Clinical Utility of Universal Germline Genetic Testing for Patients With Breast Cancer

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Abstract

IMPORTANT National Comprehensive Cancer Network guidelines currently recommend germline testing for high-risk genes in selected patients with breast cancer. The clinical utility of recommending testing all patients with breast cancer with multigene panels is currently under consideration.

OBJECTIVE To examine the implications of universal testing of patients with breast cancer with respect to clinical decision-making.

DESIGN, SETTING, AND PARTICIPANTS Patients from a previously reported cohort were assessed as in-criteria or out-of-criteria according to the 2017 guidelines and underwent testing with a multigene germline panel between 2017 to 2018. Patients were women and men aged 18 to 90 years, with a new and/or previous diagnosis of breast cancer who had not undergone either single or multigene testing. Clinicians from 20 community and academic sites documented patient clinical information and changes to clinical recommendations made according to test findings. Association between prevalence of pathogenic or likely pathogenic germline variants and previously unreported clinical features, including scores generated by the BRCA PRO statistical model, was determined. Data were analyzed from April 2020 to May 2022.

EXPOSURE New and/or previous diagnosis of breast cancer.

MAIN OUTCOMES AND MEASURES Disease management recommendations that were changed as a result of genetic testing results are reported.

RESULTS Clinicians were asked to assess changes to clinical management as a result of germline genetic testing for 952 patients. Informative clinician-reported recommendations were provided for 939 (467 in-criteria and 472 out-of-criteria) of the patients with breast cancer (936 [99.7%] female; 702 [74.8%] White; mean [SD] age at initial diagnosis, 57.6 [11.5] years). One or more changes were reported for 31 of 37 (83.8%) in-criteria patients and 23 of 34 (67.6%) out-of-criteria patients with a pathogenic or likely pathogenic variant. Recommendations were changed as a result of testing results for 14 of 22 (63.6%) out-of-criteria patients who had a variant in a breast cancer predisposition gene. Clinicians considered testing beneficial for two-thirds of patients with pathogenic or likely pathogenic variants and for one-third of patients with either negative results or variants of uncertain significance. There was no difference in variant rate between patients meeting the BRCA PRO threshold (≥10%) and those who did not (P = .86, Fisher exact test). No changes to clinical recommendations were made for most patients with negative results (345 of 349 patients [98.9%]) or variants of uncertain significance (492 of 509 patients [96.7%]).

(continued)
CONCLUSIONS AND RELEVANCE  In this cohort study, germline genetic testing was used by clinicians to direct treatment for most out-of-criteria patients with breast cancer with pathogenic or likely pathogenic germline variants, including those with moderate-risk variants. Universal germline testing informs clinical decision-making and provides access to targeted treatments and clinical trials for all patients with breast cancer.


Introduction

The value of identifying patients with highly penetrant, pathogenic or likely pathogenic germline genetic variants (PGVs) in clinical management for cancer predisposition has been well-established.1 To target high-risk variants, genetic testing guidelines developed by professional organizations are largely determined by age at diagnosis and personal and/or family history.2 Additionally, risk assessment tools such as the BRCAPRO statistical model use a patient’s personal cancer status and family history to assist in recommendation for genetic testing.3 Germline testing for BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 is currently recommended for certain patients with breast cancer by the National Comprehensive Cancer Network (NCCN) guidelines; however, studies of universal testing with multigene panels suggest that guidelines should be broadened to include testing of all individuals with solid tumors and include genes beyond those with proven breast cancer associations.4-8

Previously, we reported that in a cohort of 959 patients with breast cancer stratified according to the 2017 NCCN guidelines (version 1.2017),9 approximately 50% of PGVs would have been missed if only patients meeting the guidelines were tested.10 The guidelines have since been updated (version 1.2022) to recommend testing at any age for triple-negative breast cancer, or to aid in eligibility determination for treatment with poly (ADP-ribose) polymerase (PARP) inhibitors for patients with metastatic breast cancer and for early-stage high-risk patients with ERBB2-negative breast cancer.11,12 Testing is also now indicated when a patient does not meet family history criteria for cancer but has a probability greater than 5% of a BRCA1/2 variant according to an assessment tool such as BRCAPRO. However, recommendations that preclude universal testing of patients with breast cancer with multigene panels remain, specifically those requiring younger age at diagnosis (<45 years), combinations of age, personal and/or family history of cancer, and Ashkenazi Jewish ancestry.13

The clinical actionability associated with expanded panel testing has demonstrated its potential to alter patient care.14,15 In a prospective, multicenter study16 using germline multigene panel testing in unselected patients with cancer, 48.4% of the 397 patients with PGVs had clinically actionable findings that would not have been detected by phenotype or family history–based testing criteria. Most importantly, 28% of patients with high-penetrance PGVs had genetic data-informed changes in their clinical management and/or treatment.16

Several studies have performed cost modeling of expanding testing that accounts for appropriate screenings and risk-reducing interventions.17 An analysis of population-based germline genetic testing of unselected women aged 50 years and younger in the United Kingdom and US using a panel comprising BRCA1/2, PALB2, RAD51C, RAD51D, and BRIP1 was found to reduce breast cancer incidence and was more cost-effective than a guideline-based strategy.18

To fully assess the changes resulting from germline testing, it is vital to monitor treatment decisions and patient outcomes. Here, we report how universal germline genetic testing in our previously reported10 cohort informed clinical management and clinicians’ assessment of the overall benefit of testing to patients.
Methods

Study Population and Data Sources
A multicenter prospective registry was initiated in 2017 with 20 community and academic clinics in states including Alaska, Arizona, California, Hawaii, Illinois, Michigan, New Mexico, New York, Pennsylvania, Tennessee, Texas, and Virginia. As previously reported, a cohort of 956 female and 3 male patients with breast cancer underwent germline genetic testing and variant interpretation at Invitae (San Francisco, CA) (eTable 1 and eFigure in the Supplement). PGV penetrance was defined according to disease risk and previous modeling. Breast cancer predisposition genes are defined as those associated with risk at the time the study was conducted (including *NBN* and *RAD50*, which are no longer associated with breast cancer risk). Clinicians completed an institutional review board-approved case report form (CRF) to document patient clinical information, genetic testing results, changes to clinical recommendations made according to test findings, and assessed changes resulting from testing on patient outcomes (eTable 2 in the Supplement). Analysis of deidentified and aggregated data was approved by an independent institutional review board (WCG IRB). All enrolled patients provided written consent to have their deidentified data used in the registry, which were recorded in a Health Insurance Portability and Accountability Act–compliant electronic database. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. A list of abbreviations used in the study is available in the eAppendix in the Supplement.

Study Design
A subset of 949 female and 3 male patients from the cohort described previously was used for this study. Seven patients were excluded for not fulfilling the criteria of the study (as detailed in the eFigure in the Supplement). The final cohort comprised an equal number of in-criteria (IC) patients who met the 2017 NCCN germline genetic testing guidelines (version 1.2017) and out-of-criteria (OOC) patients who did not meet these guidelines. Two patients previously incorrectly reported as IC were recategorized as OOC. To contextualize newly reported data, clinical information that was previously reported, including PGV prevalence, patient age at testing, age at diagnosis, and self-reported race and ethnicity, were reassessed for the cohort. Self-reported race and ethnicity were assessed in this study in order to elucidate, if present, any evidence of health care disparities in this cohort, as has been previously reported to occur in the delivery of clinical genetic services to historically underrepresented patient populations. In addition, data that were collected during the course of the study but not previously reported, including type of breast cancer, hormone receptor status, and BRCAPRO score (if evaluated), were analyzed.

Clinician-Provided Data
The CRF included questions regarding any changes to surgical strategy; chemotherapy, endocrine, or radiation treatment; or follow-up plan made for the patient and patient’s relatives that were specifically changed as a result of the genetic testing results. Clinicians were also asked to assess whether genetic testing had a positive impact on patient health outcomes, which was defined as being beneficial to clinical management and/or the patients’ overall well-being at the time of CRF completion.

Statistical Analysis
The associations of patient characteristics, changes to clinical recommendations, and reported outcomes with genetic testing results were analyzed. Informative responses were defined as those in which an answer was provided and not left blank, regardless of whether any change in recommendation was noted. GraphPad QuickCalcs was used to analyze data. Fisher exact test was used to compare PGV prevalence between IC and OOC groups. Statistical significance is indicated by a 2-tailed \( P < .05 \). Data were analyzed from April 2020 to May 2022.
Results

Cohort Patient Characteristics

A total of 467 in-criteria and 472 out-of-criteria patients with breast cancer had clinical and demographic information available (936 [99.7%] female; 702 [74.8%] White; mean [SD] age at initial diagnosis, 57.6 [11.5] years). Patient clinical and demographic characteristics stratified by IC vs OOC and PGV prevalence for the analyzed cohort are shown in Table 1. Of note, patients with triple-negative hormone receptor status determined to be OOC would have been IC according to the 2021 NCCN criteria (changes to patient status according to updated NCCN criteria are presented in eTable 3 in the Supplement). The rate of PGVs for IC patients was 8.8% (42 patients) and 8.4% (40 patients) for OOC patients. For PGVs in OOC patients, 55% were in genes that were considered to be breast cancer predisposition genes at the time the study was conducted, and of those genes, the majority (68.2%) were of moderate penetrance (Table 1). Although there was a higher rate of PGVs in breast cancer predisposition genes for IC patients (32 patients [76.2%]) compared with OOC patients, the difference was not significant (P = .06, Fisher exact test) (Table 1). There were, however, significantly more high-penetrance PGVs identified in IC patients compared with OOC patients (P = .001, Fisher exact test) (Table 1).

Prevalence of PGVs According to Patient Characteristics

Stratification of PGV prevalence according to age revealed that PGV rates were similar in the IC and OOC groups across age groups (Table 1). Patients older than 65 years in the OOC group had a higher positivity rate (9.4%) than patients in the IC group (7.7%), although this was not statistically significant (P = .66, Fisher exact test). PGV prevalence for the cohort stratified according to previously reported10 clinical features are presented in eTable 4 in the Supplement.

BRCAPRO scores were assessed using the consensus threshold of 10% or greater for the likelihood of carrying a BRCA1/2 variant at the time of patient enrollment,21 and reassessed using the more recent NCCN suggestion of a greater than 5% threshold (version 1.2022).13 Using 10% or greater as the threshold, there was no statistically significant difference in PGV rate between patients scoring above the threshold compared with those below the threshold (7.9% vs 8.7%; P = .86, Fisher exact test) (Table 1). For greater than 5% as threshold, 5 additional PGV-positive patients were identified, all of whom had BRCA2 PGVs; however, 25 PGV-positive IC and 34 PGV-positive OOC patients would still have been missed using a threshold of greater than 5% as the sole criterion for testing. Screening by BRCAPRO would have missed 64 (7.4%) and 59 (6.8%) PGV-positive patients out of all scored patients using 10% or greater and greater than 5% thresholds, respectively (Table 1).

Changes to Recommendations for Patients With PGVs

Informative data regarding clinician-reported management recommendations indicated by genetic testing were available for 71 of 82 PGV-positive patients (Table 2). Since recommendation to refer family members for genetic counseling and/or testing does not change a patient’s care directly, 4 PGV-positive patients with no other new recommendations other than referrals for family members were excluded for subsequent analyses as indicated. In the present study, only 32% of all PGV-positive patients were recommended to refer their family members for genetic counseling and/or testing. For the remaining patients, at least 1 change in clinical recommendation was made for 31 of 37 (83.8%) IC and 23 of 34 (67.6%) of OOC PGV-positive patients, with a mean (SD) of 1.8 (1.2) changes to management recommendations per patient (Table 2).

The most frequent recommendations made according to testing results for OOC patients were proactive surveillance or risk-reduction recommendations or clinician specialist referrals (Figure 1). No changes to recommendations were reported for radiation or endocrine treatment strategy for either IC or OOC patients. No changes to recommendations were reported for 13 patients, and the 4 aforementioned patients received only recommendations for familial genetic testing and/or...
counseling. For this group of patients, 3 PGVs were in the high-risk gene PALB2, 7 were in moderate-risk genes, and 6 in low-risk or recessive genes. Also, 4 of the 7 genes with PGVs were breast cancer predisposition genes (eTable 5 in the Supplement).

### Table 1. Prevalence of PGVs Among Patients Who Did and Did Not Meet 2017 NCCN Criteria for Germline Genetic Testing

<table>
<thead>
<tr>
<th>Clinical features of patients</th>
<th>IC group (n = 476)</th>
<th>OOC group (n = 476)</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGV positive</td>
<td>42 (8.8)</td>
<td>434 (91.2)</td>
<td>40 (8.4)</td>
</tr>
<tr>
<td>PGV negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>434 (91.2)</td>
<td>40 (8.4)</td>
<td>436 (91.6)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variants of uncertain significance</td>
<td>NA</td>
<td>260 (54.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Cancer predisposition category and penetrance&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer risk</td>
<td>32 (76.2)</td>
<td>NA</td>
<td>22 (55.0)</td>
</tr>
<tr>
<td>High-risk</td>
<td>18 (42.9)</td>
<td>NA</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>11 (26.2)</td>
<td>NA</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Low-risk</td>
<td>3 (7.1)</td>
<td>NA</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Non-breast cancer risk&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 (23.8)</td>
<td>NA</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42 (100)</td>
<td>432 (99.5)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Age at initial breast cancer diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>57 (35-83)</td>
<td>60 (22-93)</td>
<td>57 (46-85)</td>
</tr>
<tr>
<td>≤45</td>
<td>15 (10.3)</td>
<td>130 (89.7)</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;45</td>
<td>27 (8.2)</td>
<td>304 (91.8)</td>
<td>40 (8.4)</td>
</tr>
<tr>
<td>45-65</td>
<td>21 (8.0)</td>
<td>241 (92.0)</td>
<td>25 (7.8)</td>
</tr>
<tr>
<td>≤65</td>
<td>34 (9.1)</td>
<td>338 (90.9)</td>
<td>24 (7.8)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>8 (7.7)</td>
<td>96 (92.3)</td>
<td>16 (9.4)</td>
</tr>
<tr>
<td>Time of breast cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New diagnosis within 12 mo of testing</td>
<td>31 (9.2)</td>
<td>306 (90.8)</td>
<td>34 (10.2)</td>
</tr>
<tr>
<td>Previous diagnosis &gt;12 mo before testing</td>
<td>11 (7.9)</td>
<td>128 (92.1)</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>Final histological report&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal</td>
<td>24 (8.5)</td>
<td>257 (91.5)</td>
<td>22 (8.1)</td>
</tr>
<tr>
<td>Invasive lobular</td>
<td>3 (8.8)</td>
<td>31 (91.2)</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>DCIS</td>
<td>9 (9.5)</td>
<td>86 (90.5)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Invasive ductal or DCIS</td>
<td>4 (9.3)</td>
<td>39 (90.7)</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (9.5)</td>
<td>19 (90.5)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Not provided</td>
<td>0</td>
<td>2 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>ERBB2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>7 (11.7)</td>
<td>53 (88.3)</td>
<td>3 (17.6)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>ERBB2-negative</td>
<td>22 (8.0)</td>
<td>253 (92.0)</td>
<td>22 (7.9)</td>
</tr>
<tr>
<td>ERBB2-positive</td>
<td>7 (12.3)</td>
<td>50 (87.7)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>ER-positive</td>
<td>32 (9.3)</td>
<td>311 (90.7)</td>
<td>31 (8.1)</td>
</tr>
<tr>
<td>ER-negative</td>
<td>8 (9.6)</td>
<td>75 (90.4)</td>
<td>7 (12.7)</td>
</tr>
<tr>
<td>PR-positive</td>
<td>28 (9.3)</td>
<td>272 (90.7)</td>
<td>25 (7.7)</td>
</tr>
<tr>
<td>PR-negative</td>
<td>10 (8.3)</td>
<td>110 (91.7)</td>
<td>12 (11.8)</td>
</tr>
<tr>
<td>Not provided or other&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2 (4.2)</td>
<td>46 (95.8)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Risk model score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1/1 ≤5%</td>
<td>25 (9.5)</td>
<td>237 (90.5)</td>
<td>34 (8.8)</td>
</tr>
<tr>
<td>BRCA1/1 &gt;5%</td>
<td>15 (9.1)</td>
<td>149 (90.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>BRCA1/1 &lt;10%</td>
<td>30 (9.4)</td>
<td>288 (90.6)</td>
<td>34 (8.1)</td>
</tr>
<tr>
<td>BRCA1/1 ≥10%</td>
<td>10 (9.3)</td>
<td>98 (90.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Score not provided</td>
<td>2 (4.0)</td>
<td>48 (96.0)</td>
<td>6 (15.0)</td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; IC, in-criteria; NA, not applicable; PGV, pathogenic or likely pathogenic germline variant; OOC, out-of-criteria.

<sup>a</sup> Includes patients with variants of uncertain significance.

<sup>b</sup> Fisher exact test was performed for PGV prevalence between IC and OOC groups.

<sup>c</sup> PGV genes are classified according to associated breast cancer risk at the time of the study.<sup>9</sup>

<sup>d</sup> Excludes patients who carried concurrent variants in breast cancer risk genes (BRCA1/MUTYH, RAD51C/WRN, ATM/NTHL1).

<sup>e</sup> Classified according to American Society of Clinical Oncology/College of American Pathologists guidelines.

<sup>f</sup> Patients with triple-negative hormone receptor status would have been IC according to 2021 National Comprehensive Cancer Network criteria (version 1.2022).

<sup>g</sup> Other includes the following responses: not yet tested, not available, pending, not applicable due to type of cancer.
Changes to clinical management recommendations were made for more patients 45 years and younger (13 of 15 patients [86.7%]) than those older than 45 years (41 of 56 patients [73.2%]) (Table 3). Changes were also made for most patients older than 65 years (13 of 18 patients [72.2%]). Reporting of changes to recommendations by self-reported ethnicity indicated that 75.0% of non-Hispanic White patients had 1 or more changes to recommendations made. For patients other than non-Hispanic White, 14 of 17 (82.4%) had 1 or more changes to recommendations made (Table 3).

On a per-gene basis, changes to recommendations for OOC patients included those with PGVs in breast cancer predisposition and DNA damage repair genes ATM, BRCA2, CHEK2, NBN, RAD51C.

### Table 2. Clinician-Reported Impact of Germline Genetic Testing on Patients

<table>
<thead>
<tr>
<th>Clinician-reported impact and changes to recommendations influenced by testing</th>
<th>Patients, No./total No. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health outcome was reported to be positively impacted by testing</td>
<td>28/41 (68.3)</td>
</tr>
<tr>
<td>≥1 changes made&lt;sup&gt;c&lt;/sup&gt;</td>
<td>31/37 (83.8)</td>
</tr>
<tr>
<td>Breast cancer predisposition genes</td>
<td>27/32 (84.4)</td>
</tr>
<tr>
<td>Patients with no changes to clinical recommendations made&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6/37 (16.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IC, in-criteria; OOC, out-of-criteria; PGV, pathogenic or likely pathogenic germline variant; VUS, variants of uncertain significance.

<sup>a</sup> Denominators indicate number of patients with informative (not blank) responses from clinicians regarding impact of testing on health outcomes or changes to clinical recommendations made.

<sup>b</sup> A recommendation is defined as a results-based clinical recommendation directly impacting the patient’s care.

<sup>c</sup> Excludes patients who had no new recommendations other than familial genetic testing or counseling.

<sup>d</sup> Excludes recommendations for familial genetic testing or counseling.

<sup>e</sup> Includes 4 patients who had no new recommendations other than familial genetic testing or counseling.

### Figure 1. Changes to Recommendations Made for Pathogenic Germline Genetic Variants (PGV)-Positive Patients

Clinicians made a total of 132 changes to clinical management recommendations for 58 PGV-positive patients specifically according to germline genetic testing results. Recommendations for familial genetic testing and/or counseling are excluded from subsequent analyses (including 36 total recommendations and 4 patients for whom no new recommendations were made other than for familial testing/counseling). Changes in recommendations included those for current breast cancer (orange) or related to potential future cancers (blue), or clinician referrals (brown). The darker shades indicate in-criteria patients; the lighter shades indicate out-of-criteria patients. Clinicians did not report any changes to recommendations for radiation or endocrine treatment strategy. GC indicates genetic counseling.
and RAD51D. Recommendations for both IC and OOC patients were also made for non-breast cancer risk genes, such as MSH6 and MUTYH (monoallelic carriers) (Figure 2A). The mean number of changes to recommendations per patient was higher for IC patients compared with OOC patients for BARD1, BRCA2, CHEK2, PALB2, RAD51D, and RECQL4. For ATM, MITF, and NBN, more changes per patient were made for OOC patients (Figure 2B).

Clinician-Reported Impact of Testing for Patients
Clinicians were asked to report their assessment of how genetic testing impacted patients’ health outcomes at the time of reporting. For 28 of 41 (68.3%) and 23 of 40 (57.5%) IC and OOC PGV-positive patients assessed, respectively, testing was reported to positively impact the patients’ health outcomes in terms of being beneficial to disease management and/or patient well-being at the time of CRF completion (Table 2).

Patients With Variants of Uncertain Significance or Negative Results
Clinician-reported informative data on clinical management changes were available for 509 patients with variants of uncertain significance (VUS) and 349 patients with negative results. Clinicians managed VUS and negative results similarly, in that they did not make any changes to clinical recommendations in most cases (492 [96.6%] cases for both VUS and 345 [98.9%] negative). There were more changes to clinical recommendations made for patients with VUS compared with those with negative results (17 vs 4) (Table 2). However, many of the changes reported for both groups were for more conservative surgical strategies (e.g., bilateral mastectomies were deemed unnecessary). Overall, physicians indicated that health outcomes were positively impacted by test results in 186 of 508 VUS patients (36.6%) and 122 of 349 (35.0%) of negative patients (Table 2).

Discussion
We previously demonstrated in a setting of community and academic sites that restrictive germline genetic testing guidelines led to approximately half of all patients with breast cancer with PGVs being missed. In the present cohort study, we analyzed the changes resulting from testing on clinician

Table 3. Characteristics of Patients With Pathogenic or Likely Pathogenic Germline Variants and Corresponding Impact of Testing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No./total No. (%)</th>
<th>≥1 changes to clinical recommendations</th>
<th>Clinicians reported a positive impact of testing on health outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC</td>
<td>OOC</td>
<td>Total</td>
</tr>
<tr>
<td>Self-reported race and ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian, Black/African American, Hispanic, Native American/Alaskan Native, or Native Hawaiian/other Pacific Islander</td>
<td>9/9 (100.0)</td>
<td>5/8 (62.5)</td>
<td>14/17 (82.4)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>22/27 (81.5)</td>
<td>17/25 (68.0)</td>
<td>39/52 (75.0)</td>
</tr>
<tr>
<td>Not provided/other</td>
<td>0/1</td>
<td>1/1 (50.0)</td>
<td>1/2 (50.0)</td>
</tr>
<tr>
<td>Age at initial breast cancer diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>13/15 (86.7)</td>
<td>NA</td>
<td>13/15 (86.7)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>18/22 (81.8)</td>
<td>23/43 (57.6)</td>
<td>41/56 (73.2)</td>
</tr>
<tr>
<td>≤65</td>
<td>29/32 (90.6)</td>
<td>14/22 (63.6)</td>
<td>43/54 (79.6)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>3/6 (50.0)</td>
<td>10/12 (83.3)</td>
<td>13/18 (72.2)</td>
</tr>
<tr>
<td>Time of breast cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New diagnosis within 12 mo of testing</td>
<td>24/29 (82.8)</td>
<td>19/28 (67.9)</td>
<td>43/57 (75.4)</td>
</tr>
<tr>
<td>Previous diagnosis &gt;12 mo before testing</td>
<td>7/8 (87.5)</td>
<td>4/6 (66.7)</td>
<td>11/14 (78.6)</td>
</tr>
</tbody>
</table>

Abbreviations: IC, in-criteria; OOC, out-of-criteria.

a Denominators indicate number of patients with informative (not blank) responses from clinicians regarding changes to clinical recommendations made or impact of testing on health outcomes.

b Excludes patients who had no recommendations other than familial genetic testing or counseling.

c Other includes self-reported non-Hispanic multiracial and Ashkenazi Jewish ancestry.
decision-making and overall patient outcomes assessed during the study. For most IC and OOC patients, clinicians recommended at least 1 change to clinical management according to testing results, meaning that OOC patients would not have received the same genetic data-informed care as that provided for IC patients.

Germline testing in patient care is becoming increasingly relevant as precision therapies emerge. PARP inhibitors olaparib and talazoparib were the first molecular-targeted therapies approved for patients with metastatic breast cancer who carry germline *BRCA1/2* variants. \(^2\) The

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**Figure 2. Pathogenic Germline Variant (PGV)-Positive Patients by Gene and Treatment Management**

A, All patients grouped by gene and breast cancer risk

<table>
<thead>
<tr>
<th>Penetrance (IC/OOC patients)</th>
<th>Treatment management</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Change</td>
</tr>
<tr>
<td>Moderate</td>
<td>No change or blank response</td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

Breast cancer predisposition genes

- BRCA1
- BRCA1/MUTYH
- BRCA2
- PALB2
- TP53
- ATM
- ATM/NTHL
- CHEK2
- NF1
- RAD51C
- RAD51C/WRN
- RAD50
- DIS3L2
- FH (p.Lys477 dup)
- MITF
- MSH6
- MUTYH
- MUTYH/NTHL
- RB1
- RECQL4
- RET
- VHL

Nonbreast cancer risk genes

- BLMP
- DIS3L2
- FH (p.Lys477 dup)
- MITF
- MSH6
- MUTYH
- MUTYH/NTHL
- RB1
- RECQL4
- RET
- VHL

Changes to clinical management recommendations based on genetic testing results

A, All 82 PGV-positive patients grouped according to gene and breast cancer risk are shown. The solid icons represent the 58 patients for whom at least 1 change in clinical recommendation as a result of genetic testing was made. Outlined icons represent the 24 patients for whom no changes were recommended, or no response was provided. Darker shades indicate in-criteria patients; lighter shades indicate out-of-criteria patients. B, Mean number of changes to clinical management recommendations made according to genetic testing results per patient according to the gene(s) harboring PGVs. Patients that had no new recommendations other than familial genetic testing or counseling are excluded. Penetrance of breast cancer predisposition genes is indicated as: high (orange), moderate (gray), low-penetrance/recessive (blue).

- Breast cancer predisposition genes were defined according to the National Comprehensive Cancer Network guidelines at the time of the study. \(^9\)
- Monoallelic variants in genes associated with autosomal recessive cancer risk syndromes.
- Possibly mosaic variant.
OlympIA trial demonstrated the efficacy of olaparib in improving overall and progression-free survival in patients with early-stage breast cancer. Olaparib and niraparib are now being investigated in clinical trials for non-\textit{BRCA1/2} DNA repair genes, which require germline or somatic testing to determine eligibility. Obtaining genetic testing results earlier in a diagnosis is now more important than ever for patients when considering the most up-to-date clinical management options or participating in a clinical treatment trial. Due, in part, to the success of PARP inhibitors, universal germline genetic testing for patients with breast cancer is gaining acceptance.

In 2019, the American Society of Breast Surgeons released a consensus guideline to recommend that genetic testing be offered to all patients with a personal history of breast cancer. In response, some clinicians have suggested that universal testing would entail challenges and potential harms; therefore, guidelines should be revised to include women with breast cancer at age of diagnosis of 60 years or younger or 65 years or younger, but still exclude older patients with no family history. Yet in the studies cited pointing to potentially inappropriate mastectomies or unnecessary oophorectomies performed for moderate-risk variants, the majority of patients described were aged 50 years or younger. In the present study, PGV prevalence was distributed similarly across all age groups, and for most patients older than 65 years, clinicians reported a change in clinical recommendation made and positive impact on patient health outcome as a result of testing. These data are consistent with previous findings that the prevalence of PGVs in patients with breast cancer up to 65 years or postmenopausal patients (aged 59-70 years) is sufficiently high to warrant testing even in the absence of family history. Limiting testing to patients aged 65 years or younger can exacerbate the already vast underrepresentation of older adults in clinical trials. Similarly, denying patients access to precision therapy based solely on their age seems inappropriate as life expectancy continues to increase.

Currently, the US Preventive Services Task Force recommends that all women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with \textit{BRCA1/2} PGVs be screened for genetic counseling using a risk assessment tool such as BRCAPRO, with genetic testing to follow if indicated. Despite the lower threshold currently suggested by NCCN, our data show that BRCAPRO remains limited to estimating the likelihood of \textit{BRCA1/2} variants, and is inadequate for screening patients with PGVs in other high-risk and moderate-risk genes that have NCCN recommendations for clinical management.

Clinicians in both academic and community practices demonstrated the ability to discern the clinically actionable value of PGVs from nonactionable VUS. These data agree with recent studies indicating that clinicians do not misinterpret VUS as an indication for risk-reducing interventions, as these are variants of no known clinical significance. The observation that more conservative surgical strategies were recommended for patients with VUS or negative results underscores the value of germline genetic testing in the decision to opt for more moderate treatment and follow-up recommendations. In addition, identifying PGVs in genes not associated with breast cancer predisposition can aid in screening and risk-reducing strategies for other cancers, such as colorectal and ovarian cancer for \textit{MSH6} carriers.

For OOC patients, most (68.2%) PGVs in breast cancer predisposition genes were of moderate penetrance. Our previous report presents management guidelines and clinical trial eligibility criteria that were in effect at the time of the study for these genes. Despite less established guidelines for individuals harboring other moderate-risk or low-risk variants, recommendations for these genes regarding management of breast and other cancers are available from NCCN or other published sources.

As expected, most PGVs (81.8%) in patients for whom no changes to recommendations were made were in moderate-penetrance or low-penetrance breast cancer predisposition genes. When identification of a PGV does not directly change a patient’s treatment, it should nonetheless prompt cascade testing of the patient’s relatives to identify those who will benefit from cancer surveillance and prevention protocols. In the present study, only 32% of all PGV-positive patients were reportedly referred for familial genetic counseling and/or testing. This is consistent with previous observations.
that cascade testing in clinical practice is lacking. In addition to supporting germline genetic testing for all patients with a cancer diagnosis, the recent report from the President’s Cancer Panel states that cascade testing should be offered if variants of concern are identified.

**Strengths and Limitations**

The strengths of this study include clinical practice evidence from academic and community-based practices across diverse geographical regions across the US. We evaluated the changes resulting from germline genetic testing with regards to clinical decision-making and disease management, and gauged clinicians’ assessment of the overall impact of testing on their patients’ outcomes. However, there are several limitations. First, cancer stage at diagnosis was not noted. The study sites selected were primarily breast surgery practices; thus, the patients studied were biased toward those with early-stage resectable disease. Second, the study was performed before NCCN guidelines were updated to screen patients for PARP inhibitor treatment eligibility. Third, the OOC patient representation is necessarily skewed to patients older than age 45 years, as determined by the NCCN guidelines; however, prevalence of PGVs in high-penetrance genes has been shown to be significant in women aged 60 to 65 years. Fourth, patients were not studied longitudinally to determine longer-term outcomes such as progression-free survival.

**Conclusions**

To our knowledge, this is the first prospective study to demonstrate the clinical utility of universal germline genetic testing for patients with breast cancer. These data demonstrate that clinicians assessed germline testing as positively impacting their patients’ outcomes, and underscore the obstacles that current genetic testing criteria introduce between patients and their access to precision therapy, clinical trials, and evidence-based management guidelines. Although longer-term follow-up studies are required to determine ultimate patient outcomes, these clinical decision-making and patient evaluation data are important to consider when determining the value of comprehensive germline testing for all patients with breast cancer.

**ARTICLE INFORMATION**

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Acquisition, analysis, or interpretation of data: Whitworth, Beitsch, Patel, Compagnoni, Baron, Gold, Holmes, Smith, Kinney, Grady, Clark, Barbosa, Lyons, Riley, Coomer, Curcio, Ruiz, Khan, MacDonald, Hughes, Hardwick, Heald, Munro, Nielsen, Esplin.

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Critical revision of the manuscript for important intellectual content: Whitworth, Beitsch, Patel, Rosen, Compagnoni, Baron, Brown, Gold, Holmes, Smith, Kinney, Grady, Clark, Riley, Coomer, Curcio, Ruiz, Khan, MacDonald, Hughes, Hardwick, Heald, Munro, Nielsen.

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Obtained funding: Whitworth.

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Conflict of Interest Disclosures: Dr Whitworth reported serving as CSO and Managing Partner of TME, LLC during the conduct of the study; TME LLC provides consultative and research support services for the sponsor, Invitae, and for additional diagnostic testing companies, including Myriad, Agenda, and Exact Sciences. Dr Beitsch reported being an employee and shareholder of Invitae during the conduct of the study, and reported serving on the Board of Directors of TME Breast Care Network. Dr Patel reported being an employee and shareholder of Invitae during the conduct of the study; and reported serving on the Board of Directors of TME Breast Care Network. Dr Rosen reported being managing partner and director of TME Breast Care Network. Dr Brown reported serving on the advisory board of Targeted Medical Education during the conduct of the study. Dr Gold reported receiving financial support for research staff from Targeted Medical Education during the conduct of the study; and receiving personal fees from Targeted Medical Education advisory board outside the submitted work. Dr Hughes reported receiving personal fees from Invitae, MedNeon, Ambry, Myriad, and TME during the conduct of the study; receiving honoraria from Hologic, TME, MedNeon, 23&Me, Invitae, and Ambry; having financial interest in CRA Health (Formerly Hughes RiskApps), which was acquired by Volpara in January, 2021; and being the Co-Creator of Ask2Me.Org which is freely available for clinical use and is licensed for commercial use by the Dana Farber Cancer Institute and Massachusetts General Hospital. Dr Hardwick reported receiving grants from Invitae during the conduct of the study. Dr Heald reported receiving personal fees from Invitae outside the submitted work. Dr Munro reported being an employee of Invitae and holding stock from Invitae as an employee during the conduct of the study. Dr Nielsen reported being an employee and shareholder of Invitae. Dr Esplin reported being an employee and shareholder of Invitae during the conduct of the study; and serving as a scientific advisory board member and stockholder for Taproot Health outside the submitted work. No other disclosures were reported.

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REFERENCES


**SUPPLEMENT.**

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