Description of the What Comes Next Cohort: A longitudinal study of healthcare utilization and outcomes after *BRCA1* and *BRCA2* testing

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Abstract

Background: Our understanding of the implications of *BRCA1/BRCA2* mutations and the uptake and effectiveness of cancer risk-reduction strategies comes largely from studies of women recruited from specialized genetics clinics, with limited generalizability. Additionally, how genetic testing influences healthcare decisions of women found to carry variants of uncertain significance or those testing negative is unknown. This paper describes the What Comes Next Cohort, a unique data platform collecting real-world information on women undergoing *BRCA1/BRCA2* testing, irrespective of test result.

Methods: Detailed demographic, genetic testing, and family history data were collected for adult women who underwent *BRCA1/BRCA2* testing in Ontario, Canada from 2007 to 2016 through chart review. These data were linked with population-based administrative health databases to longitudinally track healthcare utilization and outcomes. We evaluated the demographics of the cohort, indications for testing, and test results.

Results: We identified 15,986 women (mean age 52.5 years, SD 13.9) who underwent *BRCA1* and/or *BRCA2* testing, including 2,033 women who tested positive, 1,175 women with variants of uncertain significance, and 12,778 women who tested negative. The positive yield among Ashkenazi Jewish founder testing, predictive testing (for familial variants), and complete gene analysis were 10.4%, 41.0%, and 7.4%, respectively. Among women negative for Ashkenazi Jewish founder mutations who subsequently underwent complete gene analysis, 3.0% tested positive for alternate pathogenic/likely pathogenic variants in the *BRCA1* or *BRCA2* genes.

Interpretation: The What Comes Next Cohort provides a rich resource for researchers interested in evaluating real-world healthcare behaviours and outcomes of women who undergo *BRCA1/BRCA2* testing.

Introduction

Carriers of pathogenic variants in the *BRCA1/BRCA2* genes face elevated risks of breast and ovarian cancer,[1] and cancer-related mortality; however, early identification of women harbouring variants can mitigate risks. For women affected by cancer, genetic testing can guide treatment, e.g. by identifying individuals who may benefit from poly(ADP-ribose) polymerase inhibitors. When performed among women unaffected by cancer, genetic testing can identify candidates for high-risk breast cancer screening and prophylactic surgery.[2-4]

Despite availability of *BRCA1/BRCA2* testing, the impact on the health behaviours of women who undergo testing is not well understood. Studies that inform our understanding of the uptake of risk-reduction strategies among *BRCA1/BRCA2* mutation carriers have relied on patients recruited from specialized cancer or genetics clinics[5,6] and may not be generalizable to the broader population. Importantly, while there are some studies of cancer incidence, prevention, and outcomes for women with pathogenic *BRCA1/BRCA2* variants, our understanding of the implications of variants of uncertain significance (VUS) and negative test results (received by most women tested) is limited. We lack consensus on the benefit of increased surveillance and prophylactic surgery for these women, and this uncertainty can lead to variability in care.[7] Few large cohorts of women with VUS or negative results exist.[8]

The What Comes Next Cohort (WCNC) aims to provide researchers with near population-based data on women undergoing *BRCA1/BRCA2* testing. This unique data platform provides detailed genetic testing, family history, and health utilization/outcomes data for a large, unselected cohort of women who underwent testing over a 10-year period, irrespective of test result. Herein, we provide a description of the WCNC, including demographics and test results.

Methods

Overview

Since 2000, the Ontario Ministry of Health (MOH) has funded *BRCA1/BRCA2* testing.[9] In 2001, thirteen eligibility criteria for testing based on personal and family cancer history were established. Similar to criteria used elsewhere,[10] Ontario criteria were chosen with the intention of identifying individuals with ≥10% carrier probability. To assemble the WCNC, we abstracted charts at hospitals performing *BRCA1/BRCA2* testing to obtain demographic, family cancer history, and genetic testing information for women tested. We used unique encoded identifiers to deterministically link records to administrative health databases housed at ICES (formerly the Institute for Clinical Evaluative Sciences), an independent, non-profit research institute that collects and analyzes healthcare and demographic data for health system evaluation and improvement. Data captured in the WCNC and data available for future linkages are presented in **Table 1**.

Participants

The protocol for development of the WCNC has previously been described[11]; eligibility criteria are summarized here. We identified adult women (≥18 years) who underwent *BRCA1/BRCA2* testing between January 1, 2007 and April 30, 2016 at two provincial genetic testing laboratories (North York General Hospital [NYGH], Mount Sinai Hospital [MSH]). Together, these sites perform approximately 70% of *BRCA1/BRCA2* testing provincially, capturing women referred from geographically dispersed counselling centres. Women were required to have a physician order genetic testing and a genetic counselor submit a requisition form indicating testing indication, and a pedigree detailing personal and family cancer history.

Genetic Testing

From patient charts at MSH and NYGH, we extracted reason for testing, type of test performed, and result. Test types included: (1) predictive/familial testing for a specific variant known to be carried by a family member, (2) founder testing for three variants carried in highest frequency among the Ashkenazi Jewish population (*BRCA1* c.68_69delAG, c.5266dupC; *BRCA2* c.5946delT), or (3) complete analysis, defined as sequencing of coding region and splice sites using Sanger sequencing, next generation sequencing, or analysis by denaturing high-performance liquid chromatography (DHPLC), and deletion/duplication detection by multiplex ligation-dependent probe amplification (MLPA).

For women who underwent predictive testing, we categorized results as Positive or Predictive Negative based on whether the known familial variant was detected. For women who underwent Ashkenazi Jewish founder testing, results were categorized as Positive or Negative. For women who underwent complete analysis, test results were reported by the testing site using the 2007 and 2015 American College of Medical Genetics (ACMG) classification systems (ACMG).[12,13] We categorized pathogenic (ACMG category 1) and likely pathogenic (ACMG category 2) variants as Positive results; ACMG category 3 variants as VUS; and likely benign (ACMG category 4) and benign (ACMG category 5) variants as Negative results. We captured results of prior *BRCA1/BRCA2* testing if reported to or performed at the genetic testing sites, applying the same categorization system.

Family Cancer History

We abstracted information on history of breast and ovarian cancer among first- and second-degree relatives from detailed pedigrees included with requisition forms. First-degree relatives were defined as parents, siblings, or children; second-degree relatives were defined as grandparents, grandchildren, aunts, uncles, nieces, nephews, and half-siblings.

Demographic and Personal Cancer History

From genetic testing requisition forms and pedigrees, we obtained women's ethnicity, Ashkenazi Jewish ancestry, and number of biological children. Linkage with administrative databases at ICES allowed collection of additional demographic variables. We obtained postal codes for women using the Registered Persons Database (RPDB), categorizing women as living within urban (population ≥10,000) or rural (<10,000) areas at the time of testing. We used Ontario census data to determine the median neighborhood household income level, categorizing women living in urban areas into 5 groups by quintile. We determined degree of marginalization using the census-based Ontario Marginalization Index (ONMARG), which captures extent of material deprivation, residential instability, ethnic concentration, and dependency.[14] We measured healthcare utilization using the Aggregated Diagnosis Groups (ADGs) of the Johns Hopkins Adjusted Clinical Group (ACG)® System Version 10.0 (Johns Hopkins University),[15] with a two-year look-back period.

The Ontario Cancer Registry (OCR) has collected data on all incident invasive cancers, excluding non-melanoma skin cancers, since 1964 and is over 95% complete.[16] We used OCR to determine cancer history prior to genetic testing and cancer occurrence afterwards. We included fallopian tube and primary peritoneal cancers in our definition of ovarian cancer.

Follow-Up

Follow-up began on the date of the genetic test and continues until the earliest of death or last follow-up in administrative data. Vital status was identified through RPDB.

Statistical Analysis

We determined baseline characteristics of women in the WCNC at the time of their most recent genetic test. Continuous data are reported as mean (SD) and categorical data are reported

as frequencies (percentages). Groups were compared using ANOVA and chi-squared tests. Reported p-values are two-sided. Analyses were performed at ICES using R, version 3.3. In accordance with ICES policies, we suppressed cells with <6 individuals.

Ethics Approval

This study received approval from the Research Ethics Boards at MSH, NYGH, Sunnybrook Health Sciences Centre, and the University of Toronto.

Results

The WCNC includes 15,986 women who underwent *BRCA1/BRCA2* testing between 2007 and 2016 (**Figure 1**), among whom 2,329 (14.6%) underwent predictive testing, 2,072 (13.0%) underwent Ashkenazi Jewish founder testing, and 11,585 (72.5%) underwent complete *BRCA1/BRCA2* gene analysis. The cohort includes 2,033 (12.7%) women who tested positive, 1,175 (7.4%) women with a VUS, 11,437 (71.5%) women who tested negative on founder testing or complete analysis, and 1,341 (8.4%) women who tested negative on predictive testing.

Table 2 summarizes cohort demographics. The mean age of women in the cohort is 52.5 years (SD 13.9); 12.1% of women tested lived in urban neighbourhoods belonging to the lowest fifth income group, whereas 28.0% lived in urban neighbourhoods in the highest fifth income group. Although chart abstraction was performed at only two hospitals, women captured in the WCNC resided across the province of Ontario (**Figure 2**). As of September 2019, median follow-up was 5.9 years and total person-years of follow-up was 100,438 years.

Test Results

Among the 2,033 (12.7%) women who received a positive result, 50.9% (n = 1,035) had pathogenic/likely pathogenic variants in *BRCA1*, 48.7% (n = 990) in *BRCA2*, and 0.4% (n = 8) in

both *BRCA1* and *BRCA2*. Positive yields among founder testing, predictive testing, and complete analysis were 10.4% (n = 216), 41.0% (n = 955), and 7.4% (n = 862), respectively.

A VUS was identified in 9.9% of women undergoing complete analysis (n = 1,142); another 33 women underwent predictive testing for and were found to carry a familial VUS. Among women with a VUS, 376 (32.0%) women carried a variant in *BRCA1*, 754 (64.2%) women in *BRCA2*, and 45 (3.8%) women in both *BRCA1* and *BRCA2*.

743 (4.6%) women had undergone multiple *BRCA1/BRCA2* tests; 403 women with a negative Ashkenazi Jewish founder test also underwent complete gene analysis (either reflexively or subsequently). The positive yield of complete analysis in these women was 3.0% (n = 12); VUS were identified in 35 (8.9%) women.

Indications for Testing

Testing indications, based on MOH criteria, are presented in **Table 3**. The most common indications were women with breast/ovarian cancer from families with 3 or more breast/ovarian cancer cases (n = 5,293, 33.1%) and testing in a relative of a *BRCA1/BRCA2* carrier (n = 2,394, 15.0%); 2,105 (13.2%) women were tested because of a pedigree strongly suggestive of hereditary breast or ovarian cancer. The criterion with the greatest positive yield was testing undertaken in relatives of *BRCA1/BRCA2* carriers (n = 860, 35.9%), followed by testing among women with breast/ovarian cancer from families with 2 cases of ovarian cancer among first- or second-degree relatives (n = 52, 26.7%), and women with invasive serous ovarian cancer (n = 195, 14.7%). Although testing criteria were developed to capture women with ≥10% risk of testing positive, 6 criteria had <10% positive yield, one of which had <5% yield. Criteria with lowest yield included testing of women with pedigrees suggesting >10% risk of carrying a

pathogenic variant (n = 93, 4.4%) and Ashkenazi Jewish women with breast cancer and a family history of breast/ovarian cancer (n = 38, 5.5%).

Personal Cancer History

A history of prior cancer was present among 10,345 (64.7%) women undergoing testing. 8,517 (53.3%) women had a diagnosis of breast cancer (**Table 4)**. The mean age at breast cancer diagnosis was 49.72 years (SD 11.79) and was highest among women with a predictive negative result (mean 55.60, SD 13.59). 197 (8.6%) women undergoing predictive testing had a history of breast cancer prior to testing. Women undergoing predictive testing who had a history of breast cancer more often received a positive result than women without a breast cancer history (75.6% vs. 24.4%, p<0.0001). For women undergoing non-predictive testing, a greater proportion of women without a history of breast cancer received a positive result than women with a history of breast cancer (9.0% vs. 7.0%, p=0.005). This was expected as women who undergo non-predictive testing in the absence of breast cancer likely have other high risk factors, such as ovarian cancer or a strong family history. Women testing positive were younger at breast cancer diagnosis than women who received VUS or negative results (44.5 years for positive, 48.8 years for VUS, 50.3 years for negative, p<0.0001).

1,589 (9.9%) women had a history of ovarian cancer prior to genetic testing (**Table 4**). Among women undergoing non-predictive testing, those with a history of ovarian cancer more often received a positive result than those without ovarian cancer (16.9% vs. 6.7%, p<0.0001). Women testing positive were diagnosed with ovarian cancer at a younger age than women receiving VUS or negative results (53.9 for positive, 56.4 for VUS, 60.0 for negative, p<0.0001).

Family Cancer History

Family history of breast cancer in first- or second-degree relatives was present for 70.3% (n = 11,241) of women (**Table 4**). Proportionally more women undergoing predictive testing had a first-degree relative with breast cancer than women undergoing founder or complete analysis (52.6%, 43.2%, 46.0%, respectively; p<0.0001). Among women undergoing non-predictive testing, those with first-degree relatives with breast cancer tested positive as often as those with second-degree relatives with breast cancer (7.2% and 7.9%, respectively; p = 0.11).

Family history of ovarian cancer in first- or second-degree relatives was present for 23.2% (n = 3,705) of women tested (**Table 4**). The predictive testing group were most likely to have a first-degree relative affected by ovarian cancer (20.5% for predictive, 8.2% for founder, 11.6% for complete analysis; p<0.0001). Among women undergoing non-predictive testing, similar proportions of women with affected first- and second-degree relatives tested positive (12.8% and 11.0%, respectively; p = 0.13).

Interpretation

The WCNC captures approximately 70% of women in Ontario who underwent *BRCA1*/*BRCA2* testing over a 10-year period within a publicly-funded genetic testing program. The cohort includes nearly 16,000 women, with large numbers of previously understudied women with VUS and negative results. Despite the provincial goal of testing women with ≥10% carrier probability, we identified 6 testing criteria with <10% positive yield, and one criterion with <5% yield. Additionally, 3% of women who received negative results from Ashkenazi founder testing and underwent complete gene analysis carried pathogenic/likely pathogenic variants.

To date, most data important to understanding cancer development and prevention among women at high risk for breast/ovarian cancer has come from highly specialized genetics clinics.

Capture of data solely from women motivated to attend these clinics may overestimate uptake of risk-reduction strategies. Real-world data have been difficult to obtain as factors important to understanding cancer development and prevention, e.g. family history and genetic testing results,[17] are not routinely collected in administrative datasets. Additionally, it can be challenging to acquire and follow a large group of women with VUS or negative results in a prospective fashion. Through a combination of detailed chart abstraction and linkage with administrative datasets, the WCNC overcomes these challenges.

Although genetic testing was captured at two sites in Toronto, Canada, women included in the cohort came from many jurisdictions from wide-spread genetic counseling centres. As testing was provincially funded throughout the duration of the study period, affordability of testing did not limit access. By capturing indication for testing, we were able to assess the performance of testing criteria. For future studies, linkage to administrative datasets in Ontario enables tracking of all healthcare utilization (i.e. ambulatory care visits, hospital admissions, surgeries, chemotherapy, radiation therapy) before and after genetic testing with minimal attrition over long-term follow-up. Uniquely, our cohort includes all women tested, not just those with a positive result.

Limitations

Despite these strengths, the cohort does have limitations. During chart review, we were unable to identify members of a family who were undergoing testing and, therefore, could not track cascade testing. Although we captured the genetic test result, we cannot be certain of how results were communicated; this may be particularly important in understanding healthcare decisions made by women who received VUS or negative results.[18] Finally, our cohort only includes women who have undergone *BRCA1* and/or *BRCA2* testing; we do not have data on

men who underwent *BRCA1/BRCA2* testing or any individuals who underwent panel testing (implemented in Ontario in 2016).

Conclusion

The WCNC is a unique data platform that provides a source of broadly generalizable data that can be used in future studies to evaluate cancer risk, cancer treatment, and use of cancer risk-reduction strategies among women who have undergone *BRCA1/BRCA2* testing, irrespective of test result. This cohort provides the ability to perform comparative studies of women with varying test results with a sufficiently large sample size to evaluate rare outcomes and has the potential to significantly further our understanding of hereditary cancers and their treatment and prevention.

Data Sharing Statement: The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Table Legend

Table 1. Variables measured in the What Comes Next Cohort and variables available through future planned linkages

Table 2. Baseline characteristics of the What Comes Next Cohort measured at the time of genetic testing

Table 3. Indications for and yield of testing by Ontario Ministry of Health (MOH) testing criteria

Table 4. Family and personal cancer history by test result. Results are reported as n (row %) or mean (SD)

Figure Legend

Figure 1. The What Comes Next Cohort

Figure 2. Number of women captured by the What Comes Next Cohort by geographic region in Ontario. Colours represent number of women included in the cohort per 100,000 women living within each region, based on population estimates from 2016

Table 1. Variables measured in the What Comes Next Cohort and variables available for future planned linkages

Category	Source	Variables	Baseline	Follow-up
Demographics	Chart review	Ethnicity	✓	
		Ashkenazi Jewish ancestry	✓	
		Number of biological children	✓	
	RPDB	Age	✓	✓
		Vital status	✓	✓
		Urban vs. rural neighbourhood	✓	✓
		Neighbourhood income quintile	✓	✓
	ONMARG	Ontario Marginalization Index	✓	✓
	CIC	Immigration status	✓	✓
	ORGD	Cause of death		✓
Comorbidities	CIHI-DAD, NACRS, OHIP, SDS	Aggregated Diagnosis Groups	✓	✓
	Comorbidity-specific datasets*	Asthma, hypertension, diabetes, rheumatoid arthritis, kidney disease, COPD, stroke, HIV, dementia	✓	✓
Genetic testing	Chart review	Date of genetic counseling	✓	
		Site of genetic counseling	✓	
		Results from previous testing	✓	
		Reason for testing	✓	
		Date of testing	✓	
		Site of testing	✓	
		Test type	✓	
		Test result	✓	
Family cancer history	Chart review	Number of 1st-degree maternal relatives with breast cancer	✓	
		Number of 2nd-degree maternal relatives with breast cancer	✓	
		Number of 1st-degree maternal relatives with ovarian cancer	✓	
		Number of 2nd-degree maternal relatives with ovarian cancer	✓	
		Number of 1st-degree paternal relatives with breast cancer	✓	
		Number of 2nd-degree paternal relatives with breast cancer	✓	
		Number of 1st-degree paternal relatives with ovarian cancer	✓	
		Number of 2nd-degree paternal relatives with ovarian cancer	✓	
Personal cancer history	Chart review	Type of cancer	✓	
		Stage at diagnosis	✓	
		Age at diagnosis	✓	

Personal cancer history	OCR	Date of cancer diagnosis	✓	✓
		Morphologic type	✓	✓
		Histologic type	✓	✓
		Stage at diagnosis	✓	✓
Treating physicians	CPDB	Age	✓	✓
		Specialty	✓	✓
		Years in practice	✓	✓
Hospitals	INST	Hospital number	✓	✓
		Hospital setting (academic vs. non-academic)	✓	✓
Hospital admissions*	CIHI-DAD	Date of admission	✓	✓
		Reason for admission	✓	✓
		Length of stay	✓	✓
Emergency department visits*	NACRS	Date of visit	✓	✓
		Reason for visit	✓	✓
Surgical history	OHIP, CIHI-DAD, SDS	Type of surgery	✓	✓
		Date of surgery	✓	✓
Breast or pelvic screening or diagnostic imaging	OHIP, OBSP	Date of imaging	✓	✓
		Date of biopsy	✓	✓
Radiation treatment*	ALR, OHIP	Body region radiated	✓	✓
		Dates of planning and treatment	✓	✓
		Course of treatment	✓	✓
		Dose per fraction	✓	✓
		Intent of treatment	✓	✓
Chemotherapy*	ALR, NDFP	Date of treatment	✓	✓
		Line of therapy	✓	✓
		Intent of treatment	✓	✓
		Drug administered	✓	✓
		Dose administered	✓	✓

*Requires linkages not yet performed but available for future studies

Abbreviations: ALR, Cancer Activity Level Reporting; CIC, Citizenship and Immigration Canada; CIHI, Canadian Institutes of Health Information; CPDB, Corporate Provider Database; DAD, Discharge Abstract Database; INST, Institution Information System; NACRS, National Ambulatory Care Reporting System; NDFP, New Drug Funding Program; OBSP, Ontario Breast Screening Program; OCR, Ontario Cancer Registry; OHIP, Ontario Health Insurance Plan; ONMARG, Ontario Marginalization Database; ORGD, Office of the Registrar General-Deaths; RPDB, Registered Persons Database; SDS, Same Day Surgery

Table 2. Baseline characteristics of the What Comes Next Cohort measured at the time of genetic testing (n = 15,986)

Characteristic	
Age, mean (SD)	52.51 (13.92)
Ethnicity[a], n (%)	
European	10,130 (63.4)
Southeast Asian	1,048 (6.6)
Central/South Asian or Middle Eastern	1,282 (8.0)
African/Caribbean	606 (3.8)
Latin/Hispanic	495 (3.1)
Other	1,107 (6.9)
Unknown	1,378 (8.6)
Ashkenazi Jewish, n (%)	2,946 (18.4)
Neighbourhood Income	
Rural	1,340 (8.4)
Urban, lowest fifth	1,940 (12.1)
Urban, second fifth	2,378 (14.9)
Urban, third fifth	2,522 (15.8)
Urban, fourth fifth	3,298 (20.6)
Urban, highest fifth	4,481 (28.0)
Marginalization, mean (SD)	3.03 (0.77)
ADGs	
0-5	2,938 (18.4)
6-7	3,051 (19.1)
8-10	4,714 (29.5)
≥11	5,283 (33.0)
Biological children, n (%)	
Yes	11,702 (73.2)
No	2,411 (15.1)
Unknown	1,873 (11.7)
Year of testing, n (%)	
2007-2009	2,793 (17.5)
2010-2012	4,616 (28.9)
2013-2016	8,577 (53.7)
Test type, n (%)	
Founder testing	2,072 (13.0)

Predictive testing	2,329 (14.6)
Complete analysis	11,585 (72.5)
Test result, n (%)	
Positive	2,033 (12.7)
VUS	1,175 (7.4)
Negative	11,437 (71.5)
Predictive negative	1,341 (8.4)

Abbreviations: VUS, variant of uncertain significance; ADGs, Aggregated Diagnosis Groups

[a]Women may belong to >1 ethnic group; ethnicity and Ashkenazi Jewish ancestry are not mutually exclusive

Table 3. Indications for and yield of testing by Ontario Ministry of Health (MOH) testing criteria

MOH Testing Criterion*		All tested (n = 15,986)	Positive (n = 2,033)	VUS (n = 1,175)	Negative (n = 11,437)
Affected individuals					
At least one case of cancer:					
MOH1:	Ashkenazi Jewish and breast cancer <50 years, or ovarian cancer at any age	435	39 (9.0)	24 (5.5)	366 (84.1)
MOH2:	Breast cancer <35 years of age	1,036	123 (11.9)	108 (10.4)	801 (77.3)
MOH4:	Invasive serous ovarian cancer at any age	1,327	195 (14.7)	104 (7.8)	1,027 (77.4)
At least two cases of cancer on the same side of the family					
MOH5:	Breast cancer <60 years and a first- or second-degree relative with ovarian cancer or male breast cancer	1,143	147 (12.9)	115 (10.1)	880 (77.0)
MOH6:	Breast and ovarian cancer in the same individual, or bilateral breast cancer with the first case <50 years	976	127 (13.0)	86 (8.8)	763 (78.1)
MOH7:	Two cases of breast cancer, both <50 years, in first- or second-degree relatives	1,508	134 (8.9)	160 (10.6)	1,210 (80.2)
MOH8:	Two cases of ovarian cancer, any age, in first- or second-degree relatives	195	52 (26.7)	17 (8.7)	122 (62.6)
MOH9:	Ashkenazi Jewish and breast cancer at any age, and any family history of breast or ovarian cancer	691	38 (5.5)	29 (4.2)	621 (89.9)
At least 3 cases of cancer on the same side of the family					
MOH10:	Three or more cases of breast or ovarian cancer at any age	5,293	355 (6.7)	454 (8.6)	4,467 (84.4)
Unaffected individuals					
MOH11:	Relative of individual with known *BRCA1* or *BRCA2* mutation**	2,394	860 (35.9)	27 (1.1)	237 (9.9)
MOH12:	Ashkenazi Jewish and first- or second-degree relative of individual with: breast cancer <50 years, or ovarian cancer at any age, or male breast cancer, or breast cancer at any age, with no positive family history of breast or ovarian cancer	1,277	92 (7.2)	4 (0.3)	1,130 (88.5)
MOH13	A pedigree strongly suggestive of hereditary breast/ovarian cancer i.e. risk of carrying a mutation for the individual being tested is >10%	2,105	93 (4.4)	175 (8.3)	1,830 (86.9)

* MOH3 (male breast cancer) excluded from table

** 94.7% of women with a predictive negative result were tested under MOH11; therefore, results are not shown for the predictive negative group

Note: women may have had multiple indications for testing selected; indication for testing missing for 859 women

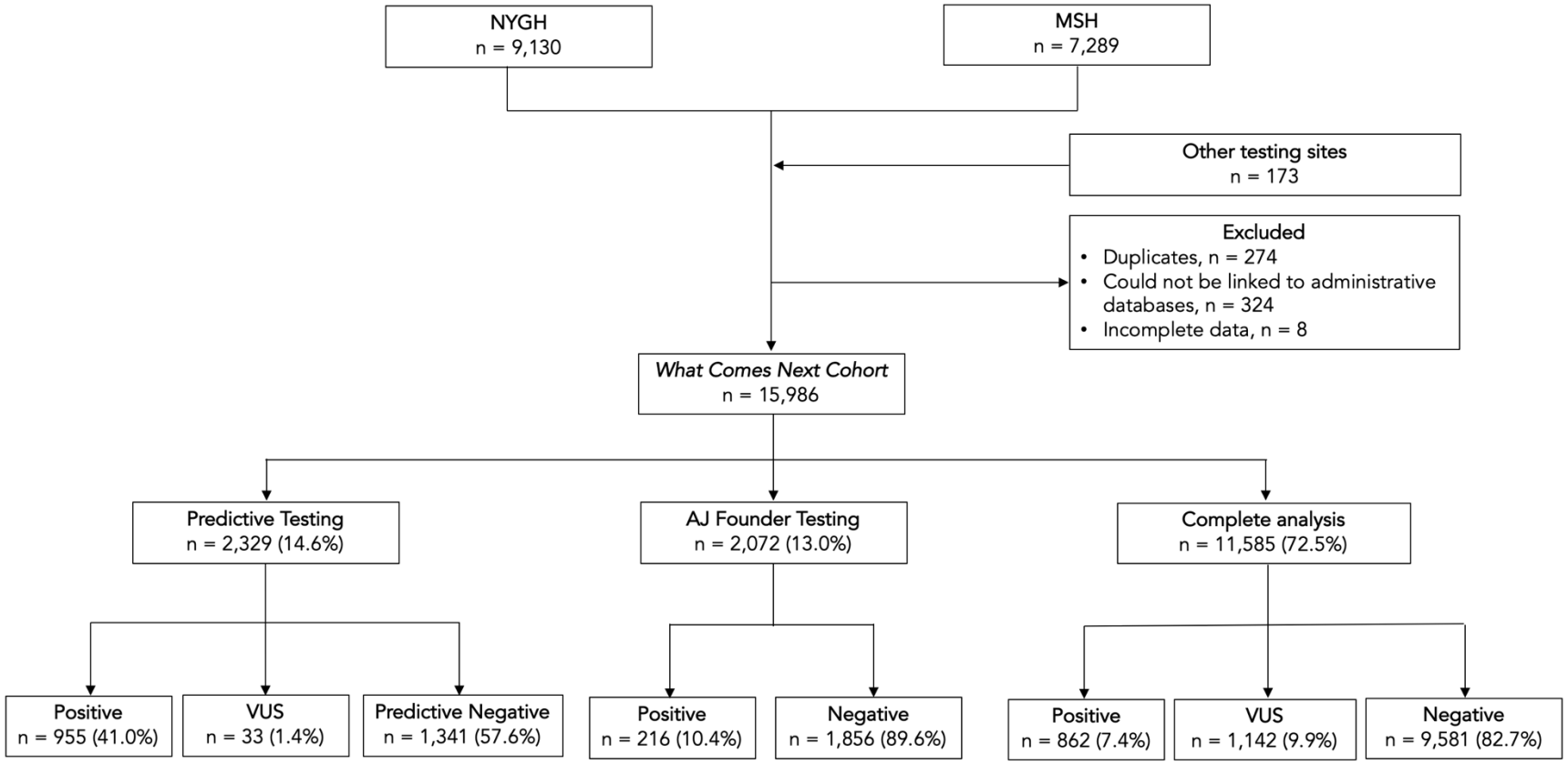
Table 4. Family and personal cancer history by test result. Results are reported as n (row %) or mean (SD)

	Predictive Testing*		Non-predictive Testing		
	Positive (n = 955)	**Negative** (n = 1,341)	**Positive** (n = 1,078)	**VUS** (n = 1,175)	**Negative** (n = 11,437)
Family Cancer History					
Breast Cancer					
1st-degree relatives with breast cancer	524 (43.7)	675 (56.3)	449 (7.2)	530 (8.5)	5,269 (84.3)
1 relative	413 (44.2)	521 (55.8)	362 (7.3)	409 (8.2)	4,201 (84.5)
≥2 relatives	111 (41.9)	154 (58.1)	87 (6.8)	121 (9.5)	1,068 (83.7)
2nd-degree relatives with breast cancer	545 (42.1)	749 (57.9)	501 (7.9)	540 (8.5)	5,275 (83.5)
1 relative	322 (43.0)	426 (57.0)	325 (8.0)	337 (8.3)	3,378 (83.6)
≥2 relatives	223 (40.8)	323 (59.2)	176 (7.7)	203 (8.9)	1,897 (83.3)
1st- or 2nd-degree relatives with breast cancer	769 (42.3)	1,050 (57.7)	717 (7.6)	802 (8.5)	7,903 (83.9)
1 relative	329 (42.5)	445 (57.5)	340 (7.7)	367 (8.3)	3,708 (84.0)
≥2 relatives	440 (42.1)	605 (57.9)	377 (7.5)	435 (8.7)	4,195 (83.8)
Ovarian Cancer					
1st-degree relative with ovarian cancer	216 (45.8)	256 (54.2)	195 (12.8)	142 (9.3)	1,187 (77.9)
1 relative	195 (45.8)	231 (54.2)	184 (12.8)	131 (9.1)	1,123 (78.1)
≥2 relatives	21 (45.7)	25 (54.3)	11 (12.8)	11 (12.8)	64 (74.4)
2nd-degree relative with ovarian cancer	225 (40.5)	330 (59.5)	175 (11.0)	144 (9.1)	1,267 (79.9)
1 relative	189 (41.7)	264 (58.3)	158 (11.4)	122 (8.8)	1,107 (79.8)
≥2 relatives	36 (35.3)	66 (64.7)	17 (8.5)	22 (11.1)	160 (80.4)
1st- or 2nd-degree relatives with ovarian cancer	392 (42.8)	523 (57.2)	323 (11.6)	255 (9.2)	2,212 (79.3)
1 relative	301 (43.7)	388 (56.3)	259 (11.4)	195 (8.6)	1,820 (80.0)
≥2 relatives	91 (40.3)	135 (59.7)	64 (12.4)	60 (11.6)	392 (76.0)
Personal Cancer History					
Breast Cancer					
Unaffected at time of testing	806 (38.4)	1,293 (61.6)	531 (9.0)	457 (7.8)	4,893 (83.2)
Affected at time of testing	149 (75.6)	48 (24.4)	547 (7.0)	718 (9.2)	6,544 (83.8)
Age at diagnosis, *mean (SD)*	47.15 (12.79)	55.60 (13.59)	44.45 (10.59)	48.82 (12.11)	50.30 (11.70)

Ovarian Cancer					
Unaffected at time of testing	920-925 (40.7-40.9)	1,335-1,341 (59.1-59.3)	817 (6.7)	1,044 (8.6)	10,289 (84.7)
Affected at time of testing	30-35 (85.7-100)	<6 (0-14.3)	261 (16.9)	131 (8.5)	1,148 (74.5)
Age at diagnosis, *mean (SD)*	54.57 (12.75)	-	53.90 (9.60)	56.39 (13.54)	60.00 (12.08)
Other cancers					
Pancreas	-	-	7 (6.6)	10 (9.4)	89 (84.0)
Colorectal	-	-	7 (9.6-10.3)	<6 (0-6.8)	61 (83.6-89.7)
Endometrial	-	-	7 (6.0)	14 (12.1)	95 (81.9)
Other	-	-	18 (3.8)	26 (5.5)	428 (90.7)
Number of cancers					
0	736 (37.3)	1,237 (62.7)	266 (7.1)	287 (7.7)	3,190 (85.2)
1	199 (68.2)	93 (31.8)	704 (7.9)	815 (9.1)	7,415 (83.0)
≥2	20 (64.5)	11 (35.5)	108 (10.7)	73 (7.2)	832 (82.1)

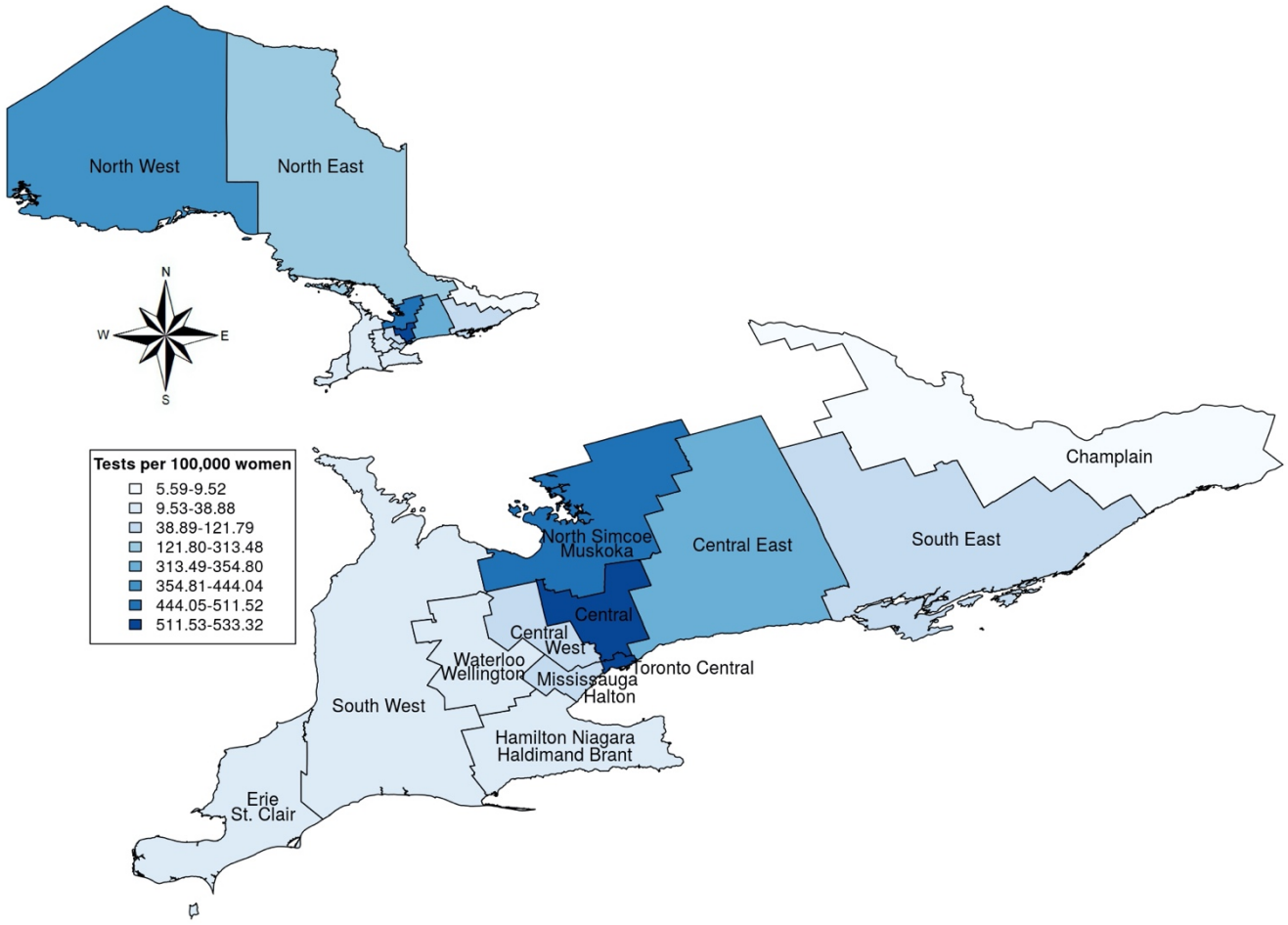
Abbreviations: VUS, variant of uncertain significance
Values for small cells presented as ranges or suppressed to prevent back-calculation
*33 women underwent predictive testing for and were found to carry a VUS previously identified among a family member; these women are included in the VUS column
Note, values suppressed where cell size <6

Figure 1. The What Comes Next Cohort



Abbreviations: NYGH, North York General Hospital; MSH, Mount Sinai Hospital; AJ, Ashkenazi Jewish; VUS, variant of uncertain significance

Figure 2. Number of women captured by the What Comes Next Cohort by geographic region in Ontario. Colours represent number of women included in the cohort per 100,000 women living within each region, based on population estimates from 2016



Population estimates obtained from: Statistics Canada. Table 17-10-0088-01 Estimates of population (2011 Census and administrative data), by age group and sex for July 1st, Canada, provinces, territories, health regions (2015 boundaries) and peer groups

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