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EPIDEMIOLOGY

Concordance with *BRCA1/2* testing guidelines among women in The Health of Women (HOW) Study®

Michelle I. Silver[1,3] · William Klein[1] · Goli Samimi[2] · Lori Minasian[2] · Jennifer Loud[3] · Megan C. Roberts[1]

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Abstract

Purpose To evaluate factors associated with compliance to the National Comprehensive Cancer Network (NCCN) guidelines for *BRCA1/2* testing and identify groups who are at risk of under- and over-use of *BRCA1/2* testing.

Methods Data included 20,758 women from Dr. Susan Love Research Foundation's The Health of Women (HOW) Study®. Multinomial logistic regression was used to examine the association of socioeconomic and demographic characteristics with whether the woman was over-, under-, or appropriately tested for *BRCA1/2* mutations, per 2015 NCCN guidelines.

Results 3894 women (18.8%) reported *BRCA1/2* testing. 5628 (27.1%) women who met NCCN criteria for testing were not tested. Among women with a history of breast cancer, those without health insurance were more likely to be under-tested (OR 2.04, 95% CI 1.15–3.60) than those with managed care insurance, and higher education was associated with a lower likelihood of under-testing (Graduate/professional degree OR 0.71, 95% CI 0.55–0.91).

Conclusion Almost 30% of women were under-tested, indicating that many high-risk women who may benefit from genetic testing are currently being missed. Without appropriate testing, providers are unable to tailor screening recommendations to those carrying mutations who are at highest risk. Patient and healthcare provider education and outreach targeted to low-income and under-served populations may assist in reducing under-testing.

Keywords Breast cancer · Genetic testing · BRCA1/2 · Guideline adherence

Introduction

In the United States, breast cancer is the leading cancer among women. With improvement in early detection and treatment, 5-year survival rates for breast cancer overall are high, approaching 90%, though 5-year prognosis for late stage diagnoses is only 26% [1]. Given this vast survival difference, breast cancer prevention efforts focus on risk assessment, risk reduction, and early detection [2–5]. Individuals with germline mutations in cancer susceptibility genes, such as *BRCA1 and BRCA2*, are at an increased likelihood of developing breast and ovarian cancer, and thus require tailored cancer prevention strategies [6, 7]. Although the average population risk of breast cancer for women is 8.3% over a lifetime, it reaches approximately 60% for *BRCA1* and 45% for *BRCA2* mutation carriers [8, 9].

Accurate identification of this high-risk group, through genetic testing, is critical for tailoring surveillance for this population through more frequent and/or more accurate breast cancer screening methods. As such, clinical guidelines have included genetic testing for high-risk women (with extensive personal and/or family cancer histories) for

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✉ Michelle I. Silver
michelle.silver@nih.gov

[1] Division of Cancer Control and Population Sciences, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA

[2] Division of Cancer Prevention, National Cancer Institute, Rockville, MD, USA

[3] Division of Cancer Epidemiology & Genetics, National Cancer Institute, Rockville, MD, USA

over a decade [3, 4, 10]. For clinical management of this high-risk population, the National Comprehensive Cancer Network (NCCN) recommends that women with *BRCA1/2* mutations begin breast cancer screening (i.e., annual mammography and MRI) at age 25 and to consider prophylactic mastectomy and bilateral salpingo-oophorectomy to reduce the risk of breast and ovarian cancer [11]. Among *BRCA1/2* patients, these preventive services are cost effective and reduce the burden of breast and ovarian cancer [3, 12].

Of note, genetic testing is not recommended for average-risk women [10, 13]. Cost-effectiveness analyses show that benefits do not outweigh the harms [14] in such women, largely because the prevalence of *BRCA1/2* mutations is low in the general population (0.2–0.3% [13]) and there are concerns regarding potential physical and psychological consequences related to genetic testing [15].

Evidence shows that use of *BRCA1/2* testing is often not in agreement with current guidelines (i.e., guideline discordant), with some women receiving potentially unnecessary tests (i.e., over-testing) and others not receiving testing despite meeting the guideline criteria (i.e., under-testing). Studies demonstrate that the majority of eligible patients do not receive *BRCA1/2* testing [16], potentially due to lack of provider recommendation [17] or cost [18]. Although uptake of *BRCA1/2* testing has increased [19–26], these increases may not reflect guideline-recommended use [27, 28] and uptake remains particularly low among under-served populations [29–31].

To date, the extent of *BRCA1/2* over-testing (i.e., *BRCA1/2* testing among low-risk populations) and under-testing (i.e., lack of *BRCA1/2* testing among high-risk populations) has not been well characterized. Dr. Susan Love Research Foundation's Health of Women (HOW) Study® is a large cohort study of women with and without breast cancer [32] for whom detailed information about breast cancer risk and genetic testing was collected. Our study leverages this rich dataset to identify patient groups who are at higher risk of guideline discordant testing for *BRCA1/2* (i.e., over-testing and under-testing). These data are critical for informing targeted interventions to reduce guideline discordant *BRCA1/2* testing and its related harms to patients and the healthcare system.

Methods

Study population

Data were obtained from Dr. Susan Love Research Foundation's The Health of Women (HOW) Study® [32], an online study that aims to better understand breast cancer causes and the experiences of breast cancer survivors. The study deployed up to six online modules between 2012 and 2015 to over 40,000 individuals with and without breast cancer. It was open to women and men aged 18 and older. There were no explicit restrictions on participation except that participants must have had access to the internet.

Because breast cancer screening and *BRCA1/2* testing availability and guidelines are country-specific, we limited our study population to only those participants who resided in the United States. Additionally, less than 0.5% of participants were male, and so we restricted our analysis to females only. Our analysis incorporates data collected through October 31, 2015, from three of the six modules: a basic health overview survey, a personal and family health history survey, and a personal breast cancer history survey. We restricted our sample to women who completed the basic health overview and personal and family health history surveys (if they did not report a history of breast cancer) and all three modules if they reported a history of breast cancer ($N = 20{,}758$). Data were obtained through a collaborative agreement with Dr. Susan Love Research Foundation. Our sample is comparable to the total population enrolled in the overall HOW Study in terms of basic demographics (age, race, education). Study procedures were reviewed and deemed exempt by the Office of Human Subjects Research Protections at the National Cancer Institute.

Data analysis

Descriptive statistics were calculated, and multivariable logistic regression was used to examine the association of patient-level factors, including clinical (i.e., personal and family cancer histories), socioeconomic (i.e., education), and demographic (i.e., age, race) characteristics, with our outcomes of interest (i.e., *BRCA1/2* testing status). Our outcome variables were based on the 2015 NCCN recommendations for genetic testing [11], with the exceptions that we could not capture (1) whether there was an identified *BRCA1/2* mutation in the family, (2) the age at which a family member was diagnosed with breast cancer, or (3) the Gleason score of a relative's prostate cancer. The resulting criteria which were used to determine whether a woman should be tested are listed in Table 1. Covariates included self-reported measures of race, personal breast cancer status, the number of family members with any type of cancer, education, health insurance status, and age.

We included two analyses: First, our primary analysis examined associations of patient-level factors with *BRCA1/2* testing status, where testing status was a binary outcome that measured guideline discordant testing (i.e., over-testing or under-testing) *versus* guideline-concordant testing (i.e., being tested or untested according to NCCN guidelines). Second, we separated our analyses of guideline discordant testing into over-testing (women who were tested but did not meet the NCCN criteria) and under-testing (women who met the criteria for testing but were not tested). Multinomial logistic regression was then performed comparing over-testing, under-testing, and guideline-concordant testing. Both analyses were stratified by whether a woman had a history of breast cancer.

Table 1 Criteria used to determine if genetic testing was recommended

- Diagnosed with breast cancer before the age of 46
- Diagnosed with breast cancer before the age of 51 AND
  - An additional primary breast cancer OR
  - At least one close blood relative with breast cancer at any age OR
  - At least one close relative with pancreatic cancer OR
  - At least one relative with prostate cancer
- Diagnosed with triple negative breast cancer before the age of 61
- Diagnosed with breast cancer at any age AND
  - At least two close blood relatives with breast cancer at any age OR
  - At least one close blood relative with ovarian cancer OR
  - At least two close blood relatives with pancreatic and/or prostate cancer at any age OR
  - A close male blood relative with breast cancer OR
  - Jewish
- Diagnosed with invasive ovarian cancer
- Diagnosed with pancreatic cancer AND
  - At least one close blood relative with breast cancer and/or invasive ovarian cancer and/or pancreatic cancer OR
  - Jewish
- First or second-degree blood relative with breast cancer AND
  - At least two close blood relatives with breast cancer at any age OR
  - At least one close blood relative with ovarian cancer OR
  - At least two close blood relatives with pancreatic and/or prostate cancer at any age OR
  - A close male blood relative with breast cancer OR
  - Jewish
- First or second-degree blood relative with invasive ovarian cancer
- First or second-degree relative with male breast cancer
- First or second-degree relative with prostate cancer AND
  - At least one close blood relative with breast cancer and/or invasive ovarian cancer and/or pancreatic cancer or prostate cancer
- First or second-degree relative with pancreatic cancer AND
  - At least one close blood relative with breast and/or invasive ovarian and/or pancreatic cancer OR
  - Jewish
- Third degree relative with breast cancer and at least two close blood relatives with breast cancer and/or invasive ovarian cancer

Results

Descriptive

The study population consisted of 20,758 women ages 18 and older, with a mean age of 53.8 years (SD: 13.0). Our study cohort was 94% white and 97.5% non-Hispanic. About 6500 (31%) women reported a personal history of breast cancer and 60% reported having at least one relative (male or female, first or second degree) with a history of breast cancer.

3,894 women (18.8%) reported that they had *BRCA1/2* testing (Figure S1). Of those tested, 3,400 were considered guideline concordant tested and 494 were considered over-tested based on the 2015 NCCN guidelines. 16,864 (81.2%) women reported not undergoing *BRCA1/2* testing; among those not tested, 5628 met NCCN criteria for *BRCA1/2* testing but were under-tested. Overall, guideline-concordant testing was reported by 70.5% of women, whereas 1.4% were over-tested and 27.1% were under-tested.

Patients who were under-tested and over-tested were older (mean age: 55.7 versus 53.1 years, $p < 0.001$) than patients

Table 2 Descriptive characteristics

	Overall $N=20,758$	Guideline concordant $N=14,636$	Over-tested $N=494$	Under-tested $N=5628$	p value
Mean age (years)	53.8	53.1	55.7	55.7	< 0.001
Race					0.775
White	94.1	94.0	94.5	94.4	
Black	1.2	1.3	1.2	1.2	
Other	4.7	4.8	4.3	4.4	
Education					0.001
High school or less	4.4	4.3	5.7	4.7	
Some college or associate degree	18.6	18	17.8	20.3	
4-Year college degree	32.7	32.8	35.8	31.9	
Graduate/professional degree	44.3	44.9	40.7	43.1	
Insurance					< 0.001
Managed care	69.1	70.2	71.6	66	
No insurance	1.8	1.8	0.2	2	
Medicaid	1.3	1.3	1.5	1.3	
Indemnity/PPO	4.7	4.7	4.2	4.7	
Medicare	19.9	18.8	18.3	22.9	
Military/VA	3.2	3.3	4.4	3.1	
Has biologic children	67.7	67.0	73.2	68.2	< 0.001
Mean number of family members with cancer	3.2	2.8	2.9	4.1	< 0.001

who were guideline concordant (Table 2). A greater proportion of under-testing occurred among those with less than a 4-year college degree, though this difference was small. Under-testing was also higher among women with Medicare and lower among women with managed care, not controlling for other factors. Women with biologic children were more likely to be over-tested than under- or appropriately tested. Under-tested women reported a greater number of total family members with a history of any cancer compared to guideline concordant women and over-tested women (4.1 versus 2.8 and 2.9, $p < 0.001$).

Guideline concordance

In a multivariate model of women without a history of cancer, we found that for each increase in the number of family members with any type of cancer, the odds of guideline-concordant *BRCA1/2* testing decreased (aOR 0.66, 95% CI 0.65–0.68) (Table 3). To explore this finding further, we examined the association of family cancer history, measured by the number of family members diagnosed with any cancer, with receipt of *BRCA1/2* testing, and found a 33% increased likelihood of receiving *BRCA1/2* testing with each additional family member with cancer (aOR 1.33, 95% CI 1.29–1.37), suggesting that while more testing is occurring with greater family history, the testing is not necessarily guideline concordant.

Table 3 Odds of guideline concordance among participants without a history of breast cancer

	aOR*	(95% CI)
Age (years)	1	(0.99–1.0)
Race		
White	1	
Black	0.97	(0.66–1.41)
Other	0.95	(0.78–1.15)
Education		
High school or less	1	
Some college or associate degree	1.04	(0.83–1.30)
4-Year college degree	1.03	(0.83–1.28)
Graduate/professional degree	0.96	(0.77–1.18)
Insurance		
Managed care	1	
No insurance	0.98	(0.74–1.29)
Medicaid	1.08	(0.72–1.63)
Indemnity/PPO	1.02	(0.85–1.24)
Medicare	1.04	(0.92–1.19)
Military/VA	1.05	(0.84–1.33)
Has biologic children	1.00	(0.92–1.10)
Number of family members with cancer	0.66	(0.65–0.68)

In a multivariate model of women with a history of breast cancer, we found that as age increased, the odds of receiving guideline-concordant testing decreased

Table 4 Odds of guideline concordance among participants with a history of breast cancer

	aOR*	(95% CI)
Age (years)	0.95	(0.95–0.96)
Race		
White	1	
Black	0.68	(0.42–1.09)
Other	0.90	(0.67–1.19)
Education		
High school or less	1	
Some college or associate degree	0.95	(0.74–1.22)
4-Year college degree	1.03	(0.81–1.31)
Graduate/professional degree	1.42	(1.12–1.80)
Insurance		
Managed care	1	
No insurance	0.55	(0.31–0.97)
Medicaid	0.74	(0.49–1.10)
Indemnity/PPO	0.94	(0.72–1.22)
Medicare	1.26	(1.07–1.47)
Military/VA	1.20	(0.88–1.64)
Has biologic children	1.21	(1.07–1.36)
Number of family members with cancer	0.98	(0.96–1.01)

(aOR 0.95, 95% CI 0.95–0.96) (Table 4). Higher levels of education were associated with greater odds of receiving guideline-concordant testing (Graduate/professional degree: aOR 1.42, 95% CI 1.12–1.80). Participants with Medicare had higher odds of receiving guideline-concordant testing than those with managed care (aOR 1.26, 95% CI 1.07–1.47), whereas those without insurance had lower odds of receiving guideline-concordant testing (aOR 0.55, 95% CI 0.31–0.97). Women with biologic children were more likely to receive guideline-concordant testing than women without biologic children (aOR 1.21, 95% CI 1.07–1.36).

Over- and under-testing

We identified several patient-level characteristics whose associations varied by over- and under- and concordant testing. For women without a history of breast cancer, we found that women with Medicare were less likely to be over-tested and more likely to be guideline concordant than women with managed care (aOR 0.46, 95% CI 0.26–0.82) (Table 5). Increasing numbers of family members with cancer were associated with a greater likelihood of both over- and under-testing than guideline concordance (over-testing: aOR 1.26, 95% CI 1.18–1.35; under-testing: aOR 1.52, 95% CI 1.49–1.56).

Among women with a history of breast cancer, increasing age was associated with greater likelihood of both over-testing and under-testing than guideline concordance (over-testing: aOR 1.06, 95% CI 1.04–1.07; under-testing: aOR 1.05, 95% CI 1.04–1.05) (Table 6). Participants with Medicare were less likely to be over-tested or under-tested and more likely to be guideline concordant than those with

Table 5 Odds of over- and under-testing among women without a history of breast cancer by key variables

	Over-testing		Under-testing	
	aOR*	(95% CI)	aOR*	(95% CI)
Age (years)	0.99	(0.98–1.00)	1	(0.99–1.01)
Race				
White	1		1	
Black	0.85	(0.21–3.47)	1.05	(0.71–1.54)
Other	1.13	(0.61–2.10)	1.05	(0.86–1.28)
Education				
High school or less	1		1	
Some college or associate degree	0.48	(0.22–1.01)	1	(0.79–1.26)
4-Year college degree	0.76	(0.39–1.50)	0.98	(0.79–1.23)
Graduate/professional degree	0.71	(0.36–1.39)	1.07	(0.86–1.34)
Insurance				
Managed care	1		1	
No insurance	–	–	1.10	(0.83–1.45)
Medicaid	0.86	(0.21–3.53)	0.93	(0.61–1.41)
Indemnity/PPO	0.55	(0.24–1.25)	1.01	(0.83–1.22)
Medicare	0.46	(0.26–0.82)	0.98	(0.86–1.12)
Military/VA	1.40	(0.73–2.70)	0.92	(0.72–1.17)
Has biologic children	1.10	(0.80–1.50)	0.99	(0.90–1.08)
Number of family members with cancer	1.26	(1.18–1.35)	1.52	(1.49–1.56)

Table 6 Odds of over- and under-testing among women with a history of breast cancer by key variables

	Over-testing		Under-testing	
	aOR*	(95% CI)	aOR*	(95% CI)
Age (years)	1.06	(1.04–1.07)	1.05	(1.04–1.05)
Race				
White	1		1	
Black	1.35	(0.47–3.82)	1.49	(0.90–245)
Other	0.96	(0.48–1.91)	1.14	(0.85–1.54)
Education				
High school or less	1		1	
Some college or associate degree	0.91	(0.53–1.58)	1.07	(0.83–1.39)
4-Year college degree	1.02	(0.60–1.73)	0.96	(0.85–1.24)
Graduate/professional degree	0.68	(0.40–1.15)	0.71	(0.55–0.91)
Insurance				
Managed care	1		1	
No insurance	0.52	(0.07–3.89)	2.04	(1.15–3.60)
Medicaid	1.34	(0.53–3.41)	1.36	(0.89–2.08)
Indemnity/PPO	1.15	(0.65–2.04)	1.05	(0.79–1.39)
Medicare	0.56	(0.38–0.81)	0.84	(0.71–0.99)
Military/VA	0.92	(0.48–1.76)	0.82	(0.59–1.14)
Has biologic children	1.05	(0.79–1.39)	0.80	(0.71–0.91)
Number of family members with cancer	0.84	(0.78–0.89)	1.04	(1.02–1.07)

managed care (over-testing: aOR 0.56, 95% CI 0.38–0.81; under-testing: aOR 0.84, 95% CI 0.71–0.99). On the other hand, women without insurance were twice as likely to be under-tested than women with managed care insurance (aOR 2.04, 95% CI 1.15–3.60). Women with biologic children were less likely to be under-tested than women without biologic children (aOR 0.80, 95% CI 0.71–0.91). Increasing numbers of family members with cancer were associated with a lower likelihood of over-testing (aOR 0.84, 95% CI 0.78–0.89) and a greater likelihood of under-testing (aOR 1.04, 95% CI 1.02–1.07).

Discussion

We found one in five women in this cohort had received *BRCA1/2* testing, consistent with recent estimates of testing among high-risk, insured women [33, 34]. This may not be surprising considering the high proportion of women reporting personal and family histories of breast cancer who self-selected into participating in the HOW Study. Among this highly motivated population of women, approximately 70% received guideline-concordant testing—that is, they received or did not receive *BRCA1/2* testing as recommended in 2015 NCCN guidelines. It is important to note that most guideline *discordant* women were under-tested rather than over-tested, indicating that many high-risk women who would benefit from genetic testing are currently being missed. Without this information, providers are unable to tailor screening recommendations to those women who are at highest risk of breast and ovarian cancer.

As the number of family members with any type of cancer increased, the likelihood of guideline discordant testing increased for both women with and without a personal breast cancer history. It may be the case that confusion over what types of cancer within a family warrant *BRCA1/2* testing contributes to this guideline discordant testing or that panel testing (that includes *BRCA1/2*) was ordered to assess the presence of a different hereditary cancer syndrome. In the first case, this may suggest a need for better patient and provider education tailored to explaining breast cancer risk and the criteria that factor into determining individual risk and whether genetic testing would be appropriate. Of note, higher levels of education were also associated with lower levels of under-testing, and so improving patient education related to risk assessment may reduce under-testing.

Insurance coverage also played a significant role in guideline-concordant testing. Those with a history of breast cancer and without health insurance had lower odds of receiving guideline-concordant testing than those with managed care, and this appears to be driven by a greater likelihood of being under-tested than those with managed cared. Women with Medicare were more likely to receive guideline-concordant (less over-testing and less under-testing) testing than those with managed care plans. It is important to note that Medicare only reimburses for genetic testing if a woman has a cancer diagnosis. As the US Preventive Services Task Force gave *BRCA1/2* testing among high-risk individuals a 'B grade' in

December 2013, insurance companies are currently required to cover the cost of this service under the Affordable Care Act. However, barriers to concordant testing may remain, such as perceived cost, lack of insurance, fears of discrimination (life insurance, employment, etc.), and access to genetic testing providers and counselors. Outreach targeted to low-income and under-served populations regarding guaranteed coverage may assist in reducing the amount of under-testing.

BRCA1/2-attributable cancers are relatively small in number, making them difficult to study. As such, current research examining *BRCA1/2* testing uptake and delivery often suffers from small sample sizes, which has limited inferences. Larger datasets from commercial claims data often lack sufficient information (*i.e.*, detailed personal and family cancer history) to determine whether patients are eligible for *BRCA1/2* testing. Through the HOW Study, we were able to leverage a large cohort study that did not restrict enrollment to high-risk women or women already diagnosed with breast cancer. This enabled us to capitalize on the extensive demographic, clinical, health services, and patient-reported outcomes that have been collected from the HOW Study cohort to examine key associations between patient characteristics and guideline discordant genetic testing, whereas many previous analyses have been underpowered to do so. In light of these study design strengths, there are also limitations.

All data were patient-reported and thus rely on accurate recall. Additionally, participants may have completed the survey modules in different orders. Study participation was based on self-selection and so there is the potential for bias in the sample towards women with a personal or family history of cancer. Further, women who did not complete all three modules were not included in this analysis, and may be different from those women who were included, though they did not differ based on age, race, or education. We did not have information on the Gleason score of a relative's prostate cancer so we included all prostate cancers where noted in the criteria. This may have caused us to slightly overestimate the number of women who met the criteria for testing and in turn overestimate those who were under-tested. We also did not have information on the age of a relative's breast cancer diagnosis, and so we excluded that criterion. We also did not know whether genetic testing had been performed in the family, and this may have influenced the decision of whether our participants were screened or not. There is also the potential for misclassification for patients with DCIS or LCIS in whether they consider themselves to have had breast cancer. This could result in a portion of women who appeared to be under-tested as they considered themselves to have a personal history of cancer where the guidelines would not include LCIS. Replicating these findings in a dataset with medical record verification will be an important next step. There were small changes to NCCN guidelines during this study period (2012–2015), but these minor modifications were unlikely to affect classification of testing concordance. Of note, some women were tested before this period when guidelines may have been different, but we were unable to capture those differences. While our sample size was well powered to examine differences in guideline-concordant testing, there was a lack of diversity in this sample demonstrating a need to examine this issue more fully in racial/ethnic and socioeconomically diverse populations. Finally, we do not have information on whether a woman received panel versus single-gene testing. Individuals with significant cancer histories in their families may be receiving panel testing, which includes BRCA1/2 despite not meeting that specific testing criteria for that gene. Thus, there may be individuals who were classified as over-tested that were appropriately given a gene panel test for hereditary cancer disorders. Future studies should examine the unique aspects of gene panel testing.

Conclusions

Genetic testing is increasingly used to assess potential risk-based prevention strategies, which is critical for guiding screening, prevention, and treatment decisions. However, almost 30% of women were under-tested, indicating that many high-risk women who may benefit from genetic testing are currently being missed. Without appropriate testing, providers are unable to tailor screening recommendations to those carrying mutations who are at highest risk. However, guideline-concordant testing alone is not enough. These tests must be administered in conjunction with pre/post-test counseling by professionals trained to interpret and explain results as well as connect patients to appropriate risk-based prevention strategies. Future studies should examine this explicitly to better understand how genetic results are being delivered and informing preventive care.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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