



BRCA testing and testing results among women 18–65 years old

Fangjian Guo^{a,b,*}, Matthew Scholl^c, Erika L. Fuchs^{a,b}, Abbey B. Berenson^{a,b},
Yong-Fang Kuo^{b,d,e}

^a Department of Obstetrics & Gynecology, University of Texas Medical Branch at Galveston, Galveston, TX, United States

^b Center for Interdisciplinary Research in Women's Health, University of Texas Medical Branch at Galveston, Galveston, TX, United States

^c School of Medicine, University of Texas Medical Branch at Galveston, Galveston, TX, United States

^d Office of Biostatistics, Department of Preventive Medicine and Population Health, University of Texas Medical Branch at Galveston, Galveston, TX, United States

^e Institute for Translational Science, University of Texas Medical Branch at Galveston, Galveston, TX, United States

ARTICLE INFO

Keywords:

BRCA
BRCA testing
Cancer prevention
Electronic health record
Trend

ABSTRACT

Since the 1990 s discovery of *BRCA1* and *BRCA2* pathogenic variants in breast or ovarian cancer patients, genetic testing has been recommended as part of a targeted, individualized approach for cancer prevention and treatment in eligible individuals. The aim of this study was to assess trends in *BRCA* test rates and results among adult women aged 18 to 65 in the US between 2007 and 2017. Using Clinformatics© Data Mart (CDM) Electronic Health Records, we included 223,211 women 18–65 years old with documented *BRCA* testing results from 1/1/2007–9/30/2017. Positive results indicated the presence of pathogenic variants. *BRCA* test rates increased significantly from 34 per 100,000 women in 2007 to 488 per 100,000 women in 2016 (APC 30.8, 95% confidence interval 26.6–35.1). Documented positive results decreased from 86.1% in 2007 to 78.0% in 2017 (APC –0.6, 95% confidence interval –1.4–0.2). From 2007 to 2017, decreasing trends in the rates of documented positive results were observed among all three age groups (18–39, 40–54, and 55–65 years; largest in 40–54 group). In 2015–2017, women with positive test results were less likely to be non-Hispanic Whites, cancer patients, or living in the Northeast or an area with average household income \geq \$50,000. Between 2007 and 2017, increasing use of *BRCA* testing for cancer prevention and treatment occurred, correlating to the observed decreasing documented positive test rate. The utilization of testing and corresponding test results differed significantly across races/ethnicities, suggestive of a divergent application of the same testing criteria.

1. Introduction

In the US, breast cancer is the second most diagnosed cancer, and is the second leading cause of cancer mortality. (Siegel et al., 2019) A small proportion of breast cancers have an inheritable genetic basis. (Network, Oct 2012) Pathogenic variants in the *BRCA1* and *BRCA2* genes make up about half of the inherited germline pathogenic variants. Pathogenic *BRCA1/2* mutations may lead to the development of breast cancers. (Nelson et al., 2019) Since the discovery in the 1990 s of *BRCA1* and *BRCA2* pathogenic variants in breast and ovarian cancer patients, (Weitzel et al., 2011) genetic testing has been a recommended component of targeted, individualized cancer prevention and treatment in

eligible individuals.

BRCA testing can be used for breast and ovarian cancer prevention if susceptible individuals are identified before the onset of cancer. Genetic testing in patients with prevalent breast or ovarian cancer can also be beneficial in several ways. For instance, identification of those with pathogenic variants may help those patients choose specific treatment options, and predict their prognoses more accurately. (Narod, Dec 2010) Additionally, carriers of pathogenic variants diagnosed with only one type of cancer (breast or ovarian) may presumably benefit from increased surveillance and risk-reducing measures for the prevention of other cancers to which they are genetically predisposed. Finally, their blood relatives may have up to a 50% chance of carrying the same

Abbreviations: CDM, Clinformatics© Data Mart; USPSTF, US Preventive Services Task Force; NCCN, National Comprehensive Cancer Network; HER, Electronic Health Records; ICD–9, International Classification of Diseases, ninth edition; ICD–10, International Classification of Diseases, tenth edition; APC, annual percentage change.

* Corresponding author at: Department of Obstetrics & Gynecology, Center for Interdisciplinary Research in Women's Health, University of Texas Medical Branch at Galveston, 301 University Blvd, Galveston, TX 77555–0587, United States

E-mail address: faguo@utmb.edu (F. Guo).

<https://doi.org/10.1016/j.pmedr.2022.101738>

Received 20 April 2021; Received in revised form 22 January 2022; Accepted 16 February 2022

Available online 19 February 2022

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pathogenic variant and can benefit from cascade testing and the subsequent cancer prevention choices. The aforementioned benefits of *BRCA* testing have led to genetic testing recommendations by the US Preventive Services Task Force (USPSTF), the National Comprehensive Cancer Network (NCCN), and other professional organizations for women whose personal histories, ethnic backgrounds, or family histories are associated with an increased risks for *BRCA* pathogenic variants. (FitzGerald et al., 1996) Currently, the testing is recommended for women who meet the guideline criteria and not for all the women with personal and/or family history of *BRCA*-related cancers.

With the celebrity publicity and the massive and intensive marketing campaigns targeting the public by Myriad Genetics and others (So and Joly, Jun 2013), the awareness of use of genetic testing has been on an increasing trend. The 2008 Genetic Information Nondiscrimination Act may also allay the fears of genetic information misuse and boost the utilization of genetic testing. Since 2011, the Affordable Care Act has mandated coverage for preventive services recommended by USPSTF, including referring eligible women for genetic counseling and *BRCA* testing. (Seiler et al., 2014 Nov-Dec 2014) Moreover, the 2013 Supreme Court ruling against Myriad Genetics's patent claims of *BRCA* mutation test and subsequent availability of the testing in other clinical labs will greatly reduce the cost of the test and further increase the testing rate. (Long and Ganz, Dec 2015; King et al., Sep 2014; Test, 2016) However, research has shown that in the US, the majority of *BRCA* pathogenic variant carriers remain unidentified. (Drohan et al., 2012) It is estimated that only 10% of unaffected carriers of *BRCA* pathogenic variants and 30% of living breast cancer patients with *BRCA* pathogenic variants know their status. (Drohan et al., 2012) The USPSTF guidelines only address *BRCA* testing in women without a personal history of *BRCA*-related cancer. Even though unaffected young women < 40 years old benefit the most from prophylactic treatment, only 20% of tests are performed in this demographic group. (Guo et al., 2017) Previously, using claims data from the Clinformatics® Data Mart Database, we reported on trends in the use of *BRCA* testing in unaffected women vs cancer patients among US adult women aged 20–65 years old. (Guo et al., 2017) *BRCA* testing had been used mainly in women already diagnosed with breast or ovarian cancer and in cascading tests, and we observed a gradual shift towards the use of *BRCA* testing in cancer prevention. (Guo et al., 2017) The extensive Electronic Health Record data provides the opportunity to assess trends in *BRCA* test results among free-living adult women in the US. In this study, we evaluate how the rate of documented positive results for *BRCA* testing changed over time and the influence of race/ethnicity on the trends among adult US women.

2. Methods

2.1. Ethics statement

This study was exempt from full board review by the Institutional Review Board at University of Texas Medical Branch. All patient information was deidentified.

Data from Optum® de-identified Clinformatics® Data Mart Database (Eden Prairie, MN) were used to study the trends in *BRCA* test rate, which contains de-identified insurance claim records on a population representative of the working US population. (Palmer et al., 2020; Hu et al., 2020) Data from Clinformatics® Data Mart (CDM) Electronic Health Records (EHR) (Optum, Eden Prairie, MN) were used to study *BRCA* test result. As of 2018, CDM EHR data integrated 85 health systems across all 50 states and represented > 140,000 providers for a cumulative 91 million lives. This longitudinal, comprehensive, structured EHR data contains deidentified information on demographics, diagnosis, hospitalizations, lab results, medications, observations, outpatient visits, provider notes, and procedures. Important clinical information can also be extracted from provider notes using natural language processing software. Broad geographic and demographic

representations with similar compositions in age, sex, race, and income to the US population are available.

Current Procedural Terminology codes and Healthcare Common Procedure Coding System for the *BRCA* pathogenic variant test (81162, 81211–81217, 81432, 81433, S3818–S3820, S3822, and S3823) were used to identify women who received *BRCA* testing in the CDM dataset. We included 223,211 women aged 18–65 years old with *BRCA* testing results noted in their EHR's from 1/1/2007 to 9/30/2017. *BRCA* test results were obtained from lab results and were also extracted from provider notes using natural language processing. Positive test results indicated the presence of pathogenic variants and a genetic predisposition for certain cancers. Only true pathogenic variants were classified as positive results.

Age at *BRCA* testing was categorized into three groups: 18–39 years, 40–54 years, and 55–65 years. Race/ethnicity was classed as Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian and other. Region of residence was divided according to the U.S. Census Regions (South, Northeast, Midwest, and West). Percentage of people with a college degree and annual household income were based on zip code data. Cases of previously diagnosed breast cancer were identified by the International Classification of Diseases, ninth edition (ICD-9) code V10.3 and the International Classification of Diseases, tenth edition (ICD-10) code Z85.3 for personal history of malignant neoplasm of breast, ICD-9 code 174.x and ICD-10 code C50 for malignant neoplasm of female breast, and ICD-9 code 233.0 and ICD-10 code D05 for carcinoma in situ of breast. Cases of previously diagnosed ovarian cancer were identified by ICD-9 code V10.43 and ICD-10 code Z85.43 for personal history of malignant neoplasm of ovary and ICD-9 code 183.0 and ICD-10 code C56 for malignant neoplasm of ovary. Family history of breast cancer was identified by ICD-9 code V16.3 and ICD-10 code Z80.3. Family history of ovarian cancer was identified by ICD-9 code V16.41 and ICD-10 code Z80.41. This study was exempt from full board review by the Institutional Review Board.

2.2. Statistical analysis

BRCA testing rates were calculated by using the female beneficiary population aged 18–65 years old of the health plan in each year from 2007 to 2017 as the denominator and women with *BRCA* tests in that year as the numerator. As we did not have data on the whole year of 2017, annual test rates were calculated based on data from 2007 to 2016. Rates of documented positive test results were calculated using the female population with documented *BRCA* test results in each year as the denominator and women with pathogenic variants noted in their EHR during that year as the numerator. Then, the linear trends in documented *BRCA* testing rates and positive test result rates were assessed. The annual percentage change (APC) of total *BRCA* testing and the APC of test results were also calculated. APC was calculated as $(\exp[\beta]-1)*100$, where the regression coefficient (β) was estimated by fitting a least-squares regression line to the natural logarithm of the rates, using the calendar year as a regressor variable. The differences in characteristics between women with and without pathogenic variants were assessed by the χ (Network CGA, 2012) test. Multivariable logistic regression models were used to assess the trends. Covariates assessed included age, race/ethnicity, and region of residence. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute; Cary, NC). A 2-sided p value of < 0.05 was considered statistically significant.

3. Results

From the collected data, 223,211 women had *BRCA* testing results noted in their EHRs during 2007–2017 (Table A.1) with a mean age of 46.8 years. Most (81.1%) of those women were non-Hispanic Whites, and 44.2% resided in the Midwest (Table 1). Of the 223,211 women, 32.7% had a prior history of diagnosed breast cancer before *BRCA*

Table 1
Characteristics of adult women who had BRCA test noted in their electronic health records in 2007–2017.

	Mean or Percentage (95% Confidence Interval)		
	All	Positive	Not positive
N	223,211	171,645	51,566
Age (mean, year)	46.8 (46.7–46.8)	46.8 (46.7–46.9)	46.7 (46.5–46.8)
Race/ethnicity			
Non-Hispanic White	81.1 (80.9–81.2)	80.4 (80.3–80.6)	83.1 (82.8–83.4)
Non-Hispanic Black	6.7 (6.6–6.8)	7.2 (7.0–7.3)	5.0 (4.8–5.2)
Non-Hispanic Asian	2.1 (2.1–2.2)	2.2 (2.1–2.2)	2.0 (1.9–2.1)
Other	6.4 (6.3–6.5)	6.3 (6.2–6.4)	6.6 (6.4–6.9)
Hispanic	3.8 (3.7–3.9)	3.9 (3.9–4.0)	3.2 (3.1–3.4)
Region			
South	20.1 (19.9–20.2)	20.6 (20.4–20.8)	18.5 (18.1–18.8)
West	19.6 (19.4–19.8)	21.6 (21.4–21.8)	12.8 (12.5–13.1)
Midwest	44.2 (44.0–44.4)	44.3 (44.1–44.5)	43.8 (43.4–44.3)
Northeast	12.2 (12.1–12.4)	9.5 (9.4–9.6)	21.4 (21.0–21.7)
Percent with college education (%)	25.6 (25.5–25.6)	25.1 (25.1–25.1)	27.2 (27.1–27.2)
Annual household income ≥ \$50,000	14.3 (14.2–14.5)	12.1 (11.9–12.2)	21.9 (21.5–22.3)
family history of breast cancer	32.7 (32.5–32.9)	31.2 (31.0–31.4)	37.4 (37.0–37.8)
family history of ovarian cancer	8.5 (8.4–8.6)	8.7 (8.6–8.8)	7.7 (7.5–8.0)
personal history of breast cancer	25.9 (25.7–26.1)	23.4 (23.2–23.6)	34.3 (33.9–34.7)
personal history of ovarian cancer	2.4 (2.4–2.5)	2.5 (2.4–2.6)	2.3 (2.1–2.4)

testing, 8.5% had a prior history of diagnosed ovarian cancer before documented BRCA testing, 25.9% had a family history of breast cancer before documented BRCA testing, and 2.4% had a family history of ovarian cancer before documented BRCA testing. Among women with pathogenic variants, 7.2% were non-Hispanic Blacks, 3.9% were Hispanics, 21.6% resided in the West, and 9.5% resided in the Northeast. Among women without pathogenic variants, 5.0% were non-Hispanic Blacks, 3.2% were Hispanics, 12.8% resided in the West, and 21.4% resided in the Northeast.

A significant increase in BRCA test rates occurred, from 34 per 100,000 women in 2007 to 488 per 100,000 women in 2016 (Fig. 1). APC 30.8, 95% confidence interval 26.6–35.1). The BRCA test rate in 2016 was highest among non-Hispanic Whites (582 per 100,000), while

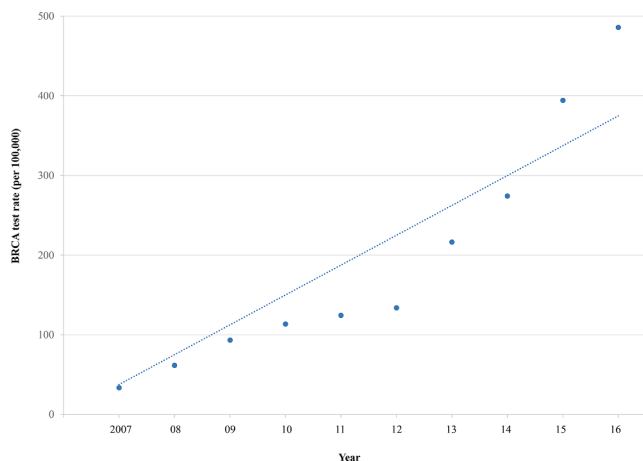


Fig. 1. Trends in documented BRCA testing rate among women aged 18–65 years, 2007–2016.

it was 313 per 100,000 in non-Hispanic Black women, 310 per 100,000 in Hispanic Women, and 281 per 100,000 in women of other races/ethnicities.

Documented positive test results decreased from 86.1% in 2007 to 78.0% in 2017 (Fig. 2). APC -0.6 , 95% confidence interval -1.4 – 0.2). From 2007 to 2017, decreasing trends in documented positive rates were observed among all three age groups (Fig. 3A). 18–39, 40–54, and 55–65 years; largest decrease in 40–54 group). Documented positive test rates decreased in patients residing in the Midwest and the Northeast, but increased in the West (Fig. 3B). Among patients with breast or ovarian cancer, positive results decreased from 85.3% to 62.4% (Fig. 3C). Among those without breast or ovarian cancer, documented positive results decreased from 86.2% to 80.9% (APC -3.2 vs. -0.1 , $p < 0.001$). Similar patterns were observed among women with breast cancer vs. women without breast cancer (Fig. A.1), and among women with ovarian cancer vs. women without ovarian cancer (Fig. A.2). Documented positive test result rates decreased in non-Hispanic White women but increased in Hispanics (Fig. 3D). Among women with breast or ovarian cancer, documented positive test result rates decreased across time among all racial/ethnic groups (Fig. A.3). Among women without breast or ovarian cancer, documented positive rates were relatively constant across time and even increased in Hispanic women (Fig. A.4). Documented positive test result rates remain constant among women with no personal or family history of breast or ovarian cancer, while the rates continuously decreasing in women have personal or family history of breast or ovarian cancer and women with both personal and family history of cancer seemed to have higher documented positive rates (Fig A.5).

In 2015–2017, women with documented positive test results were less likely to be cancer patients or non-Hispanic Whites. During the same period, women with positive test results were also less likely to live in the Northeast or an area with average household income \geq \$50,000. The percentage of positive results was lowest among non-Hispanic White women tested (75.7%), and highest among non-Hispanic Black test takers (85.1%). After adjusting for age, region of residence, education, income, and family history of breast or ovarian cancer, adjusted odds ratio for having a positive test among non-Hispanic Black women tested vs. non-Hispanic White women tested was 1.71, 95% confidence interval 1.61–1.82 (Table A.2). Similarly, the adjusted odds ratio for Hispanics vs non-Hispanic Whites was 1.21, 95% confidence interval 1.13–1.31.

4. Discussion

Using data from large insurance claim and EHR datasets, we assessed

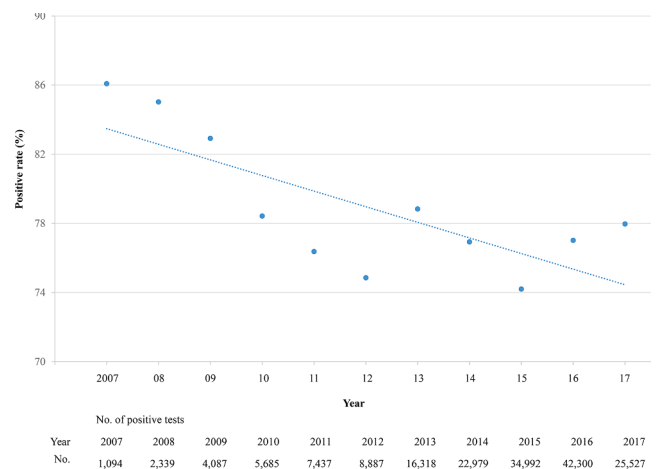


Fig. 2. Documented positive BRCA test rates among women aged 18–65 years, 2007–2017.

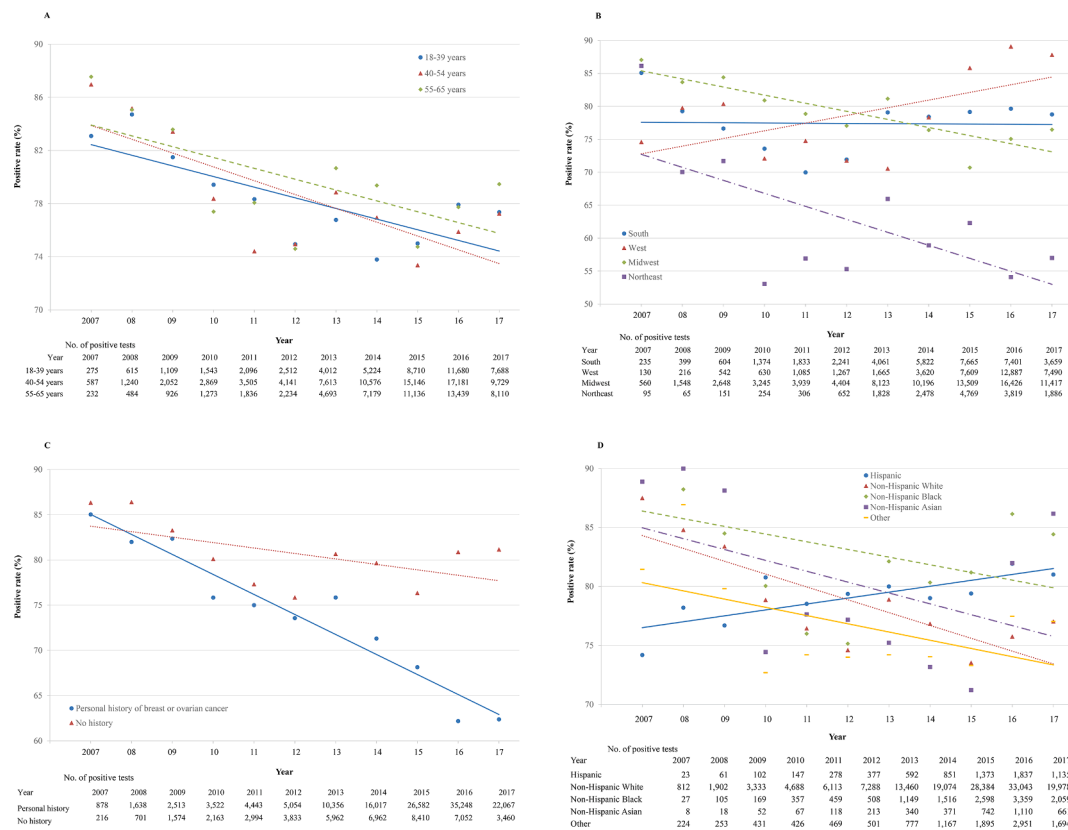


Fig. 3. Documented positive BRCA test rates by age group, region of residence, personal history of breast or ovarian cancer, and race/ethnicity, 2007–2017. A. Age group; B. Region of residence; C. Personal history of breast or ovarian cancer; D. Race/ethnicity.

trends in BRCA testing and documented positive testing results among adult US women. An increasing BRCA testing and decreasing documented positive test rate were found, which may be partly due to a loosening of testing criteria for testing subject selection over the evaluated period. Differences in positive rates of documented BRCA testing across races/ethnicities, with the highest positive rate in non-Hispanic Black women, suggest that more stringent test selection criteria were applied to this underserved population.

A striking observation seen from this study is the high positive rate compared to that reported by others. For example, in high risk patients meeting testing criteria for BRCA1/2, 33% were positive for pathogenic variants; (LaDuca et al., 2020) in African American women with breast cancer, 5%–10% were positive; (Palmer et al., 2020) in invasive breast cancer patients, about 4% were positive; (Hu et al., 2020) and among families affected by breast cancer, about 4% of those families had individuals with identified pathogenic variants of BRCA1/2. (Maxwell et al., 2016) The reason why the positivity rate found in our study far exceeds the positivity rates of any other study is that we only studied BRCA test documented in EHR and would miss many BRCA tests that were not documented in EHR, especially those with negative results. Our observed high positive rate is likely the result of under-documentation of negative BRCA testing results in the electronic health records. Positive results omitted in clinical documentation are possible though less likely, because positive results can be acted on in clinical settings. Our findings only reflect the clinical practice of documentation of BRCA testing results in EHR.

The testing rate of 488 per 100,000 women in 2016 in this study is relatively high compared to other countries. Our test rates were similar to those in 2009–2014 and 2003–2014 in the US calculated using private claim data and publicly reported revenues from the primary BRCA testing provider. (Chen et al., 2018; Kolor et al., 2017) The number of BRCA genetic tests in 2016/2017 was 54.2 per 100,000 women in

England and 69.8 per 100,000 women in Scotland. (Kroese et al., 2018) In France, the number of genetic consultations were 77,478 in 2017. (Institut national du cancer, 2019) 54,936 of these consultations were due to breast or ovarian cancer concerns, of which 18,180 women received BRCA testing. Consultation rates varied across France, from 65 per 100,000 women the center of France to 172 per 100,000 women in Pays de la Loire. The reason why testing rate is higher in the US in our study compared to other developed countries is unknown and warrants further study. Affordable care act coverage and other policy changes (loosening test selection criteria) may play a part in increasing the test rate in the US. (Chen et al., 2018)

An examination of the selection criteria for BRCA testing and genetic counseling in clinical guidelines from the USPSTF and NCCN shows that the selection criteria has gradually loosened over time. (Nelson et al., 2005; Nelson et al., 2014; Daly et al., 2014; Daly et al., Feb 2006; Daly et al., May 2010) In our study, we observed an ongoing decrease in positive rates of BRCA test results among breast or ovarian cancer patients. This is consistent with the loosening of testing selection criteria, because as the pool of people tested grows and becomes increasingly less likely to contain those with a BRCA pathogenic variant the rate of positive BRCA test results should decrease. Loosened guidelines may lead to a lower positive rate. However, lower positive rate is not necessarily the result of loosened guidelines or application of the guidelines. Due to most young female breast or ovarian cancer patients not having a family history of breast or ovarian cancer or Ashkenazi Jewish ancestry, even those who are BRCA pathogenic variant carriers do not qualify under the current standards to undergo BRCA testing prior to their cancer diagnosis. (Kwon et al., 2010) The goal of this testing, in terms of benefits to family members, is to identify the mutation that runs in the family, ideally for single site testing. This is one reason why previous and ongoing proposals and evaluations of genetic testing for all women with breast or ovarian cancer are necessary. (Kwon et al., 2010; Beitsch et al.,

2019) Population-wide *BRCA* screening in women may identify those women prior to their cancer diagnosis and provide them an opportunity to prevent breast and ovarian cancers. However, whether this approach is feasible and cost-effective needs further investigation.

The main strength of this study is the use of a large and comprehensive sample of electronic medical records to examine documentation of *BRCA* testing and positive rates of the testing results over time. The CDM EHR data are longitudinal, comprehensive and structured, covering over 140,000 providers and 91 million lives across 50 states. The national data provides reliable estimates of documented positive rates of *BRCA* testing in electronic health records. Additionally, using the EHR rather than processed claims for calculating documented positive test rate means that claims that were denied are still included in the sample. Limitations to this study include the generalizability of the data used and the potential for incorrect or missed documentation in EHR. As awareness of *BRCA* testing has increased, documentation of negative results likely has increased. Also, documentation of negative results might vary by indication (personal vs. family history of cancer). The possibility of under-documentation of negative results for patients in some racial and ethnic minority groups might also be possible. Properly documented negative results may help avoid unnecessary screening and save healthcare costs. Necessary measures are needed to improve the documentation of these negative results. Positive results omitted in clinical documentation are possible though less likely, because positive results can be acted on in clinical settings. (Nelson et al., 2019; Nelson et al., 2019) Our data included more people in the Midwest and more non-Hispanic Whites compared to the standard US population. Our data also only covered those who went to the health systems integrated into CDM EHR data and may not be applicable to women who visit other health systems. Additionally, we only studied *BRCA* test documented in EHR and the findings only reflect the clinical practice of documentation of *BRCA* testing results in EHR. Our study would miss many *BRCA* tests that were not documented in EHR, especially those with negative results. Any further interpretation of those findings should be with caution.

5. Conclusions

Between 2007 and 2017, there was an increasing use of *BRCA* testing for cancer prevention and treatment. In women with breast or ovarian cancer, a significantly decreasing positive rate of documented *BRCA* test results indicates an increasingly loose criteria for testing subject selection. The documentation of testing and corresponding test results differed significantly across races/ethnicities, suggestive of a differential application of the testing criteria. Documented testing rate was highest in non-Hispanic Whites, who were also the least likely to have a positive test result documented. Non-Hispanic Black women tested were more likely to have a positive test result documented, suggesting the most stringent application of testing selection criteria for this underserved population.

CRedit authorship contribution statement

Fangjian Guo: Conceptualization, Methodology, Visualization, Software, Writing – original draft. **Matthew Scholl:** Writing – review & editing. **Erika L. Fuchs:** Writing – review & editing. **Abbey B. Berenson:** Conceptualization, Writing – review & editing. **Yong-Fang Kuo:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Part of the results were presented at the 2018 Annual BIRCWH Meeting – Building Interdisciplinary Research Careers in Women's Health. November 28, 2018. Bethesda, MD, and the AACR (American Association for Cancer Research) Annual Meeting 2019. March 29 – April 3, 2019. Atlanta, Georgia.

Dr. Guo is currently supported by the National Cancer Institute of NIH under Award Number K07CA222343. At the time the study was initially performed, Drs. Guo and Fuchs were previously supported by a research career development award (K12HD052023: Building Interdisciplinary Research Careers in Women's Health Program-BIRCWH; Berenson, principal investigator) from the Office of Research on Women's Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

No financial disclosures were reported by the authors of this paper.

Data availability statement

Data from Clinformatics® Data Mart (CDM) Electronic Health Records are available through Optum.com. The authors are not allowed to share data with third party due to legal restrictions. For analytical data of individual beneficiaries, investigators need to sign a data reuse agreement following the procedure specified by Optum. The authors did not have any special access privileges that others would not have.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pmedr.2022.101738>.

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