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ORIGINAL REPORT

Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer

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A B S T R A C T

Purpose

Genetic testing for breast cancer risk is evolving rapidly, with growing use of multiple-gene panels that can yield uncertain results. However, little is known about the context of such testing or its impact on treatment.

Methods

A population-based sample of patients with breast cancer diagnosed in 2014 to 2015 and identified by two SEER registries (Georgia and Los Angeles) were surveyed about genetic testing experiences (N = 3,672; response rate, 68%). Responses were merged with SEER data. A patient subgroup at higher pretest risk of pathogenic mutation carriage was defined according to genetic testing guidelines. Patients' attending surgeons were surveyed about genetic testing and results management. We examined patterns and correlates of genetic counseling and testing and the impact of results on bilateral mastectomy (BLM) use.

Results

Six hundred sixty-six patients reported genetic testing. Although two thirds of patients were tested before surgical treatment, patients without private insurance more often experienced delays. Approximately half of patients (57% at higher pretest risk, 42% at average risk) discussed results with a genetic counselor. Patients with pathogenic mutations in *BRCA1/2* or another gene had the highest rates of BLM (higher risk, 80%; average risk, 85%); however, BLM was also common among patients with genetic variants of uncertain significance (VUS; higher risk, 43%; average risk, 51%). Surgeons' confidence in discussing testing increased with volume of patients with breast cancer, but many surgeons (higher volume, 24%; lower volume, 50%) managed patients with *BRCA1/2* VUS the same as patients with *BRCA1/2* pathogenic mutations.

Conclusion

Many patients with breast cancer are tested without ever seeing a genetic counselor. Half of average-risk patients with VUS undergo BLM, suggesting a limited understanding of results that some surgeons share. These findings emphasize the need to address challenges in personalized communication about genetic testing.

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INTRODUCTION

Genetic testing has permeated faster and further into the management of breast cancer than of any other disease. Together with advances in sequencing efficiency and decreasing costs,[1,2] recent media coverage and public awareness of hereditary breast cancer have fueled patients' interest in genetic testing.[3,4] Practice guidelines have reinforced an increase in testing use with a shift toward more inclusive testing criteria for patients with breast cancer,[5] on the basis of emerging studies that suggest the wider relevance of genetic testing.[6-14] However, few studies have examined the patient experience in this rapidly changing landscape of genetic testing for cancer susceptibility after a breast cancer diagnosis.

Clinicians face challenges in using genetic testing to inform breast cancer treatment decisions. Germline genetic testing requires a patient's substantial involvement,[15-17] which is unusual among tests that doctors order for patients with breast cancer. Incorporating genetic test results into treatment decision making is difficult, because the results relate largely to future

ASSOCIATED CONTENT

Appendix
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cancer risks of the patient and her relatives. Pretest counseling is demanding because it requires assessment both of the patient's risk of mutation carriage and her desire for testing. Furthermore, results are increasingly complex because multiple-gene panel testing often yields pathogenic mutations with poorly defined cancer risks, along with a high rate of genetic variants of uncertain significance (VUS).[6,7,9,18,19] However, the genetic counselor workforce is insufficient to meet the growing demand for timely incorporation of testing into treatment decisions.[20] Thus, surgeons, medical oncologists, and other physicians may feel increasing pressure to counsel patients about genetic testing. Given the many competing management priorities for patients newly diagnosed with breast cancer and the limited genetic experience and confidence of some clinicians, this counseling will be difficult.[21,22] In this challenging context, it may be particularly hard to target the right patient for the right test, counsel her about the implications of her results, and incorporate test results into timely treatment decision making.

We recently reported that genetic counseling and testing are not well matched to clinical need, even among patients with higher pretest risk of genetic mutation carriage.[23] Yet little is known about testing logistics and timing in the cancer management workflow. There is growing concern about the impact of increasingly complex results on treatment decision making, particularly if patients do not receive expert genetic counseling.[24] We examined the patterns, correlates, and timing of genetic counseling and testing, and the impact of results on surgical decisions, in a large, diverse, population-based sample of patients newly diagnosed with breast cancer. We also examined attending surgeons' perspectives and attitudes about integrating testing into treatment decision making.

METHODS

Study Sample and Data Collection

After institutional review board approval, we selected women age 20 to 79 years with stages 0 to II breast cancer who were reported to the SEER registries of Georgia and Los Angeles County. Eligible patients were identified via pathology reports from surgical procedures. Patients diagnosed in 2014 to 2015 were selected approximately 2 months after surgery. Patients with stage III or IV disease, tumors greater than 5 cm, or greater than three involved nodes were excluded. Black, Asian, and Hispanic women were oversampled in Los Angeles, as we previously reported.[25] Questionnaire content was developed using a conceptual framework, research questions, and hypotheses. We developed measures drawing from the literature and our prior research.[26,27] We assessed content validity, including systematic review by design experts, cognitive pretesting with patients, and clinical pilot studies.[23]

Data Collection

Patient surveys were mailed approximately 2 months after surgery. We provided a $20 cash incentive and used a modified Dillman method,[28] including reminders to nonrespondents. All materials were in English. We added Spanish-translated materials for all women with surnames suggesting Hispanic ethnicity. Survey responses were merged with SEER data. Nearly all patients (98%) reported their surgeon's name, and these doctors were surveyed (using a similar Dillman approach) toward the end of the patient data collection period.

Measures

Patients provided information about genetic testing (defined as "testing for cancer risk, often called *BRCA* tests or multi-gene panel tests"), including discussion with any health professional (yes or no), counseling receipt (phrased as "Did you have a counseling session with a genetic counseling expert—that is, an appointment where the whole discussion is about genetic risk for breast cancer?"; yes or no), and testing receipt (yes or no). Patients reported test timing (before diagnosis, after diagnosis but before surgery, or after surgery) and results (no mutations; a mutation in a gene [*BRCA1*, *BRCA2*, or another] that increases the risk of breast cancer; a mutation in a gene [*BRCA1*, *BRCA2*, or another] but not one that is known to increase the risk of breast cancer, sometimes called a VUS; other or unknown).

Patients reported on health care provider(s) who ordered the genetic test and who discussed results with them (surgeon, medical oncologist, primary care provider, genetic counselor, or other). Patients reported surgical procedures (lumpectomy, mastectomy on one breast, or mastectomy on both breasts). Race or ethnicity (Hispanic, non-Hispanic black, non-Hispanic Asian, or non-Hispanic white); family history of breast, ovarian, and other cancers (yes or no, number and relationship of affected relatives); Ashkenazi Jewish ancestry (yes or no); insurance coverage (Medicaid, Medicare, private or other insurance, or not insured); education (at least some college or less); and household income ($< $40,000, $40,000 to $89,999, or $\geq$ $90,000) were self-reported by patients.

SEER registries provided age at diagnosis (years), cancer stage (0, I, or II), and biomarkers including expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. Tumors lacking estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression were considered triple negative.

We constructed a measure of higher risk for genetic mutation carriage based on criteria for hereditary breast/ovarian cancer syndrome testing according to guidelines of the National Comprehensive Cancer Network,[5] contemporaneous to patients' diagnosis dates. Patients were categorized as higher risk if they had one or more of the following: age at breast cancer diagnosis $\leq$ 45 years; triple-negative breast cancer diagnosed at age less than 60 years; any relative with ovarian cancer, sarcoma, or male breast cancer; two or more first-degree relatives with breast cancer (for patients diagnosed at age $\leq$ 50 years, one or more first-degree relative with breast cancer); Ashkenazi Jewish ancestry; or family history of a mutation conferring high risk (eg, *BRCA1/2*).

Surgeons were asked about the number of new patients with breast cancer they had treated in the past year. We asked surgeons about confidence in discussing the pros and cons of genetic testing with patients and how often they did the following for patients who were testing candidates: refer patient for genetic counseling; order testing without counseling referral; and delay surgery until testing results are obtained. We also asked surgeons whether they would offer breast-conserving therapy to some *BRCA1/2* mutation carriers as a reasonable option or manage a patient with a *BRCA1/2* VUS the same way as a *BRCA1/2* mutation carrier.

Statistical Methods

We conducted descriptive statistics and examined the patterns and timing of testing and results discussion. We used two separate logistic regression models to model the following two outcomes: bilateral mastectomy (BLM) receipt (yes or no) and whether testing occurred after surgery (yes or no). Both models considered the following potential predictors: pretest risk of pathogenic mutation carriage, age, race or ethnicity, insurance, study site, education, comorbidities, and cancer stage (Table 1). We retained test results and pretest risk in the BLM model regardless of statistical significance, given their relevance. In both models, we used a backward-selection method predictive modeling approach to eliminate variables that did not reach a significance level of $P = .10$. On the basis of the BLM model, we calculated the adjusted probability of BLM for a typical patient who is non-Hispanic white, older than age 50 years, and privately insured.

Patient respondents were more likely to be white or have stage I cancer ($P < .05$) than nonrespondents, and response rates differed slightly between two study sites ($P < .001$). Survey design and nonresponse

Table 1. Demographic and Clinical Characteristics of Patients Who Reported Undergoing Genetic Testing

Characteristic	Weighted % of Patients (N = 666)
Genetic test result	
No pathogenic mutation or VUS	72
VUS only, no pathogenic mutation	9
Pathogenic mutation in *BRCA1/2* or another gene that increases risk of breast cancer	7
Missing	12
Age at time of survey, years	
≥ 50	64
< 50	36
Mean age (standard deviation)	56.0 (0.48)
Study site	
Georgia	53
Los Angeles County	47
Race/ethnicity	
White	56
Black	18
Hispanic	14
Asian	9
Other/unknown/missing	3
Education	
High school graduate or less	18
Some college	31
College graduate or more	48
Missing	3
Partnered	
No	31
Yes	67
Missing	2
Annual family income, $	
< 20,000	8
20,000-60,000	26
≥ 60,000	52
Unknown	14
Insurance status	
Medicaid	7
Medicare or Veterans Affairs	18
Private or other	62
None	14
No. of comorbidities*	
0	81
1	16
> 1	3
Tumor grade	
1	22
2	40
3	34
Missing	4
Cancer stage	
0	22
I	48
II	27
Missing	3
Tumor size, cm	
≤ 1	30
> 1, ≤ 2	36
> 2, ≤ 5	28
Missing	6
Tumor ER and PR expression	
ER positive only	9
PR positive only	0
ER and/or PR positive	72
Missing	19
Tumor HER2 status	
Negative	66
Positive	10
Missing	25
Lymph nodes involved by tumor	
No	82
Yes	16
Missing	2
Surgical treatment	
Breast-conserving surgery	55
Unilateral mastectomy	15
Bilateral mastectomy	29
Missing	1
Pretest risk of pathogenic mutation carriage†	
Average risk	39
Higher risk	59
Missing	2

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; VUS, variant of uncertain significance.

*Comorbidities: None, one, or two or more of the following four major comorbid conditions: stroke, myocardial infarction, diabetes, or chronic obstructive pulmonary disease.

†Patients were categorized as higher risk if they had one or more of the following: age at breast cancer diagnosis ≤ 45 years; bilateral breast cancer; triple-negative breast cancer diagnosed at age < 60 years; any relative with ovarian cancer, sarcoma, or male breast cancer; two or more first-degree relatives with breast cancer (or, for patients diagnosed at age ≤ 50 years, one or more first-degree relative with breast cancer); Ashkenazi Jewish ancestry; or family history of a deleterious genetic mutation (*BRCA1/2* or another mutation associated with increased breast cancer risk, eg, *TP53*). All other patients were categorized as average risk.

weights were used in all analyses to compensate for the differential probability of patient selection and survey nonresponse among subgroups with various demographic and/or clinical characteristics.[23,29-31] We used an inverse probability weighting method as a sensitivity analysis on missing data and reached similar conclusions (results not shown). Surgeon responses were analyzed according to volume of patients with newly diagnosed breast cancer seen in the last year, categorized as low (zero to 20 patients), moderate (21 to 50 patients), and high (≥ 51 patients). All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Results

Patient characteristics. We selected 3,930 women diagnosed in 2014 to 2015. Among these patients, 258 were ineligible as a result of having prior cancer diagnosis or stage III or IV disease; having residence outside the SEER registry area; or being deceased, too ill, or unable to complete a survey in Spanish or English. Of the 3,672 eligible women remaining, 1,170 could not be contacted or did not participate, leaving 2,502 respondents (68%). As described earlier, all analyses were weighted to control for potential bias as a result of nonresponse. We excluded 115 women as a result of bilateral cancer, 1,535 women as a result of no genetic testing, and 186 women as a result of no information on tumor laterality or testing. This left 666 patients (30%) who reported genetic testing as the analytical sample (Appendix Fig A1, online only). The sample was

racially diverse, with 57% non-Hispanic whites, 18% blacks, 14% Hispanics, and 9% Asians (Table 1).

Timing, ordering, and discussion of genetic testing. Among all tested patients, 59% met criteria for higher pretest risk of mutation carriage (higher risk), and 39% did not (average risk; Table 1). Test timing was as follows: before diagnosis (higher risk, 6%; average risk, 2%), after diagnosis but before surgery (higher risk, 67%; average risk, 64%), and after surgery (higher risk, 27%; average risk, 34%; Table 2). Providers who ordered testing were surgeons (higher risk, 48%; average risk, 42%), medical oncologists (higher risk, 31%; average risk, 40%), and genetic counselors (higher risk, 21%; average risk, 18%). Patients reported results discussion by surgeons only (higher risk, 19%; average risk, 18%), medical oncologists only (higher risk, 17%; average risk, 31%), genetic counselors only (higher risk, 57%; average risk, 42%), and multiple health professionals (high risk, 7%; average risk, 10%).

Correlates of testing delay. Because genetic test results may inform surgery decisions, we defined delay as testing after surgery. In a multivariable model adjusted for age, race, education, stage, comorbidities, and study site, the only factors associated with delay were insurance and pretest risk. Compared with patients with private insurance, patients were more likely to be tested after surgery if they had Medicare (odds ratio [OR], 2.6; 95% CI, 1.6 to 4.2), Medicaid (OR, 2.3; 95% CI, 1.1 to 4.5), or no insurance (OR, 2.5; 95% CI, 1.5 to 4.3). Average-risk patients were more likely than higher- risk patients to be tested after surgery (OR, 1.4; 95% CI, 1.0 to 2.1)

Genetic testing results and surgical decisions. Among tested patients (n = 666), 72% stated no mutation was detected, 9% indicated VUS, and 7% indicated a mutation in *BRCA1/2* or another risk-associated gene; 12% of patients did not report results (Table 1). Figure 1 shows adjusted ORs from a multivariable logistic regression model of BLM receipt. BLM recipients were more likely to have a pathogenic mutation (*v* no mutation; OR, 7.7; 95% CI, 3.9 to 15.3), be white (*v* black; OR, 3.2; 95% CI, 1.7 to 5), be age $\leq$ 50 years (*v* $>$ 50 years; OR, 2.5; 95% CI, 1.6 to 3.9), and have private insurance (*v* Medicare; OR, 3.3; 95% CI, 1.6 to 6.9). Figure 2 shows adjusted probabilities of BLM by pretest risk and test results, calculated using the model from Figure 1 for a typical patient with non-Hispanic white race, age greater than 50 years, and private insurance. Higher-risk women were likely to have BLM (80%) if they had a pathogenic mutation, but less so if they had VUS (43%) or no mutation (34%). BLM receipt was similar in average-risk patients (85% with pathogenic mutation, 51% with VUS, and 30% with no mutation).

Surgeon Results

A total of 377 surgeons responded (response rate, 78%); 38% had a lower volume of patients (one to 20 patients with breast cancer in prior year), 30% had a moderate volume (21 to 50 patients), and 29% had a higher volume ($>$ 51 patients), with 3% missing data. Confidence in discussing testing was higher among surgeons with higher (73%) versus lower (35%) volume (Fig 3). Up to one third of surgeons rarely referred patients for genetic counseling and ordered testing without referral. The minority of surgeons (17% of higher-volume surgeons and 38% of lower-volume surgeons) never delayed surgery for test results. Fewer than half of surgeons offered breast-conserving therapy to some *BRCA1/2* mutation carriers (43% of higher-volume, 25% of moderate-volume, and 36% of lower-volume surgeons). Half of lower-volume surgeons and one quarter of higher-volume surgeons reported managing patients with *BRCA1/2* VUS the same way as *BRCA1/2* mutation carriers (Fig 3).

DISCUSSION

We examined experiences and perspectives on genetic testing in a large, diverse sample of patients with newly diagnosed breast cancer immediately after a major testing expansion. We also examined perspectives and attitudes of these patients' attending surgeons regarding genetic counseling, testing, and results management. We began accruing patients shortly after a US Supreme Court ruling against gene patents enabled the rapid entry of

Table 2. Clinicians Who Ordered Genetic Testing and Discussed Results and Test Timing According to Patient Pretest Risk for Pathogenic Mutation Carriage

Factor	Average-Risk Patients		Higher-Risk Patients	
	Weighted %	95% CI	Weighted %	95% CI
Clinician who ordered genetic test				
Surgeon	42	35 to 49	48	42 to 54
Medical oncologist	40	34 to 47	31	26 to 36
Genetic counselor	18	12 to 23	21	16 to 25
Clinician who discussed genetic test results (mutually exclusive)*				
Surgeon only	18	12 to 23	19	14 to 23
Medical oncologist only	31	24 to 37	17	13 to 21
Genetic counselor	42	35 to 49	57	52 to 63
Multiple health professionals†	10	6 to 14	7	4 to 10
When patient was tested				
Before diagnosis	2	0.4 to 4	6	4 to 9
After diagnosis but before surgery	64	57 to 70	67	62 to 72
After surgery to treat breast cancer	34	28 to 40	27	22 to 32

*Excludes 36 patients who stated that their primary care physician or other health professionals, instead of surgeons, medical oncologists, or genetic counselors, discussed the genetic results with them.
†Either surgeon or medical oncologist discussed the genetic results.

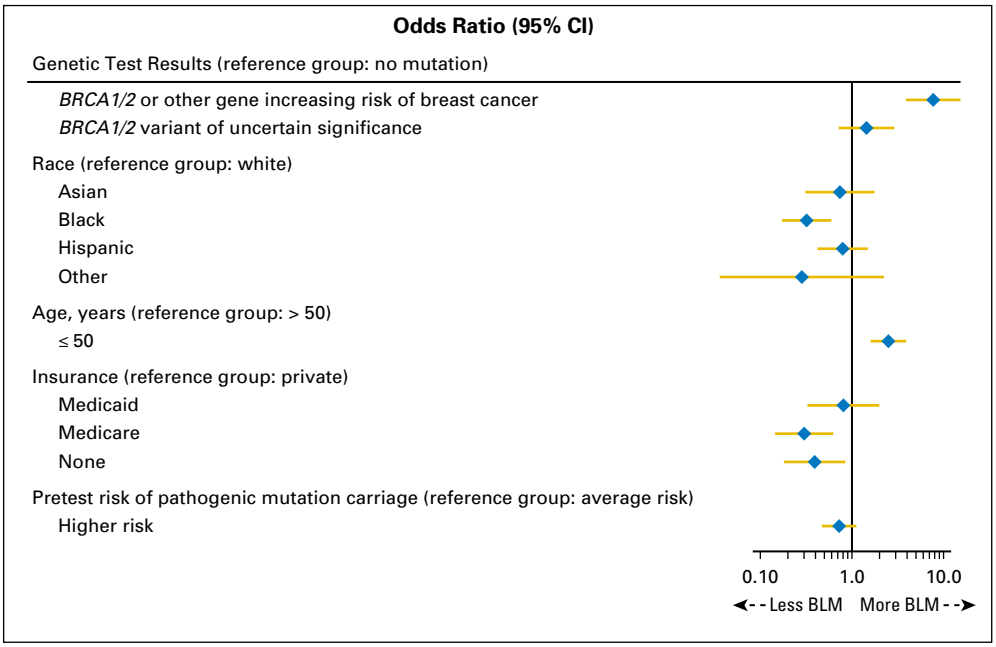

Fig 1. Results from logistic regression model on the likelihood of receiving bilateral mastectomy (BLM). The model also controlled for geographic site as a potential confounder.

companies offering cheaper testing.[10] Out-of-pocket costs for testing without insurance coverage have decreased from greater than $3,000 in early 2013 to as low as $250 today, increasing access. Simultaneously, the growth of multiplex panel testing markedly increased the complexity of results.[1] This study offers a unique window into a transformative period for precision medicine and the challenge of implementing advances in genomic technology into breast cancer treatment.

Effective genetic testing requires clinicians to assess pretest risk, counsel patients on testing implications, order an appropriate test, communicate results, and develop an appropriate management plan. Furthermore, there is urgency for a patient with newly diagnosed breast cancer; genetic tests are often desired to inform surgical decision making,[32] yet patients may fear that the 3-week testing process will dangerously postpone treatment. Reassuringly, we found that two thirds of patients reported testing after diagnosis yet before surgery; however, 27% of higher-risk and 33% of average-risk patients had testing after surgery. Although some patients may prefer to defer testing until after the hectic period of initial decision making, for others, this delay may represent suboptimal care. In addition, it is concerning that a substantial proportion of surgeons, particularly those who saw the fewest patients with breast cancer, never postponed surgery until test results were available.

Guidelines advise pretest genetic counseling, particularly in the new era of more complicated multiple-gene testing.[33] Yet fewer

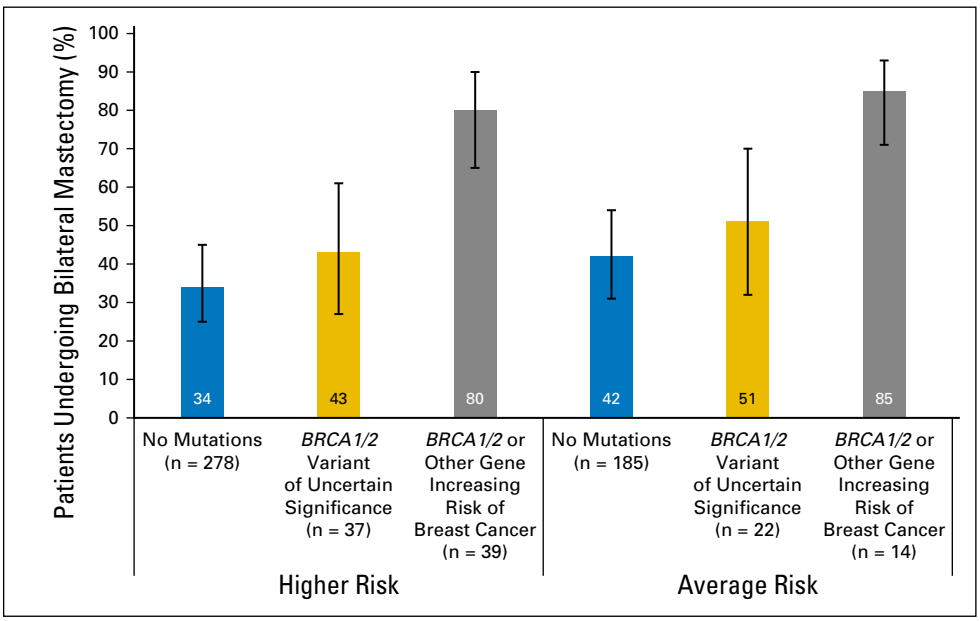

Fig 2. Adjusted probability of receiving bilateral mastectomy and its 95% CI according to genetic testing results and patient pretest risk for genetic mutation carriage. This figure depicts adjusted probability of receiving bilateral mastectomy by the genetic testing results and pretesting risk levels, based on results from a logistic regression model on the likelihood of receiving bilateral mastectomy, controlling for the significant confounders of age, race, insurance type, and site. The adjusted probability is calculated for a typical patient who is non-Hispanic white, is older than age 50 years, and has private insurance.

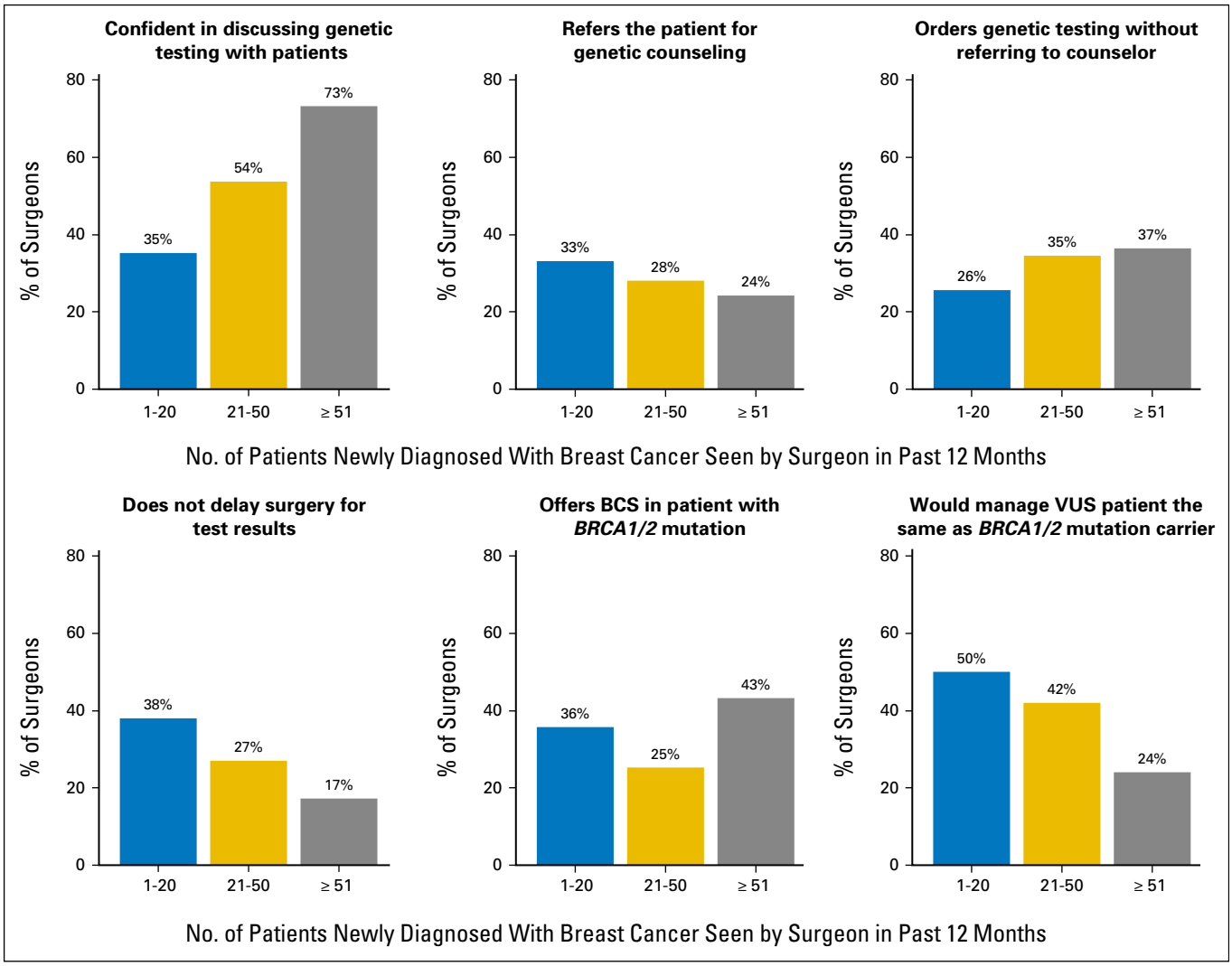

Fig 3. Attending surgeons' perspectives on referral to genetic counseling, ordering genetic tests, and managing test results, according to surgeons' volume of newly diagnosed patients with breast cancer seen in the past year. BCS, breast-conserving surgery; VUS, variant of uncertain significance.

than 20% of patients reported that a genetic counselor ordered their test; at least one quarter of surgeons rarely referred patients to genetic counseling and ordered testing without referral. Adequate pretest counseling may have been provided by other means, but this raises the possibility that only one in five patients received optimal pretest care. Of particular concern, lower-volume surgeons were least likely to refer to genetic counseling even though they were least confident about discussing testing. Higher-risk patients were similarly unlikely to have a genetic counselor order testing as average-risk patients (20% *v* 17%, respectively). This may reflect the recognized shortage of genetic counselors nationwide[20]; we lack information about surgeons' perceived access to genetic counseling services. However, our findings also suggest suboptimal triage of higher-risk patients to early counseling. It may be that clinicians fail to recognize higher-risk patients, consistent with our recent work.[23] Although more patients met with a genetic counselor after testing, many reported no counselor contact. Although the causes of this shortfall remain to be defined, insurance status was the sole significant predictor of testing delay. This suggests a persistent cost barrier to effective testing for some patients, despite recent price reductions.[2]

We and others have reported substantial recent increases in BLM use, which confers no survival advantage to most women.[34-36] Women who carry pathogenic mutations in genes such as *BRCA1/2* are the rare exceptions who may benefit from BLM.[37-39] Thus, it is essential that patients understand the meaning of their results and that BLM be discussed with mutation carriers but not recommended for women with negative or VUS results.[5] However, we found that up to half of surgeons did not recognize this distinction, reporting no difference in their management of patients with *BRCA1/2* VUS versus pathogenic mutations. This reinforces the urgent need to improve both surgeons' and patients' genetic knowledge. We found that *BRCA1/2* mutation carriage predicted BLM receipt. Notably, however, patients with VUS frequently underwent BLM, particularly those with average pretest risk. The decision for BLM is a complicated one, with many determinants beyond second cancer risk.[26,40] However, our findings raise concern that average-risk patients in particular may not have

understood their VUS results; alternatively, their desire for BLM may not have been affected by test results. The findings highlight another dilemma—meeting the information needs of a growing number of patients who lack high risk yet desire testing nonetheless. This underscores the urgency to develop effective testing communication strategies for these patients.

Aspects of the study merit comment. Its strengths include a large diverse sample accrued immediately after a major testing expansion, detailed clinical information, survey data from patients and their attending surgeons, and a high participation rate. However, there were limitations. The source of testing data was patient report, which might be incorrect; however, we previously validated patient report of genetic testing in comparison with medical records in a diverse preliminary sample. Nonresponse may have biased results, but analyses weighted for survey nonresponse were used to address this bias. Relatively few patients had VUS or pathogenic mutation results of genetic testing. Results are limited to two large regions of the United States.

The need for physicians to engage with patients with breast cancer about genetic testing is growing rapidly. As the scope of analyzed genes and diseases expands, genetic counseling expertise is increasingly critical.[24] However, our findings underscore the inadequate engagement of genetic counselors in breast cancer treatment. Addressing these problems will require expanding the genetic counselor workforce and new strategies to integrate counseling more efficiently into the rapid pace of treatment decision making.[41]

A busy cancer doctor's major challenge is to test the right patient for the right genes soon enough to guide time-sensitive treatment decisions such as BLM. Thus, a key priority is to improve clinicians' communication skills and support their assessment of patients' genetic risk and desire for testing. With more thorough understanding of patients' risk and interest, physicians can optimize triage by directing higher-risk patients to expedited genetic counseling and interested average-risk patients to another form of discussion. This discussion might begin with a clinical decision support tool for average-risk patients, which could offer much of the information provided in a counseling session, yet reserve the scarce resource of timely in-person counseling for higher-risk patients who need it most. Our findings reinforce the need to address challenges in personalized communication about genetic testing. Clinicians' skill in communicating about precision medicine technologies will determine whether these advances translate into better care and outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Domchek SM, Bradbury A, Garber JE, et al: Multiplex genetic testing for cancer susceptibility: Out on the high wire without a net? J Clin Oncol 31: 1267-1270, 2013
2. Kurian AW, Ford JM: Multigene panel testing in oncology practice: How should we respond? JAMA Oncol 1:277-278, 2015
3. Evans DG, Wisely J, Clancy T, et al: Longer term effects of the Angelina Jolie effect: Increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women. Breast Cancer Res 17:143, 2015
4. Noar SM, Althouse BM, Ayers JW, et al: Cancer information seeking in the digital age: Effects of Angelina Jolie's prophylactic mastectomy announcement. Med Decis Making 35:16-21, 2015
5. Daly MB, Pilarski R, Axilbund JE, et al: Genetic/familial high-risk assessment: Breast and Ovarian, Version 2.2015. J Natl Compr Canc Netw 14: 153-162, 2016
6. Desmond A, Kurian AW, Gabree M, et al: Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. JAMA Oncol 1:943-951, 2015
7. Kurian AW, Hare EE, Mills MA, et al: Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol 32: 2001-2009, 2014
8. LaDuca H, Stuenkel AJ, Dolinsky JS, et al: Utilization of multigene panels in hereditary cancer predisposition testing: Analysis of more than 2,000 patients. Genet Med 16:830-837, 2014
9. Maxwell KN, Wubbenhorst B, D'Andrea K, et al: Prevalence of mutations in a panel of breast cancer susceptibility genes in BRCA1/2-negative patients with early-onset breast cancer. Genet Med 17:630-638, 2015
10. Offit K, Bradbury A, Storm C, et al: Gene patents and personalized cancer care: Impact of the Myriad case on clinical oncology. J Clin Oncol 31: 2743-2748, 2013
11. Thompson ER, Rowley SM, Li N, et al: Panel testing for familial breast cancer: Calibrating the tension between research and clinical care. J Clin Oncol 34:1455-1459, 2016
12. Tung N, Lin NU, Kidd J, et al: Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol 34:1460-1468, 2016
13. Couch FJ, Hart SN, Sharma P, et al: Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol 33:304-311, 2015
14. Moreno L, Linossi C, Esteban I, et al: Germline BRCA testing is moving from cancer risk assessment to a predictive biomarker for targeting cancer therapeutics. Clin Transl Oncol 18:981-987, 2016
15. Bradbury AR, Patrick-Miller L, Domchek S: Multiplex genetic testing: Reconsidering utility and informed consent in the era of next-generation sequencing. Genet Med 17:97-98, 2015
16. Bradbury AR, Patrick-Miller L, Long J, et al: Development of a tiered and binned genetic counseling model for informed consent in the era of multiplex testing for cancer susceptibility. Genet Med 17:485-492, 2015
17. Stadler ZK, Schrader KA, Vijai J, et al: Cancer genomics and inherited risk. J Clin Oncol 32:687-698, 2014
18. Easton DF, Pharoah PD, Antoniou AC, et al: Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 372:2243-2257, 2015
19. Balmaña J, Digiovanni L, Gaddam P, et al: Conflicting Interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the Prospective Registry of Multiplex Testing. J Clin Oncol 34:4071-4078, 2016
20. Delikurt T, Williamson GR, Anastasiadou V, et al: A systematic review of factors that act as

barriers to patient referral to genetic services. Eur J Hum Genet 23:739-745, 2015

21. Gray SW, Hicks-Courant K, Cronin A, et al: Physicians' attitudes about multiplex tumor genomic testing. J Clin Oncol 32:1317-1323, 2014

22. Yu PP, Vose JM, Hayes DF: Genetic cancer susceptibility testing: Increased technology, increased complexity. J Clin Oncol 33:3533-3534, 2015

23. Kurian AW, Griffith KA, Hamilton AS, et al: Genetic testing and counseling among patients with newly diagnosed breast cancer. JAMA 317:531-534, 2017

24. Robson ME, Bradbury AR, Arun B, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660-3667, 2015

25. Hamilton AS, Hofer TP, Hawley ST, et al: Latinas and breast cancer outcomes: Population-based sampling, ethnic identity, and acculturation assessment. Cancer Epidemiol Biomarkers Prev 18: 2022-2029, 2009

26. Hawley ST, Jagsi R, Morrow M, et al: Social and clinical determinants of contralateral prophylactic mastectomy. JAMA Surg 149:582-589, 2014

27. Jagsi R, Griffith KA, Kurian AW, et al: Concerns about cancer risk and experiences with genetic testing in a diverse population of patients with breast cancer. J Clin Oncol 33:1584-1591, 2015

28. Dillman DA, Smyth JD, Christian LM: Internet, Mail, and Mixed-Mode Surveys: The Tailored Design Method (ed 3). Hoboken, NJ, John Wiley & Sons, 2009

29. Kish L: Survey Sampling. New York, NY, John Wiley & Sons, 1965

30. Kurian AW, Friese C, Bondarenko I, et al: Second opinions from medical oncologists for early-stage breast cancer: Prevalence and consequences. JAMA Oncol 3:391-397, 2017

31. Groves RM, Fowler F, Couper MP, et al: Survey Methodology (ed 2). New York, NY, John Wiley & Sons, 2009

32. Weitzel JN, McCaffrey SM, Nedelcu R, et al: Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Arch Surg 138: 1323-1329, 2003

33. Robson ME, Storm CD, Weitzel J, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 28:893-901, 2010

34. Kurian AW, Lichtensztajn DY, Keegan TH, et al: Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998-2011. JAMA 312:902-914, 2014

35. Tuttle TM, Habermann EB, Grund EH, et al: Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. J Clin Oncol 25: 5203-5209, 2007

36. Tuttle TM, Jarosek S, Habermann EB, et al: Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol 27:1362-1367, 2009

37. Antoniou A, Pharoah PD, Narod S, et al: Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 72: 1117-1130, 2003

38. Domchek SM, Friebel TM, Singer CF, et al: Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304:967-975, 2010

39. Rebbeck TR, Friebel T, Lynch HT, et al: Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol 22:1055-1062, 2004

40. Rosenberg SM, Tracy MS, Meyer ME, et al: Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: A cross-sectional survey. Ann Intern Med 159:373-381, 2013

41. Kinney AY, Butler KM, Schwartz MD, et al: Expanding access to BRCA1/2 genetic counseling with telephone delivery: A cluster randomized trial. J Natl Cancer Inst 106:dju328, 2014

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Appendix

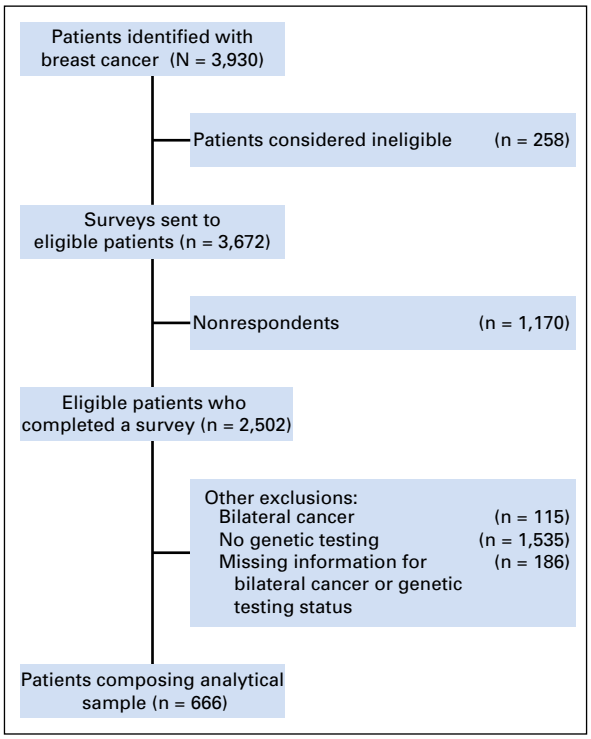

Fig A1. Patient flow diagram depicting the flow of patients into the study from those initially identified to the final analytic sample.