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Inequities in multi-gene hereditary cancer testing: Lower diagnostic yield and higher VUS rate in individuals who identify as Hispanic, African or Asian and Pacific Islander as compared to European

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Abstract

The identification of germline pathogenic/likely pathogenic (P/LP) variants in cancer predisposition genes can guide treatment and management decisions for the individual being tested and potentially at-risk relatives. Prior studies have raised concerns of racial/ethnic disparities in the detection rates of P/LP variants and variants of uncertain significance (VUSs). In 2018, Color Genomics™, a commercial laboratory, made de-identified, aggregate genetic and clinical information from 50,000 individuals who completed testing for 30 cancer predisposition genes publicly available. It is the largest publicly available database of its kind from a single laboratory. An analysis of individuals from this database with a negative personal history of cancer that identify as European (n = 31920), Hispanic (n = 1700), African (n = 462) or Asian and Pacific Islander (n = 2602), demonstrated that the VUS rate in the hereditary breast and ovarian cancer syndrome and Lynch syndrome genes was higher for all non-European groups as compared to the European group; Hispanic (7.1% vs 5.8%; p=0.029), African (12.3% vs 5.8%; p<0.001), Asian and Pacific Islander (13.1% vs 5.8%; p<0.001). In the other cancer genes (OCGs), the P/LP rate was lower; Hispanic (5.1% vs 7.6%; p <0.001), African (2.4% vs 7.6%; p<0.001), and Asian and Pacific Islander (4.3% vs 7.6%; p<0.001). The VUS rate was also higher in the OCGs; Hispanic (16.2% vs 12.2%; p<0.001), African (21.6% vs 12.2%; p<0.001), Asian and Pacific Islander

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(24.4% vs 12.2%; p<0.001). Our study emphasizes the reality of disparities in the results of cancer genetic testing and highlights factors that propagate these inequities.

Keywords

Cancer genetic testing; BRCA1/2; Hereditary cancer; Health disparities

Introduction

The availability of gene-specific guidance on cancer risk reduction and management, and the continued decline in the cost of DNA sequencing has fueled the growth of germline genetic testing for hereditary cancers. In 2015 the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) introduced variant classification criteria which have been widely implemented in clinical genetics [1]. The ACMG/AMP variant classification criteria include an assessment of population allele frequency, computational, functional and segregation data.

The identification of pathogenic/likely pathogenic (P/LP) variants facilitates tailored approaches to cancer risk assessment, prevention strategies and management. After a P/LP variant in a cancer predisposition gene is identified, management can potentially include earlier screening or risk reducing surgery. Conversely, identification of variants of uncertain significance (VUSs) can be challenging for clinicians and families as VUSs may represent normal human variation or indicate an increased risk for cancer. Mismanagement of VUSs remains a concern and can expose patients and their families to harm. Including potentially unnecessary and invasive surveillance, surgical intervention, or misinformed family planning. The majority of VUSs that are eventually reclassified are downgraded to benign or likely benign [2].

In this study, we examined European, Hispanic, African and Asian and Pacific Islanders who underwent multi-gene hereditary cancer testing. On the basis of a positive or negative personal history of cancer we compared the detection rates for P/LP variants and VUSs in the non-European groups with the European group. This database's size and comprehensive demographic data make it the largest public database of its kind. Prior research has highlighted the issue of racial/ethnic differences in variant classification rates but with several limitations including: small cohort sizes, low number of genes assessed, and issues of inter-laboratory discordance in variant classification in the case of studies that utilized data from multiple labs [3, 4]. Disparities in classification rates are concerning because the results of genetic testing can guide treatment and management decisions not only for the individuals being tested, but also for their potentially at-risk relatives.

Materials and Methods

We accessed a database that contains 50,000 affected and unaffected individuals who completed hereditary cancer testing through Color Genomics™ (https://data.color.com/). A detailed description of the informed consent process, the sequencing and bioinformatics pipeline, and the methodology utilized in the construction of this database has been recently

published [5]. Briefly; patients were from the United States, 18 years of age or older and submitted saliva or blood samples. Individuals self-reported their clinical, demographic, and health history. All participants consented to the use of their de-identified data. All tests were ordered by a healthcare provider. The genes included in the panel were *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A (p14ARF and p16INK4a), CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11*, and *TP53*. We divided the genes into two groups; the first group being the hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome (LS) genes and the second being "other cancer genes" (OCGs). Individuals were assigned to one of four ancestral groups on the basis of their self-reported ethnicity; European, Hispanic, African or Asian and Pacific Islander. We calculated the proportions of P/LP variants and VUSs in the Hispanic, African and Asian and Pacific Islander groups and used Chi-square tests to compare these proportions to the rates in the European group. Individuals with a positive or negative personal history of cancer were included in this analysis. Individuals with more than one VUS or P/LP variant were also included. Individuals with a personal history of a cancer type not specified in the database (n = 3265), or those who reported multiple ethnicities (n = 3193) or Native American (n = 116) ancestry were excluded. Statistical analysis was performed using GraphPad (https://www.graphpad.com/). We did not perform an adjustment for multiple comparisons because the comparisons were complementary.

Results

Individuals with a positive personal history of cancer

There were 5822 Europeans, 267 Hispanics, 128 Africans and 235 Asian and Pacific Islanders with a positive personal history of cancer (Table 1A). The majority were female across all groups; European (74%), Hispanic (88%), African (63%) and Asian and Pacific Islander (84%). The most commonly reported cancer types were breast and prostate cancer (Table 1A). The Asian and Pacific Islander group had a higher P/LP rate among HBOC and LS genes compared to the European group (8.9% vs 4.3%; p=0.001). The African and the Asian and Pacific Islander groups both had higher VUS rates in the HBOC and LS genes compared to the European group, 18.8% vs 6.1%; p<0.001 and 16.6% vs 6.1%; p<0.001 respectively.

In the OCGs, the African group had a lower P/LP rate than the European group (≤ 3.1% vs 9.6%; p=0.019). The Asian and Pacific Islander group had a higher VUS rate than the European group (23.8% vs 13.4%; p<0.001).

Individuals with a negative personal history of cancer

There were 31920 Europeans, 1700 Hispanics, 462 Africans and 2602 Asian and Pacific Islanders with a negative personal history of cancer (Table 1B). All groups were predominantly female; European (82%), Hispanic (85%), African (78%) and Asian and Pacific Islander (56%). The Asian and Pacific Islander group had a lower P/LP rate among the HBOC and LS genes compared to the European group (2.7% vs. 3.7%; p=0.006). There was no difference in the P/LP rate in the HBOC and LS genes when the African or Hispanic

groups were compared to the European. All non-European groups had a higher VUS rate in the HBOC and LS genes compared to the European group; Hispanic (7.1% vs 5.8%; p=0.029), African (12.3% vs 5.8%; p<0.001), Asian and Pacific Islander (13.1% vs 5.8%; p<0.001).

In the OCGs, all non-European groups had a lower P/LP rate compared to the European group; Hispanic (5.1% vs 7.6%; p <0.001), African (2.4% vs 7.6%; p<0.001), and Asian and Pacific Islander (4.3% vs 7.6%; p<0.001). Additionally, all non-European groups had a higher VUS rate compared to the European group; Hispanic (16.2% vs 12.2%; p<0.001), African (21.6% vs 12.2%; p<0.001), Asian and Pacific Islander (24.4% vs 12.2%; p<0.001). Within each of the individual non-European groups, there was a markedly higher VUS rate in the OCGs than in the HBOC & LS genes; Hispanics (16.2% vs 7.1%); Africans (21.6% vs 12.3%); Asian and Pacific Islanders (24.4% vs 13.1%). Exclusion of *CHEK2* from among the OCGs was insufficient to resolve the disparities between patients of European descent as compared to patients of non-European descent.

Discussion

Among African and Hispanic individuals with a personal history of cancer, we observed no statistical differences in P/LP rates in the HBOC and LS genes as compared to the European group. While the Asian and Pacific Islander group had a higher P/LP rate than the European group, this was likely due to a higher proportion of ovarian cancer cases (7% vs 3.7%). The African and the Asian and Pacific Islander groups both had higher VUS rates in the HBOC and LS genes, 18.8% vs 6.1%; p<0.001 and 16.6% vs 6.1%; p<0.001 respectively. Our findings are consistent with recent work by other groups including Kurian et al. [6] and provide further support that racial/ethnic disparities exist primarily in the VUS rate and not in the overall P/LP rate in individuals with positive personal histories of cancer.

In contrast, disparities in P/LP and VUS rates were more frequently observed among members of non-European groups with no personal history of cancer when compared to their European counterparts. Of note, these disparities were more consistently observed in the OCGs. In these OCGs, a lower P/LP rate and higher VUS rate was observed in all non-European groups as contrasted with the European group. While these OCGs are less commonly implicated causes of hereditary cancer, they can contribute significantly to the disparities in P/LP and VUS rates observed between European and non-European groups. In these understudied groups, variant classification disparities in these lower penetrance genes emphasize our relative lack of insight into the genetic architecture of non-European groups. A greater understanding of population specific founder mutations in populations of European descent including the Ashkenazi Jewish population also account for the observed disparities in P/LP rates. Hereditary cancer gene sequencing in an ethnically diverse population that includes individuals with no personal history of cancer highlights some of the potential challenges of testing at a population level. Differences in P/LP and VUS rates translates to the benefits of genetic testing (e.g., potential early diagnosis; changes in management) being primarily realized among those of European ancestry, and the risks (e.g., lower diagnostic yield for affected individuals; VUS related mismanagement) being disproportionately realized among non-European groups.

Multiple factors account for racial/ethnic P/LP and VUS disparities. Ancestral diversity in the populations participating in genomic medicine in clinical or research contexts is lacking. The Genome Aggregation Database (gnomAD) is the largest population allele frequency database (http://gnomad.broadinstitute.org/about) and is routinely utilized in clinical variant classification [7]. gnomAD contains 141,456 unrelated individuals from several large-scale sequencing projects. However, 58.2% of the individuals in gnomAD are European (Finnish; Non-Finnish European; Ashkenazi Jewish), as compared to 12.5% Latino, 8.8% African/ African American, 7.1% East Asian, and 10.8% South Asian. The underrepresentation of non-European groups in this and similar databases makes variant interpretation more challenging in these groups. Recent work highlights the lack of ancestral diversity in the populations participating in genomic research. A recent publication reviewing genome-wide association study (GWAS) cohorts from 2005 to 2018 demonstrated that participants of European ancestry have thus far accounted for 86% and 77% of GWAS discovery and replication studies respectively [8].

The historic and present realities of discrimination also make racial/ethnic minority populations reticent to voluntarily participate in the genomics era [9]. Due to socioeconomic factors, minority populations often have more restricted access to specialty care centers which typically serve as the gateways to genomic medicine. Minority populations are also less likely to be referred to clinical genetics providers even when they meet referral guidelines [10]. The lack of diversity within the research and clinical community itself also serves to exacerbate these disparities. Implicit biases and gaps in culturally competent care among clinicians and researchers are additional factors that contribute to the lack of participation from racial/ethnic minority populations.

The primary strength of this current analysis is its use of a large and diverse cohort and inclusion of comprehensive demographic data. However, there are some notable limitations. First, as currently constructed, the database does not allow us to ascertain the proportion of individuals from each group with family members affected by cancer. It is not clear if individuals of European ancestry have a higher proportion of affected relatives. A lower rate of P/LP variants identified in non-European groups would be expected if significantly more individuals of European ancestry, had a positive family history of cancer. Non-European groups are also underrepresented in this database which makes broad generalizations challenging. Additionally, men are underrepresented in the database likely due to the fact that breast, ovarian and endometrial cancers, all cancers of the female reproductive system, continue to be a primary indications for cancer genetic testing. Despite these limitations, this dataset is presented in a demographically rich context and is an excellent source of insight into hereditary cancer testing. It is our hope that the availability of datasets like this one encourages other private and academic laboratories to pursue similar initiatives and thereby broaden our insight into the real world application of genomics technologies. Such databases also demonstrate the leading role commercial laboratories can play in moving this field forward by sharing large de-identified datasets at a scale that most academic laboratories cannot match.

Effective strategies to ameliorate these disparities will only be realized as similar databases are made available to the wider genomics community. Additionally, initiatives like the

National Institutes of Health's (NIH) *All of Us* Research Program (https://allofus.nih.gov/) and Human Heredity and Health in Africa (H3Africa; https://h3africa.org/) which aim to diversify genomic data and the genomics workforce are examples of noteworthy efforts to turn the tide of racial and ethnic inequity in genomics. In doing so, all groups may soon reap the benefits of the genomics revolution.

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References

1. Richards S, Aziz N, Bale S, et al. (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17(5): 405–24 DOI 10.1038/gim.2015.30 [PubMed: 25741868]
2. Mersch J, Brown N, Pirzadeh-miller S, et al. Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing. JAMA. 2018;320(12):1266–1274 [PubMed: 30264118]
3. Caswell-Jin JL, Gupta T, Hall E, et al. (2018) Racial/ethnic differences in multiple-gene sequencing results for hereditary cancer risk. Genet Med 20(2): 234–9 DOI 10.1038/gim.2017.96 [PubMed: 28749474]
4. Ricker C, Culver JO, Lowstuter K, et al. (2016) Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort. Cancer Genet 209(4): 130–7 DOI 10.1016/j.cancergen.2015.12.013 [PubMed: 26908360]
5. Barrett R, Neben CL, Zimmer AD, et al. (2019) A scalable, aggregated genotypic-phenotypic database for human disease variation. Database (Oxford) 2019: DOI 10.1093/database/baz013
6. Kurian AW, Ward KC, Howlader N, et al. Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovarian Cancer Patients. J Clin Oncol. 2019;37(15):1305–1315 [PubMed: 30964716]
7. Lek M, Karczewski KJ, Minikel EV, et al. (2016) Analysis of protein-coding genetic variation in 60,706 humans. Nature 536(7616): 285–91 DOI 10.1038/nature19057 [PubMed: 27535533]
8. Mills MC, Rahal C (2019) A scientometric review of genome-wide association studies. Commun Biol 2: 9 DOI 10.1038/s42003-018-0261-x [PubMed: 30623105]
9. George S, Duran N, Norris K (2014) A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. Am J Public Health 104(2): e16–31 DOI 10.2105/AJPH.2013.301706
10. Muller C, Lee SM, Barge W, et al. (2018) Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening. Clin Gastroenterol Hepatol 16(12): 1911–8.e2 DOI 10.1016/j.cgh.2018.08.038 [PubMed: 30130624]

Table 1:

Demographic and Clinical Histories

A.	**Positive Personal History of Cancer**[a]			
	European	**Hispanic**	**African**	**Asian and Pacific Islander**
	Caucasian (5243); Ashkenazi Jewish (579)	Hispanic (267)	African (128)	Asian, not specified (96); Chinese (64); Filipino (33); Indian (10); Japanese (29); Pacific Islander (3)
Cohort size	5822	267	128	235
Gender				
Male	1492	33	47	38
Female	4330	234	81	197
HBOC & LS				
P/LP[b]	251/5822 = 4.3%	17/267 = 6.4%	10/128 = 7.8%	21/235 = 8.9%*
VUS[c]	355/5822 = 6.1%	23/267 = 8.6%	24/128 = 18.8%**	39/235 = 16.6%**
Other cancer genes				
P/LP	561/5822 = 9.6%	19/267 = 7.1%	*< 5 individuals***	15/235 = 6.4%
VUS	778/5822 = 13.4%	46/267 = 17.2%	24/128 = 18.8%	56/235 = 23.8%**
Reported cancer types[d]				
Breast	3245 (52.2%)	193 (70.2%)	67 (50.8%)	165 (67.6%)
Colorectal	276 (4.4%)	11 (4.0%)	9 (6.8%)	19 (7.8%)
Gastric	21 (0.3%)	2 (0.7%)	2 (1.5%)	2 (0.8%)
Melanoma	892 (14.3%)	6 (2.2%)	0 (0.0%)	1 (0.4%)
Ovarian	229 (3.7%)	17 (6.2%)	4 (3.0%)	17 (7.0%)
Pancreatic	136 (2.2%)	6 (2.2%)	6 (4.5%)	8 (3.3%)
Prostate	1203 (19.3%)	25 (9.1%)	41 (31.1%)	24 (9.8%)
Uterine	218 (3.5%)	15 (5.5%)	3 (2.3%)	8 (3.3%)
Mean Age of Onset ± Standard Deviation				
Breast	52.98 ± 10.90	47.57 ± 9.67	50.22 ± 10.08	49.16 ± 10.71
Colorectal	55.34 ± 13.86	51.27 ± 8.21	47.11 ± 10.88	49.74 ± 12.89
Gastric	62.24 ± 15.87	35.50 ± 0.71	35.00 ± 9.90	52.00 ± 11.31
Melanoma	46.22 ± 14.42	41.00 ± 18.12	N/A	21.00
Ovarian	50.28 ± 15.16	46.75 ± 10.42	35.50 ± 12.79	50.69 ± 19.37
Pancreatic	64.11 ± 10.70	53.17 ± 13.01	62.80 ± 6.14	58.00 ± 11.06
Prostate	61.41 ± 8.41	54.80 ± 8.49	55.20 ± 8.37	61.58 ± 9.57
Uterine	50.00 ± 14.53	41.60 ± 15.12	50.00 ± 13.00	47.63 ± 12.28
B.	**Negative Personal History of Cancer**			
	European	**Hispanic**	**African**	**Asian and Pacific Islander**
	Caucasian (28538); Ashkenazi Jewish (3382)	Hispanic (1700)	African (462)	Asian, not specified (1335); Chinese (877); Filipino (180); Indian (98); Japanese (96); Pacific Islander (16)

Cohort size	31920	1700	462	2602
Gender				
Male	5683	263	101	1145
Female	26237	1437	361	1457
HBOC & LS				
P/LP	1196/31920 = 3.7%	59/1700 = 3.5%	14/462 = 3%	70/2602 = 2 7% ****
VUS	1837/31920 = 5.8%	120/1700 = 7 l% *****	57/462 = 12.3% **	340/2602 = 13.1% **
Other cancer genes				
P/LP	2410/31920 = 7.6%	86/1700 = 5.1% **	11/462 = 2.4% **	112/2602 = 4.3% **
VUS	3887/31920 = 12.2%	275/1700 = 16.2% **	100/462 = 21.6% **	636/2602 = 24.4% **

[a] Breast, Colorectal, Gastric, Melanoma, Ovarian, Pancreatic, Prostate, Uterine

[b] Pathogenic/likely pathogenic variants

[c] Variants of uncertain significance

[d] Some individuals with multiple cancer types

* p=0.001

** p<0.001

*** p=0.019

**** p=0.006

***** p=0.029