BRCA1 and *BRCA2* Testing Referral Indications among Patients in the Hereditary Cancer Network Database

Background: Healthy People 2030 and Michigan state cancer plan objectives promote referral to genetic services for any individual with a strong personal or family history of breast and/or ovarian cancer. This may be indicative of hereditary breast and/or ovarian cancer (HBOC) syndrome, which is brought about by a mutation in specific genes, such as the *BRCA1* or *BRCA2*. A mutation in *BRCA1* or *BRCA2* can increase an individual's cancer risk by as much as 87%.[1] For individuals identified with HBOC, earlier and increased cancer screenings and preventive interventions can be considered to significantly reduce cancer risks. The National Comprehensive Cancer Network (NCCN) provides guidelines on who should be referred for genetic services. According to the NCCN guidelines, an individual needs to meet at least 1 of the 25 criteria in order to be referred for *BRCA1* and *BRCA2* testing. The Michigan Department of Health and Human Services (MDHHS) Cancer Genomics Program aims to reduce incidence and mortality rates of HBOC by educating providers on the importance of collecting a full personal and family history. In collecting this information and being aware of the NCCN guidelines, more patients can be appropriately referred to genetic services.

Methods: The Hereditary Cancer Network Database (HCN) collects non-identifiable information for patients seeking counseling for HBOC. Eighteen clinics have contributed information to this database. This database does not account for all genetic services in Michigan and provides only a sample of the population who are receiving genetic counseling and testing in the state. Looking at the patients seen in the HCN, a total of 27,940 individuals sought genetic counseling between 2008 and 2017 and had a strong personal or family history of a cancer related to HBOC. This report describes the various NCCN criteria that were met by individuals from the HCN database. Due to low frequencies for select criteria this report focuses on the characteristics for 15 of the criteria. Significance was based on chi-square analyses with a significance value set to be $p < 0.05$ and odds ratio analyses with a 95% confidence interval that did not include one.

Initial Visits and Genetic Testing Ordered for Specific NCCN Criteria for *BRCA1* and *BRCA2* Testing

- Patients who had no personal history, but a significant family history had the highest frequency for patients who sought genetic counseling; however, only 50.2% of these patients had testing, and of those who were tested, 19.2% were positive for a *BRCA1* or *BRCA2* mutation.
- Of patients with a history of breast cancer and of Ashkenazi Jewish heritage, 89.8% were referred to testing and 9.7% were positive for a *BRCA1* or *BRCA2* mutation.
- Of patients with a known familial mutation, 75.0% were referred to testing and 45.0% were positive for a *BRCA1* or *BRCA2* mutation.

Patients Meeting Select NCCN Guidelines from the HCN Database, 2008-2017

NCCN Criteria [1]	Initial Visit N (%)	*BRCA1* or *BRCA2* Test Ordered N (%)	Positive Result Received N (%)
Significant Family Hx Only [2]	10,518 (37.6)	5,278 (50.2)	1,011 (19.2)
Known Familial Mutation	3,155 (10.9)	2,367 (75.0)	1,065 (45.0)
BC at age 45	4,810 (17.2)	3,897 (81.0)	456 (11.7)
Multiple BC Primaries	538 (1.9)	461 (85.7)	86 (18.7)
BC ≤ 50 + Family Hx of BC	1,159 (4.2)	1,040 (89.7)	163 (15.7)
BC ≤ 50 + Family Hx of Prostate Cancer	511 (1.8)	460 (90.0)	64 (13.9)
BC ≤ 50 + Family Hx of Pancreatic Cancer	183 (0.7)	172 (94.0)	30 (17.4)
BC ≤ 60 + Triple Negative Breast Cancer	313 (1.1)	289 (92.3)	54 (18.7)
BC + ≥ 2 Relatives with a BRCA Related Cancer	2,044 (7.3)	1,752 (85.7)	230 (13.1)
BC + ≥ 1 Relative with BC ≤ 50	2,975 (10.7)	2,325 (78.2)	341 (14.7)
BC + ≥1 Relative with OC	563 (2.0)	506 (89.9)	79 (15.6)
BC + ≥ 1 Male Relatives w/ BC	668 (2.4)	454 (68.0)	90 (19.8)
BC + Ashkenazi Jewish Heritage	610 (2.2)	548 (89.8)	53 (9.7)
Male Breast Cancer	222 (0.8)	183 (82.4)	22 (12.0)
Ovarian Cancer	1,466 (5.3)	1,144 (78.0)	209 (18.3)
Total Patients	**27,940 (100)**	**17,659 (63.2)**	**2,379 (13.5)**

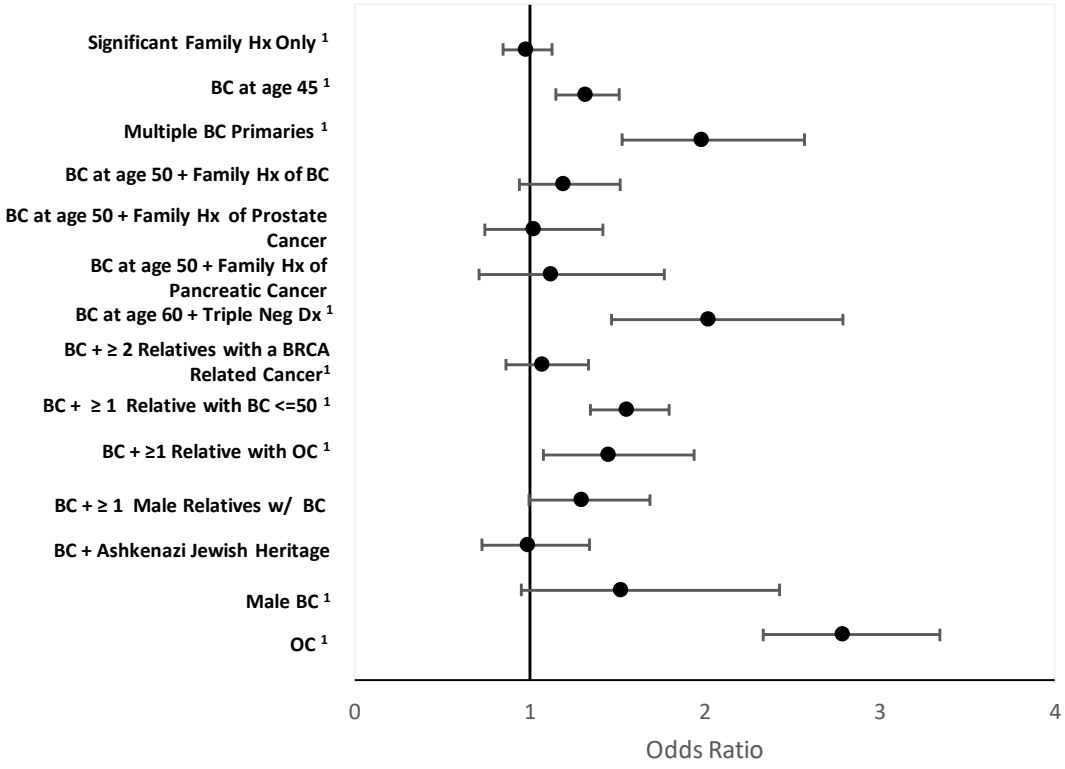
Abbreviations: Hx=History
BC= Breast Cancer
OC= Ovarian Cancer

[1] Criteria are not mutually exclusive, and individuals may fall under more than one category.
[2] Defined as having 1 or more family member with ovarian cancer, a male family member with breast cancer, a family member diagnosed with breast cancer at age 50 or younger, or 2 or more family members with either breast, prostate or pancreatic cancer.

NCCN Guidelines for *BRCA1* and *BRCA2* Testing Referral and Having a Pathogenic Mutation

- The odds of having a BRCA mutation were significantly higher among patients with a known familial mutation compared to patients without (OR=11.4) (Data not Shown).
- The odds of having a BRCA mutation were significantly higher among patients diagnosed with triple negative breast cancer at age 60 or younger compared to those patients who did not meet this guideline (OR=2.0).
- The odds of having a BRCA mutation were significantly higher among patients diagnosed with breast cancer at age 45 or younger compared to those patients who did not meet this guideline (OR=1.3).
- The odds of having a BRCA mutation were significantly higher among patients with ovarian cancer compared to those without ovarian cancer (OR=2.8).

Odds of having a Pathogenic Mutation for a *BRCA1* or *BRCA2* Mutation by Specific NCCN Criteria for Patients in the HCN Database, 2008-2017

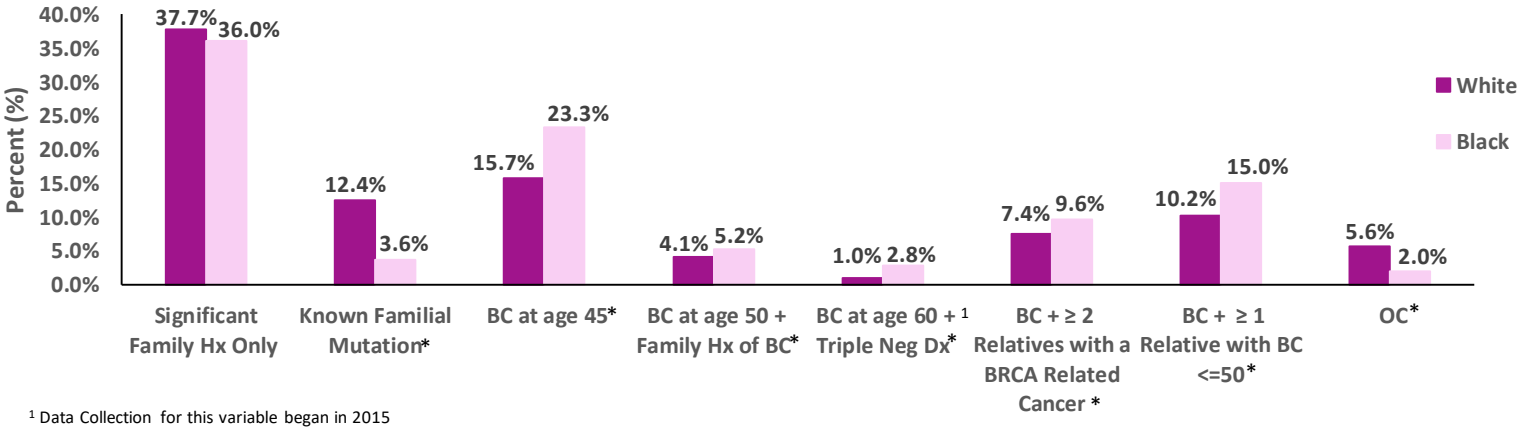


Abbreviations: HX=History; KFM=Known Familial Mutation; BC= Breast Cancer; OC= Ovarian Cancer

[1] Statistically significant at $p < 0.0001$

NCCN Guidelines for *BRCA1* and *BRCA2* Testing Referral by Race

NCCN Criteria for *BRCA1* or *BRCA2* Testing Referral that were Significantly Different between black and white Patients in the HCN Database, 2008-2017



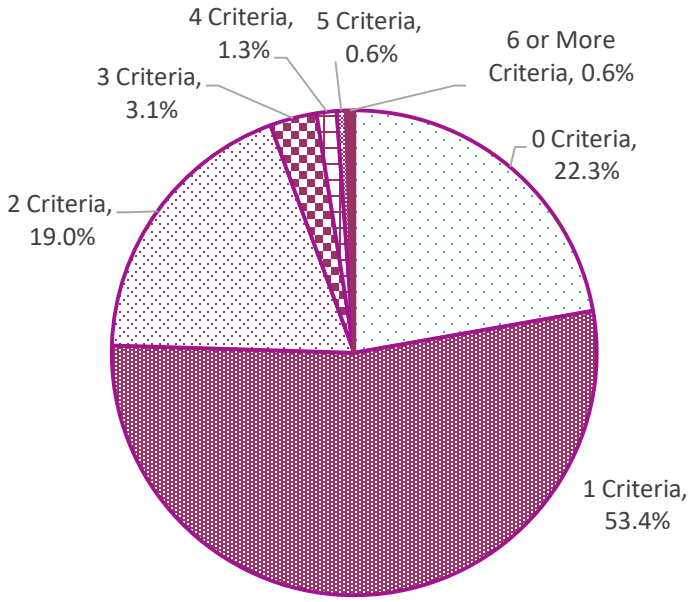
[1] Data Collection for this variable began in 2015
*Variable is statistically significant at $p < 0.05$

- White patients were significantly more likely to report having a known familial mutation (12.4%) compared to black patients (3.6%).
- Black patients were significantly more likely to report a diagnosis of breast cancer at age 45 or younger (23.3%) compared to white patients (15.7%).
- Significantly more black patients reported having Triple Negative breast cancer (2.8%) compared to white patients (1.0%).
- Significantly more white patients reported having ovarian cancer (5.6%) compared to black patients (2.0%).

Number of NCCN Guidelines Met for *BRCA1* and *BRCA2* Testing

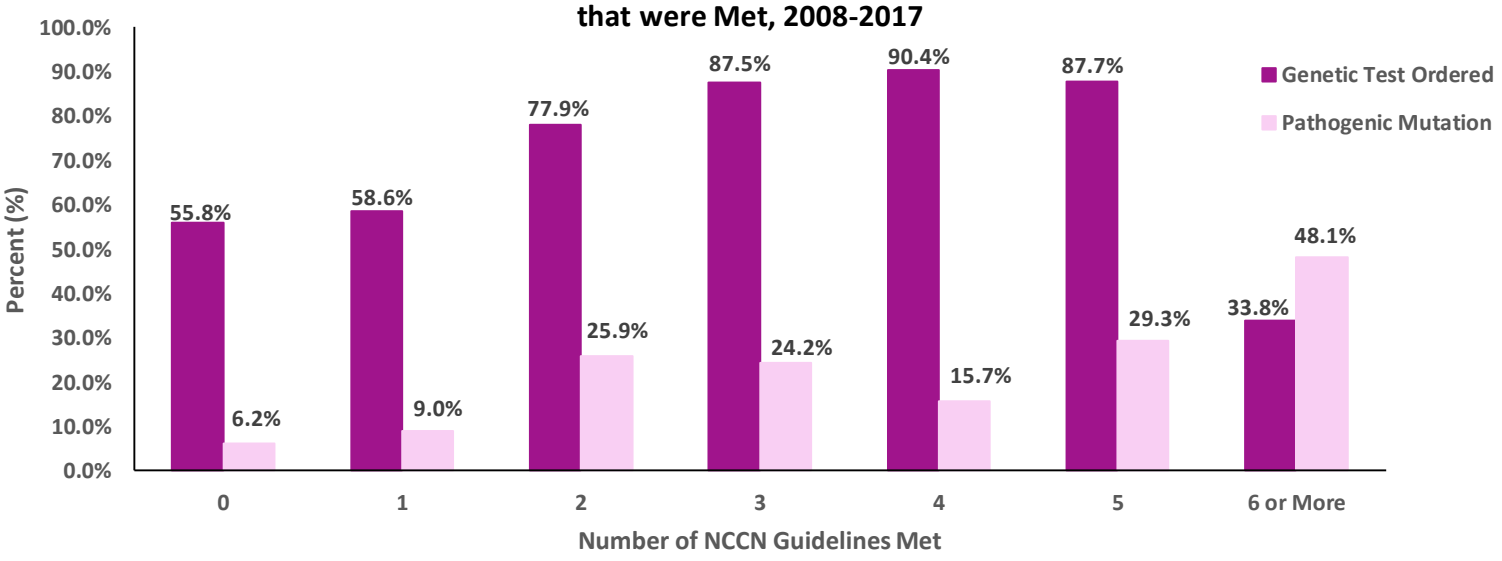
- Of all the patients who have a family or personal history of breast, ovarian, prostate, or pancreatic cancer, 28.9% did not meet any of the NCCN guidelines for *BRCA1* or *BRCA2* testing referral.
- Several patients met more than one criteria (24.2%).
  - Of those who met at least two criteria, 36.0% had both a known familial mutation and a significant family history.
- Significant racial differences existed in the distribution of the number of NCCN guidelines that were met by patients.
  - Black patients were more likely to meet three or more guidelines compared to white patients (6.8% vs 5.2%; Data not shown).

Number of NCCN Guidelines Patients Met for *BRCA2* and *BRCA2* Testing among Patients in the HCN Database, 2008-2017



Number of NCCN Guidelines Met for *BRCA1* and *BRCA2* Testing and Genetic Testing Ordered

Genetic Testing and Mutation Detection among Patients in the HCN Database by the Number of NCCN Guidelines that were Met, 2008-2017

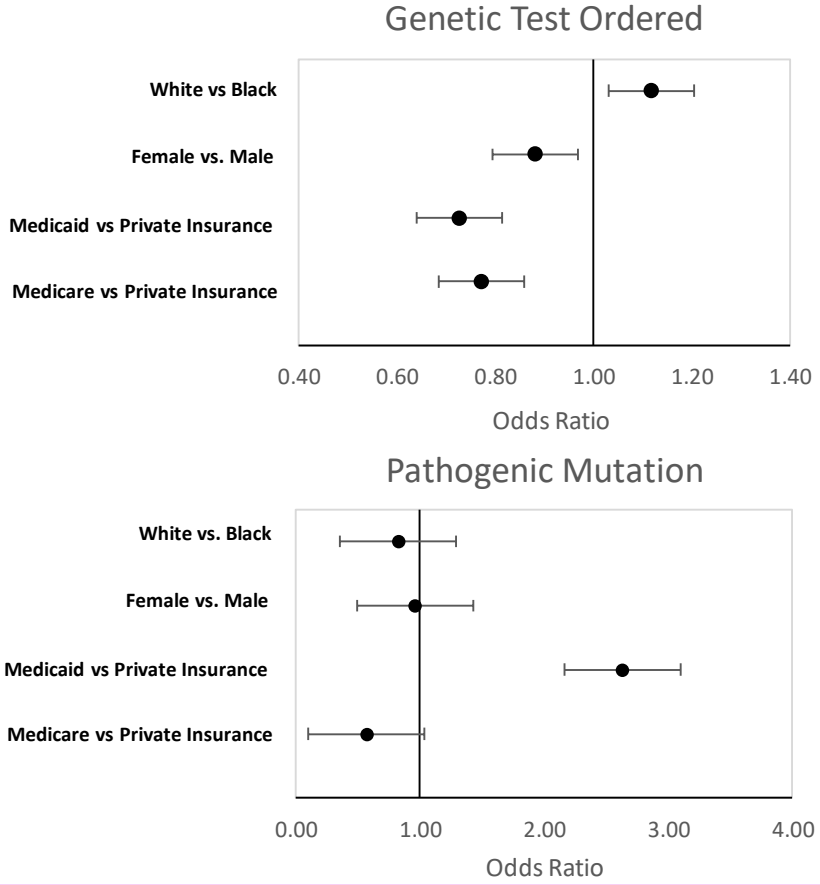


- The number of NCCN guidelines met was statistically significant with having a genetic test ordered.
- The number of NCCN guidelines met was statistically significant with having a pathogenic mutation.
  - Of those patients who did not meet any NCCN guidelines, 55.8% had a genetic test, and of those patients 6.2% had a pathogenic mutation.
  - Of those patients who met two NCCN guidelines, 77.9% had a genetic test, and of those patients 25.9% had a pathogenic mutation.
  - Of those patients who met six or more NCCN guidelines, 33.8% had a genetic test, and of those patients 48.1% had a pathogenic mutation.

Characteristics of Patients who had Genetic Testing

- Black patients were 22.8% less likely to have a genetic test ordered compared to white patients when controlling for the number of NCCN guidelines met.
- Patients on Medicaid were 11.8% less likely to have a genetic test ordered compared to patients with private insurance when controlling for the number of NCCN guidelines met.
- The odds of a black patient having a pathogenic mutation was 43.0% less likely compared to white patients when controlling for the number of NCCN guidelines met.
- The odds of a male having a pathogenic mutation was 2.6 times that of a female when controlling for the number of NCCN guidelines met.
- The odds of a patient on Medicare having a pathogenic mutation was 17.4% less likely compared to patients with private insurance when controlling for the number of NCCN guidelines met.

Characteristics of Patients in the HCN Database who had a Genetic Test Ordered and a Detected Pathogenic Mutation, Controlling for Number of NCCN Guidelines Met, 2008-2017



Summary

By examining the NCCN criteria that were met by patients from the HCN database, certain characteristics and disparities can be highlighted. Having a known familial mutation increased one's odds for having a pathogenic mutation detected the most, however there was a significant difference in reporting a familial mutation between white and black patients. Racial disparities also existed in the number of the criteria met. black patients on average met more of the criteria compared to white patients. Only one of these criteria needs to be met to meet the testing referral guideline indicating that black patients may need a stronger family or personal history to obtain a referral for testing compared to white patients. When holding the number of NCCN criteria met constant, black patients still were less likely to have a genetic test ordered. Further programmatic work is needed to address these disparities to ensure all people meeting at least one of these criteria are referred for genetic testing.

For More Information:

Visit www.Michigan.gov/hereditarycancer to learn more about hereditary cancers.
Visit www.Michigan.gov/cge to view more data on hereditary cancers.

MDHHS
Michigan Department of Health & Human Services
GRETCHEN WHITMER, GOVERNOR | ROBERT GORDON, DIRECTOR

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References:
1. Petrucelli N, Daly MB, Pal T. BRCA1 and BRCA2 Associated Hereditary Breast and Ovarian Cancer. Gene Reviews (2016)

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