Restrictive testing guidelines miss Canadians at risk of hereditary cancer

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Introduction

Current hereditary cancer testing guidelines employ strict criteria based on personal and family history of cancer to determine eligibility for genetic testing. In Canada, guidelines are set by individual genetics clinics or provincial health ministries, and therefore may vary by province. These guidelines are typically more restrictive than the National Comprehensive Cancer Network (NCCN) guidelines employed in the United States. However, the decreasing cost of multi-gene panel tests has facilitated a broader testing approach and has revealed that testing individuals excluded by current guidelines may be appropriate. Here, we analyzed mutation carrier rates for Canadian individuals who met or did not meet criteria derived from select Canadian clinics, as described below. We sought to determine the mutational burden that would be missed if testing was only carried out in individuals meeting criteria.

Methods

We analyzed the first 558 people in Canada who received the Color Test, a 30-gene panel for hereditary cancer risk including: *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*. Variants were classified according to current American College of Medical Genetics and Genomics (ACMG) guidelines.

We determined eligibility using combined guidelines and practices from the provinces most represented in the cohort. The most inclusive criteria based off self-reported health history was used, as described in Table 1. Study limitations include relying on self-reported health history information and a possible selection bias of clients who sought testing through Color Genomics.

Table 1: Qualification Methods

Cancer Type	Qualification Criteria
Breast and Ovarian Cancer	NCCN (Genetic/Familial High-Risk assessment: Breast and Ovarian version 2.2107), with the following changes: • Age of personal history of breast cancer lowered from age 45 to age 35 • Family history of prostate and pancreatic cancers were not considered • Qualification based on family history: At least 2 family members with cancer under age 50 or 3 family members with at least 1 under the age of 50
Lynch syndrome	Personal history of colorectal cancer before the age of 50 or 3 family members with colorectal or endometrial cancer under age 50
Colon Cancer (*APC, MUTYH, SMAD4*, and *BMPR1a*)	Personal history of 3 or more colon polyps
Gastric Cancer (*CDH1*)	One or more of the following: • 2 or more family members with gastric cancer, with at least one diagnosed under the age of 50 • 3 or more family members with gastric cancer diagnosed at any age • A personal history of gastric cancer diagnosed before age 40 • A personal history of gastric cancer and at least 1 family member with gastric cancer or lobular carcinoma.

Conclusions

- Due to the stringency of current testing guidelines, approximately one third of hereditary cancer mutation carriers would not have qualified for genetic testing.
- Individuals who would not have met guidelines had a mutation carrier rate of 8.0% (excluding low-penetrance alleles).
- Many of these missed mutation carriers did not qualify because the age of onset of personal or family cancer exceeded current cut-offs.
- These data suggest that in order to broadly reveal clinically actionable information, current guidelines should be revisited and broadened, and testing should be considered in individuals who do not strictly meet current criteria.

Results

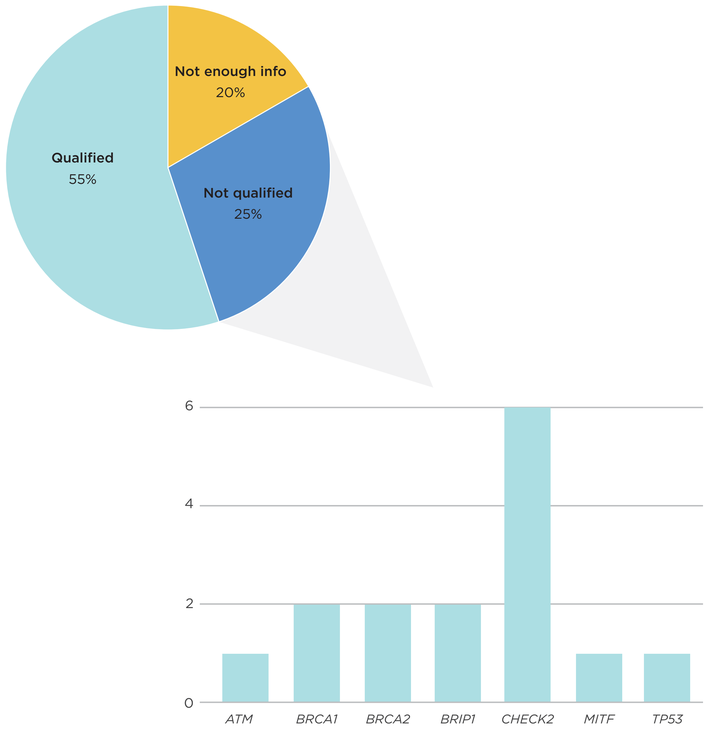
Demographics of cohort

Table 2: A majority of the cohort was caucasian, female, over the age of 50, and did not report a personal history of cancer.

		Number	Fraction of population	Number Positive	Positive Rate
Total		558	1.00	78	14.0%
Gender	Female	498	0.89	72	14.5%
	Male	60	0.11	6	10.0%
Age	18-30	22	0.04	5	22.7%
	31-40	105	0.19	14	13.3%
	41-50	150	0.27	22	14.7%
	51-65	193	0.35	25	13.0%
	65+	88	0.16	12	13.6%
Ethnicity	African	1	0.00	0	0.0%
	Ashkenazi Jewish	15	0.03	1	6.7%
	Asian	49	0.09	6	12.2%
	Caucasian	362	0.65	53	14.6%
	Hispanic	7	0.01	0	0.0%
	Multiple Ethnicity	15	0.03	2	13.3%
	Native American	1	0.00	0	0.0%
	Unknown	108	0.19	16	14.8%
Personal History of Cancer	Breast Cancer	198	0.36	28	14.1%
	Ovarian Cancer	17	0.03	0	0.0%
	Pancreatic Cancer	7	0.01	1	14.3%
	Melanoma	10	0.02	1	10.0%
	Other Cancer	17	0.03	1	5.9%
	No Cancer	322	0.58	46	14.3%

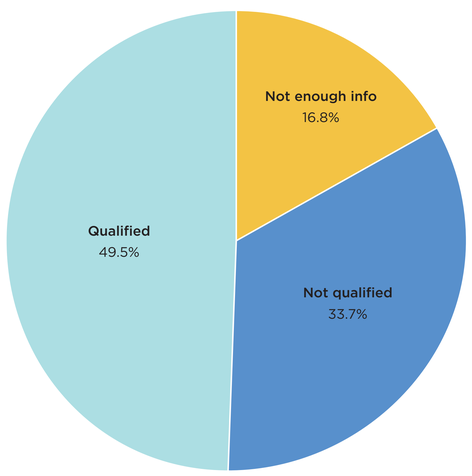
Positives by qualification

Figure 3: Excluding low penetrance alleles, 25% of mutation carriers did not meet criteria and would have been missed. 27% of these missed mutations were in *BRCA1/2*.



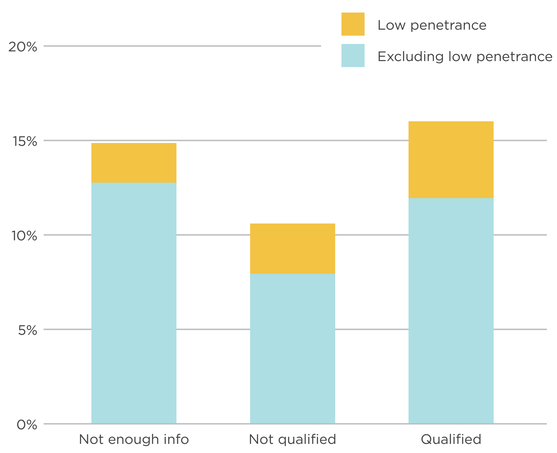
Canadian guideline qualification in cohort

Figure 1: 49.5% of the cohort qualified, 33.7% did not qualify for testing based on personal/family history, and 16.8% did not provide sufficient information to determine eligibility.



Mutation carrier rate by qualification

Figure 2: Excluding common low penetrance alleles (*MUTYH* heterozygotes, *APC* I1307K, and *CHEK2* I157T), pathogenic or likely pathogenic mutations were found in 10.8% of individuals: 12.0% among those that qualified, 8.0% among those that did not qualify, and 12.8% amongst those that did not provide enough information.



Characteristics of positives who did not meet criteria

Figure 4: Detailed analysis of those that received a positive result but did not meet testing criteria. The most common reason for failing to meet criteria was having a personal history of breast cancer, but at an age above the criteria cut-off. The average age of diagnosis was 46.4 years, and 3 of the 7 would have qualified under NCCN guidelines, as they were diagnosed at the age of 39. Similarly, the next most common category was individuals with a family history of breast cancer, but the affected relatives were too old to qualify. Additional reasons for not qualifying were: no suggestive personal or family history, family history is too remote, and incomplete health history information to assess.