Abstract #10525: Closing the gap: Trends in inconclusive rates in hereditary cancer testing across racial/ethnic groups

Authors: Foluso Olabisi Ademuyiwa, MD, MPH[1], Carolyn Horton, MS[2], Holly LaDuca, MS[2], Tim Komala, BS[2], Tina Pesaran, MS[2], Jessica Profato, MS[2]

1) Washington University, St. Louis, MO 63110; 2) Ambry Genetics; Aliso Viejo, CA 92656

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Background:

- Several groups have described disparities in genetic test results for inherited breast cancer predisposition, with a disproportionate number of variants of unknown significance (VUS) reported in non-Caucasian individuals.
- VUS results lead to ambiguity in risk management and counseling.
- Little data exists on how ethnicity- and gene-specific VUS rates have changed over time and whether such disparities have improved or worsened.

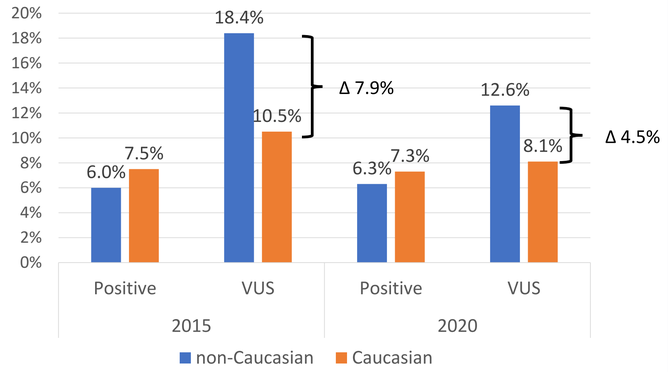
Methods:

- Demographic and results data were retrospectively reviewed in individuals who self-reported as African American, Asian, Caucasian, or Hispanic as specified by the test requisition form, and whose testing included five commonly tested breast cancer predisposition genes with published management guidelines (*ATM, BRCA1, BRCA2, CHEK2, PALB2*).
- The frequency of germline variants of unknown significance (VUS) in the five genes was assessed for each racial/ethnic group in September 2015 and September 2020

Cohort Description

Characteristic	2015 Total n=44,147	2020 Total n=284,130
Sex		
Female	42369 (96.0%)	258,073 (90.8%)
Male	1,817 (4.0%)	26,057 (9.2%)
Ethnicity		
African American	2,870 (6.5%)	26,140 (9.2%)
Asian	2,031 (4.6%)	15,059 (5.3%)
Caucasian	36,554 (82.8%)	219,948 (77.2%)
Hispanic	2,649 (6.0%)	23,867 (8.4%)
Average Age at Testing	53.1y (SD 12.8)	45.9y (SD 12.4)
Personal History		
Affected with any cancer	37220 (84.3%)	209,811 (73.8%)
Not affected with cancer	6927 (15.7%)	74319 (26.2%)

Absolute Difference in VUS and Positive Rate in Five Evaluated Genes



The difference in VUS rate between Caucasians and non-Caucasians decreased from 7.9% in 2015 to 4.5% in 2020.

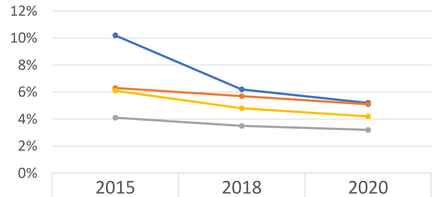
Take Home Points

1) Overall, VUS rates are declining in commonly tested breast cancer predisposition genes.
2) Between 2015 and 2020, the overall VUS rate for the five included genes was reduced by 32.0% in non-Caucasians compared to 23.6% in Caucasians.

Corresponding author: chorton@ambrygen.com

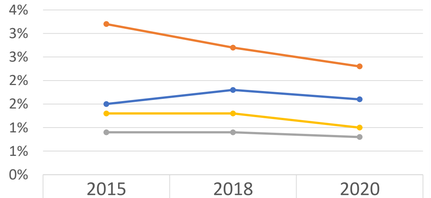
VUS Rates by Gene Over Time

ATM



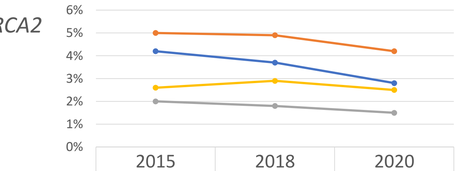
	2015	2018	2020
African American	10.2%	6.2%	5.2% *
Asian	6.3%	5.7%	5.1% *
Caucasian	4.1%	3.5%	3.2% *
Hispanic	6.1%	4.8%	4.2% *

BRCA1



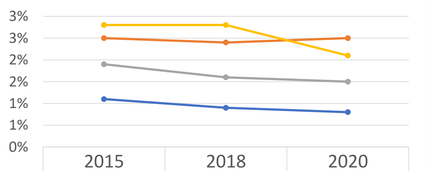
	2015	2018	2020
African American	1.5%	1.8%	1.6%
Asian	3.2%	2.7%	2.3% *
Caucasian	0.9%	0.9%	0.8%
Hispanic	1.3%	1.3%	1.0% *

BRCA2



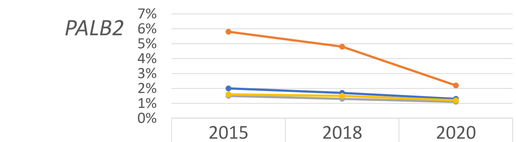
	2015	2018	2020
African American	4.2%	3.7%	2.8% *
Asian	5.0%	4.9%	4.2% *
Caucasian	2.0%	1.8%	1.5% *
Hispanic	2.6%	2.9%	2.5%

CHEK2



	2015	2018	2020
African American	1.1%	0.9%	0.8% *
Asian	2.5%	2.4%	2.5%
Caucasian	1.9%	1.6%	1.5% *
Hispanic	2.8%	2.8%	2.1% *

PALB2



	2015	2018	2020
African American	2.0%	1.7%	1.3% *
Asian	5.8%	4.8%	2.2% *
Caucasian	1.5%	1.3%	1.1% *
Hispanic	1.6%	1.5%	1.2% *

*denotes statistically significant decrease

Future Directions for Research:

These findings may be indicative of efforts by clinicians and laboratories to reduce disparities in VUS rates. Clinical utility and accuracy of genetic testing in non-Caucasians may be improved through efforts such as

1) Increased referral for and adoption of genetic testing by non-Caucasians
2) More robust representation of non-Caucasians in reference population databases
3) Diversified approaches to variant classification