Genetic testing by ethnicity in a population-based, publicly funded hereditary cancer program

Part I: Patient ethnicity and index genetic testing

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Land Acknowledgment

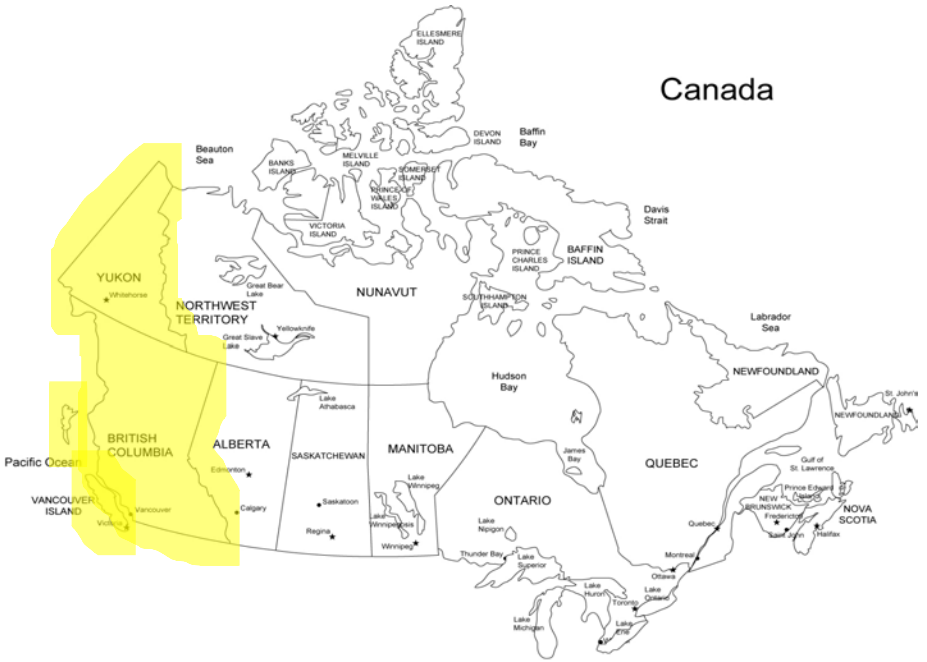
I respectfully acknowledge that I live and work on the traditional, ancestral and the unceded territory of the Coast Salish Peoples, including the territories of the xʷməθkwəy̓əm (Musqueam), Skwxwú7mesh (Squamish), and Sə́lílwətaɬ/Selilwitulh (Tsleil-Waututh) Nations.

Disclosures

I have received honoraria from AstraZeneca Canada

Experience of a population-based Hereditary Cancer Program

- Offering genetic testing since 1996 to population of BC and Yukon
- Criteria based referral and genetic testing
- Adoption of new testing criteria over the years
- The goal has been to have a mutation detection rate ~10%
- Recently this bar has been lowering



Centralized service delivery with outreach

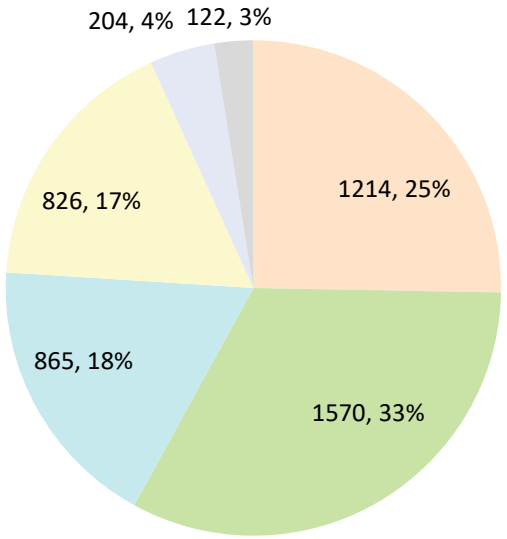
Clinics

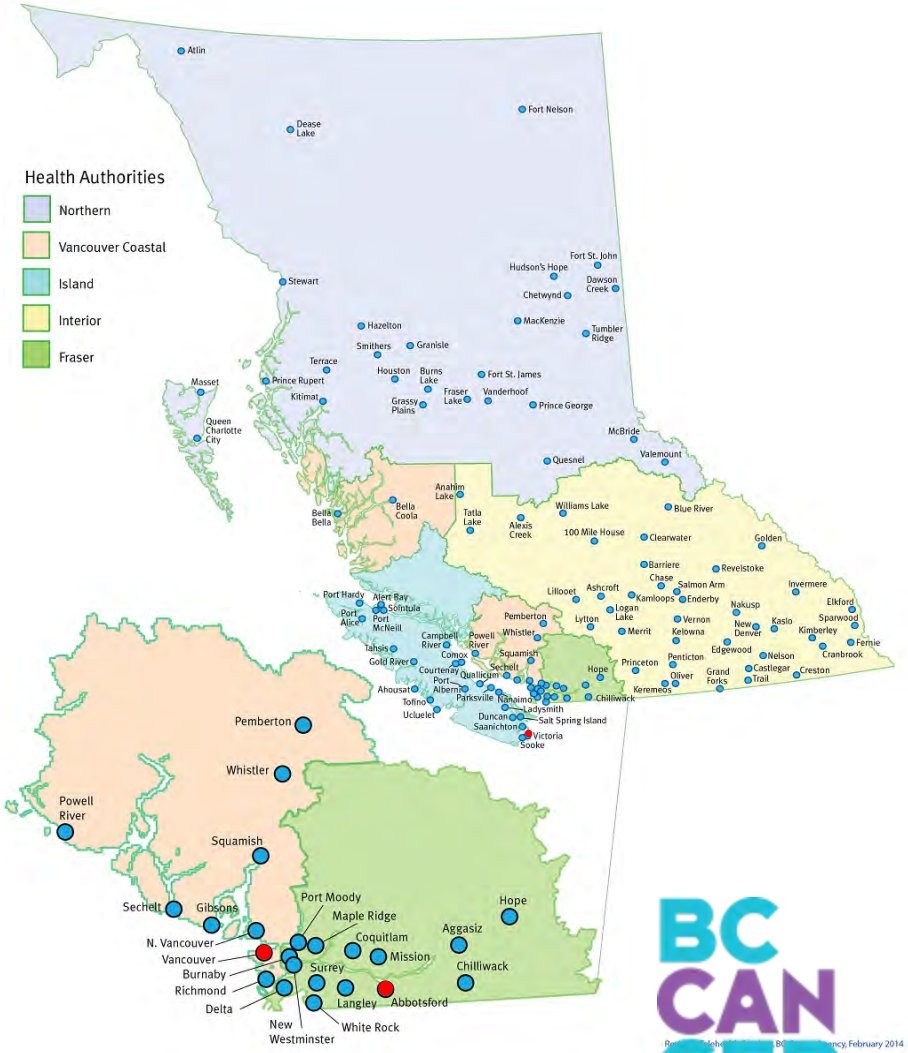
- Vancouver
- Abbotsford
- Victoria

Outreach

- Surrey
- Kelowna
- Prince George

Videoconference/Telehealth





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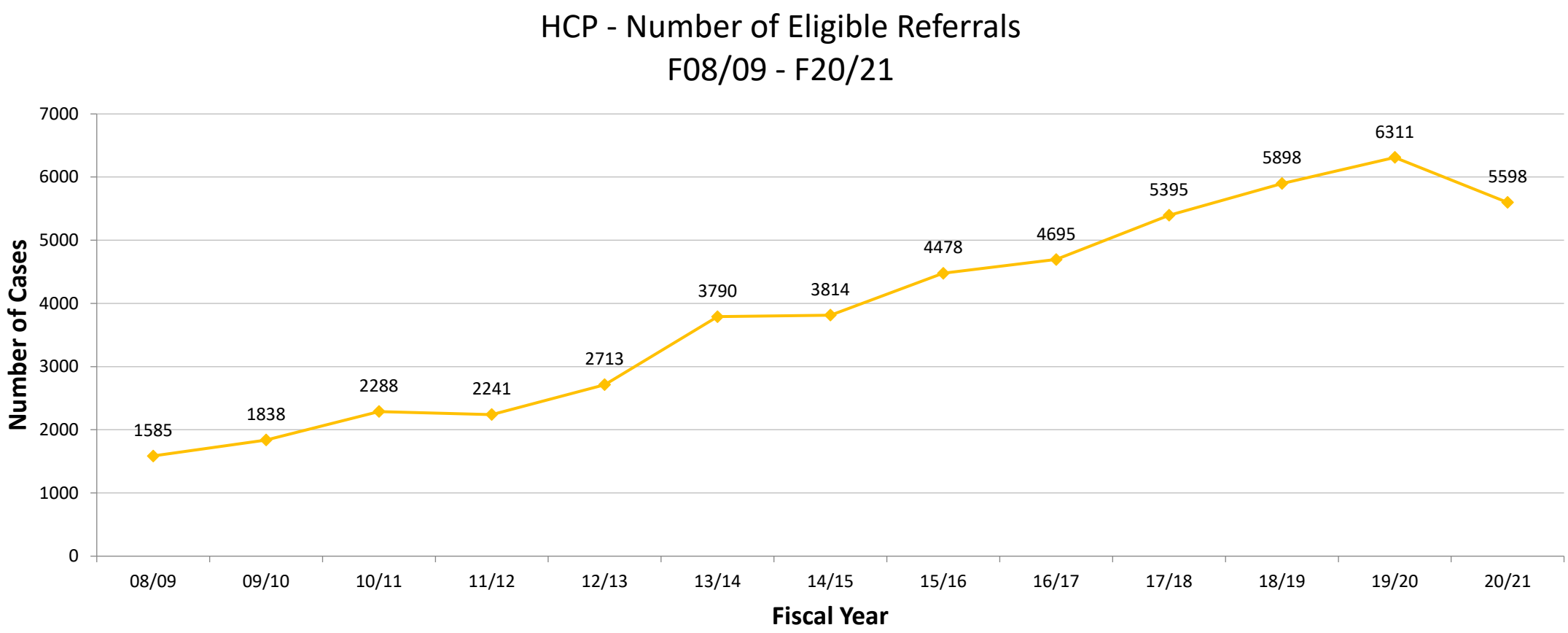
Increasing demand for hereditary cancer services in BC/Yukon



Cancer genetics clinics are already over capacity

- 85% percent of what we test for relates to HBOC
- But we have likely only identified less than 5% of *BRCA1*/*BRCA2* carriers under current models of care
- Review of ethnic breakdowns within the tested population are not reflective of the population census, suggesting we are not evenly testing minorities within the population

Retrospective study of standardized multigene panel testing

- Patients ≥ age 18 undergoing index genetic testing using a 14 or 17 gene testing panel (October 2014 to August 2017)
- Ethnicity defined as patient's "self-expressed racial identity" using a patient ethnicity questionnaire
  - European, Asian (East Asian, South Asian, Southeast Asian), Latin American, Black Canadian, Middle Eastern, Pacific Islander, Indigenous, and Ashkenazi Jewish.
  - more than one racial identity they were placed into a mixed category

Richardson 2020, *Examination of a new model of genetic counselling and assessing a demographically diverse patient population attending hereditary cancer genetic counselling services*

Patient demographics receiving genetic testing and counselling at the BC HCP (n=2051)

Patient Demographics	Total Population	UNINF	VUS	PV
Patient Age at First Cancer Diagnosis – years (SD)	52.0 (13.5)	53.4 (13.4)	49.9 (13.7)	49.6 (12.7)
Sex – N (%)				
Female	1936 (94.39%)	1131 (58.42%)	617 (31.87%)	280 (14.46%)
Male	115 (5.61%)	48 (41.74%)	48 (41.74%)	32 (27.83%)
Ethnicity – N (%)				
European	1334 (65.04%)	843 (63.19%)	359 (26.91%)	179 (13.41%)
Asian	358 (17.45%) *	144 (40.22%)	172 (48.04%) *	78 (21.79%) **
Middle Eastern	36 (1.76%)	19 (52.78%)	13 (36.11%)	8 (22.22%)
Pacific Islander	5 (0.24%) *	2 (40.00%)	2 (40.00%)	1 (20.00%)
Black Canadian	8 (0.39%) *	3 (37.50%)	5 (62.50%) *	1 (12.50%)
Indigenous	22 (1.07%) *	10 (45.45)	10 (45.45%)	2 (9.09%)
Ashkenazi Jewish	34 (1.66%)	16 (47.59%)	11 (32.35%)	10 (29.41%) **
Latin American	18 (0.88%) *	5 (27.78%)	13 (72.22%) *	3 (16.67%)
Mixed	136 (6.63%)	75 (55.15%)	51 (37.5%)	19 (13.97%)
No Patient Ethnicity Data	100 (4.88%)	62 (62.00%)	29 (29.00%)	11 (11.00%)

*Significantly underrepresented at HCP compared with BC population from 2016 BC Census (21.69%; 0.74%; 1.07%; 2.05%; 1.70%; respectively) (all $p < 0.002$). * Significantly higher VUS rate and ** Significantly higher proportion of PV compared to patients of European ethnicity

Richardson et al in preparation

Patients that self-report only Indigenous ethnicity are significantly (p=0.002) under-represented at the HCP compared to the BC Census

- A total of 115 patients at the HCP self-reported Indigenous ethnicity and received genetic testing
- Compared to the BC Census of all residents that self-reported Indigenous ethnicity the HCP population is not significantly under-represented (p=0.066)

Ethnicity – N (%)	Total	BC 2016 Census Proportion
Indigenous	22 (1.07%)	2.05%
Mixed	136 (6.63%)	
Indigenous	93 (4.53%)	
All Patients Reporting Indigenous Ethnicity	**115 (5.61%)**	**6.64%**

Richardson et al in preparation

Patient Populations Experiencing Negative Psychological Outcomes

- Multigene panel testing or single gene carrier testing between September 2015 to November 2018, completed the MICRA survey, did not require an interpreter, and were ≥ 18.
- A total of 1,671 patients were sent MICRA surveys and 917 patients completed them (response rate of 55.1%).

- Factors with a negative influence on psychological outcomes included genetic test result, cancer diagnosis, age, ethnicity, hereditary cancer referral syndrome and sex

Patient demographics and MICRA scores

Patient Demographics	Index N (%)	Carrier N (%)	MICRA – Total (SD)	MICRA – Distress (SD)	MICRA – Positive Experiences (SD)	MICRA – Uncertainty (SD)
Sex						
Female[a]	544 (86.1%)	198 (70.7%)	17.06 (13.58)	3.68 (5.51)	4.86 (5.21)	8.52 (7.45)
Male	88 (13.9%)	82 (29.3%)	15.69 (11.88)	2.61 (4.10)*	5.99 (5.49)*	7.09 (7.22)*
Ethnicity						
European[a]	424 (67.1%)	194 (69.3%)	16.39 (13.10)	3.31 (5.24)	5.12 (5.26)	7.96 (7.28)
Asian	57 (9.0%)	17 (6.1%)	22.39 (14.86)*	5.32 (6.19)*	5.38 (5.68)	11.69 (7.99)*
Middle Eastern	8 (1.3%)	2 (0.7%)	15.55 (11.60)	3.82 (5.04)	3.00 (3.90)	8.73 (7.02)
Pacific Islander	N/A	1 (0.4%)	15.00 (N/A)	7.00 (N/A)	0 (N/A)	8.00 (N/A)
African	1 (0.2%)	N/A	41.00 (N/A)	10.00 (N/A)	2.00 (N/A)	29.00 (N/A)*
Indigenous	3 (0.5%)	1 (0.4%)	15.75 (18.28)	3.00 (6.00)	7.00 (9.45)	5.75 (7.80)
Ashkenazi Jewish	11 (1.7%)	4 (1.4%)	12.13 (7.61)	1.53 (2.20)	3.40 (3.87)	7.20 (5.28)
Mixed	110 (17.4%)	41 (14.6%)	16.55 (12.85)	3.33 (5.06)	5.19 (5.40)	8.04 (7.23)
No Patient Ethnicity Data	18 (2.8%)	20 (7.1%)	14.29 (13.61)	3.45 (5.22)	4.32 (4.47)	6.53 (7.96)

Patients of Asian ethnicity scored higher than those of European ethnicity on the distress and uncertainty subscale

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Patients with high or moderate penetrance PV experienced higher distress, uncertainty, and feelings of negative experiences.

Patient Demographics	Index N (%)	Carrier N (%)	MICRA – Total (SD)	MICRA – Distress (SD)	MICRA – Positive Experiences (SD)	MICRA – Uncertainty (SD)
Cancer Diagnoses						
No Diagnoses[a]	59 (9.3%)	201 (71.8%)	14.95 (13.07)	3.41 (5.14)	5.25 (5.51)	6.29 (6.50)
One Diagnosis	406 (64.2%)	66 (23.6%)	17.71 (13.41)*	3.69 (5.40)*	4.81 (5.07)	9.20 (7.76)*
Multiple Diagnoses	167 (26.4%)	13 (4.6%)	17.10 (13.08)*	3.04 (5.21)	5.8 (5.46)	8.58 (7.27)*
Genetic Test Result						
UNINF (Index Test)[a]	400 (63.3%)	N/A	13.86 (10.84)	2.06 (3.81)	4.08 (5.06)	7.72 (7.12)
High Penetrance PV (Index Test)[b]	74 (11.7%)	N/A	27.87 (15.61)*	8.09 (7.38)*	7.81 (3.82)*	11.98 (8.08)*
High Penetrance PV (Carrier Test)[b]	N/A	101 (36.1%)	27.79 (14.34)*	7.65 (6.80)*	9.28 (4.34)*	10.86 (7.48)*
Moderate Penetrance PV (Index Test)[c]	26 (4.1%)	N/A	22.41 (18.90)*	5.20 (7.38)*	8.32 (6.40)*	8.89 (9.46)
Moderate Penetrance PV (Carrier Test)[c]	N/A	14 (5.0%)	29.03 (10.91)*	7.50 (5.43)*	9.64 (3.43)*	11.88 (7.53)*
Low Penetrance PV (Index Test)[d]	20 (3.2%)	N/A	18.12 (11.92)	3.87 (5.03)	4.20 (3.53)	10.05 (7.61)
Low Penetrance PV (Carrier Test)[d]	N/A	1 (0.4%)	12.00 (N/A)	0.00 (N/A)	10.00 (N/A)	2.00 (N/A)
Recessive[e]	N/A	1 (0.4%)	7.00 (N/A)	1.00 (N/A)	6.00 (N/A)	0 (N/A)
VUS (Index Test)	112 (17.7%)	N/A	16.16 (11.99)	2.69 (4.27)	4.31 (5.28)	9.16 (7.82)
True Negative (Carrier Test)	N/A	163 (58.2%)	10.28 (8.13)	2.06 (3.29)	3.24 (4.85)	4.98 (5.34)

* Significantly (p=0.017) associated with a higher MICRA score than the baseline outcome
a. Baseline outcomes for each variable are the first outcome in their respective variable section
b. *APC, ATM* (c.7271T>G), *BRCA1, BRCA2, CDH1, CDKN2A, DICER1, FH, FLCN, MLH1, MSH2, MSH6, MUTYH* biallelic, *PALB2, PMS2, SDHA, SDHB, SDHC, SDHD, TP53*
c. *ATM, BRIP1, CHEK2, MITF, NBN, PTEN, RAD51C, RAD51D*
d. *APC* (c.3920T>A), *AXIN, CHEK2* (c.470TC), *MSH6* (c.3117C>G), *MUTYH* monoallelic
e. *FH* (c.1431 1433dupAAA). All scores are the averaged unadjusted raw MICRA scores.

Patient demographics and patient responses to the MICRA Survey for each demographic are presented in table 1. A high MICRA score represents a negative psychological response and a low MICRA score represents a positive psychological response. All scores are the averaged unadjusted raw MICRA scores.

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New models of testing can decrease wait times and improve capacity

GENONC
- Oncologist-initiated genetic testing, cancer genetics results appointment

Large Scale Group
- Groups of 50 offered genetic testing

DNA Direct
- Abbreviated pre-test telephone appointment

Patient-led approaches
- Digital pre-test information video and chatbot

Richardson M, Min HJ, Hong Q, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. *Cancers* (Basel). 2020;12(2):338. Published 2020 Feb 3. doi:10.3390/cancers12020338
Bedard, A et al. DNA-direct: A trial of a new approach to genetic service delivery, abstract, CAGC 2017
Lohn Z. et al. Large Scale Group Genetic Counselling: Evaluation of a Novel Service Delivery Model in a Canadian Hereditary Cancer Clinic. Accepted *Journal of Genetic Counseling.* 2021

Additional approaches are needed to meet full demand

Reflex tumour sequencing

Complete index testing outside of cancer genetics clinics
- population-based genetic testing

Subsequent referral of patients with pathogenic and likely pathogenic variants and/or personal and family histories suspicious for hereditary cancer

Vos JR. et al; OPA Working Group. Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition. J Natl Cancer Inst. 2020 Feb 1;112(2):161-169. doi: 10.1093/jnci/djz080. PMID: 31076742; PMCID: PMC7019087.

Opportunities to address disparities in uptake/access to testing

- Systematic interventions
  - Re-examining genetic testing criteria in certain populations
  - Reflex sequencing of tumours prospectively
  - Prospective registry based identification and retrospective re-identification of high-risk cases/families in population

Refocusing cancer genetics services towards aggressive case finding

- Cascade genetic testing
- Follow-up of pathogenic variant carriers
- Specialized assessment of suspicious personal and family history of cancer

However, similar ethnic disparities in index testing are also seen in cascade genetic testing…

Offit K, Tkachuk KA, Stadler ZK, et al. Cascading After Peridiagnostic Cancer Genetic Testing: An Alternative to Population-Based Screening. J Clin Oncol. 2020;38(13):1398-1408. doi:10.1200/JCO.19.02010

Frey MK, Kahn RM, et al. Prospective Feasibility Trial of a Novel Strategy of Facilitated Cascade Genetic Testing Using Telephone Counseling. J Clin Oncol. 2020 May 1;38(13):1389-1397. doi: 10.1200/JCO.19.02005. Epub 2020 Jan 10. PMID: 31922918; PMCID: PMC7193751.

Braley EF, Bedard AC, et al. Patient ethnicity and cascade genetic testing: a descriptive study of a publicly funded hereditary cancer program. Fam Cancer. 2021 Jul 7. doi: 10.1007/s10689-021-00270-0. Epub ahead of print. PMID: 34232459.

Genetic testing by ethnicity in a population-based, publicly funded hereditary cancer program

Part II: Patient ethnicity and cascade genetic testing

Angela Bedard, MS, CGC

Genetic Counsellor, Hereditary Cancer Program, BC Cancer

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Land Acknowledgment

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Disclosures

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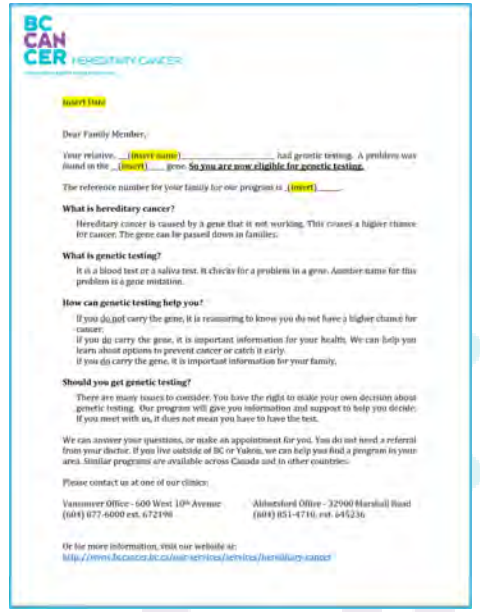
Pathway to cascade carrier testing

Proband receives diagnoses → Proband disseminates information regarding GC/GT to eligible relatives → Relative contacts genetics clinic or family doctor for a referral

- BC Cancer facilitates communication through a family letter given to the proband to disseminate

- Family letter provided to additional relatives who test positive to disseminate - cascade



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Insert Date

Dear Family Member,

Your relative, __(insert name)_____ had genetic testing. A problem was found in the __(insert)____ gene. **So you are now eligible for genetic testing.**

The reference number for your family for our program is __(insert)_____

What is hereditary cancer?

Hereditary cancer is caused by a gene that is not working. This causes a higher chance for cancer. The gene can be passed down in families.

What is genetic testing?

It is a blood test or a saliva test. It checks for a problem in a gene. Another name for this problem is a gene mutation.

How can genetic testing help you?

If you do not carry the gene, it is reassuring to know you do not have a higher chance for cancer.
If you do carry the gene, it is important information for your health. We can help you learn about options to prevent cancer or catch it early.
If you do carry the gene, it is important information for your family.

Should you get genetic testing?

There are many issues to consider. You have the right to make your own decision about genetic testing. Our program will give you information and support to help you decide. If you meet with us, it does not mean you have to have the test.

We can answer your questions, or make an appointment for you. You do not need a referral from your doctor. If you live outside of BC or Yukon, we can help you find a program in your area. Similar programs are available across Canada and in other countries.

Please contact us at one of our clinics:

Vancouver Office - 600 West 10th Avenue
(604) 877-6000 ext. 672198

Abbotsford Office - 32900 Marshall Road
(604) 851-4710, ext. 645236

Or for more information, visit our website at:
http://www.bccancer.bc.ca/our-services/services/hereditary-cancer

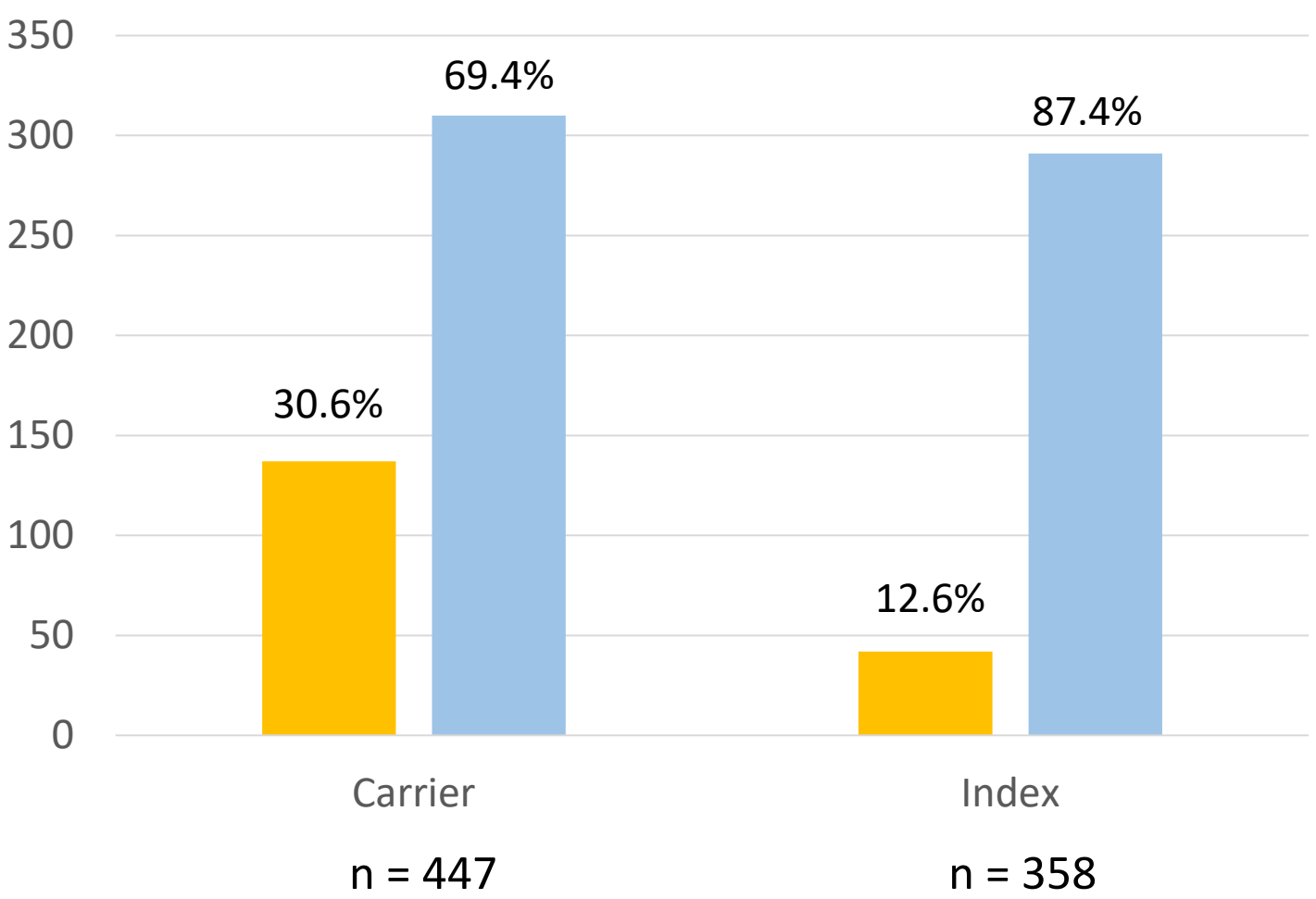
Analysis of Cascade Carrier Testing by Patient Ethnicity

- Retrospective analysis of **mutation-positive index cases** and the corresponding **carrier tests** of their family members performed between **February 3, 2015 and March 7, 2019.**

- Index cases for 2015-2018, and Carrier cases for 2015-2019

Acknowledgement: Eryn Braley
UFV Biology
UBC School of Public Health

The number of carrier and index tests by gender



Age

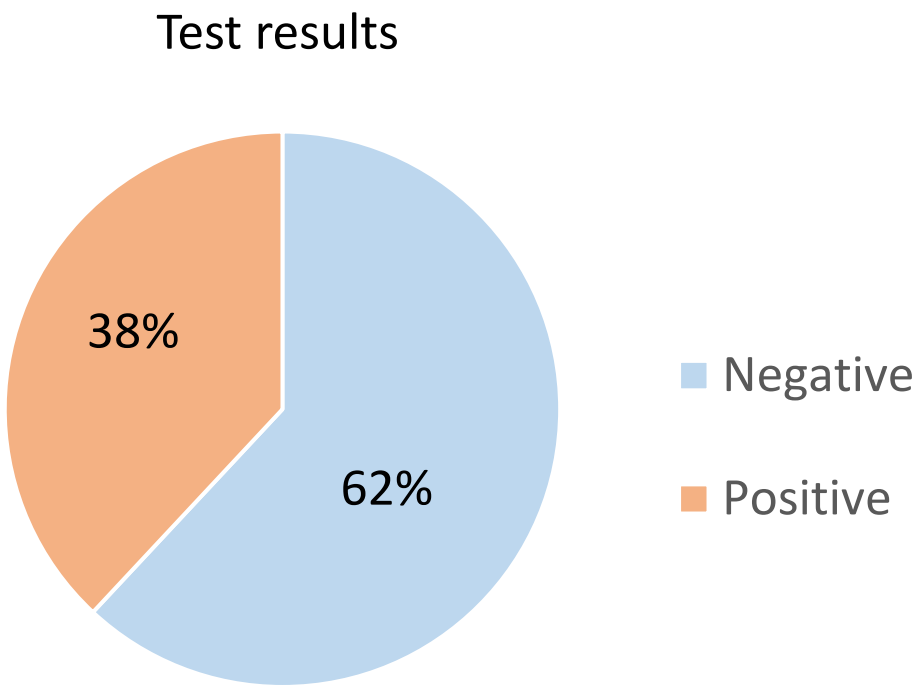
- Mean age at carrier testing: **49** (SD: 18)
- Mean age at index testing: **55** (SD: 13)

Testing uptake

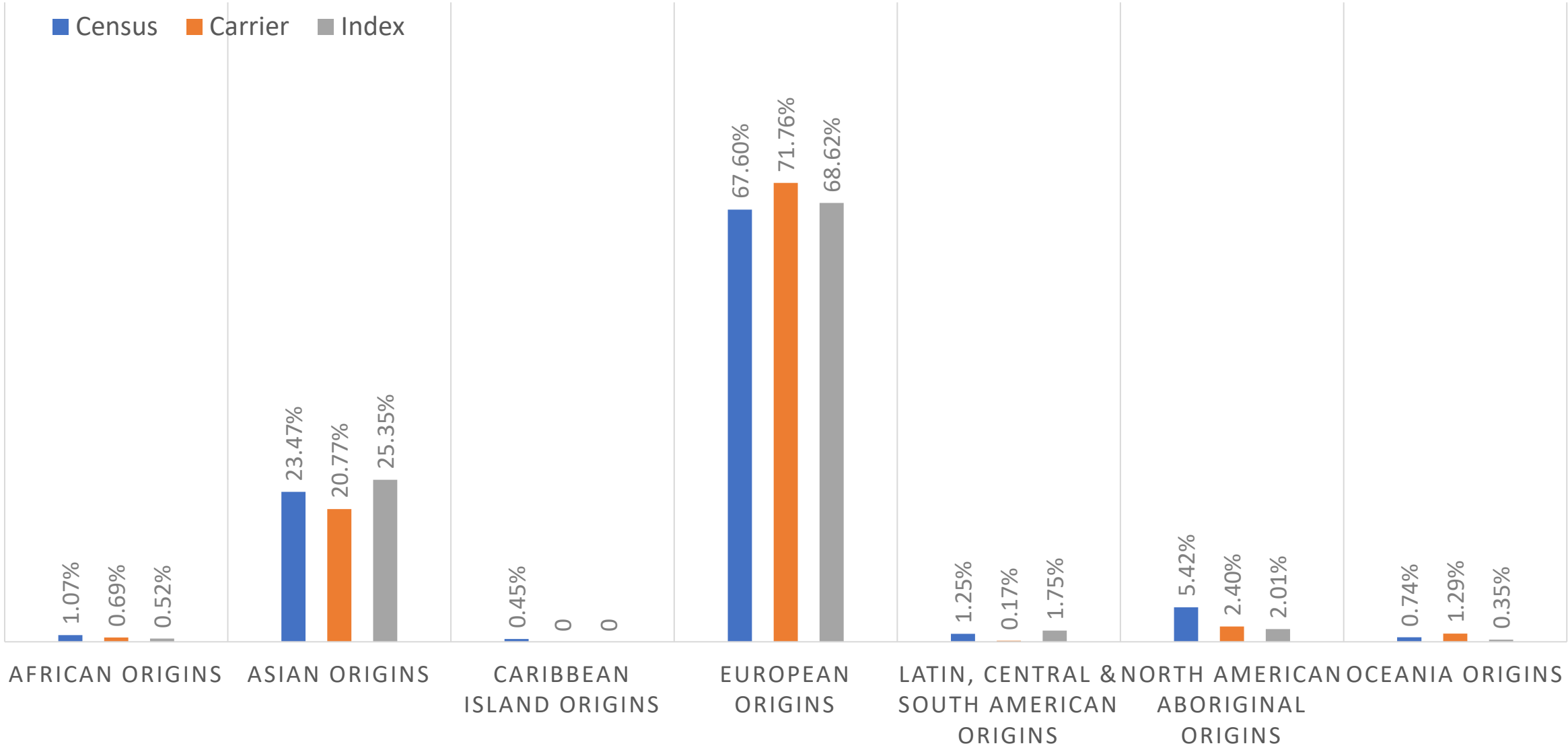
- **1.25** carriers per index

Carrier Testing - Genes tested

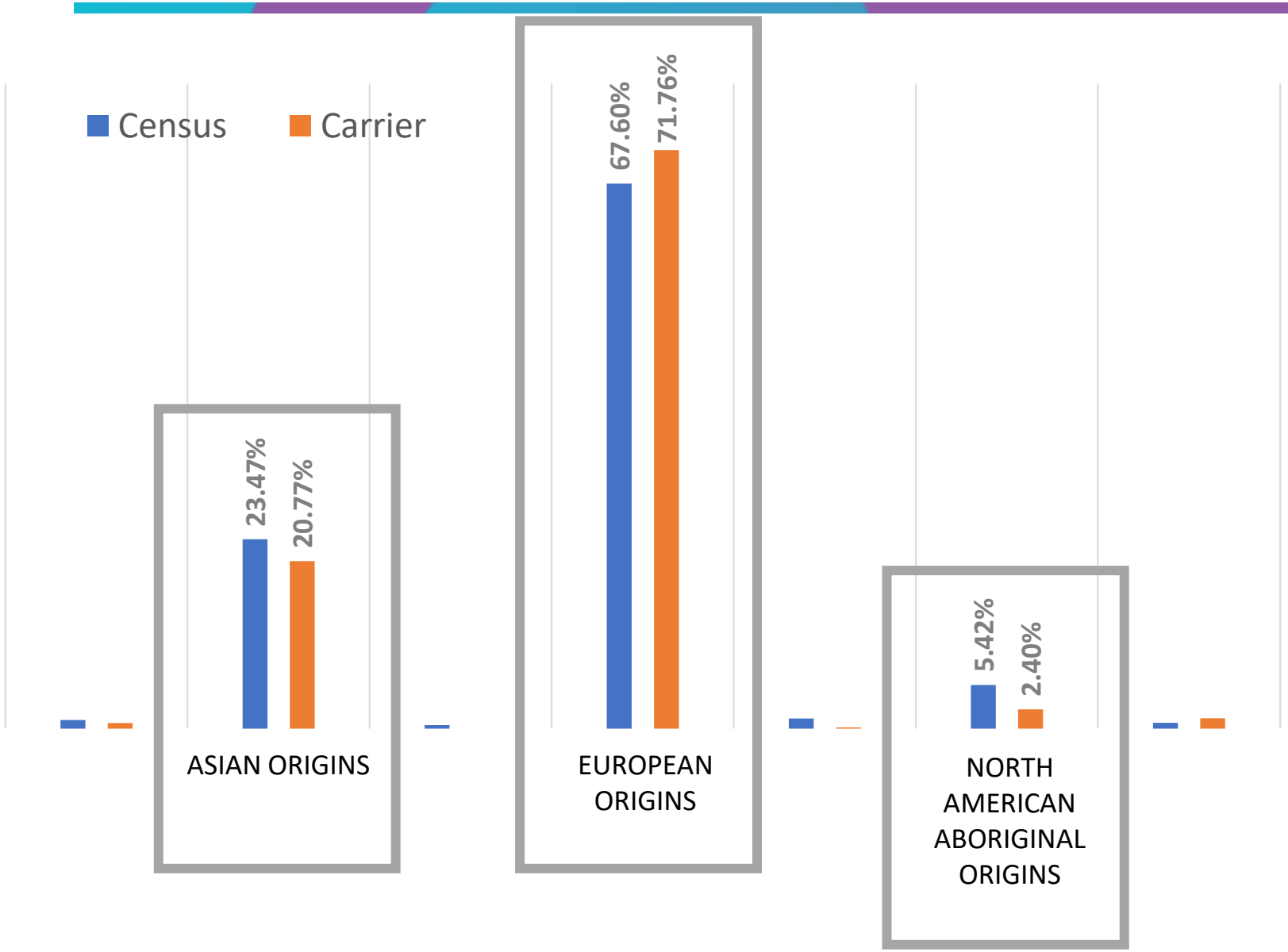
Gene Tested	n	%
HBOC (BRCA1/BRCA2)	271	58.9
Lynch (MLH1/MSH2/MSH6/PSM2)	86	18.7
TP53	9	2.0
APC	10	2.2
SDHA/SDHB/SDHD	10	2. 2
MEN1	6	1.3
CDKN2A	6	1.3
RET	5	1.1
VHL	0	0
Other	57	12.4
Total	460	



The ethnic makeup of BC and the testing populations

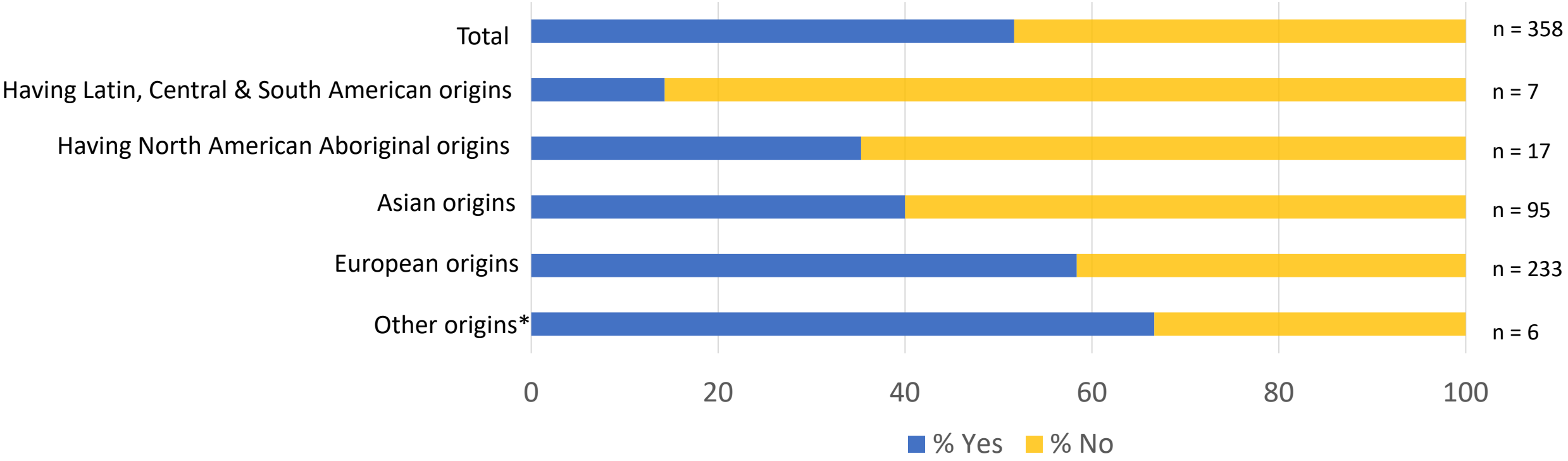


The ethnic makeup of BC and the carrier testing population



There was a significant difference between the proportion of ethnicities in the carrier testing population and the general BC population ($p<0.05$).

Carrier testing within pedigree



- There is a significant difference among ethnicities for pedigrees containing carrier testing ($p<0.05$).

* Other origins (n = 6) includes African, Mixed Asian and African, Oceania, Mixed Oceania and European, and Mixed Asian and European

Discussion

- Underrepresentation of Indigenous individuals in cancer genetic testing is also seen in other cancer screening studies
  - e.g. breast and colon screening

- Racism experienced within the healthcare system is an ongoing issue
  - e.g. recent report from BC “In Plain Sight” concerning Indigenous individuals

- Indigenous individuals more likely to experience poorer cancer survival outcomes

- Asian individuals make up the largest minority group in BC, with Asia being the largest source of more recent immigration.

Strategies

- Exploring a supported direct contact approach
- Developing partnerships to improve culturally competent care
- Increasing focus on cascade carrier testing

Thank you

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