

Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?

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abstract

PURPOSE An estimated 10% of breast and ovarian cancers result from hereditary causes. Current testing guidelines for germ line susceptibility genes in patients with breast carcinoma were developed to identify carriers of *BRCA1/2* variants and have evolved in the panel-testing era. We evaluated the capability of the National Comprehensive Cancer Network (NCCN) guidelines to identify patients with breast cancer with pathogenic variants in expanded panel testing.

METHODS An institutional review board–approved multicenter prospective registry was initiated with 20 community and academic sites experienced in cancer genetic testing and counseling. Eligibility criteria included patients with a previously or newly diagnosed breast cancer who had not undergone either single- or multigene testing. Consecutive patients 18 to 90 years of age were consented and underwent an 80-gene panel test. Health Insurance Portability and Accountability Act–compliant electronic case report forms collected information on patient demographics, diagnoses, phenotypes, and test results.

RESULTS More than 1,000 patients were enrolled, and data records for 959 patients were analyzed; 49.95% met NCCN criteria, and 50.05% did not. Overall, 8.65% of patients had a pathogenic/likely pathogenic (P/LP) variant. Of patients who met NCCN guidelines with test results, 9.39% had a P/LP variant. Of patients who did not meet guidelines, 7.9% had a P/LP variant. The difference in positive results between these groups was not statistically significant (Fisher’s exact test $P = .4241$).

CONCLUSION Our results indicate that nearly half of patients with breast cancer with a P/LP variant with clinically actionable and/or management guidelines in development are missed by current testing guidelines. We recommend that all patients with a diagnosis of breast cancer undergo expanded panel testing.

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INTRODUCTION

Approximately 330,000 patients are diagnosed with breast cancer every year in the United States.¹ An estimated 10% of these cancers likely result from hereditary causes.² Studies have estimated that less than 10% of all *BRCA1* and *BRCA2* carriers have been identified.³ Moreover, 50% to 80% of individuals at risk have not received genetic testing, in part because they do not meet the family history criteria of current testing guidelines,^{4,5} and insurance seldom reimburses testing in such cases. An estimated 35,000 patients with breast cancer have pathogenic *BRCA1/2* variants; however, only 30% have been identified.^{3,4} A recent study of Medicare patients with breast cancer found no significant difference in the germ line pathogenic/likely

pathogenic (P/LP) rate from multigene panel tests between patients who did and did not meet genetic testing guidelines.⁶

In addition to enhanced cancer screening, risk reduction, and surgical treatment, germ line genetic results are increasingly relevant to systemic therapy,⁷⁻⁹ and results in affected individuals also yield valuable information for cascade family variant testing and thus efficient discovery of unaffected carriers, facilitating prevention of breast and other cancers.

Recent studies have identified the clinical actionability associated with expanded multigene panels, and these management strategies are now an accepted part of clinical guidelines.^{6,10} For example, a study of 488 patients with breast cancer (stage I to III) at

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Appendix

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a single center yielded a P/LP variant in 10.7% of women, only 6.1% of whom were *BRCA1/2*.¹¹ In other studies, up to 10% of women who tested negative for *BRCA1/2* had P/LP variants in other cancer predisposition genes, providing additional information that might change management of these patients.¹²

National Comprehensive Cancer Network (NCCN) guidelines for genetic testing were established approximately 20 years ago to identify patients with the highest likelihood of carrying *BRCA1/2* variants to reduce the number needed to test at a time when *BRCA1/2* genetic testing cost \$2,000 to \$5,000 per test and in line with known management implications at the time. However, with the landmark Supreme Court case on *BRCA1/2* in 2013, which overturned patents on naturally occurring genes, and with next-generation sequencing (NGS) spurring competition, the availability and cost of testing has dropped (as low as \$250 per test¹³). Simultaneously management guidelines are developing rapidly and have been revised multiple times. However, testing guidelines have become more complicated and have not been sufficiently reevaluated in the panel-testing era. Testing guidelines remain limited for *BRCA1/2*, *TP53*, and *PTEN*. The use of multigene panels is pointing to additional genes beyond *BRCA1/2* that may be implicated in breast cancer (and other cancers) and for which management guidelines have been proposed or are in development.

Accumulating evidence suggests that the rate of germ line pathogenic variants in the US population is higher than originally suspected and that *BRCA1/2* mutation prevalence may be as high as one in 200.¹⁴ A recently published study in which the exomes of 50,000 patients were sequenced found that close to 50% of patients with *BRCA1/2* variants did not meet published guidelines for clinical testing.¹⁴ A study by Buys et al¹⁵ of 35,000 patients with breast cancer who were tested with a 25-gene panel found a P/LP variant rate of 9.3%, with more than 50% of these variants in genes other than *BRCA1/2*; a study by Susswein et al¹⁶ reporting NGS testing of 10,000 patients—two thirds of whom had a cancer diagnosis—found a similar P/LP variant rate.

We created a cohort of patients with breast cancer seen in practice and who agreed to participate in largely community-based clinics using a multigene panel. The primary objective was to determine whether there was a difference in the incidence of actionable variants between patients who met 2017 NCCN testing guidelines and those who did not.

METHODS

Investigator Selection

An institutional review board (IRB)–approved multicenter prospective registry was initiated with 20 community and academic breast practices experienced in cancer genetic

risk assessment and management. IRB approval and oversight were provided by Western Institutional Review Board (Puyallup, WA) or via a local IRB. Sites were selected with the aim of having the ethnicity of participants commensurate with US ethnicity demographics and in the interest of generating hereditary genetic testing data for traditionally underrepresented and underserved ethnic populations.

Participant Accrual

Patients were eligible to participate if they were 18 years of age or older, had a personal diagnosis of breast cancer, were either currently being treated or had previously been treated, and had not previously undergone either single- or multigene germ line testing. Patients were enrolled in two equal cohorts—those who met NCCN genetic testing guidelines¹⁷ and those who did not. Sites identified consecutive patients meeting enrollment criteria (breast cancer, no previous germ line genetic testing), with each site enrolling equivalent numbers of patients who met guidelines and who did not, per study design. Site clinicians classified patients as meeting or not meeting NCCN (version 2.2017) guidelines based on their responses to a multipart question developed with the assistance of a cancer genetic counselor. If a clinician answered no to this question for a particular patient, the patient did not meet guidelines for testing. Sites stopped enrolling when they met their individual enrollment goals. All enrolled patients consented to have their deidentified data included in the registry.

Genetic Testing

All patients underwent germ line genetic testing with a multicancer panel of 80 genes (Appendix Table A1, online only). Among these genes, 11 (*BRCA1*, *BRCA2*, *ATM*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, *STK11*, *TP53*) are referenced in NCCN management guidelines and commonly included in diagnostic breast cancer panels. Full-gene sequencing, deletion/duplication analysis, and variant interpretation were performed at Invitae (San Francisco, CA), as previously described.^{12,18}

Test results were deidentified and recorded in a Health Insurance Portability and Accountability Act–compliant electronic study registry (Genae, Belgium), along with other relevant clinical data including demographic and clinical data and whether and how patients met 2017 NCCN criteria. All reported patients had their variant findings source verified and confirmed by independent review of the test results by a medical geneticist. Patients were informed of their test results, and physicians initiated appropriate management actions if indicated by current guidelines and as they saw fit.

Statistical Analysis

This noninferiority study was powered to detect a difference in P/LP variant rate of 4 percentage points between those

meeting and not meeting testing guidelines with statistical significance (Fisher's exact test $P < .05$). Participant characteristics and genetic testing results were tabulated, with descriptive statistics including medians, means, and standard deviations for continuous data and proportions with 95% CIs for categorical data. All P values are two tailed.

RESULTS

Participant Characteristics

Participating sites enrolled 1,001 patients with breast cancer from April 2017 to September 2018. Forty-two patients were excluded from analysis because their data were incomplete or could not be source verified. A total of 959 patients meeting all study requirements and having all required data collected and available were included in our evaluation. Among the 959 unselected patients with breast cancer in this cohort, 479 (49.95%) met established 2017 NCCN germ line genetic testing guidelines, and 480 (50.05%) did not meet these guidelines for genetic testing. Age, sex, ethnicity, and personal and family cancer history information of the in-guideline and out-of-guideline patient groups is listed in Table 1. The cohort included 650 patients who were recently diagnosed (within 12 months of consent) and 309 who were not recently diagnosed. There were 106 patients with a previous cancer other than breast cancer.

Pathogenic Variants in Cancer Genes

Overall, 83 (8.65%) of 959 patients had a P/LP variant. Of these, 45 (9.39%) of 479 patients who met NCCN testing guidelines and 38 (7.9%) of 480 patients who did not meet guidelines had a P/LP variant. The difference of positive cases between the two groups was not statistically significant ($P = .4241$). Overall, 47 patients (4.9%) had a P/LP variant if only an 11-gene breast cancer panel was considered, and only 15 patients (1.56%) had a P/LP variant if only *BRCA1/2* mutation were considered (Table 2). When only results from *BRCA1* and *BRCA2* testing were

considered, the positive rate of the in-guideline group was four-fold that of the out-of-guideline group (2.51% v 0.63%; $P = .0201$; Table 2). Variant of uncertain significance (VUS) rates were virtually identical between the two groups. The overall VUS rate was 54.22% for the entire patient population. Accordingly, almost half of the patients with breast cancer tested had either a P/LP variant or a completely negative test with no P/LP variant or VUS found in 80 genes.

Clinical Implications of P/LP Variants

The P/LP variants identified for both patient groups occurred in genes associated specifically with breast cancer, as well as in known cancer genes traditionally associated with other hereditary cancers (Fig 1). The spectrum of P/LP variants differed somewhat between the two groups, with some overlap. The yield of P/LP variants from the 80-gene panel was greater than that with an 11-gene panel (8.65% v 4.90%), and with few exceptions, the genes in which P/LP variants were identified have published management recommendations and are clinically actionable for treatment of a patient's cancer, post-treatment surveillance and prophylaxis, or cascade testing for at-risk family members (Table 3).

DISCUSSION

The rate of P/LP variants in a large 80-gene panel was similar among patients with breast cancer who did and did not meet 2017 NCCN guidelines for genetic testing; the difference was not statistically significant. In fact, the results of our study suggest that a strategy that simply tests all patients with a personal history of breast cancer would almost double the number of patients identified as having a clinically actionable genetic test result.

Advances in NGS technologies have dramatically reduced the cost of *BRCA1/2* testing and enabled simultaneous sequencing and deletion/duplication testing of *BRCA1/2* concomitantly with dozens of additional risk genes for breast, ovarian, and/or other cancers (eg, *PALB2*, *PTEN*, *ATM*, *CHEK2*). Furthermore, current testing guidelines do not adequately account for the full range of clinical presentations described to date as associated with breast cancer, and carriers of clinically actionable variants in genes other than *BRCA1/2* are likely to fall outside of the current guidelines.

The rate of *BRCA1/2* P/LP variants we observed was lower among both groups of patients with breast cancer than the 6% to 9% rate estimates of previous reports. This is not surprising for our in-guideline patient cohort, because this registry specifically excluded patients who had previously been tested. Previously diagnosed patients at our research sites with clearly identifiable personal and family histories consistent with NCCN testing guidelines (ie, *BRCA1/2* positive) were likely to have already undergone testing and therefore would have been excluded from this study. Our study population was tested using a comprehensive

TABLE 1. Characteristics of Patients Who Met and Did Not Meet NCCN Guidelines

Group	Positive Result (%)		
	<i>BRCA1/2</i> Alone	HBOC Guidelines Panel (11 genes)	Large Cancer Panel (80 genes)
In guideline	2.51	6.26	9.39
Out of guideline	0.63	3.54	7.92

NOTE. Information on personal and family histories of cancer based on data available for patients as provided by clinicians. In-guideline versus out-of-guideline *BRCA1/2* alone: results for testing only *BRCA1* and *BRCA2*; hereditary breast and ovarian cancer guideline panel includes genes recommended for germ line testing by the National Comprehensive Cancer Network guidelines and have recommendations for modifying breast and ovarian cancer risk management; large cancer panel is a large hereditary cancer panel of 80 genes.

Abbreviations: HBOC, hereditary breast and ovarian cancer; NCCN, National Comprehensive Cancer Network.

TABLE 2. Patient Genetic Test Positive Result Rate
Clinical Trial Eligibility for Breast Cancer*

Management Guideline	Clinical Trial Eligibility for Breast Cancer*
ATM	
Annual mammography†	NCT02401347
Consider breast MRI	
Genetic counseling	
Cascade FVT	
BRCA1	
Annual breast MRI†	NCT03286842 (treatment)
Consider RRM	NCT03495609 (prevention)
Recommend RRSO	
Genetic counseling	
Cascade FVT	
BRCA2	
Annual breast MRI†	NCT03286842 (treatment)
Consider RRM	NCT03495609 (prevention)
Recommend RRSO	
Genetic counseling	
Cascade FVT	
CHEK2	
Annual mammography†	NCT02401347
Consider breast MRI	
Colonoscopy screening at age 40 years	
Genetic counseling	
Cascade FVT	
MSH6	
Colonoscopy screening at age 20 years‡	NCT03495544
Upper endoscopy at age 35 years	
Consider RRHyst, RRSO	
Genetic counseling	
Cascade FVT	
MUTYH	
Consider colonoscopy at age 40 years‡ per family history of CRC	NCT03495544
Genetic counseling	
Cascade FVT	
PALB2	
Annual mammography†	NCT02401347
Consider breast MRI	
Genetic counseling	
Cascade FVT	

(continued in next column)

TABLE 2. Patient Genetic Test Positive Result Rate (continued)
Clinical Trial Eligibility for Breast Cancer*

Management Guideline	Clinical Trial Eligibility for Breast Cancer*
RAD50	
No current guidelines	NCT02401347
RAD51C	
Recommend RRSO†	NCT02401347
Genetic counseling	
Cascade FVT	
RAD51D	
Recommend RRSO†	NCT02401347
Genetic counseling	
Cascade FVT	

NOTE. Clinical trials listed indicate a selection of ongoing trials for which patients with breast cancer may be eligible and in which a germ line pathogenic/likely pathogenic variant in the specified gene is among the inclusion criteria for enrollment.

Abbreviations: CRC, colorectal cancer; FVT, family variant testing; MRI, magnetic resonance imaging; RRHyst, risk-reducing hysterectomy; RRM, risk-reducing mastectomy, RRSO, risk-reducing salpingo-oophorectomy.

*From ClinicalTrials.gov.

†National Comprehensive Cancer Network (NCCN) breast and ovarian cancer guideline.¹⁹

‡NCCN colorectal cancer guideline.²⁰

multigene panel strategy, which identified a substantial number of patients with P/LP variants in genes such as *PALB2*, *ATM*, *CHEK2*, *MSH6*, *MUTYH*, *RAD50*, *RAD51C*, and *RAD51D* that would have been missed by a restrictive testing strategy (Fig 1). Furthermore, of the patients with P/LP variants who did not meet NCCN germ line testing guidelines, 56% were potentially eligible for precision therapeutic clinical treatment trials, 76% for established clinical management recommendations, and 82% overall for clinical treatment trials and/or established management recommendations based in part on their germ line test results.

These management implications are invaluable to clinicians caring for these patients, including breast specialists who observe their patients over many years and are in position to test and counsel patients and make recommendations for next steps; this is critical as evidence emerges on cancer genes, guidelines change, and information about VUSs evolves. This proposed expansion of testing will require surgeons and other physicians who order testing to be comfortable either counseling patients appropriately about their risk profiles or referring them to genetic counselors.

The rate of VUSs observed in our study is not surprising given the number of genes included in the panel. Given the lack of definitive clinical significance for these variants, participating physicians counseled their patients not to be

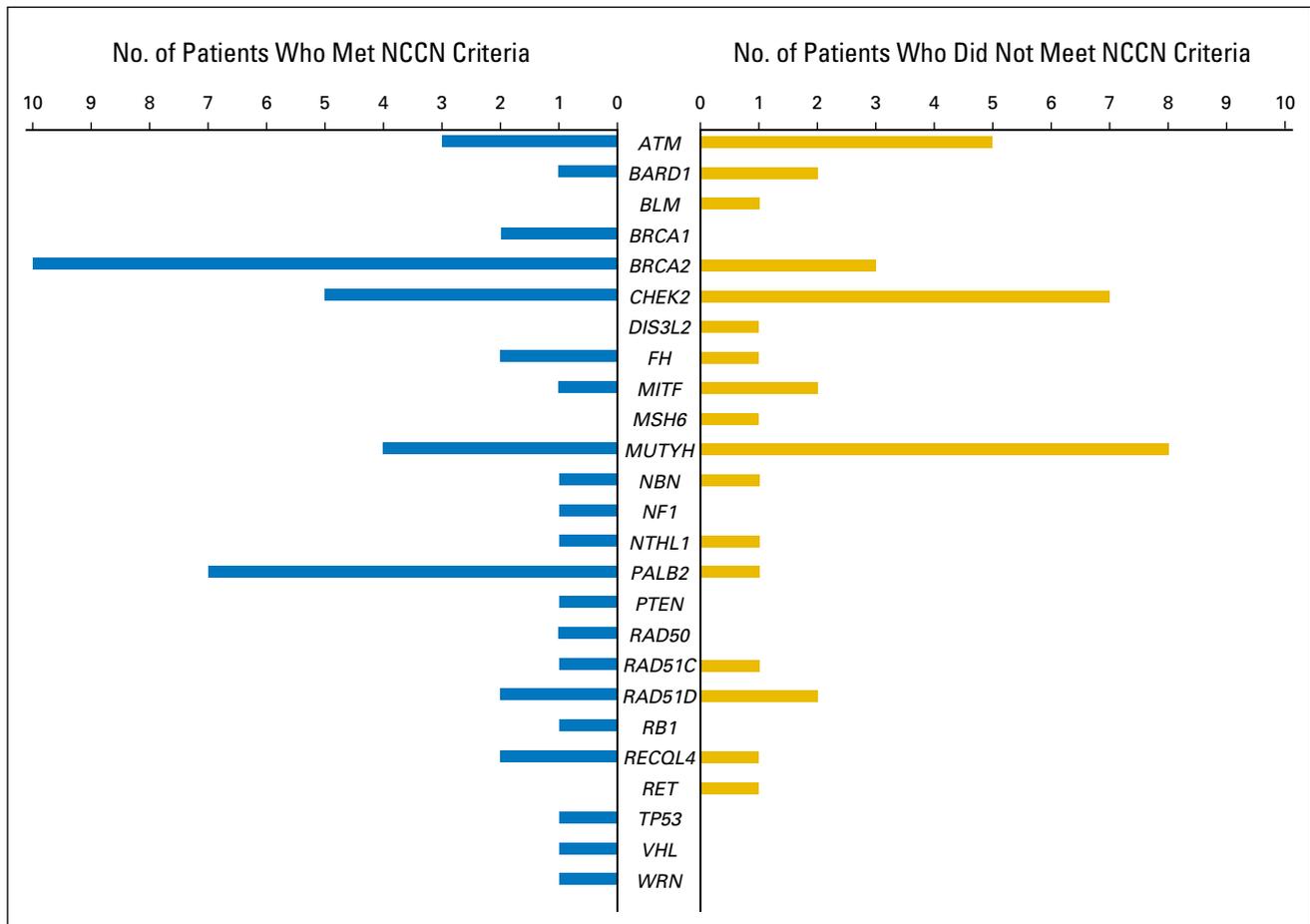


FIG 1. Pathogenic/likely pathogenic variants identified by gene. Includes *BRCA1* and *BRCA2* and other genes associated with breast cancer, genes associated with breast and/or gynecologic cancers, and genes associated with other cancers. NCCN, National Comprehensive Cancer Network.

concerned about VUSs, and they did not use VUSs to alter patient management with regard to cancer treatment or the testing of family members. This does represent a future opportunity to have patients return to be counseled as evidence emerges and supports the reclassification of an identified VUS. This requires that diagnostic laboratories provide VUS updates to clinicians over time, which is already the practice of some commercial laboratories. It also necessitates that clinicians stay current with management guidelines and access reliable information resources to implement these updates effectively for their patients (eg, cancer genetic counselors, resources such as ASK2me²¹).

The results of this study suggest that a substantial modification of the scope and intent of existing genetic testing guidelines is critically overdue. We conclude that guidelines should be expanded immediately to include genetic testing of all patients with breast cancer. This conclusion is not as radical as it may seem. Our proposal is analogous to published studies and recommendations supporting universal germ line genetic testing of patients with pancreatic or metastatic prostate cancer, which have been incorporated into NCCN guidelines, as well as recently published data calling for tumor sequencing of all colorectal

cancers.²²⁻²⁴ Furthermore, geneticist Mary Claire King has suggested that all women older than 30 years of age have *BRCA1/2* testing.^{24a}

Testing would facilitate informed decision making for patients with breast cancer and identify family members through cascade testing before they develop cancer, thereby activating surveillance and risk-reduction options. Any conversation about universal germ line genetic testing for all patients with breast cancer needs to acknowledge the implementation burden such testing would create. Because of the persisting shortage of genetic professionals, consideration and research must be devoted to developing novel genetics service delivery models for pretest counseling, delivery of the associated volume of test results, and coordination of appropriate specialty follow-up as indicated. These are issues with which the American Society of Breast Surgeons, the National Society of Genetic Counselors, the American College of Medical Genetics and Genomics, and independent researchers are actively engaged. For example, a variety of models for delivering genetic counseling with improved access have been proposed, including novel genetic counselor extender models.²⁵⁻³¹

TABLE 3. Clinical Actionability by Gene

Characteristic	No. (%)	
	Met NCCN Criteria	Did Not Meet NCCN Criteria
Sex		
Female	477 (99.58)	479 (99.79)
Male	2 (0.42)	1 (0.21)
Age at initial diagnosis, years		
Median	54	60
Range	24-93	40-89
Ethnicity		
African American/black	33 (6.89)	30 (6.25)
Asian	29 (6.05)	36 (7.50)
White	389 (81.21)	383 (79.79)
Multiracial	14 (2.92)	13 (2.71)
Native American or Alaskan Native	4 (0.84)	2 (0.42)
Native Hawaiian or other Pacific Islander	2 (0.42)	9 (1.88)
Unknown	8 (1.67)	7 (1.46)
Cancer history		
With other cancers	54 (11.27)	52 (10.83)
No other cancers	425 (88.73)	428 (8.75)
Family history		
With positive family history	374 (78.08)	254 (52.92)
No positive family history	102 (21.29)	221 (46.04)
Unknown	3 (0.63)	5 (1.04)

Abbreviation: NCCN, National Comprehensive Cancer Network.

The scope of this study did not allow for patient-reported outcomes to document patient experiences in receiving test results, which is a limitation. These are important aspects of testing and merit additional research. Determination of the economic implications and cost effectiveness of germ line genetic testing in patients with breast cancer, including testing under broadened criteria, was also outside the scope of this study but warrants additional study and dedicated research efforts. Studies investigating these crucial issues have already generated evidence supporting the cost effectiveness of germ line genetic testing and cascade family variant testing for patients with breast cancer,^{32,33} and additional research is needed.

Although the additional cost of germ line testing for all patients with breast cancer is not negligible, it is approximately 10 times less than it was at the time the genetic testing guidelines were originally established, and the cost will continue to decrease. Naturally, this cost needs to be weighed in the context of current practices considered standard of care. For example, insurers currently pay for mammography/three-dimensional mammograms (current standard of care regionally in the United States) and routine population screening using advanced lipid panels that are repeated yearly. By contrast, hereditary testing is a one-time

cost with information that may be valuable over the lifetime of a patient—a value likely to increase over time commensurate with the ever-advancing understanding of medical genetics by the medical community. Furthermore, the finite cost of genetic testing for all patients with breast cancer must be considered against the potentially dramatic cost of such patients undergoing prolonged/failed treatments because genetic information necessary to apply the most effective treatment/clinical trial was not generated. It must also be considered in the context of weighing the opportunity for preventive management, including screening patients with breast cancer for other cancers for which they have identified genetic risk, against the high cost of treating the catastrophic presentation of a late-stage malignancy in patients with a genetic risk that was not identified. Additionally, the opportunity for true prevention, which is cost effective, may be afforded to affected patients' family members through cascade testing and subsequent risk-reduction decisions.

The availability of germ line genetic information for the routine clinical care of patients with cancer is one of the most significant opportunities to revolutionize the practice of medicine today. Genetic information expands clinicians' ability to apply precision treatments and personalize risk assessment and management options for patients and their

families. Key to accomplishing this is increasing access to germ line genetic testing. As the cost of testing falls, it becomes more accessible to all patients. Current testing guidelines represent another barrier that, if relaxed, would increase access to genetic testing, particularly as more insurance companies cover the delivery of this clinically vital information and commercial laboratories offer testing programs to facilitate access for Medicare recipients, low-income patients, and other underserved populations. Although broader clinical implementation of genetic testing requires additional clinical education to inform patient management, it also holds the promise of greater access to targeted interventions and increased cost effectiveness from interventional and preventive care tailored to individuals and their families. Universal genetic testing of patients with breast cancer, including currently underserved populations, with a comprehensive gene panel has the potential to reveal the full component that genetics

play in breast cancer development regardless of the age or family history of the patient.

Expanded panel testing can provide information that may present additional treatment and follow-up options, including clinical trials, for all patients with breast cancer, not just those who meet testing guidelines.

Additional research is needed to quantify the impact on clinical outcomes when all patients with a personal history of breast cancer are eligible to undergo genetic testing (ie, elimination of additional guidelines), including multigene panel testing; however, our results suggest that approximately 45% of patients with breast cancer with clinically actionable germ line variants are being missed when testing is restricted to patients meeting current NCCN guidelines and when testing strategies are limited to panels containing only *BRCA1/2* or to less comprehensive panels. We propose that testing criteria be expanded to include all patients with breast cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT**Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?**

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APPENDIX

TABLE A1. Multigene Panel Gene List (n = 80 genes)

Gene
ALK
APC
ATM
AXIN2
BAP1
BARD1
BLM
BMPR1A
BRCA1
BRCA2
BRIP1
CASR
CDC73
CDH1
CDK4
CDKN1B
CDKN1C
CDKN2A
CEBPA
CHEK2
DICER1
DIS3L2
EGFR
EPCAM
FH
FLCN
GATA2
GPC3
GREM1
HOXB13
HRAS
KIT
MAX
MEN1
MET
MITF
MLH1
MSH2
MSH6
MUTYH
NBN
NF1

(continued in next column)

TABLE A1. Multigene Panel Gene List (n = 80 genes) (continued)

Gene
NF2
PALB2
PDGFRA
PHOX2
BPMS2
POLD1
POLE
POT1
PRKAR1A
PTCH1
PTEN
RAD50
RAD51C
RAD51D
RB1
RECQL4
RET
RUNX1
SDHA
SDHAF2
SDHB
SDHC
SDHD
SMAD4
SMARCA4
SMARCB1
SMARCE1
STK11
SUFU
TERC
TERT
TMEM127
TP53
TSC1
TSC2
VHL
WRN
WT1

NOTE. List of genes with variants in more than two patients in our study population and associated with established management guidelines.