background, 3.7% of Cuban background, 3.2% of Dominican background, 2.4% of Guatemalan background, and the remainder

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are of other origins.[2] Although the terms *Hispanic* and *Latino/Latina* are often interchangeably used, we selected the term *Latina* for the current manuscript as we feel it extends beyond spoken language to reflect both origin and cultural traditions of women from Latin America.

Breast cancer is the most common cancer diagnosed among Latinas in the United States and is the leading cause of cancer-related death in this population.[3] Although the overall prevalence of breast cancer in Latinas is lower than in non-Latina whites, Latinas tend to be diagnosed at a later stage and have worse prognostic features (eg, triple-negative disease, *ERBB2* [formerly *HER2* or *HER2/neu*]–positive disease).[4] A myriad of socioeconomic and cultural factors contribute to health disparities in breast cancer among Latinas,[5-7] but biological factors — particularly genomics — remain an important but understudied consideration.

High and Moderate Penetrance Genes

Approximately 10% to 15% of breast cancer cases are attributed to inherited gene mutations.[8] Although multiple genes confer an inherited risk for cancer,[9] *BRCA* mutations are the most prevalent and penetrant mutations, accounting for the majority of hereditary types of breast cancer.[10] *BRCA* mutations result in an increased lifetime risk of breast cancer of up to approximately 60% to 70% and a lifetime ovarian cancer risk of up to 40%.[11-13] Among Latinas, breast cancer is often diagnosed at younger ages and with worse prognostic features, including increased rates of triple-negative disease, than their non-Hispanic white counterparts.[3,14-16] Triple-negative disease and premenopausal breast cancer are both clinical characteristics associated with a higher probability of having a *BRCA1* or *BRCA2* mutation.[17,18]

Prevalence of BRCA

The prevalence of *BRCA* mutations in the general US population is estimated to be 1 in 400, excluding women of Ashkenazi Jewish descent in whom the prevalence is 1 in 40.[19-21] However, less is known about the prevalence among racial and ethnic minority groups, including Latinas as a whole or by subethnicity based on country of origin. A review examined the spectrum of *BRCA1* and *BRCA2* mutations in Latin America and the Caribbean using studies published between the years 1994 and 2015.[22] Six of the 33 studies were conducted among Latinas living in the United States, with the vast majority of participants drawn from clinic-based samples of patients of Mexican origin with breast cancer residing in California, Arizona, and Texas.[22] Prevalence estimates of carrying a *BRCA* mutation for this US Latina group ranged from 0.7% to 42.0% and varied based on whether cases were selected or unselected for family history or clinical characteristics (eg, affected vs unaffected, age at diagnosis), cancer site (eg, breast, ovarian), and type of testing (eg, inclusion of large rearrangement testing).[22] In the cohorts of unselected patients with breast cancer, the *BRCA* mutation prevalence was 1.2% to 4.9%, which was consistent with expected rates.[22]

BRCA mutations have also been documented in all residents of Latin American countries where these genes have been studied, including Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Mexico, Peru, Puerto Rico, Uruguay, and Venezuela.[23-54] Most studies have focused on the spectrum of *BRCA* mutations.[22,55] In a review of *BRCA1* and *BRCA2* mutations in persons living in Latin America and the Caribbean, 36% of the 33 studies primarily focused on Mexican or Mexican American patients.[22] Of the Mexican study population, the mutation prevalence was between 4.3% and 23.0%.[22] For other Latina subethnic groups, the mutation prevalence estimates of each country studied were: Colombia (1.2%–15.6%; 2 studies), Costa Rica (4.5%; 1 study), Cuba (2.6%; 1 study), Peru (4.9%; 1 study), Uruguay (17%; 1 study), and Venezuela (17.2%; 1 study).[22] These studies provide insight into areas of future research of *BRCA* mutation distribution and frequency based on country of origin, the role of specific founder mutations, the contribution of large genomic rearrangements to the spectrum of mutations across various Latina subethnic groups, and the consideration of other non-*BRCA* genes that increase the risk of breast cancer.

Although recurrent mutations were identified within most studies, the specific mutation varied by study and country.[22] *BRCA1* 185delAG has also been documented in Latinas across Latin America and the United States.[40,42-44,47,56-58] One of the 3 Jewish founder mutations, *BRCA1* 185delAG is estimated to have arisen about 800 years ago or earlier and is believed to have been introduced into Latin America about 650 years ago.[59] When this mutation is identified in Latinos, haplotype analysis supports that this mutation is of the same origin as the Jewish founder mutation, rather than a separate genetic event.[60,61] Pooled mutation estimates performed by Porchia et al[55] found that *BRCA1* 185delAG is the second most prevalent *BRCA1* mutation and its frequency is not significantly different between Mexico and other Latin American countries ($P = .70$). However, it is worth noting that not all Central and South American countries were represented in their analysis.[55]

The most common *BRCA1* mutation in the same meta-analysis was deletion of exons 9 to 12.[55] This mutation is estimated to have originated nearly 1,500 years ago near Puebla Mexico.[48,58] However, to date, it has been reported in Mexicans and Mexican Americans alone.[22,32,55,61,62] The contribution of large genomic re-

arrangements to *BRCA1* in Latin American patients was evaluated in a study of US Latinas and described the prevalence of rearrangements by racial and ethnic groups.[63] Large rearrangements were significantly more common in individuals who reported Latin American ancestry, and the prevalence of rearrangements was two-fold higher than in the overall population tested.[63] This laboratory-based cohort extracted ethnicity data from genetic testing request forms; therefore, no data about subethnicity was available.[63] However, the 2 most frequent *BRCA1* rearrangements identified in this study were deletion of exons 9 to 12 and deletion of exons 1 and 2, likely reflecting the underlying US Latino population in whom the majority is of Mexican ancestry.[63] In a Puerto Rican study, *BRCA1* deletion of exons 1 to 2 was seen in nearly 20% of study patients positive for *BRCA1*.[49] Because Puerto Ricans represent the second largest US Latino group after those of Mexican ancestry, these findings support utilizing an assay that includes large rearrangements when testing Latinos.[49] The study results also highlight the importance of understanding more granular aspects of ethnicity, such as country of origin, to ensure that all mutations that contribute significantly are captured.

Dutil et al[22] noted that most Latin American studies they reviewed identified a higher proportion of *BRCA1* than *BRCA2* mutations, a finding similar to reports in other populations. However, studies from 4 different countries (Costa Rica,[37] Cuba,[35] Puerto Rico,[49] Uruguay[64]) reported more *BRCA2* mutations than those in *BRCA1*. While these studies may have been limited by sample size and the mutation-detection strategies and technologies,[35,37,49,64] this finding has been also reported in a single US-based clinical site and may warrant further exploration.[65]

The meta-analysis performed by Porchia et al[55] identified recurrent *BRCA2* mutations across all studies with the following pooled prevalence: H372N (0.88%; 95% confidence interval [CI]: 0.24–1.92), E49X (0.38%; 95% CI: 0.13–0.75), and 3492insT (0.32%; 95% CI: 0.24–0.53). *BRCA2* 3492insT has been identified in different regions of Spain with a frequency as high as 2.08%.[65-71] Although it is possible that this mutation was introduced in Latin America by the Spaniards, no haplotype studies of this specific mutation were identified to confirm a shared ancestry rather than a separate mutational event.[49]

BRCA1 and *BRCA2* account for the majority of hereditary breast cancer, but other high- and moderate-risk genes also predispose individuals to breast cancer, including *TP53, PTEN, CDH1, STK11, CHEK2, PALB2,* and *ATM*, among others.[26,27,54,72-80] Limited studies have been performed of non-*BRCA* genes in Latina breast-cancer cohorts, leaving much to be learned about the prevalence and spectrum of mutations in these genes among Latinas with breast cancer (Table 1).[26,27,54,72-80]

One exception is the Brazilian founder mutation in *TP53*, R337H. Mutations in *TP53* cause Li-Fraumeni syndrome, which is associated with an elevated risk for a wide spectrum of cancers, including adrenal cortical carcinoma, soft-tissue and bone sarcomas, brain tumors, and breast cancer.[81-83] The overall contribution of *TP53* mutations to breast cancer is estimated to be less than 1%, unless selecting for early-onset breast cancer.[84,85] In studies of women diagnosed with breast cancer at or before the age of 30 or 35 years, 5% to 8% had *TP53* mutations.[81,86-88]

TP53 R337H was first identified in individuals with childhood adrenal cortical carcinomas living in southern Brazil.[89] This mutation occurs in 2.4% to 8.6% of Brazilian women with breast cancer.[78,79,89,90] In a large study, which included 403 patients with breast cancer diagnosed at 45 years or younger, 12.1% carried the *TP53* R337H mutation. Although the mutation was significantly more frequent in younger patients compared with those diagnosed at 55 years or older ($P < .001$), 5.1% of the older group carried the mutation.[79] To date, no other populations have been identified in whom *TP53* makes such a significant contribution to breast cancer. The prevalence of this mutation in southern Brazil has been estimated to be approximately 0.3%.[91,92] Additional haplotype analyses support the hypothesis that this recurrent mutation is a founder mutation from a shared ancestor.[79,93]

Historically, the genetic assessment for hereditary breast cancer involved the formation of a differential diagnosis followed by a syndrome-by-syndrome evaluation through the sequential testing of genes. However, the rapid integration of next-generation sequencing has enabled simultaneous testing of multiple inherited cancer genes, thereby expanding the use of multigene panels in clinical testing at a reduced cost.[94] This expansion is reflected in the emerging body of literature on breast cancer focused on multigene panel findings from the research, clinical, and laboratory settings.[95-103]

These literature cohorts are predominantly non-Hispanic whites, with Latinas representing less than 1.0% to 7.4% of study participants, thus highlighting another area where future research is needed.[95-97,99-102] One study of 475 patients undergoing multigene panel testing included 228 Latino patients (47.6% of the study population), and it reported that the likelihood of detecting a deleterious mutation was no different among the ethnic and racial groups represented.[96] Of the patients with breast cancer (n = 197), 14.8% (n = 28) carried mutations, and, as expected, *BRCA1* and *BRCA2* were the most commonly mutated genes; however, 16 mutations were identified in other genes (*CDH1* = 4, *CHEK2* = 3, *MUTYH* = 3, *PALB2* = 2,

TP53 = 1, *RAD50* = 1, *RAD51D* = 1, *BARD1* = 1).[96] Of note, the likelihood of identifying more than 1 variant of uncertain significance in Latinos was significantly higher than that of non-Hispanics whites.[104] Thus, a need exists for further research to better classify rare variants, especially given the under-representation of Latinos in laboratory and research databases.

Genetic Counseling and Testing

Patient- and Health Care–Related Factors

An important step toward understanding the role of *BRCA* and other high- and moderate-risk breast cancer genes in Latinas is to increase the number of individuals who receive genetic counseling and subsequently elect to undergo testing. However, growing evidence identifies disparities in awareness of and access to genetic counseling among Latinas compared with non-Hispanic white women. Data from health interview surveys from 2000, 2005, and 2010 show that Latinas had the lowest level of awareness about genetic testing for inherited cancer risk than all of the other US racial ethnic groups.[105-107] Using telephone surveys, Gammon et al[108] studied 63 Latinas and 84 non-Hispanic whites at increased risk for carrying a *BRCA1* or *BRCA2* mutation, examining their awareness, cognition level, and psychosocial needs related to genetic

Table 1. — Select Non-*BRCA* Genes Observed in Latina Populations

Study	Country	Cohort		Gene	Analysis	Findings
		No. of Patients	Inclusion Criteria			
Assumpção[78]	Brazil	123	Family history of breast cancer Family history of ovarian cancer Sporadic breast cancer	*TP53*	Site-specific analysis of *TP53* R337H	2.4% of cases carried the mutation (P = .0442)
Carraro[54]		54	Early-onset breast cancer diagnosis < 30 y	*BRCA1* *BRCA2* *CHEK2* *TP53*	Coding introns/exons of *BRCA1/2, TP53,* and site-specific analysis of *CHEK2* (c.1100delC)	22% carried mutations mostly in *BRCA1/2* 2% (n = 1) had *TP53* mutation
Felix[26]		106	HBOC testing	*BRCA1/2* *CHEK2* *TP53*	PCR of each exon of *BRCA1* Site-specific analyses of *BRCA2* (c.5946_5946delT; c.156_157insAlu), *CHEK2* (c.1100delC; c.444+1G>A; p.I157T), and *TP53* (p.R337H)	2.8% carried mutations (*BRCA* = 2, *TP53* = 1)
Giacomazzi[79]		874	Family history of cancer (group 1) Consecutive breast cancer (group 2)	*TP53*	Single-site analysis for p.R337H	p.R337H identified in 3.4% (group 1) and 8.6% (group 2) Higher prevalence when diagnosed ≤ 45 y (12.1%) vs 55 y (5.1%; P < .001)
Silva[27]		120	HBOC testing	*ATM* *BRCA1/2* *BRIP1* *CDH1* *CDKN2A* *CTNNB1–CHEK2* *MLH1* *MSH6* *NBN* *PALB2* *PTEN* *RAD50* *RAD51* *TP53*	Coding introns/exons of *BRCA1/2* Site-specific analysis of *CHEK2* (c.1100delC) and *TP53* (p. R337H) Array comparative genomic hybridization for CNVs in other 14 genes	26% (n = 31) mutations (*BRCA1/2* = 27, *CHEK2* = 1, *TP53* = 3)

Continued on next page

Table 1. — Select Non-*BRCA* Genes Observed in Latina Populations, continued

Study	Country	Cohort		Gene	Analysis	Findings
		No. of Patients	Inclusion Criteria			
González-Hormazábal[72]	Chile	137 (*BRCA*⁻ = 126, *BRCA*⁺ = 11)	≥ 2 family members with breast cancer ≥ 2 family members with ovarian cancer Family history of male breast cancer Early-onset breast cancer with no family history	*ATM*	PCR-based analysis of coding sequence and exon/intron boundaries of *ATM* Analysis of *ATM* 5557G>A, IVS38-8T>C, IVS24-9delT	5557G>A, IVS38-8T>C, IVS24-9delT associated with elevated risk of breast cancer if *BRCA*⁻ Identification of composite genotype that confers 3.19-fold risk for breast cancer
Jara[80]		143 (*BRCA*⁻ = 131, *BRCA*⁺ = 12)	≥ 2 family members with breast cancer ≥ 2 family members with ovarian cancer Family history of male breast cancer Early-onset breast cancer with no family history	*RAD51D*	PCR-based analysis of coding sequence and exon-intron boundaries of *RAD51D* Analysis of *RAD51D,* c.135G>C	No mutations detected in *RAD51D* c.135G>C associated with elevated breast cancer risk if *BRCA*⁻
Leyton[73]		436	*BRCA*⁺ ≥ 2 family members with breast cancer ≥ 2 family members with ovarian cancer Single case of early-onset diagnosed ≤ 50 y	*PALB2*	Full gene sequencing in 100 "high-risk" cases Analysis of identified variants	No pathogenic mutations identified 3 variants identified (c.1676A>G[a], c.2993C>T[a], c.1861C>A)
Calderón-Zúñiga[74]	Mexico	94	Familial breast cancer Early-onset breast cancer	*ATM*	PCR-FLP of 3 specific mutations (IVS24-9delT, IVS38-8T>C, 5557G>A)	5557G>A (13%) IVS24-9delT (21% vs 8% controls; *P* = .0122) IVS38-8T>C (< 1%)
Bell[76]	United States	362[b]	Early-onset breast cancer	*CHEK2*	169 cases diagnosed ≤ 40 y had sequencing of coding region of *CHEK2* Specific analysis of 1100delC, H143Y, and 8 other *CHEK2* variants/mutations	Data not reported by ethnicity, but reported "infrequency" of c.1100delC among Latinas
Bretsky[75]		101[b]	Personal history of breast cancer	*ATM*	20 specific *ATM* missense mutations or polymorphisms	L546V had modest but not significant predictor of risk; almost exclusive to African American women (found in 2 Latinas)
Damiola[77]		158[b]	Breast cancer diagnosed ≤ 45 y	*MRE11* *RAD50* *NBN*	PCR-based analysis of coding sequence and exon/intron boundaries of *MRE11, RAD50, NBN*	Data not reported by ethnicity *MRE11, RAD50, NBN* are intermediate-risk genes

[a]These variants play a role in risk of breast cancer.
[b]Latinas were part of a larger multiethnic cohort.
CNV = copy number variation, FLP = fragment length polymorphism, HBOC = hereditary breast and ovarian carcinoma, PCR = polymerase chain reaction.

counseling and testing. Among those who had not previously undergone genetic counseling (53 of the 120), Latinas were more unaware than their white counterparts of the availability of testing (56.9% vs 34.8%, respectively).[108] Vadaparampil et al[109] reported on a sample of Latinas with a personal or family history of breast cancer, all of whom reported an awareness of genetic risk for breast cancer (ie, family history). However, none of the Latinas had a clear understanding of what genetic testing was and had not received physician referral for genetic testing.[109] Findings did differ based on country of origin — an important area to consider in future work, given the diversity of Hispanic populations across the United States.[109] In another report, Kaplan et al[110] reported differences in awareness of genetic testing by race and ethnicity, such that 19.4% of Latinas had heard of genetic testing compared with 59.4% of whites, 26.1% of Asian Americans, and 31.0%

of black women.

In a study of more than 2,400 patients completing a family cancer history form, Mays et al[111] found that, overall, despite low levels of initial awareness, 65 patients (2.7%) met criteria for cancer risk assessment; of those, 72.3% expressed interest in receiving genetic counseling. Furthermore, no differences in interest in genetic services were reported across all racial and ethnic groups.[111] Among 1,536 women with nonmetastatic breast cancer, Jagsi et al[112] found that Latinas had a greater desire for genetic counseling than other groups (58.8% of Spanish-speaking Latinas; 36.7% of English-speaking Latinas; 27.1% of non-Latina whites; and 28.1% of blacks). In addition, Lagos et al[113] examined social, cognitive, and cultural variables among Latinas prior to an appointment for genetic counseling. Fifty low-income, underserved Latinas completed the assessment, and the results demonstrated their readiness (having the necessary skills for the genetic-counseling process), low fatalism, and high rate of self-efficacy, and social support.[113] However, this study was conducted in women who showed up to their genetic counseling appointments, thus representing a unique group of women.[113] Vadaparampil et al[114] studied a group of Puerto Rican women (living in Puerto Rico or central Florida) with a family or personal history of breast cancer and found that the vast majority of participants said they would undergo genetic testing within the next 6 months if it was available. Barriers included the potential physical pain associated with the test.

Uptake of Services

Given lower levels of patient awareness, physician recommendations may provide a critical approach to increasing the utilization of genetic counseling and testing for hereditary risk of breast cancer. However, available studies suggest a missed clinical opportunity, because both English- and Spanish-speaking Latina survivors of breast cancer may be more likely to have unmet needs for discussion with a health care professional about genetic testing for cancer than their non-Hispanic white counterparts. For example, Jagsi et al[112] reports that minority patients were the most likely to express an unmet need for a discussion about genetic testing, although they also showed a strong desire for such testing.

Preliminary studies support the uptake of genetic counseling when services are offered.[115-118] One study of predominantly Latina patients (71.4%) offered genetic counseling at a safety-net hospital found that 88.0% kept their appointments.[115] Another study of women (69.6% were Latinas) seen in a safety-net hospital setting reported that 96.4% of them underwent *BRCA* testing when it was recommended to them.[116] Once Latinas were referred, Olaya et al[117] found that they are equally likely as the general population to complete *BRCA* testing. Overall, 52% completed genetic testing, and no differences by race and ethnicity were observed.[117] Woodson et al[118] reported on the utilization of group pretest genetic counseling in a community clinic made up of mostly Latinas (62.3%) with breast cancer; the majority (86.7%) underwent *BRCA* genetic testing when offered.

Overall, these studies have focused on the delivery of genetics services for cancer to majority Latina cohorts, demonstrating that genetic counseling and testing is likely well-received by Latinas with breast cancer; however, these studies were all conducted in safety-net hospitals or in community, low-resource settings and were aimed at the provision of service to low-income, uninsured patients.[115-118] Although Latinas continue to be disproportionally uninsured or underinsured, these study findings might not generalize to other health care settings. Thus, further studies are needed across various clinical settings and in a wider representation of Latinas with breast cancer to better understand the utilization of genetic testing as well as the barriers for referrals.

Common Genetic Polymorphisms and Risk of Breast Cancer

Genome-Wide Association Studies

Progress in the discovery of germline genetic polymorphisms associated with breast cancer risk changed pace when technological advances in genotyping made it possible to characterize genome-wide genetic variation at a relatively low cost.[119] In 2007, the first breast cancer genome-wide association studies were published, and they reported a handful of single nucleotide polymorphisms (SNPs) associated with a modest increase in risk.[120-122] Since then, more than 100 common variants that either increase risk for or are protective against developing breast cancer have been discovered and, including replication efforts, data from more than 120,000 women have been analyzed.[120-143] A small proportion of samples included in these major initiatives are from minority populations in the United States (eg, Latinas, African Americans),[120-143] and the first results of genome-wide association studies of Latinas with breast cancer were published in 2014.[144] This latter study represents important but limited progress, considering that the sample size was one-tenth of that available for genome-wide association studies involving women of European origin.[120-122,144]

Until the first genome-wide association studies of breast cancer in women of European origin were published, the search for risk-predisposing genetic variants was focused on finding polymorphisms within genes that, for known or hypothesized involvement in the biology of the disease, were likely to contribute to breast cancer risk.[120-122] These studies in US Latinas or Latin American women typically consisted of the replication of previously associated polymorphisms reported in Europeans, with few of these studies looking for varia-

tion in samples of Latinas before further testing specific polymorphisms for associations in larger samples.[145,146]

Compared with the hundreds of genome-wide association studies in non-Hispanic white women, we identified 13 case-control studies or cohorts that include US Latina or Latin American women.[147-160] These studies include populations of women of no more than 100 and up to approximately 5,000 women of Latin American origin; combined, the study populations tally approximately 5,000 Latina women with breast cancer and 11,000 Latina healthy controls.[147-160]

Candidate Gene or Pathway Studies

Multiple breast cancer–association studies of candidate genes or pathways have been reported for US Latina and Latin American women during the last 20 years. Genes or pathways studied have included those related to hormone metabolism, hormone receptors, hormone coactivators or supressors,[145,161-166] growth factors,[146,167-173] matrix metalloproteinases,[174,175] inflammation and energy balance,[149,176-181] metabolism of xenobiotic compounds and oxidative stress,[150,182-184] DNA repair,[151,152,154,186] and angiogenesis.[187] Results reported in these publications should be interpreted with caution, given that approximately 60% of the candidate gene analyses included did not adjust for genetic ancestry, which is a known confounder in genetic association studies in admixed populations.[188,189] In addition, no associations in candidate gene or pathways studies, nor any of the interactions with risk factors, genetic ancestry, or tumor characteristics, have been replicated in independent samples of Latinas.

Replication of Identified Single Nucleotide Polymorphisms

Few studies have included Latinas and tested the association between SNPs discovered in genome-wide association studies of breast cancer conducted in samples of European or Asian women.[190-195] The first study genotyped previously reported SNPs in the 2q35 region and *FGFR2*, *TOX3*, and *MAP3K1*, reporting statistically significant replications for the polymorphisms in *FGFR2* and 2q35.[190] Two different studies published the results of analyses conducted in the same sample of high-risk families from Chile and healthy controls, testing associations between previously reported variants in *FGFR2, MAP3K1,* and *TOX3* and the 2q35 and 8q24 regions and breast cancer risk.[194,195] They replicated the associations for *FGFR2, MAP3K1, TOX3,* and 2q35 but not for 8q24.[194,195] An analysis conducted in a pooled sample of Latina cases and controls from the Four-Corners study, San Francisco Bay Area Breast Cancer Study, and a study in Mexico, investigated the association between 10 identified polymorphisms in genome-wide association studies (in region 2q35 and in or near *RELN, MRPS30, RNF146, FGFR2, TOX3, LSP1, TLR1, MAP3K1,* and *RAD51L1)* and breast cancer risk.[192] They replicated associations for the polymorphisms in *RELN, FGFR2, TOX3,* and *TLR1* and 2q35 and found heterogeneity by ancestry for the *RELN*, 2q35, and *TLR1* SNPs.[192] A follow-up study reported that the heterogeneity by ancestry for the 2q35 polymorphism was likely due to the association between genetic ancestry, use of hormone therapy, and breastfeeding.[191] Another analysis of the *FGFR2* polymorphism in the Mexican study reported an interaction between the *FGFR2* polymorphism and alcohol intake.[193] The first genome-wide association study of breast cancer in US Latinas also replicated previous associations, with most of the SNPs being concordant in terms of direction and magnitude of association with those reported in European or Asian populations.[144] Twenty-three of the 83 variants tested had probability values below .05.[144]

Ancestry

Admixture mapping leverages the demographical history of admixed populations to find genomic regions that may carry trait-associated variants.[196-204] An admixed population results from the combination of 2 or more ancestral groups.[200] The principle of admixture mapping is to identify genomic regions in which cases share more of the same genetic ancestry than either population-based controls (case-control analysis) or compared with the average ancestry of the rest of the genome among cases (case-only analysis).[202] This approach has identified risk variants or risk regions for multiple complex traits, including obesity, hypertension, and cancer.[196-199,201,203,204] The incidence of breast cancer varies across different racial and ethnic groups in the United States, and Latinas have lower incidence rates than non-Latina whites but higher rates than American Indian women.[205] Genetic ancestry has also been associated with breast cancer risk in US Latinas and Mexican women after adjusting for nongenetic risk factors, suggesting that a genetic component could be responsible for the difference in risk.[149,206,207] An admixture mapping study in Latinas reported a statistically significant association between a region in the long arm of chromosome 6 (6q25) near *ESR1* and risk of breast cancer and a suggestive association on chromosome 11.[208] Higher Indigenous American ancestry at chromosome 6q25 was associated with lower risk of breast cancer.[208] This finding was concordant with the previous reports of lower rates of risk of breast cancer among Latinas with high American Indian ancestry compared with women with high European ancestry after adjusting for possible risk factors such as socioeconomic status, number of full-term pregnancies, and breast feeding.[206-208]

One included a discovery phase and replication in 3 additional studies.[144] The study reported genome-wide results that were statistically significant

for 2 linked SNPs 56kb upstream of *ESR1* (rs140068132 and rs147157845).[144] These SNPs have a frequency of between 5% and 23% in Latin American populations and are absent in most all other groups.[144] The minor allele was protective, with an associated odds ratio (OR) of 0.60 (95% CI: 0.53–0.67) per allele and was more protective for *ER*-negative disease than for *ER*-positive disease (OR for *ER*-negative disease 0.34; 95% CI: 0.21–0.54).[144]

Treatment

Tumor Genomics

A growing body of evidence suggests differences in the tumor biology of breast carcinoma across various races and ethnicities. Several studies have evaluated the prevalence of phenotypic subtypes of breast cancer in Latinas compared with other population groups.[209-215] Most data have shown a higher proportion of *HR*-negative disease types among Latinas when compared with non-Hispanic whites (Table 2).[4,209-213] However, those results have not always been concordant, and the differences seen across these studies could represent small sample sizes, patient age, or unadjusted rates for genetic ancestry. Although studies based on data from the California Cancer Registry indicated a higher proportion of triple-negative tumors,[214] this finding was not confirmed in a Colorado study.[209] In a retrospective study performed in Brazil, patients in the southern regions with a higher percentage of European ancestry and higher socioeconomic status presented with the highest proportion of luminal tumors, whereas the more aggressive subtypes were seen in the northern parts of Brazil, an area with a higher African ancestral influence.[215]

Approximately 15% of breast cancer types overexpress human epidermal growth factor receptor 2 (ERBB2; formerly HER2 or HER2/neu) protein.[216] High levels of ERBB2 expression identify those women who benefit from treatment with ERBB2-targeted agents, which have been shown to increase survival in the adjuvant and metastatic settings.[217,218] Most studies with ERBB2-targeted therapies have enrolled majority populations of non-Hispanic whites, although consistent evidence demonstrates that a higher proportion of *ERBB2*-positive tumors exist among Latinas, even after adjusting for other tumor characteristics (eg, grade, stage, *ER* status) and breast cancer risk factors (eg, number of children, alcohol consumption).[209]

Further tumor characterization has been made possible due to advances in molecular tumor profiling. Oncotype DX (Genomic Health, Redwood City, CA) is a 21-gene breast cancer assay — known as a recurrence score — that provides prognostic and predictive information regarding the benefits of adjuvant chemotherapy in patients with *ER*-positive tumors. Use of Oncotype DX is part of several guidelines from professional medical organizations, including the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society for Medical Oncology.[219-221] The characteristics of this assay and the impact of its results on treatment decisions among Latinas with breast cancer are lacking in the medical literature. Kalinsky et al[222] studied 74 Latinas and 145 non-Hispanic white women matched for age, disease stage, and nodal status, and they observed no differences in the overall recurrence score, *ER* or *PR* status, or *ERBB2* expression by Oncotype DX. However, Latinas had a higher expression of *CCNB1* and *AURKA*, 2 genes that are part of the proliferation score and heavily weighted in the calculation of the

Table 2. — Comparison of *ER* and *ERBB2* Status in Latina, Black, and White Women

Study	No. of Patients	Latina	White	Black
Chlebowski[211]	N = 3,800 n = 103 Latinas	*ER*$^+$: 83.0%	*ER*$^+$: 87.0%	*ER*$^+$: 71.0%
Dunnwald[212]	N = 209,276 n = 5,585 Latinas	*ER*$^+$: 70.2%	*ER*$^+$: 78.4%	*ER*$^+$: 60.5%
Hausauer[213]	N = 243,906 n = 15,355 Latinas	*ER*$^+$: 53.2% (unknown *ER* status: 29.4%)	*ER*$^+$: 63.5% (unknown *ER* status: 22.3%)	*ER*$^+$: 46.4% (unknown *ER* status: 29.4%)
Hines[209]	N = 285 n = 69 Latinas	*ER*$^+$: 63.8% *ERBB2*$^+$: 31.9% TNBC: 17.4%	*ER*$^+$: 77.3% *ERBB2*$^+$: 14.3% TNBC: 15.1%	—
Li[210]	N = 124,934 n = 7,219 Latinas	*ER*$^+$: 68.7%	*ER*$^+$: 78%	*ER*$^+$: 53.4%
Parise[4]	N = 143,184 n = 24,078 Latinas	*ER*$^+$: 74.6 % *ERBB2*$^+$: 22.2% TNBC: 15.9%	*ER*$^+$: 82.7% *ERBB2*$^+$: 17.2% TNBC: 11.2%	*ER*$^+$: 66.5% *ERBB2*$^+$: 20.1% TNBC: 24.5%

TNBC = triple-negative breast cancer.

recurrence score.

Multiple trials whose study populations were mostly comprised of non-Hispanic white women have shown that use of Oncotype DX affects treatment recommendations and leads to an increase in physician and patient confidence in treatment decisions.[223-226] A small study of 96 patients with breast cancer treated in Mexico showed that use of the Oncotype DX changed treatment decisions for 32% of patients, a finding suggesting that its use has a meaningful impact on recommendations for adjuvant treatment.[227] Results from cost-effectiveness analyses indicated that use of the Oncotype DX assay was projected to improve rates of life expectancy when compared with the current standard of care.[228]

Pharmacogenomics

Several factors cause variations in an individual's response to drugs, including age, body mass index, diet, and genetic variation.[229-231] SNPs in genes related to drug-metabolizing enzymes have been recognized as important determinants of variability to drug response.[232] Most studies have not been sufficiently powered to determine whether specific chemotherapy agents used to treat breast cancer have different rates of effectiveness and toxicities based on race or ethnicity.[233] However, differences in the metabolism of endocrine therapies have been well documented according to race and ethnicity.[234-237]

In a study that evaluated clinical data and blood samples from patients with breast cancer undergoing adjuvant tamoxifen therapy, mostly non-Hispanic white women (68%) and Latinas (26%) had significantly higher serum levels of tamoxifen and 4-hydroxytamoxifen, one of the tamoxifen metabolites ($P = .02$ and $P = .007$, respectively).[234] In 2 other studies, genetic polymorphisms in *CYP2D6* associated with lower plasma concentrations of the active metabolites of tamoxifen were described in Mexican, Puerto Rican, and Spanish patients.[235,236] A higher prevalence of this poor metabolizer phenotype has also been observed in non-Hispanic whites.[237] In an attempt to clarify whether CYP2D6 allele status influences outcomes from tamoxifen, investigators assessed data from 2 large prospective trials and found that CYP2D6 allele status did not predict clinical benefit of adjuvant tamoxifen in terms of risk of recurrence.[238,239] Therefore, changes in treatment decisions based on CYP2D6 allele status alone are not recommended. Differences in the incidence of polymorphisms of the aromatase gene among different ethnic groups have also been reported and could potentially lead to different outcomes and toxicities among populations.[240] One trial evaluated the benefit of extended hormonal therapy with an aromatase inhibitor after 5 years of tamoxifen treatment in non-Hispanic whites (n = 4,708) and minority women (n = 352; 1.5% were Latinas).[241] In general, the researchers found that, compared with non-Hispanic whites, minorities had fewer associated toxicities and no definitive survival benefit with aromatase inhibitors.[241] However, these results should be cautiously interpreted, because the minority participants were less adherent to hormonal therapy and the study was not powered to detect survival benefit in the subgroups.[241]

Conclusions

Several genetic and genomic factors are related to the health disparities of breast cancer in Latinas. Increasing our knowledge about the contribution of high- and moderate-penetrance mutations to the risk of breast cancer among Latinas overall and for subgroups based on country of origin is an important priority. Although genetic counseling and testing for inherited susceptibility to breast cancer has been clinically available for nearly 20 years, disparities in awareness, referral to services, and access persist. Therefore, interventions to address barriers related to low levels of awareness and lacking physician referrals are critical.[105-110]

Even though multiple candidate gene studies have been conducted in this population, only identified variants in genome-wide association studies have been systematically replicated. Much larger sample sizes will be required if we expect to discover similar results in Latinas as would be identified for the European genome in view of their Indigenous American component. We cannot assume that overlapping variants alone between different ancestral genomes will be associated with rate of risk, so our efforts should be focused on reducing research disparities by expanding available resources to include large cohorts and case-control studies of diverse populations in and outside the United States.

Latinas remain systematically underrepresented in pharmacogenomics studies and the current studies were not powered to detect outcome differences. They are also underrepresented in clinical treatment trials and other patient-reported outcomes research. Future research should draw from the few models of success in prior studies that have recruited sufficient numbers of Latinas.[242-245] Lessons can also be learned from successful examples of recruiting other racial and ethnic minority patients who have survived breast cancer.[246] Elements that appear to bolster success include partnering with community-based organizations that provide services to Latinas and the provision of language-concurrent clinical care.[247-249] The heterogeneity of the US Latina population must also be considered, because different cultural influences, levels of awareness of, and interest in genetic and genomic services appear to vary by country of origin.[109]

An urgent need exists to ensure that existing genomic research considers the unique needs of this

Latina population. As the US population continues to diversify with up to one-third identifying as Hispanics by 2060,[1] extending genetic and genomic research into this underserved and understudied population will be critical. By understanding the risk of breast cancer among diverse populations, we will be better positioned to make advancements in the number of women diagnosed at earlier stages, identify more effective and less toxic treatment regimens, and increase rates of survival. Meeting these goals will contribute to reducing the current health disparities in these patients with breast cancer.

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References

1. Colby SL, Ortman JM. Projections of the size and composition of the US population: 2014 to 2060. *Curr Pop Rep.* 2014:1-13 https://www.census.gov/content/dam/Census/library/publications/2015/demo/p25-1143.pdf. Accessed September 14, 2016.

2. Pew Research Center. Statistical portrait of hispanics in the United States, 2014. http://www.pewhispanic.org/files/2016/04/Statistical-Portrait-of-Hispanics-in-the-United-States-2014-final.pdf. Accessed September 14, 2016.

3. American Cancer Society. *Cancer Facts & Figures for Hispanics/Latinos 2015-2017.* http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-046405.pdf. Accessed September 14, 2016.

4. Parise CA, Caggiano V. The Influence of socioeconomic status on racial/ethnic disparities among the ER/PR/HER2 breast cancer subtypes. *J Cancer Epidemiol.* 2015;2015:813456.

5. Quinn GP, McIntyre JQ, Vadaparampil ST. Challenges in recruiting Mexican women for cancer genetics research. *J Community Genet*. 2011;2(1):43-47.

6. Giuliano AR, Mokuau N, Hughes C, et al. Participation of minorities in cancer research: the influence of structural, cultural, and linguistic factors. *Ann Epidemiol*. 2000;10(8 suppl):S22-S34.

7. Lantz PM, Mujahid M, Schwartz K, et al. The influence of race, ethnicity, and individual socioeconomic factors on breast cancer stage at diagnosis. *Am J Public Health.* 2006;96(12):2173-2178.

8. Ellsworth RE, Decewicz DJ, Shriver CD, et al. Breast cancer in the personal genomics era. *Curr Genomics.* 2010;11(3):146-161.

9. Lindor NM, McMaster ML, Lindor CJ, et al. Concise handbook of familial cancer susceptibility syndromes - second edition. *J Natl Cancer Inst Monogr.* 2008(38):1-93.

10. Euhus DM, Robinson L. Genetic predisposition syndromes and their management. *Surg Clin North Am.* 2013;93(2):341-362.

11. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007;25(11):1329-1333.

12. Antoniou A, Pharoah P, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003;72(5):1117-1130.

13. Litton JK, Ready K, Chen H, et al. Earlier age of onset of BRCA mutation-related cancers in subsequent generations. *Cancer.* 2012;118(2):321-325.

14. Miranda PY, Wilkinson AV, Etzel CJ, et al. Policy implications of early onset breast cancer among Mexican-origin women. *Cancer.* 2011;117(2):390-397.

15. Boyle T, McPadden E. Breast cancer presents at an earlier age in Mexican American women. *Breast J.* 2004;10(5):462-464.

16. Lara-Medina F, Pérez-Sánchez V, Saavedra-Pérez D, et al. Triple-negative breast cancer in Hispanic patients. *Cancer.* 2011;117(16):3658-3669.

17. Claus EB, Schildkraut JM, Thompson WD, et al. The genetic attributable risk of breast and ovarian cancer. *Cancer.* 1996;77(11):2318-2324.

18. Hartman AR, Kaldate RR, Sailer LM, et al. Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. *Cancer.* 2012;118(11):2787-2795.

19. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. *Br J Cancer.* 2000;83(10):1301-1308.

20. Whittemore AS, Gong G, John EM, et al. Prevalence of BRCA1 mutation carriers among US non-Hispanic Whites. *Cancer Epidemi Biomark Prev.* 2004;13(12):2078-2083.

21. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med.* 1997;336(20):1401-1408.

22. Dutil J, Golubeva VA, Pacheco-Torres AL, et al. The spectrum of BRCA1 and BRCA2 alleles in Latin America and the Caribbean: a clinical perspective. *Breast Cancer Res Treat.* 2015;154(3):441-453.

23. Gomes MC, Costa MM, Borojevic R, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. *Breast Cancer Res Treat.* 2006;103(3):349-353.

24. Esteves V, Thuler L, Amêndola L, et al. Prevalence of BRCA1 and BRCA2 gene mutations in families with medium and high risk of breast and ovarian cancer in Brazil. *Brazl J Med Biol Res.* 2009;42(5):453-457.

25. Ewald IP, Izetti P, Vargas FR, et al. Prevalence of the BRCA1 founder mutation c. 5266dupin Brazilian individuals at-risk for the hereditary breast and ovarian cancer syndrome. *Hered Cancer Clin Pract.* 2011;9:12.

26. Felix GE, Abe-Sandes C, Machado-Lopes TM, et al. Germline mutations in BRCA1, BRCA2, CHEK2 and TP53 in patients at high-risk for HBOC: characterizing a Northeast Brazilian population. *Human Genome Variation.* 2014;1:14012.

27. Silva FC, Lisboa BC, Figueiredo MC, et al. Hereditary breast and ovarian cancer: assessment of point mutations and copy number variations in Brazilian patients. *BMC Medi Genet.* 2014;15(1):1.

28. Gallardo M, Silva A, Rubio L, et al. Incidence of BRCA1 and BRCA2 mutations in 54 Chilean families with breast/ovarian cancer, genotype–phenotype correlations. *Breast Cancer Res Treat.* 2006;95(1):81-87.

29. Sanchez A, Faundez P, Carvallo P. Genomic rearrangements of the BRCA1 gene in Chilean breast cancer families: an MLPA analysis. *Breast Cancer Res Treat.* 2011;128(3):845-853.

30. Jara L, Ampuero S, Santibáñez E, et al. BRCA1 and BRCA2 mutations in a South American population. *Cancer Genet Cytogenet.* 2006;166(1):36-45.

31. Gonzalez-Hormazabal P, Gutierrez-Enriquez S, Gaete D, et al. Spectrum of BRCA1/2 point mutations and genomic rearrangements in high-risk breast/ovarian cancer Chilean families. *Breast Cancer Res Treat.* 2011;126(3):705-716.

32. Torres D, Rashid MU, Seidel-Renkert A, et al. Absence of the BRCA1 del (exons 9–12) mutation in breast/ovarian cancer families outside of Mexican Hispanics. *Breast Cancer Res Treat.* 2009;117(3):679-681.

33. Torres D, Rashid MU, Gil F, et al. High proportion of BRCA1/2 founder mutations in Hispanic breast/ovarian cancer families from Colombia. *Breast Cancer Res Treat.* 2006;103(2):225-232.

34. Sanabria MC, Muñoz G, Vargas CI. Mutations in the BRCA1 gene (185delAG and 5382insC) are not present in any of the 30 breast cancer patients analyzed from eastern Colombia [in Spanish]. *Biomedica.* 2009;29(1):61-72.

35. Rodriguez RC, Esperon AA, Ropero R, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Cuba. *Familial Cancer.* 2008;7(3):275-279.

36. Hernandez J, Llacuachaqui M, Palacio GV, et al. Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from medellín, Colombia. *Hered Cancer Clin Pract.* 2014;12(11):11.

37. Gutiérrez Espeleta G, Llacuachaqui M, García-Jiménez L, et al. BRCA1 and BRCA2 mutations among familial breast cancer patients from Costa Rica. *Clin Genet.* 2012;82(5):484-488.

38. García-Jiménez L, Gutiérrez-Espeleta G, Narod SA. Descriptive epidemiology and molecular genetics of hereditary breast cancer in Costa Rica. *Revis Biol Trop.* 2012;60(4):1663-1668.

39. Rodríguez AO, Llacuachaqui M, Pardo GG, et al. BRCA1 and BRCA2 mutations among ovarian cancer patients from Colombia. *Gynecol Oncol.* 2012;124(2):236-243.

40. Ruiz-Flores P, Sinilnikova OM, Badzioch M, et al. BRCA1 and BRCA2 mutation analysis of early-onset and familial breast cancer cases in Mexico. *Hum Mutat.* 2002;20(6):474-475.

41. Calderón-Garcidueñas AL, Ruiz-Flores P, Cerda-Flores RM, et al. Clinical follow up of Mexican women with early onset of breast cancer and mutations in the BRCA1 and BRCA2 genes. *Salud Publica Mex.* 2005;47(2):110-115.

42. Vaca-Paniagua F, Alvarez-Gomez RM, Fragoso-Ontiveros V, et al. Full-exon pyrosequencing screening of BRCA germline mutations in Mexican women with inherited breast and ovarian cancer. *PloS One.* 2012;7(5):e37432.

43. Vidal-Millan S, Taja-Chayeb L, Gutierrez-Hernandez O, et al. Mutational analysis of BRCA1 and BRCA2 genes in Mexican breast cancer patients. *Eur J Gynaecol Oncol.* 2009;30(5):527-530.

44. Villarreal-Garza C, Weitzel J, Llacuachaqui M, et al. The prevalence of BRCA1 and BRCA2 mutations among young Mexican women with triple-negative breast cancer. *Breast Cancer Res Treat.* 2015;150(2):389-394.

45. Villarreal-Garza C, Alvarez-Gómez RM, Pérez-Plasencia C, et al. Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexico. *Cancer.* 2015;121(3):372-378.

46. Nahleh Z, Otoukesh S, Dwivedi AK, et al. Clinical and pathological characteristics of Hispanic BRCA-associated breast cancers in the American-Mexican border city of El Paso, TX. *American journal of cancer research.* 2015;5(1):466.

47. Torres-Mejía G, Royer R, Llacuachaqui M, et al. Recurrent BRCA1 and BRCA2 mutations in Mexican women with breast cancer. *Cancer Epidemi Biomark Prevent.* 2015;24(3):498-505.

48. Abugattas J, Llacuachaqui M, Allende YS, et al. Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from Peru. *Clin Genet.* 2015;88(4):371-375.

49. Dutil J, Colon-Colon JL, Matta JL, et al. Identification of the preva-

lent BRCA1 and BRCA2 mutations in the female population of Puerto Rico. *Cancer Genet.* 2012;205(5):242-248.

50. Delgado La, Fernández G, González A, et al. Hereditary breast cancer associated with a germline BRCA2 mutation in identical female twins with similar disease expression. *Cancer Genet Cytogenet.* 2002;133(1):24-28.

51. Lara K, Consigliere N, Pérez J, et al. BRCA1 and BRCA2 mutations in breast cancer patients from Venezuela. *Biol Res.* 2012;45(2):117-130.

52. Solano AR, Aceto GM, Delettieres D, et al. BRCA1 And BRCA2 analysis of Argentinean breast/ovarian cancer patients selected for age and family history highlights a role for novel mutations of putative south-American origin. *Springerplus.* 2012;1:20.

53. Dufloth RM, Carvalho S, Heinrich JK, et al. Analysis of BRCA1 and BRCA2 mutations in Brazilian breast cancer patients with positive family history. *Sao Paulo Med J.* 2005;123(4):192-197.

54. Carraro DM, Folgueira MA, Lisboa BCG, et al. Comprehensive analysis of BRCA1, BRCA2 and TP53 germline mutation and tumor characterization: a portrait of early-onset breast cancer in Brazil. *PloS One.* 2013;8(3):e57581.

55. Porchia LM, Gonzalez Mejia ME, Calderilla-Barbosa L, et al. Common BRCA1 and BRCA2 butations among Latin American breast cancer subjects: a meta-analysis. *J Carcinogen Mutagen.* 2015;2015. http://www.omicsonline.org/open-access/common-brca1-and-brca2-mutations-among-latin-american-breast-cancer-subjects-a-metaanalysis-2157-2518-1000228.pdf. Accessed September 15, 2016.

56. John EM, Miron A, Gong G, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. *JAMA.* 2007;298(24):2869-2876.

57. Mullineaux LG, Castellano TM, Shaw J, et al. Identification of germline 185delAG BRCA1 mutations in non-Jewish Americans of Spanish ancestry from the San Luis Valley, Colorado. *Cancer.* 2003;98(3):597-602.

58. Weitzel JN, Clague J, Martir-Negron A, et al. 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. *J Clin Oncol.* 2013;31(2):210-216.

59. Laitman Y, Feng B-J, Zamir IM, et al. Haplotype analysis of the 185delAG BRCA1 mutation in ethnically diverse populations. *Eur J Hum Genet.* 2013;21(2):212-216.

60. Ah Mew N, Hamel N, Galvez M, et al. Haplotype analysis of a BRCA1: 185delAG mutation in a Chilean family supports its Ashkenazi origins. *Clin Genet.* 2002;62(2):151-156.

61. Weitzel JN, Lagos V, Blazer KR, et al. Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. *Cancer Epidemiol Biomark Prevent.* 2005;14(7):1666-1671.

62. Weitzel JN, Lagos VI, Herzog JS, et al. Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk Hispanic families. *Cancer Epidemiol Biomark Prevent.* 2007;16(8):1615-1620.

63. Judkins T, Rosenthal E, Arnell C, et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. *Cancer.* 2012;118(21):5210-5216.

64. Delgado L, Fernández G, Grotiuz G, et al. BRCA1 and BRCA2 germline mutations in Uruguayan breast and breast–ovarian cancer families. Identification of novel mutations and unclassified variants. *Breast Cancer Res Treat.* 2011;128(1):211-218.

65. Esteban Cardeñosa E, Bolufer Gilabert P, de Juan Jimenez I, et al. Broad BRCA1 and BRCA2 mutational spectrum and high incidence of recurrent and novel mutations in the eastern Spain population. *Breast Cancer Res Treat.* 2010;121(1):257-260.

66. Miramar M, Calvo M, Rodriguez A, et al. Genetic analysis of BRCA1 and BRCA2 in breast/ovarian cancer families from Aragon (Spain): two novel truncating mutations and a large genomic deletion in BRCA1. *Breast Cancer Res Treat.* 2008;112(2):353-358.

67. Infante M, Durán M, Esteban-Cardeñosa E, et al. High proportion of novel mutations of BRCA1 and BRCA2 in breast/ovarian cancer patients from Castilla-Leon (central Spain). *J Hum Genet.* 2006;51(7):611-617.

68. de la Hoya M, Osorio A, Godino J, et al. Association between BRCA1 and BRCA2 mutations and cancer phenotype in Spanish breast/ovarian cancer families: implications for genetic testing. *Int J Cancer.* 2002;97(4):466-471.

69. Blay P, Santamaría I, Pitiot AS, et al. Mutational analysis of BRCA1 and BRCA2 in hereditary breast and ovarian cancer families from Asturias (Northern Spain). *BMC Cancer.* 2013;13(1):1.

70. Bolufer P, Munárriz B, Santaballa A, et al. BRCA1 and BRCA2 mutations in patients with familial breast cancer [In Spanish]. *Med Clin.* 2005;124(1):10-12.

71. de Juan Jiménez I, Casado ZG, Suela SP, et al. Novel and recurrent BRCA1/BRCA2 mutations in early onset and familial breast and ovarian cancer detected in the Program of Genetic Counseling in Cancer of Valencian Community (eastern Spain). Relationship of family phenotypes with mutation prevalence. *Fam Cancer.* 2013;12(4):767-777.

72. González-Hormazábal P, Bravo T, Blanco R, et al. Association of common ATM variants with familial breast cancer in a South American population. *BMC Cancer.* 2008;8(1):1.

73. Leyton Y, Gonzalez-Hormazabal P, Blanco R, et al. Association of PALB2 sequence variants with the risk of familial and early-onset breast cancer in a South-American population. *BMC Cancer.* 2015;15(1):1.

74. Calderón-Zúñiga Fdel C, Ocampo-Gomez G, Lopez-Marquez FC, et al. ATM polymorphisms IVS24-9delT, IVS38-8T>C, and 5557G>A in Mexican women with familial and/or early-onset breast cancer. *Salud Publica Mex.* 2014;56(2):206-212.

75. Bretsky P, Haiman CA, Gilad S, et al. The relationship between twenty missense ATM variants andb cancer risk the multiethnic cohort. *Cancer Epidemiol Biomark Prevent.* 2003;12(8):733-738.

76. Bell DW, Kim SH, Godwin AK, et al. Genetic and functional analysis of CHEK2 (CHK2) variants in multiethnic cohorts. *Int J Cancer.* 2007;121(12):2661-2667.

77. Damiola F, Pertesi M, Oliver J, et al. Rare key functional domain missense substitutions in MRE11A, RAD50, and NBN contribute to breast cancer susceptibility: results from a breast cancer family registry case-control mutation-screening study. *Breast Cancer Res.* 2014;16(3):R58.

78. Assumpção JG, Seidinger AL, Mastellaro MJ, et al. Association of the germline TP53 R337H mutation with breast cancer in southern Brazil. *BMC Cancer.* 2008;8(1):1.

79. Giacomazzi J, Graudenz MS, Osorio CA, et al. Prevalence of the TP53 p. R337H mutation in breast cancer patients in Brazil. *PloS One.* 2014;9(6):e99893.

80. Jara L, Acevedo ML, Blanco R, et al. RAD51 135G> C polymorphism and risk of familial breast cancer in a South American population. *Cancer Genet Cytogenet.* 2007;178(1):65-69.

81. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *J Clin Ocol.* 2009;27(8):1250-1256.

82. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes correlation between tumor type, family structure, and TP53 genotype. *Cancer Res.* 2003;63(20):6643-6650.

83. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res.* 1988;48(18):5358-5362.

84. Børresen A-L, Andersen TI, Garber J, et al. Screening for germ line TP53 mutations in breast cancer patients. *Cancer Res.* 1992;52(11):3234-3236.

85. Sidransky D, Tokino T, Helzlsouer K, et al. Inherited p53 gene mutations in breast cancer. *Cancer research.* 1992;52(10):2984-2986.

86. Lalloo F, Varley J, Moran A, et al. BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. *Eur J Cancer.* 2006;42(8):1143-1150.

87. Ginsburg OM, Akbari MR, Aziz Z, et al. The prevalence of germ-line TP53 mutations in women diagnosed with breast cancer before age 30. *Fam Cancer.* 2009;8(4):563-567.

88. McCuaig JM, Armel SR, Novokmet A, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? *Fam Cancer.* 2012;11(4):607-613.

89. Ribeiro RC, Sandrini F, Figueiredo B, et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. *Proceed Natl Acad Sci.* 2001;98(16):9330-9335.

90. Gomes M, Kotsopoulos J, de Almeida GL, et al. The R337H mutation in TP53 and breast cancer in Brazil. *Hered Cancer Clin Pract.* 2012;10(1):3.

91. Custódio G, Parise GA, Kiesel Filho N, et al. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. *J Clin Oncol.* 2013;31(20):2619-2626.

92. Palmero EI, Schüler-Faccini L, Caleffi M, et al. Detection of R337H, a germline TP53 mutation predisposing to multiple cancers, in asymptomatic women participating in a breast cancer screening program in southern Brazil. *Cancer Lett.* 2008;261(1):21-25.

93. Garritano S, Gemignani F, Palmero EI, et al. Detailed haplotype analysis at the TP53 locus in p. R337H mutation carriers in the population of southern Brazil: evidence for a founder effect. *Hum Mutat.* 2010;31(2):143-150.

94. Blazer KR, Nehoray B, Solomon I, et al. Next-generation testing for cancer risk: perceptions, experiences, and needs among early adopters in community healthcare settings. *Genet Test Molec Biomark.* 2015;19(12):657-665.

95. Maxwell KN, Wubbenhorst B, D'Andrea K, et al. Prevalence of mutations in a panel of breast cancer susceptibility genes in BRCA1/2-negative patients with early-onset breast cancer. *Genet Med.* 2014;17(8):630-638.

96. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer.* 2015;121(1):25-33.

97. Kapoor NS, Curcio LD, Blakemore CA, et al. Multigene panel testing detects equal rates of pathogenic BRCA1/2 mutations and has a higher diagnostic yield compared to limited BRCA1/2 analysis alone in patients at risk for hereditary breast cancer. *Ann Surg Oncol.* 2015;22(10):3282-3288.

98. Li J, Meeks H, Feng B-J, et al. Targeted massively parallel sequencing of a panel of putative breast cancer susceptibility genes in a large cohort of multiple-case breast and ovarian cancer families. *J Med Genet.* 2016;53(1):34-42.

99. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol.* 2015;33(4):304-311.

100. Desmond A, Kurian AW, Gabree M, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol.* 2015;1(7):943-951.

101. Doherty J, Bonadies DC, Matloff ET. Testing for hereditary breast cancer: panel or targeted testing? Experience from a clinical cancer genetics practice. *J Genet Counsel.* 2015;24(4):683-687.

102. Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multi-

ple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol.* 2014;32(19):2001-2009.

103. Lincoln SE, Kobayashi Y, Anderson MJ, et al. A systematic comparison of traditional and multigene panel testing for hereditary breast and ovarian cancer genes in more than 1000 patients. *J Molec Diagnost.* 2015;17(5):533-544.

104. Ricker C, Culver JO, Lowstuter K, et al. Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort. *Cancer Genet.* 2016; 209(4):130-137.

105. Mai PL, Vadaparampil ST, Breen N, et al. Awareness of cancer susceptibility genetic testing: the 2000, 2005, and 2010 National Health Interview Surveys. *Am J Prevent Med.* 2014;46(5):440-448.

106. Vadaparampil ST, Wideroff L, Breen N, et al. The impact of acculturation on awareness of genetic testing for increased cancer risk among Hispanics in the year 2000 National Health Interview Survey. *Cancer Epidemiol Biomark Prevent.* 2006;15(4):618-623.

107. Wideroff L, Thomas Vadaparampil S, Breen N, et al. Awareness of genetic testing for increased cancer risk in the year 2000 National Health Interview Survey. *Pub Health Genom.* 2004;6(3):147-156.

108. Gammon AD, Rothwell E, Simmons R, et al. Awareness and preferences regarding BRCA1/2 genetic counseling and testing among Latinas and non-Latina white women at increased risk for hereditary breast and ovarian cancer. *J Genet Counsel.* 2011;20(6):625-638.

109. Vadaparampil ST, McIntyre J, Quinn GP. Awareness, perceptions, and provider recommendation related to genetic testing for hereditary breast cancer risk among at-risk Hispanic women: similarities and variations by sub-ethnicity. *J Genet Counsel.* 2010;19(6):618-629.

110. Kaplan CP, Haas JS, Pérez-Stable EJ, et al. Breast cancer risk reduction options: awareness, discussion, and use among women from four ethnic groups. *Cancer Epidemiol Biomark Prevent.* 2006;15(1):162-166.

111. Mays D, Sharff ME, DeMarco TA, et al. Outcomes of a systems-level intervention offering breast cancer risk assessments to low-income underserved women. *Fam Cancer.* 2012;11(3):493-502.

112. Jagsi R, Griffith KA, Kurian AW, et al. Concerns about cancer risk and experiences with genetic testing in a diverse population of patients with breast cancer. *J Clin Oncol.* 2015;33(14):1584-1591.

113. Lagos VI, Perez MA, Ricker CN, et al. Social-cognitive aspects of underserved Latinas preparing to undergo genetic cancer risk assessment for hereditary breast and ovarian cancer. *Psycho-Oncology.* 2008;17(8):774-782.

114. Vadaparampil ST, Quinn GP, Dutil J, et al. A pilot study of knowledge and interest of genetic counseling and testing for hereditary breast and ovarian cancer syndrome among Puerto Rican women. *J Comm Genet.* 2011;2(4):211-221.

115. Ricker C, Lagos V, Feldman N, et al. If we build it… will they come?–establishing a cancer genetics services clinic for an underserved predominantly Latina cohort. *J Genet Counsel.* 2006;15(6):505-514.

116. Komenaka IK, Nodora JN, Madlensky L, et al. Participation of low-income women in genetic cancer risk assessment and BRCA 1/2 testing: the experience of a safety-net institution. *J Comm Genet.* 2015:1-7.

117. Olaya W, Esquivel P, Wong JH, et al. Disparities in BRCA testing: when insurance coverage is not a barrier. *Am J Surg.* 2009;198(4):562-565.

118. Woodson AH, Profato JL, Rizvi SH, et al. Service delivery model and experiences in a cancer genetics clinic for an underserved population. *J Health Care Poor Underserv.* 2015;26(3):784-791.

119. Macconaill LE, Garraway LA. Clinical implications of the cancer genome. *J Clin Oncol.* 2010;28(35):5219-5228.

120. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature.* 2007;447(7148):1087-1093.

121. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor–positive breast cancer. *Nat Genet.* 2008;40(6):703-706.

122. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet.* 2007;39(7):870-874.

123. Garcia-Closas M, Couch FJ, Lindstrom S, et al. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet.* 2013;45(4):392-398.

124. Fletcher O, Johnson N, Orr N, et al. Novel breast cancer susceptibility locus at 9q31. 2: results of a genome-wide association study. *J Natl Cancer Inst.* 2011;103(5):425-435.

125. Gold B, Kirchhoff T, Stefanov S, et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22. 33. *Proceed Natl Acad Sci.* 2008;105(11):4340-4345.

126. Turnbull C, Ahmed S, Morrison J, et al. Genome-wide association study identifies five new breast cancer susceptibility loci. *Nat Genet.* 2010;42(6):504-507.

127. Gaudet MM, Kuchenbaecker KB, Vijai J, et al. Identification of a BRCA2-specific modifier locus at 6p24 related to breast cancer risk. *PLoS Genet.* 2013;9(3):e1003173.

128. Long J, Cai Q, Sung H, et al. Genome-wide association study in east Asians identifies novel susceptibility loci for breast cancer. *PLoS Genet.* 2012;8(2):e1002532.

129. Couch FJ, Wang X, McGuffog L, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genet.* 2013;9(3):e1003212.

130. Li J, Humphreys K, Darabi H, et al. A genome-wide association scan on estrogen receptor-negative breast cancer. *Breast Cancer Res.* 2010;12(6):R93.

131. Murabito JM, Rosenberg CL, Finger D, et al. A genome-wide association study of breast and prostate cancer in the NHLBI's Framingham Heart Study. *BMC Med Genet.* 2007;8(1):1.

132. Antoniou AC, Wang X, Fredericksen ZS, et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet.* 2010;42(10):885-892.

133. Cai Q, Long J, Lu W, et al. Genome-wide association study identifies breast cancer risk variant at 10q21. 2: results from the Asia Breast Cancer Consortium. *Hum Molec Genet.* 2011;20(24):4991-4999.

134. Kim H-c, Lee J-Y, Sung H, et al. A genome-wide association study identifies a breast cancer risk variant in ERBB4 at 2q34: results from the Seoul Breast Cancer Study. *Breast Cancer Res.* 2012;14(2):1-12.

135. Elgazzar S, Zembutsu H, Takahashi A, et al. A genome-wide association study identifies a genetic variant in the SIAH2 locus associated with hormonal receptor-positive breast cancer in Japanese. *J Hum Genet.* 2012;57(12):766-771.

136. Long J, Cai Q, Shu X-O, et al. Identification of a functional genetic variant at 16q12. 1 for breast cancer risk: results from the Asia Breast Cancer Consortium. *PLoS Genet.* 2010;6(6):e1001002.

137. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet.* 2015;47(4):373-380.

138. Thomas G, Jacobs KB, Kraft P, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11. 2 and 14q24. 1 (RAD51L1). *Nat Genet.* 2009;41(5):579-584.

139. Siddiq A, Couch FJ, Chen GK, et al. A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. *Hum Molec Genet.* 2012;21(24):5373-5384.

140. Michailidou K, Hall P, Gonzalez-Neira A, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet.* 2013;45(4):353-361.

141. Chen F, Chen GK, Stram DO, et al. A genome-wide association study of breast cancer in women of African ancestry. *Hum Genet.* 2013;132(1):39-48.

142. Haiman CA, Chen GK, Vachon CM, et al. A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nat Genet.* 2011;43(12):1210-1214.

143. Zheng W, Long J, Gao Y-T, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25. 1. *Nat Genet.* 2009;41(3):324-328.

144. Fejerman L, Ahmadiyeh N, Hu D, et al. Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25. *Nat Comm.* 2014;5.

145. Haiman CA, Stram DO, Pike MC, et al. A comprehensive haplotype analysis of CYP19 and breast cancer risk: the multiethnic cohort. *Hum Molec Genet.* 2003;12(20):2679-2692.

146. Cheng I, Penney KL, Stram DO, et al. Haplotype-based association studies of IGFBP1 and IGFBP3 with prostate and breast cancer risk: the multiethnic cohort. *Cancer Epidemiol Biomark Prevent.* 2006;15(10):1993-1997.

147. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19(1):61-109.

148. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol.* 2003;13(9):S18-S77.

149. Slattery ML, John EM, Torres-Mejia G, et al. Genetic variation in genes involved in hormones, inflammation and energetic factors and breast cancer risk in an admixed population. *Carcinogenesis.* 2012;33(8):1512-1521.

150. Ramírez-Patiño R, Figuera LE, Puebla-Pérez AM, et al. Intron 4 VNTR (4a/b) polymorphism of the endothelial nitric oxide synthase gene is associated with breast cancer in Mexican women. *J Korean Med Sci.* 2013;28(11):1587-1594.

151. Quintero-Ramos A, Gutiérrez-Rubio S, Del Toro-Arreola A, et al. Association between polymorphisms in the thymidylate synthase gene and risk of breast cancer in a Mexican population. *Genet Mol Res.* 2014;13(4):8749-8756.

152. Jara L, Dubois K, Gaete D, et al. Variants in DNA double-strand break repair genes and risk of familial breast cancer in a South American population. *Breast Cancer Res Treat.* 2010;122(3):813-822.

153. Oliveira CB, Cardoso-Filho C, Bossi LS, et al. Association of CYP1A1 A4889G and T6235C polymorphisms with the risk of sporadic breast cancer in Brazilian women. *Clinics.* 2015;70(10):680-685.

154. Pérez-Mayoral J, Pacheco-Torres AL, Morales L, et al. Genetic polymorphisms in RAD23B and XPC modulate DNA repair capacity and breast cancer risk in Puerto Rican women. *Molec Carcinogen.* 2013;52(suppl 1):127-138.

155. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol.* 2000;151(4):346-357.

156. Kolonel LN, Altshuler D, Henderson BE. The multiethnic cohort study: exploring genes, lifestyle and cancer risk. *Nat Rev Cancer.* 2004;4(7):519-527.

157. John EM, Phipps AI, Davis A, et al. Migration history, acculturation,

and breast cancer risk in Hispanic women. *Cancer Epidemiol Biomark Prevent.* 2005;14(12):2905-2913.
158. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population the san francisco Bay area breast cancer study. *Cancer Epidemiol Biomark Prevent.* 2003;12(11):1143-1152.
159. John EM, Hopper JL, Beck JC, et al. The breast cancer family registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. *Breast Cancer Res.* 2004;6(4):R375-R389.
160. Slattery ML, Sweeney C, Edwards S, et al. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. *Breast Cancer Res Treat.* 2007;102(1):85-101.
161. Slattery ML, Sweeney C, Herrick J, et al. ESR1, AR, body size, and breast cancer risk in Hispanic and non-Hispanic white women living in the southwestern United States. *Breast Cancer Res Treat.* 2007;105(3):327-335.
162. Gallegos-Arreola MP, Figuera LE, Flores-Ramos LG, et al. Association of the Alu insertion polymorphism in the progesterone receptor gene with breast cancer in a Mexican population. *Arch Med Science.* 2015;11(3):551.
163. Haiman CA, Garcia RR, Hsu C, et al. Screening and association testing of common coding variation in steroid hormone receptor co-activator and co-repressor genes in relation to breast cancer risk: the multiethnic cohort. *BMC Cancer.* 2009;9(1):1.
164. Boone SD, Baumgartner KB, Baumgartner RN, et al. Associations between CYP19A1 polymorphisms, Native American ancestry, and breast cancer risk and mortality: the Breast Cancer Health Disparities Study. *Cancer Cause Control.* 2014;25(11):1461-1471.
165. Moreno-Galván M, Herrera-González NE, Robles-Pérez V, et al. Impact of CYP1A1 and COMT genotypes on breast cancer risk in Mexican women: a pilot study. *Int J Biol Mark.* 2009;25(3):157-163.
166. Weston A, Pan C, Bleiweiss IJ, et al. CYP17 genotype and breast cancer risk. *Cancer Epidemiol Biomark Prevent.* 1998;7(10):941-944.
167. Sarkissyan M, Mishra DK, Wu Y, et al. IGF gene polymorphisms and breast cancer in African-American and Hispanic women. *Int J Oncol.* 2011;38(6):1663-1673.
168. Slattery ML, John EM, Stern MC, et al. Associations with growth factor genes (FGF1, FGF2, PDGFB, FGFR2, NRG2, EGF, ERBB2) with breast cancer risk and survival: the Breast Cancer Health Disparities study. *Breast Cancer Res Treat.* 2013;140(3):587-601.
169. Connor AE, Baumgartner RN, Baumgartner KB, et al. Epidermal growth factor receptor (EGFR) polymorphisms and breast cancer among Hispanic and non-Hispanic white women: the Breast Cancer Health Disparities study. *Int J Molec Epidemiol Genet.* 2013;4(4):235.
170. Boone SD, Baumgartner KB, Baumgartner RN, et al. Associations between genetic variants in the TGF-β signaling pathway and breast cancer risk among Hispanic and non-Hispanic white women. *Breast Cancer Res Treat.* 2013;141(2):287-297.
171. Slattery ML, John EM, Torres-Mejia G, et al. Genetic variation in bone morphogenetic proteins and breast cancer risk in hispanic and non-hispanic white women: The breast cancer health disparities study. *Int J Cancer.* 2013;132(12):2928-2939.
172. Ingles SA, Garcia DG, Wang W, et al. Vitamin D receptor genotype and breast cancer in Latinas (United States). *Cancer Cause Control.* 2000;11(1):25-30.
173. Connor AE, Baumgartner RN, Baumgartner KB, et al. Associations between TCF7L2 polymorphisms and risk of breast cancer among Hispanic and non-Hispanic White women: the Breast Cancer Health Disparities study. *Breast Cancer Res Treat.* 2012;136(2):593-602.
174. Slattery ML, John E, Torres-Mejia G, et al. Matrix metalloproteinase genes are associated with breast cancer risk and survival: the Breast Cancer Health Disparities study. *PloS One.* 2013;8(5):e63165.
175. Delgado-Enciso I, Cepeda-Lopez FR, Monrroy-Guizar EA, et al. Matrix metalloproteinase-2 promoter polymorphism is associated with breast cancer in a Mexican population. *Gynecol Obstet Invest.* 2008;65(1):68-72.
176. Slattery ML, Herrick JS, Torres-Mejia G, et al. Genetic variants in interleukin genes are associated with breast cancer risk and survival in a genetically admixed population: the Breast Cancer Health Disparities study. *Carcinogenesis.* 2014:bgu078.
177. Slattery ML, Lundgreen A, Hines L, et al. Energy homeostasis genes and breast cancer risk: The influence of ancestry, body size, and menopausal status, the breast cancer health disparities study. *Cancer Epidemiol.* 2015;39(6):1113-1122.
178. Connor A, Baumgartner RN, Kerber RA, et al. ADRB2 G–G haplotype associated with breast cancer risk among Hispanic and non-Hispanic white women: interaction with type 2 diabetes and obesity. *Cancer Cause Control.* 2012;23(10):1653-1663.
179. Connor AE, Baumgartner RN, Baumgartner KB, et al. Associations between ALOX, COX, and CRP polymorphisms and breast cancer among Hispanic and non-Hispanic white women: the breast cancer health disparities study. *Molec Carcinogen.* 2015;54(12):1541-1553.
180. Kaklamani VG, Hoffmann TJ, Thornton TA, et al. Adiponectin pathway polymorphisms and risk of breast cancer in African Americans and Hispanics in the Women's Health Initiative. *Breast Cancer Res Treat.* 2013;139(2):461-468.
181. Flores-Ramos LG, Escoto-De Dios A, Puebla-Pérez A, et al. Association of the tumor necrosis factor-alpha-308G>: a polymorphism with breast cancer in Mexican women. *Genet Mol Res.* 2013;12:5680-5693.
182. Pellatt AJ, Wolff RK, John EM, et al. SEPP1 influences breast cancer risk among women with greater native american ancestry: the breast cancer health disparities study. *PLoS One.* 2013;8(11):e80554.
183. Baumgartner KB, Schlierf TJ, Yang D, et al. N-acetyltransferase 2 genotype modification of active cigarette smoking on breast cancer risk among hispanic and non-hispanic white women. *Toxicol Sci.* 2009:kfp199.
184. Cardenas-Rodriguez N, Lara-Padilla E, Bandala C, et al. CYP2W1, CYP4F11 and CYP8A1 polymorphisms and interaction of CYP2W1 genotypes with risk factors in Mexican women with breast cancer. *Asian Pac J Cancer Prevent.* 2012;13(3):837-846.
185. Gutierrez-Rubio S, Quintero-Ramos A, Duran-Cardenas A, et al. 1236 C/T and 3435 C/T polymorphisms of the ABCB1 gene in Mexican breast cancer patients. *Genet Mol Res.* 2015;14(1):1250-1259.
186. Ramos-Silva A, Figuera L, Soto-Quintana O, et al. Association of the C677T polymorphism in the methylenetetrahydrofolate reductase gene with breast cancer in a Mexican population. *Genet Mol Res.* 2015;14(2):4015.
187. Slattery ML, John EM, Torres-Mejia G, et al. Angiogenesis genes, dietary oxidative balance and breast cancer risk and progression: the Breast Cancer Health Disparities study. *Int J Cancer.* 2014;134(3):629-644.
188. Tsai H-J, Choudhry S, Naqvi M, et al. Comparison of three methods to estimate genetic ancestry and control for stratification in genetic association studies among admixed populations. *Hum Genet.* 2005;118(3-4):424-433.
189. Tang H, Quertermous T, Rodriguez B, et al. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. *Am J Hum Genet.* 2005;76(2):268-275.
190. Slattery ML, Baumgartner KB, Giuliano AR, et al. Replication of five GWAS-identified loci and breast cancer risk among Hispanic and non-Hispanic white women living in the southwestern United States. *Breast Cancer Res Treat.* 2011;129(2):531-539.
191. Fejerman L, Stern MC, John EM, et al. Interaction between common breast cancer susceptibility variants, genetic ancestry, and nongenetic risk factors in Hispanic women. *Cancer Epidemiol Biomark Prevent.* 2015;24(11):1731-1738.
192. Fejerman L, Stern MC, Ziv E, et al. Genetic ancestry modifies the association between genetic risk variants and breast cancer risk among Hispanic and non-Hispanic white women. *Carcinogenesis.* 2013;34(8):1787-1793.
193. Murillo-Zamora E, Moreno-Macías H, Ziv E, et al. Association between rs2981582 polymorphism in the FGFR2 gene and the risk of breast cancer in Mexican women. *Arch Med Res.* 2013;44(6):459-466.
194. Jara L, Gonzalez-Hormazabal P, Cerceño K, et al. Genetic variants in FGFR2 and MAP3K1 are associated with the risk of familial and early-onset breast cancer in a South-American population. *Breast Cancer Res Treat.* 2013;137(2):559-569.
195. Elematore I, Gonzalez-Hormazabal P, Reyes JM, et al. Association of genetic variants at TOX3, 2q35 and 8q24 with the risk of familial and early-onset breast cancer in a South-American population. *Molec Biol Rep.* 2014;41(6):3715-3722.
196. Cheng C-Y, Kao WL, Patterson N, et al. Admixture mapping of 15,280 African Americans identifies obesity susceptibility loci on chromosomes 5 and X. *PLoS Genet.* 2009;5(5):e1000490.
197. Jia L, Landan G, Pomerantz M, et al. Functional enhancers at the gene-poor 8q24 cancer-linked locus. *PLoS Genet.* 2009;5(8):e1000597.
198. Reich D, Nalls MA, Kao WL, et al. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. *PLoS Genet.* 2009;5(1):e1000360.
199. Nalls MA, Wilson JG, Patterson NJ, et al. Admixture mapping of white cell count: genetic locus responsible for lower white blood cell count in the Health ABC and Jackson Heart studies. *Am J Hum Genet.* 2008;82(1):81-87.
200. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics.* 2000;155(2):945-959.
201. Reich D, Patterson N, Ramesh V, et al. Admixture mapping of an allele affecting interleukin 6 soluble receptor and interleukin 6 levels. *Am J Hum Genet.* 2007;80(4):716-726.
202. Winkler CA, Nelson GW, Smith MW. Admixture mapping comes of age. *Ann Rev Genom Hum Genet.* 2010;11:65-89.
203. Deo RC, Patterson N, Tandon A, et al. A high-density admixture scan in 1,670 African Americans with hypertension. *PLoS Genet.* 2007;3(11):e196.
204. Freedman ML, Haiman CA, Patterson N, et al. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. *Proceed Natl Acad Sci.* 2006;103(38):14068-14073.
205. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60(5):277-300.
206. Fejerman L, John EM, Huntsman S, et al. Genetic ancestry and risk of breast cancer among US Latinas. *Cancer Res.* 2008;68(23):9723-9728.
207. Fejerman L, Romieu I, John EM, et al. European ancestry is positively associated with breast cancer risk in Mexican women. *Cancer Epidemiol Biomark Prevent.* 2010;19(4):1074-1082.
208. Fejerman L, Chen GK, Eng C, et al. Admixture mapping identifies a locus on 6q25 associated with breast cancer risk in US Latinas. *Hum Molec Genet.* 2012;21(8):1907-1917.
209. Hines LM, Risendal B, Byers T, et al. Ethnic disparities in breast tumor

phenotypic subtypes in Hispanic and non-Hispanic white women. *J Women Health.* 2011;20(10):1543-1550.
210. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Arch Intern Med.* 2003;163(1):49-56.
211. Chlebowski RT, Chen Z, Anderson GL, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J Natl Cancer Inst.* 2005;97(6):439-448.
212. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. *Breast Cancer Res.* 2007;9(1):R6.
213. Hausauer AK, Keegan T, Chang ET, et al. Recent breast cancer trends among Asian/Pacific Islander, Hispanic, and African-American women in the US: changes by tumor subtype. *Breast Cancer Res.* 2007;9(6):R90.
214. Parise CA, Bauer KR, Brown MM, et al. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1999–2004. *Breast J.* 2009;15(6):593-602.
215. Carvalho FM, Bacchi LM, Pincerato KM, et al. Geographic differences in the distribution of molecular subtypes of breast cancer in Brazil. *BMC Women Health.* 2014;14(1):1.
216. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst.* 2014;106(5):dju055.
217. Swain SM, Baselga J, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med.* 2015;372(8):724-734.
218. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005;353(16):1673-1684.
219. Harris LN, Ismaila N, McShane LM, et al; American Society of Clinical Oncology Clinical Practice Guideline. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer. *J Clin Oncol.* 2016;34(10):1134-1150.
220. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi7-23.
221. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Pratice Guidelines in Oncology: Breast Cancer. v2.*2016. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 15, 2016.
222. Kalinsky K, Lim EA, Andreopoulou E, et al. Increased expression of tumor proliferation genes in Hispanic women with early-stage breast cancer. *Cancer Invest.* 2014;32(9):439-444.
223. Eiermann W, Rezai M, Kümmel S, et al. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. *Annals of oncology.* 2012:mds512.
224. Partin JF, Mamounas EP. Impact of the 21-gene recurrence score assay compared with standard clinicopathologic guidelines in adjuvant therapy selection for node-negative, estrogen receptor-positive breast cancer. *Ann Surg Oncol.* 2011;18(12):3399-3406.
225. Geffen D, Abu-Ghanem S, Sion-Vardy N, et al. The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. *Ann Oncol.* 2011:mdq769.
226. Lo SS, Mumby PB, Norton J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol.* 2010;28(10):1671-1676.
227. Bargallo JE, Lara F, Shaw-Dulin R, et al. A study of the impact of the 21-gene breast cancer assay on the use of adjuvant chemotherapy in women with breast cancer in a Mexican public hospital. *J Surg Oncol.* 2015;111(2):203-207.
228. Bargalló-Rocha JE, Lara-Medina F, Pérez-Sánchez V, et al. Cost-effectiveness of the 21-gene breast cancer assay in Mexico. *Adv Ther.* 2015;32(3):239-253.
229. Kalow W, Gunn DR. Some statistical data on atypical cholinesterase of human serum. *Ann Hum Genet.* 1959;23(3):239-250.
230. Kalow W, Staron N. On distribution and inheritance of atypical forms of human serum cholinesterase, as indicated by dibucaine numbers. C*A J Biochem Physiol.* 1957;35(12):1305-1320.
231. Evans DAP, Manley KA, McKusick VA. Genetic control of isoniazid metabolism in man. *Br Med J.* 1960;2(5197):485.
232. Li J, Bluth MH. Pharmacogenomics of drug metabolizing enzymes and transporters: implications for cancer therapy. *Pharmgenomics Pers Med*. 2011;4:11-33.
233. O'Donnell, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. *Clin Cancer Res*. 2009;15(15):4806-4814.
234. Grabinski J, Smith L, Chisholm G, et al. Relationship between CYP2D6 and estrogen receptor alpha polymorphisms on tamoxifen metabolism in adjuvant breast cancer treatment. *ASCO Ann Meet Proceed*. 2006;24(18 suppl):505.
235. Alcazar-González GA, Calderón-Garcidueñas AL, Garza-Rodríguez ML, et al. Comparative study of polymorphism frequencies of the CYP2D6, CYP3A5, CYP2C8 and IL-10 genes in Mexican and Spanish women with breast cancer. *Pharmacogenomics*. 2013;14(13):1583-1592.
236. González-Tejera G, Gaedigk A, Corey S. Genetic variants of the drug-metabolizing enzyme CYP2D6 in Puerto Rican psychiatry patients: a preliminary report and potential implications for breast cancer patients. *P R Health Sci J.* 2010;29(3):299-304.
237. Bernard S, Neville KA, Nguyen AT, et al. Interethnic differences in genetic polymorphisms of CYP2D6 in the US population: clinical implications. *Oncologist.* 2006;11(2):126-135.
238. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol.* 2010;11(12):1135-1141.
239. Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol.* 2007;25(5):486-492.
240. Ma CX, Adjei AA, Salavaggione OE, et al. Human aromatase: gene resequencing and functional genomics. *Cancer Res.* 2005;65(23):11071-11082.
241. Moy B, Tu D, Pater J, et al. Clinical outcomes of ethnic minority women in MA.17: a trial of letrozole after 5 years of tamoxifen in postmenopausal women with early stage breast cancer. *Ann Oncol.* 2006;17(11):1637-1643.
242. Allman R, Dite GS, Hopper JL, et al. SNPs and breast cancer risk prediction for African American and Hispanic women. *Breast Cancer Res Treat.* 2015;154(3):583-589.
243. Parra A, Karnad AB, Thompson IM. Hispanic accrual on randomized cancer clinical trials: a call to arms. *J Clin Oncol.* 2014;32(18):1871-1873.
244. Gordon NP, Iribarren C. Health-related characteristics and preferred methods of receiving health education according to dominant language among Latinos aged 25 to 64 in a large Northern California health plan. *BMC Public Health.* 2008;8(1):1.
245. Merchant G, Buelna C, Castañeda SF, et al. Accelerometer-measured sedentary time among Hispanic adults: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prevent Med Rep.* 2015;2:845-853.
246. Bonner D, Cragun D, Reynolds M, et al. Recruitment of a population-based sample of young black women with breast cancer through a state cancer Registry. *Breast J.* 2016;22(2):166-172.
247. Darling M, Gonzalez F, Graves K, et al. Practical tips for establishing partnerships with academic researchers: a resource guide for community-based organizations. *Prog Community Health Partnersh.* 2015;9(2):203-212.
248. Rush CL, Darling M, Elliott MG, et al. Engaging Latina cancer survivors, their caregivers, and community partners in a randomized controlled trial: Nueva Vida intervention. *Qua Life Res.* 2015;24(5):1107-1118.
249. Detz A, Mangione CM, de Jaimes FN, et al. Language concordance, interpersonal care, and diabetes self-care in rural Latino patients. *J Gen Intern Med.* 2014;29(12):1650-1656.