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Mutations in context: implications of *BRCA* testing in diverse populations

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Abstract Cancer is a common non-communicable disease worldwide, although it exhibits differential population trends in incidence and mortality rates. The differences relate to population structure, environmental risk factors as well as health system organization. This article discusses the potential impact of genetic testing on population health, focusing in particular on the mutational spectrum of breast cancer susceptibility genes in diverse populations. We identify the need for improved access to, and increased investment in, comprehensive cancer risk assessment and genetic testing as well as cancer control measures that take into account lifestyle, environmental, and social factors in understudied minority groups.

Keywords Genetic testing · Breast cancer · Disparity · Precision medicine

Introduction

Globally, non-communicable diseases (NCDs) currently contribute to more than 38 million deaths worldwide each year, with cancer accounting for 8.2 million of these deaths. Breast cancer is the leading cause of death among women worldwide. The disparities in incidence and mortality rates of breast cancer observed between developed and developing countries are substantial [1]. Personalized cancer risk assessment and prevention offers a new approach to breast cancer early detection and treatment that may alleviate global disparities in breast cancer outcomes, but more work is required in order to implement precision medicine for all.

Breast cancer is not one disease. Rather, it is a complex group of genetically driven diseases caused by the progressive accumulation of genomic alterations involving "driver" and "passenger" mutations. In all populations, a fraction of breast cancer can be explained by inherited mutations in breast cancer susceptibility genes. To date, variants identified to be associated with breast cancer risk account for nearly 50% of the heritability of breast cancer [2]. By identifying non-genetic risk factors such as age, family history of cancer, early menarche, late menopause, age at first birth, nulliparity, exogenous hormone use, obesity, exposure to radiation, alcohol consumption, healthcare professionals can assess patients' risk of the disease and work together with the patients to mediate these risks. It is possible to reduce modifiable risk factors, alter environmental factors, and adjust screening methods to prevent advanced-stage diagnosis in women at risk of the most aggressive breast cancer phenotypes.

The Precision Medicine Initiative (PMI), now renamed "All of Us" [3] asserts that it is not only important to lower disease prevalence in populations, but also to ensure individualized care and prevention based on patients' unique environmental, lifestyle, and genomic differences. The prior use of "one-size-fits-all" recommendations and treatment approaches is inefficient and ineffective, as overdiagnosis can be costly and dangerous for false positives,

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and under-diagnosis fails to identify all individuals at risk. Through the application of precision medicine, there is great potential to decrease incidence, prevalence, and mortality rates of all NCDs, especially cancer.

Genetic testing is one means of identifying those with a predisposition to cancer and of more accurately determining the individual's risk. Now that sequencing technologies have improved and that genetic testing has become more affordable than in the past decade, it is possible to sequence and analyze the entire human genome in one day with next-generation sequencing (NGS) methodology [4, 5]. As such, individual and population-wide genetic assessments are feasible in clinical settings. Genetic profiles of individuals and populations reveal important information about the degree of genetic admixture and susceptibility to genetic diseases [6]. Unfortunately, there is currently paucity of data on genetic basis of disease in non-European ancestry groups. To improve population health and reduce health disparities, there is an urgent need for data on "All of Us", as envisaged by PMI.

Accordingly, the next decade will usher in the era of personalized cancer prevention and early detection. As data from sequencing becomes more comprehensive than that obtained from prior technologies, extracting meaningful findings from Big Data will be key in driving precision prevention that benefits high-risk patients. In this review, lessons learned over the past 20 years since the identification of *BRCA1* and *BRCA2* genes are presented in order to examine the clinical context and the impact of genetic testing in diverse populations across the globe.

BRCA1, BRCA2 and the risk of breast cancer in populations

The discoveries of the *BRCA1* and *BRCA2* genes were one of the greatest findings to date in human genetics [7, 8]. Mutations in these two genes account for at least 20% of hereditary breast cancer cases and an estimated 5–10% of all cases in some inbred populations. Previous retrospective studies found that penetrance assessments for *BRCA1* and *BRCA2* mutation carriers is substantial and the estimate of cumulative breast cancer risk by age 70 years was reported with wide confidence intervals (*BRCA1*: 40–87%; *BRCA2*: 27–84%) [9, 10]. These observations support the hypothesis that genetic and lifestyle/hormonal factors modify cancer risks for women with these mutations. Based on a recent prospective cohort study of 6036 *BRCA1* and 3,820 *BRCA2* female mutation carriers, the cumulative breast cancer risk by age 80 years was 72 and 69% for *BRCA1* and *BRCA2*, respectively [11].

Germline pathogenic mutations in *BRCA1* and *BRCA2* are inherited in an autosomal dominant manner. As such, mutations in these two genes should be suspected if the individual or her/his family has a history of early-onset breast cancer. However, because of the penetrance of these mutations, there can be differences in the age of breast cancer onset both among and within families. Regardless, breast cancer onset for individuals with a *BRCA1* or *BRCA2* mutation is typically before age 50 [12, 13]. Knowledge of the burden of aggressive, early-onset breast cancer caused by *BRCA* mutations has led to recommendations of cascade testing in families to identify all family members at risk once a mutation is identified, and, in some instances, calls for large-scale population screening to identify at-risk individuals. However, there is paucity of data in non-European populations, which makes accurate risk estimates for diverse populations difficult to provide. Moreover, the economic, social and cultural barriers to widespread adoption of genetic testing remain poorly understood, which underscores the need for additional research on how best to disseminate advances in cancer genetics to benefit all populations.

Research teams around the world, including in Africa [14], Europe [15], Latin America [16], Oceania [17], and Asia [18], have described pathogenic mutations in these genes that contribute to defective transcripts and malfunctioning proteins and their segregation with breast and ovarian cancer in high-risk families. Some of these pathogenic *BRCA* mutations are fixed in certain populations as "founder mutations." Founder mutations are informative and valuable for developing cancer gene screening panels, which help to analyze genetic susceptibility profiles rapidly and inexpensively when the patient's ancestral background is known. For example, *BRCA1* c.68_69delAG (185delAG), *BRCA1* c.5266dupC (5382insC), and *BRCA2* c.5946_5946delT (6174delT) are fixed in Ashkenazi Jewish population [19, 20]. However, further research revealed these mutations in other populations in Europe, Latin America, and North Africa, which then led to the hypothesis that these mutations were not, in fact, Jewish founder mutations; haplotype analysis has shown that these mutations entered Ashkenazi populations after they arose in an ancestral individual in Northern Europe [15, 16, 21–26].

BRCA1 and *BRCA2* founder (or recurrent) mutations have been observed throughout the world (Table 1) and have led population geneticists to examine how these mutations became fixed in populations. The fixation of these *BRCA1* and *BRCA2* founder mutations in the Ashkenazi Jewish population can be explained by the unique degree of homogeneity and intra-group marriage compared to other populations since the degree of genetic admixture of one population is associated with how the population was formed. For example, the number of ancestral populations contributing to the resulting population and under which conditions, often influence the degree of genetic admixture factors such as cultural barriers, geographical location, wars, economics,

Table 1 Examples of *BRCA1* and *BRCA2* recurrent/founder mutations in diverse populations

Continent	Population	*BRCA1* mutation		*BRCA2* mutation		References
		BIC	HGVS, NM_007294.3	BIC	HGVS, NM_000059.3	
Africa	Egyptian	185delAG, 5454delC, 4446C>T	c.68_69delAG, c.5335delC, c.4327C>T	999del5	c.771_775del5	[101]
	Nigerian	Y101X, 1742insG, 4241delTG, 4359insC, M1775R, C64Y, 1623delTTAAA, Q1090X	c.303T>G, c.1623dupG, c.4122_4123delTG, c.4240dupC, c.5324T>G, c.191G>A, c.1504_1508delTTAAA, c.3268C>T	2630del11, 9045delGAAA, 1538delAAGA	c.2402_2412del11, c.8817_8820delGAAA, c.1310_1313delAAGA	[41, 102]
	South Africans	E881X, 185delAG, 5382insC, 1493delC	c.2641G>T, c.68_69delAG, c.5266dupC, c.1374delC	–	–	[103]
Americas	African Americans	943ins10, 1832del5, 5296del4, IVS13+1G>A, IVS1616T>C, 5370C>T, 5443T>G, 5506C>A	c.824_825ins10, c.1713_1717delAGAAT, c.5177_5180del4, c.4357+1G>A, c.498616T>C, c.5251C>T, c.5324T>G, c.5387C>A	4699del4	c.4471_4474delCTGA	[9, 104, 105]
	Argentines	185delAG, 5382insC	c.68_69delAG, c.5266dupC	3034del4, 6174delT	c.2808_2811del4, c.5946_5946delT	[106]
	Bahamians	IVS13+1G>A, 185delAG, IVS1616T>C, 943ins10, 4730insG, T5443G	c.4357+1G>A, c.68_69delAG, c.498616T>C, c.824_825ins10, c.4611_4612insG, c.5324T>G	8128delA	c.7900delA	[42–44, 107]
	Brazilians	185delAG, 5382insC, R71G, 3450del4, 2156delGinsCC, C1201G, C3522T	c.68_69delAG, c.5266dupC, c.211A>G, c.3331_3334delCAAG, c.2037delGinsCC, c.1082C>G, c.3403C>T	c.156_157insAlu, 6174delT, p.S2219X, p.C1290Y, 6633del5, 5878del10, 5036delA	c.156_157insAlu, c.5946_5946delT, c.6656C>G, c.3869G>A, c.6405_6409delCTTAA, c.5650_5659del10, c.4808delA	[21, 22, 33–35, 37, 108]
	Chilean	185delAG, 2605delTT, 3450del4	c.68_69delAG, c.2486_2487delTT, c.3331_3334delCAAG	4969insTG, 5374del4, 6503delTT	c.4740_4741insTG, c.5146_5149del4, c.6275_6276delTT	[109, 110]
	Colombian	3450del4, A1708E, 233G>A	c.3331_3334delCAAG, c.5123C>A, c.114G>A	1991del4, 6252insG, ex1-14del, 3034 delACAA	c.1763_1766delATAA, c.6024dupG, ex1-14del, c.2808_2811del4	[47, 48]
	Costa Rican	–	–	5531delTT, 6174delT, C5507G	c.5303_5304delTT, c.5946_5946delT, c.5279C>G	[111]
	Cuban	–	–	3394C>T	c.3166C>T	[112]
	French Canadians	C4446T	c.4327C>T	8765delAG	c.8537_8538delAG	[113]

Table 1 (continued)

Continent	Population	*BRCA1* mutation		*BRCA2* mutation		References
		BIC	HGVS, NM_007294.3	BIC	HGVS, NM_000059.3	
	Mexican	ex9-12del, IVS5+1G>A, ex18-19del, ex8-9dup	c.548-?_4185 ?del, c.212+1G>A, ex18-19del, ex8-9dup	–	–	[114]
	Peruvian	185delAG, 2080delA	c.68_69delAG, c.1961delA	3036del4	c.2808_2811del4	[115]
Asia	Ashkenazi Jewish	185delAG, 5382insC	c.68_69delAG, c.5266dupC	6174delT	c.5946_5946delT	[20, 116]
	Chinese	1100delAT, 1584G>T, 5589_5586del8	c.981_982delAT,c.1465G>T,c.5470_5477del8	2060C>A, 6819_6820delTG	c.1832C>A, c.6591_6592delTG	[117–119]
	Cypriot	–	–	8984delG	c.8756delG	[120]
	Indian	185delAG, 295delCA, 3050del4, 2983C>A, 4213delT, 5267T>G	c.68_69delAG, c.178_179delCA, c.3331_3334delCAAG, c.2864C>A, c.4094delT, c.5148T>G	4866InsT, 6079delAGTT, 8345A>G, 5007A>C	c.4638dupT, c.5851_5854del4, c.8117A>G, c.4779A>C	[121, 122]
	Iraqi	185delAG	c.68_69delAG	–	–	[26]
	Japanese	L63X, Q934X	c.188T>A, c.2800C>T	–	–	[123]
	Pakistanis	2080insA, 3889delAG, 4184del4, 4284delAG, 3337C>T	c.1961dupA, c.3770_3771delAG, c.4065_4068delTCAA, c.4165_4166delAG, c.3109C>T	–	–	[124]
	Syrian	185delAG	c.68_69delAG	–	–	[125, 126]
	Vietnamese	185insA	c.66dupA	4705del4	c.4478_4481delAAAG	[127]
	Yemeni	185delAG	c.68_69delAG			[126]
Europe	Austrians	2795delA, C61G, 5382insC, Q1806stop	c.2676_2679delAAAG, c.181T>G, c.5266dupC, c.1687C>T	8591G>A, IVS21-1G>A, 4088delA	c.8363G>A, c.8754+1G>A, c.3860delA	[15, 128, 129]
	Belgians	2804delAA, IVS5+3A>G	c.2685_2686delAA, c.212+3A>G	–	–	[130, 131]
	Dutch	2804delAA, IVS12-1643del3835, 185delAG, 5382insC, IVS20+1G>A	c.2685_2686delAA, c.4186 − 1643_4357+2020del, c.68_69delAG, c.5266dupC, c.5277+1G>A	5579insA, 6503delTT	c.5351dupA, c.6275_6276delTT	[132, 133]
	Finnish	3745delT, IVS11-2A>G	c.3626delT, c.4097-2A>G	8555T>G, 999del5, IVS23-2A>G	c.8327T>G, c.771_775delTCAAA, c.9118-2A>G	[134]
	French	3600del11, G1710X, 5149del4	c.3481_3491delGAAGATACTAG, c.5128G>T, c.5030_5033delCTAA	–	–	[135, 136]
	Hungarians	300T>G, 5382insC, 185delAG	c.181T>G, c.5266dupC, c.68_69delAG	9326insA	c.9097dupA	[137]

Table 1 (continued)

Continent	Population	*BRCA1* mutation		*BRCA2* mutation		References
		BIC	HGVS, NM_007294.3	BIC	HGVS, NM_000059.3	
	Icelandics	–	–	999del5	c.771_775delTCAAA	[138, 139]
	Sardinians	–	–	8765delAG	c.8537_8538delAG	[140]
	Scottish/ Northern Irish	2800delAA	c.2681_2682delAA	6503delTT	c.6275_6276delTT	[141]
	Norwegians	816delGT, 1135insA, 1675delA, 3347delAG	c.697_698delGT, c.1016_1017insA, c.1556delA, c.3228_3229delAG	–	–	[142, 143]
	Polish	300T>G, 5382insC, C61G, 4153delA, 3819del5	c.181T>G, c.5266dupC, c.181T>G, c.4034delA, c.3700_3704del5	–	–	[144, 145]
	Portuguese	–	–	c.156_157insAlu	c.156_157insAlu	[146, 147]
	Russians	5382insC, 4153delA, 300T>G	c.5266dupC, c.4034delA, c.181T>G	–	–	[148, 149]
	Slovenians	5382insC, 1806C>T, 300T>G	c.5266dupC, c.1687C>T, c.181T>G	IVS16-2A>G	c.7806-2A>G	[150, 151]
	Spanish (Northern)	R71G, c.2900_2901dupCT, 3450del4	c.211A>G, c.2900_2901dupCT, c.3331_3334delCAAG	3034delAAAC, c.4030_4035delinsC, 2041insA, 2323C>T	c.2808_2811del4, c.4030_4035delinsC, c.1813dupA, c.2095 C>T	[152, 153]
	Swedish (Western)	3171ins5	c.3048_3052dupTGAGA	–	–	[154, 155]

politics, and religion could limit the amount of admixture in any population.

In contrast to Ashkenazi Jewish population, the Brazilian population for example is highly admixed. Each region of Brazil has yielded populations with distinct genetic ancestries, with a greater African ancestry contribution in the northeast, and a greater European ancestry contribution in the south [27–31]. These differences began as a result of how these populations were formed during settlement in 1500 C.E. by the Portuguese. However, other populations from Europe, Asia, and Africa also arrived in Brazil at different periods in time [32]. Thus, *BRCA1* and *BRCA2* founder mutations from Europeans, Africans, and Asians can be found in Brazilians. Founder mutations in Brazilians include *BRCA1* c.5266dupC (5382insC, Northern European origin), *BRCA1* c.3331_3334delCAAG (3450del4, Hispanic origin), *BRCA1* c.211A>G (p.R71G, Hispanic origin), *BRCA2* c.156_157insAlu (Portuguese origin), and many others [21, 33–38]. As such, the *BRCA1* and *BRCA2* mutation spectra in the Brazilian population reflect its ancestral populations, but it is not identical due to bottleneck and drift events.

To date, the spectrum of recurrent mutations in diverse populations suggest that all populations have genetic predispositions toward breast cancer, but that the burden of inherited mutations is variable due to differences in population structure across populations [14–18]. Depending on how populations are structured, some risk alleles could become major risk alleles, as seen in Ashkenazi Jewish individuals. Because these genetic factors vary by both individual and population, efforts to improve the health of individuals should also be different according to individual- and population-specific risks.

Though much has been learned about mutations in breast cancer susceptibility genes, there has been a lag in research and analysis of distinct (and often minority) populations. Initially, very little was known about mutations in African Americans. Gao et al. [39] provided one of the first descriptions of the *BRCA1* mutation spectrum in African American families affected by breast cancer and noted recurrent *BRCA1* mutations, including three novel mutations that were unique to the population: c.1713_1717delAGAAT (1832del5), c.5177_5180del4 (5296del4), and c.3764dupA (3883insA). These findings were later confirmed by Nanda et al. [40], who noted vast differences in the spectra of *BRCA1* and *BRCA2* mutations between families of European and African descent. These were also corroborated by recent findings showing that the genetic profile of African American women affected by breast cancer are different than that of Caucasian American, Ashkenazi Jewish, Hispanic, and Asian women, as shown in Table 1. In a Southwest Nigeria population, Fackenthal et al. [41] showed that Nigerian breast cancer patients have an exceptionally high frequency of *BRCA1* and *BRCA2* mutations (7.1 and 3.9%, respectively) and the data support enrichment for genetic risk factors in this relatively young cohort. By evaluating *BRCA1* and *BRCA2* mutations in 396 black women with breast cancer under 50 years old recruited in Florida, Pal et al. [9] reported a similarly high prevalence (12.4%) of *BRCA1* and *BRCA2* mutations and eight recurrent mutations accounted for 49% of all the deleterious mutations. In Caribbean populations, 23% of breast cancer patients carried one of the seven founder mutations identified in a Bahamas population [42–44] and the prevalence of *BRCA1* and *BRCA2* mutations was 5.6 and 3.7% in Trinidad and Tobago [45]. In Latin America, the prevalence of *BRCA1* and *BRCA2* mutations in unselected breast cancer patients was reported to be low in Colombians (approximately 1.2%) [46]. However, another study showed that the frequencies of two *BRCA1* founder mutations (c.3331_3334delCAAG and c.5123C>A) and two *BRCA2* founder mutations (c.1763_1766delATAA and c.2808_2811delACAA) in 1,022 Colombian unselected breast cancer cases were 5.5 and 1.5%, respectively [47, 48]. Furthermore, the frequencies of deleterious mutations in *BRCA1* and *BRCA2* among African and Latin populations undergoing clinical testing at Myriad Genetic Laboratories are much higher than other groups at 15.6 and 14.8%, respectively, compared to other populations of European ancestry groups that vary between 12.1 and 13.5% [49].

Other breast cancer susceptibility genes

With advances in genomic technologies, researchers have made significant discoveries in clinical cancer genetics in the past three decades. Important genes that play key roles in the development of cancer such as *RB1* [50–53] and *TP53* [54–56] were discovered in the 1980s, *APC* [57, 58], *MSH2* [59–61], *MLH1* [62, 63], *CDKN2A* [64–67], *CDH1* [68, 69], and *BRCA1* and *BRCA2* [7, 8] in the 1990s. In the era of NGS, we can now examine a large panel of cancer susceptibility genes simultaneously in a reliable and robust manner. Recently, a cancer susceptibility gene panel, the BROCA panel [70], was designed for massive parallel sequencing to capture more than 50 genes associated with different cancers. Using this panel in 289 African Americans with breast cancer, Churpek et al. [71] detected 57 different pathogenic mutations in eight different genes among 65 patients. It supports the clinical utility of simultaneous multi-gene NGS, rather than relying on a limited cancer screening panel or a gene-by-gene approach. Most of the mutations identified (76%) were in the *BRCA1* or *BRCA2* genes, but other genes (*BARD1, PALB2, CHEK2, ATM, PTEN* and *TP53*) also appeared to have pathogenic mutations. The penetrance of these genes and their relative contribution to the breast cancer burden in diverse populations remain understudied.

It has been suggested that *CHEK2*, a gene included in most breast cancer panels as a breast cancer susceptibility gene with the highest frequencies of deleterious mutations in populations of Northern and Eastern Europe ancestries, remains poorly studied in Non-European populations. Cybulski et al. [72, 73] reported that germline mutations in *CHEK2* are associated with a two-fold increased susceptibility to breast, prostate, colon, thyroid, and renal cancers in Poland. The most recurrent mutations in the *CHEK2* gene, c.1100delC, c.444+1>A, and c.470T>C, are founder mutations. The association of the *CHEK2* c.1100delC deleterious mutation and breast cancer was noticeably demonstrated in a population-based study done by the CHEK2 Breast Cancer Consortium [74]. The study encompasses breast cancer cases and control who are non-carriers of *BRCA1* or *BRCA2* mutations from the United Kingdom, Germany, the Netherlands, and the United States. *CHEK2* c.1100delC mutation was found in the control group with a frequency of 1.1%, but it had a statistically significantly higher frequency in the breast cancer group (5.1%). However, previous studies using a more diverse population of breast cancer cases and controls in the United States had suggested that *CHEK2* was not an important susceptibility gene for breast cancer because of the low frequency of *CHEK2* c.1100delC among breast cancer cases (<2%) [75, 76]. These conflicting conclusions underscore the need for studies in diverse populations because mutation spectra vary in different populations with distinct genetic makeups. Unfortunately, minority groups in the United States are grossly underrepresented in genetic epidemiology studies to make more accurate risk estimates of specific mutations in individual patients.

In addition to the BROCA panel, other multi-gene testing panels for breast cancer were constructed, including BreastNext from Ambry Genetics, OncoGeneDx from GeneDx, myRisk from Myriad Genetics, TruSight Cancer from Illumina, and others [77]. Given the higher incidence of aggressive, early-onset breast cancer among women of African ancestry, and the potential heterogeneous inherited mutation spectrum in the African diaspora, it is necessary to evaluate breast cancer susceptibility genes in large, population-based cohorts of breast cancer patients of African and other understudied ancestries. After more than two decades of research to establish the contribution of other genes, *BRCA* and *BRCA2* remain the most important predictors of breast cancer risk in all populations. There is ongoing debate about screening all unaffected young women for *BRCA* mutations by age 30 [78]. This population-based screening approach could be beneficial for disease prevention and early detection and would be an incredible advancement in the field. More research is urgently needed to examine penetrance of *BRCA* mutations in diverse populations and to refine breast cancer risk prediction models that can be integrated into population-based screening strategy in different countries. The aggressive nature of BRCA-associated breast cancers makes this a high priority for more effective cancer control efforts and health equity.

BRCA-associated breast cancer phenotype

As a complex disease, breast cancer can be categorized by different subtypes, based on immunohistochemistry or gene expression profiling. Triple-negative breast cancer (TNBC, lack of expression of estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]), is an aggressive subtype that confers poor prognosis and it is overrepresented in women of African ancestry. In a population-based study of invasive breast cancer patients, Clarke et al. [79] found the highest percent of TNBC among African Americans (20%), followed by Hispanic (13%), Asian (9%) and Caucasian (9%) groups. In addition, Huo et al. [80] observed that the majority of tumors from indigenous African women were hormone-receptor–negative, and only 25% were hormone-receptor-positive. Furthermore, a recent study in The Cancer Genome Atlas revealed that, after adjusting for age, black breast cancer patients had a higher odds of basal-like and HER2-enriched subtypes than white patients [81]. Differences in tumor subtype distribution across populations suggest heterogeneity in breast cancer etiology.

Breast cancer phenotype is a result of interactions of genotype and environmental factors, we can observe considerable differences when looking at the phenotype of breast cancer patients. The differences observed in the genotypes among populations are greater when taking into account the disease phenotypes, which increase the degree of heterogeneity of breast cancer [80, 82, 83]. Sorlie et al. [84], observed that women with germline *BRCA1* mutations exhibit basal-like expression in their tumors while the tumors of *BRCA2* mutation carriers exhibit luminal A expression patterns. Grushko et al. [85] verified the non-amplification of HER2/*neu* in *BRCA1*-associated tumors compared to sporadic tumors. In addition, other studies that mainly focused on whites have reported that *BRCA1* mutation carriers have an increased risk of TNBC [86–88]. By analogy, the high prevalence of TNBC in the Nigerian population [80, 92] can be explained, at least in part, by the high *BRCA1* mutation rate in the same population [41]. Therefore, a better understanding of breast cancer genotype-phenotype correlation in diverse populations can be beneficial to improve clinical strategies for mutation screening and to develop risk-prediction algorithms accordingly, by taking bother mutational and clinical-pathological characteristics into account.

Breast cancer risk prediction models

Differences in genetic profiles and environments across populations require the careful development and calibration of risk prediction models. Such risk prediction models will be needed for population risk stratification and precision medicine to improve clinical outcomes in at-risk individuals. While there are several risk prediction models in clinical use, their performance in diverse populations varies greatly. Nanda et al. [40] initially found differences in the performance of the BRCAPRO risk prediction model in populations of European versus African ancestry. The predicted risk of having *BRCA1* or *BRCA2* mutations and the observed incidence among the groups varied; BRCAPRO underestimated risk at the lowest quartile, while overestimating it at the highest quartile in African Americans. Huo et al. [89] also tested the performance of BRCAPRO model among ethnic minority families (African American, Hispanic, and Asian) compared to Caucasians. Again, the BRCAPRO model did not perform as well in predicting the risk of *BRCA1* or *BRCA2* mutations in African American families compared to Non-African American families.. These studies highlight the importance of having a reliable genetic predictor tool, especially for those in developing countries (particularly within African, Asian, and Latin American populations) that cannot easily afford genetic testing. In these already budget-constrained nations, reliable and affordable tools would be particularly helpful to efficiently and effectively assess portions of the population that are at the highest risk for more concerted interventions to reduce risk and promote early detection of breast cancer.

Fischer et al. [90] analyzed the performance of four genetic risk models (BOADICEA, IBIS, BRCAPRO and Claus) in 7352 families from Germany. In contrast to previous work by Nanda et al. [40] and Huo et al. [89] in women of African descendant, BRCAPRO and BOADICEA performed better than the other risk predictor models in breast cancer families from Germany. BRCAPRO has been recently upgraded for estimating the risk of contralateral breast cancer [91]. Kurian et al. [92] also evaluated the performance of BOADICEA and BRCAPRO in Hispanic, African American, and Caucasian women. Although the performance of the BOADICEA and BRCAPRO was previously reported to be similar, Kurian et al. [92] found that the prediction models were most accurate for non-Ashkenazi Jewish whites than for the two minority groups studied (African Americans and Hispanics). Data from these studies demonstrate the importance of calibrating breast cancer risk prediction models in each population before widespread adoption.

Besides the calibration of the prediction models in each population, the inclusion of others risk factors could also improve the performance and the accuracy of risk prediction. For instance, BOADICEA included pathology information to improve the prediction accuracy since *BRCA1* tumors often have a distinct basal-like phenotype. Consequently, for women of African ancestry (who present with higher incidence of this type of tumor and also have higher rates of *BRCA1* mutations), the BOADICEA could be a useful tool and needs to be validated in populations of African ancestry [40, 43–47].

It is crucial to ensure sufficient representation from minority groups in databases that curate genotypes and phenotypes for breast cancer. It is known that African Americans, Asians, Latin Americans, and Native Americans are underrepresented and underserved populations in breast cancer genetics databases [93]. With investment in research among diverse populations, translation of such research in the clinic could improve quality of cancer care. In addition to knowledge gaps about minority groups, access to genetic testing and preventive health care is also limited due to lack of health insurance coverage and poor personal risk awareness. Even among health care professionals there is lack of breast cancer risk awareness and poor utilization of genetic services [94].

Summary

Global health disparities across different populations exist and the gap is likely to continue to widen. Health professionals have to think globally, but act locally, in order to reduce the death rates of cancer, because each population is unique. Understanding the genetic profile of a population is important, because each population has a unique degree of genetic admixture in addition to environmental, social, and cultural factors. Researchers now know that individuals who carry alterations in breast cancer susceptibility genes can be empowered to use this knowledge to preempt and prevent disease [95]. The medical benefit of having knowledge about patients' genetic susceptibility profile after the disease is diagnosed is undoubtedly suboptimal [96]. Early screening and detection, as an outcome of a differentiated, individualized approach, is a more appropriate model than "one-size-fits-all" [97]. Studies have indicated that enhanced screening technologies such as Magnetic Resonance Imaging more accurately reflect breast architecture, which allows more precise detection of small cancers [98]. Additionally, information gained from genetic testing could be utilized to predict the disease before symptoms even begin [96]. Beyond utilizing appropriate technologies, we also have to increase public awareness about cancer and how individuals can be empowered to modify their own risk. In order to achieve this, we have to reach widespread consensus about the risks posed for each population group by identifying more precisely the unique intrinsic and extrinsic factors that play key roles in breast cancer development. Finally, with

this data, we can make adequate and effective health care policies in cancer prevention and provide adequate treatment for each distinct population [99, 100].

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Compliance with ethical standards

Conflict of interest OIO is a Co-Founder at CancerIQ.

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