Clinical outcomes and Oncotype DX Breast Recurrence Score® in early-stage BRCA-associated hormone receptor-positive breast cancer

Rachel M. Layman1 | Heather Lin2 | Angelica M. Gutierrez Barrera1 | Meghan S. Karuturi1 | Clinton Yam1 | Banu K. Arun1

Abstract

Background: BRCA-associated breast cancers tend to have distinctive features compared to sporadic breast cancers; further characterization can aid in optimizing treatment.

Methods: The study evaluated a patient cohort with early-stage estrogen receptor positive, HER2 negative invasive breast cancer who had Oncotype DX Breast Recurrence Score® analysis and genetic testing for hereditary breast and ovarian cancer syndrome. Data on patients and their breast cancers with outcomes were collected and analyzed.

Results: 745 patients were included, of whom 33 had pathogenic BRCA mutations (8 BRCA1, 25 BRCA2). Patients with BRCA mutations were younger and received more adjuvant chemotherapy, but less endocrine therapy and radiation therapy. BRCA-associated breast cancers had less progesterone receptor expression, higher nuclear grade, and higher Oncotype DX Breast Recurrence Scores® with median Recurrence Score® 29, compared to 16 in cancers without mutations (p < 0.0001). Breast cancer recurrence developed in 18% of patients with BRCA mutations and 9% of patient without mutations, although multivariate analysis of relapse-free survival was not significant, HR 1.519 (95% confidence interval [CI] 0.64–3.58; p = 0.3401). After adjusting for Recurrence Score®, overall survival by BRCA status was improved HR 0.448 (95% CI 0.06–3.34; p = 0.4333).

Conclusions: BRCA-associated early-stage hormone receptor-positive breast cancers have higher Oncotype DX Breast Recurrence Score® compared to those without mutations. BRCA status did not significantly impact relapse-free survival and overall survival. Larger clinical trials are needed to further assess the findings, and if confirmed, could impact clinical management of BRCA-associated breast cancers.

Keywords

BRCA1, BRCA2, breast cancer, estrogen receptor, gene expression profiling, survival analysis
INTRODUCTION

While most breast cancers are sporadic, approximately 20% are considered to be familial and about 5%–10% develop due to a single mutation in a breast cancer susceptibility gene. Mutations in BRCA1 and BRCA2, which cause Hereditary Breast and Ovarian Cancer Syndrome (HBOC), account for around 80% of the 5%–10% of breast cancer cases related to rare mutations. Individuals with BRCA1/BRCA2 mutations have up to a 70% life-time risk of developing breast cancer and up to 45% risk of developing ovarian cancer.

Several small studies have reported differences in pathologic and clinical characteristics of both HBOC and non-BRCA familial breast cancer. Breast carcinomas arising from a BRCA1 mutation have been shown to be somewhat distinctive, more often high grade and negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2). BRCA1-associated breast cancers are more likely to be invasive ductal type versus invasive lobular, tend to have a high mitotic rate and more frequently manifest a pattern of lymphocytic infiltration. In contrast, BRCA2-associated breast cancers are not well-defined overall.

BRCA2-associated breast cancers are more likely to be hormone receptor positive (HR+) and have lower tumor grade and mitotic counts compared to BRCA1-associated breast cancers. Women with BRCA2 mutations have an increased risk of invasive lobular breast cancer, as opposed to BRCA1 mutation carriers. While the observations would be expected to have strong implications on prognosis, data on BRCA-associated (BRCAm) breast cancers are inconsistent. Most studies describing characteristics of BRCAm cancers are small and descriptive involving data from multiple institutions.

The Oncotype DX Breast Recurrence Score® test (Exact Sciences Corporation) is a 21 gene expression assay that provides prognostic and predictive information for patients with early-stage HR+ breast cancer. Higher Recurrence Score® results (RS) are associated with worse prognosis and greater benefit from chemotherapy. As BRCAm breast cancers appear to have inherent differences from those without BRCA mutations (BRCAwt), it is important to understand the interaction between BRCAm breast cancers and RS, as this can impact systemic therapy treatment decision making.

Herein, we report the outcomes and characteristics of patients and breast cancers, including RS, in a large cohort of patients with BRCAm and BRCAwt early-stage HR+, HER2-negative breast cancer.

MATERIALS AND METHODS

Patient population

Patients with invasive HR+, HER2-negative breast cancers who have had Oncotype DX Breast Recurrence Score® testing and who underwent genetic testing in the Breast Medical Oncology and the Breast Clinical Cancer Genetics Clinic at the University of Texas MD Anderson Cancer Center (MDACC) were identified from the prospectively maintained Breast Cancer and the Genetics research registries.

For patients diagnosed with more than one invasive breast cancer, only the first cancer was included in the data and analysis. Patients with ER-negative or HER2-positive breast cancers were excluded.

Assessment

The following data were collected and analyzed as part of this study: demographic information, reproductive history (age at menarche, pregnancy history, and oral contraceptive and hormonal therapy use), genetic testing results, tumor characteristics (including gene profiling, Oncotype DX Breast Recurrence Score®), family history, cancer treatment, chemotherapy treatments, and response to chemotherapy, recurrence/metastasis information and survival data. Data collection was performed through August 28, 2020.

Informed consent and data confidentiality procedures

Patients at MDACC had previously provided consent for their data to be used for future research on protocols LAB03-0479, LAB99-402, and 2003–321. In addition, waiver of consent for the study was provided by the MDACC Institutional Review Board since this retrospective study involves no more than minimal risk, does not adversely affect the rights or welfare of the patients, and otherwise could not reasonably be carried out.

The information was kept in a database on a password-protected computer in a secure office and the data was only accessible to the study investigators. After the clinical information was obtained, all patient identifying information were deleted and replaced by unique study numbers in the analytic file. No patient identifiers were used when analyzing or reporting the data and were deleted after data analysis.
3 | STATISTICAL ANALYSIS

The study objectives were to assess the associations between BRCA status and recurrence-free survival (RFS) and overall survival (OS) among all patients, and to assess the association between BRCA status and the RS among the patients who underwent Oncotype DX Breast Recurrence Score® testing.

Univariate analyses were performed to evaluate the associations of patient’s demographic and clinical characteristics, including the RS, with BRCA mutation status, using chi-square tests for categorical variables and t tests/ANOVA or the counterparts of the non-parametric approaches (Wilcoxon rank-sum or Kruskal–Wallis for continuous variables). The distributions of RFS and OS were estimated by the Kaplan–Meier method. Log-rank test was performed to test the differences in survival between groups. Regression analyses of survival data based on the Cox proportional hazards model were conducted on RFS defined as from the time of diagnosis to the time of local recurrence, distant metastasis, or death, whichever occurred first, and OS defined as from the time of diagnosis to the time of death. Time was censored at the last contact at which the patient was known to be recurrence-free for RFS and the last time the patient was known to be alive for OS. SAS version 9.4 and S-Plus version 8.2 were used to carry out the computations for all analyses.

4 | RESULTS

4.1 | Patients

A total of 745 patients met the eligibility criteria and were included in the analysis. Patient characteristics are shown in Table 1. Thirty-three (4.4%) patients had identified pathogenic BRCA1 (8) or BRCA2 (25) germline mutations. The majority of patients (57%) were under the age of 50 at breast cancer diagnosis. A family history of breast cancer was reported in 67% of patients and 16% had a family history of ovarian cancer.

All patients had ER+ breast cancer, and most were also PR positive. Most cancers were Stage I (66%) with only 15% having documented positive lymph nodes.

| Patient characteristics (n = 745) | n (%) |
|----------------------------------|-------|
| BRCA status                      |       |
| BRCA1                            | 8 (1.1)|
| BRCA2                            | 25 (3.3)|
| Negative                         | 712 (95.6)|
| Age at diagnosis                 |       |
| ≤50                              | 423 (56.8)|
| >50                              | 322 (43.2)|
| Race                             |       |
| White                            | 519 (69.7)|
| Black                            | 36 (4.8)|
| Hispanic                         | 126 (16.9)|
| Asian                            | 52 (7.0)|
| Other                            | 12 (1.6)|
| Breast cancer, 1st degree relative |     |
| 0                                | 486 (65.2)|
| ≥1                               | 199 (26.7)|
| Unknown                          | 60 (8.1)|
| Breast Cancer Family Hx          |       |
| 0                                | 182 (24.4)|
| ≥1                               | 501 (67.3)|
| Unknown                          | 62 (8.3)|
| Ovarian cancer, 1st degree relative |     |
| 0                                | 649 (87.1)|
| 1                                | 36 (4.8)|
| Unknown                          | 60 (8.1)|
| Ovarian Cancer Family Hx         |       |
| 0                                | 564 (75.7)|
| ≥1                               | 119 (16.0)|
| Unknown                          | 62 (8.3)|

Abbreviation: Hx, history.
Over 90% of the patients received endocrine therapy, while approximately 1/3 received chemotherapy. Cancer characteristics and treatment are summarized in Table 2.

### Association of BRCA status on patient and cancer characteristics

No statistically significant difference in baseline patient characteristics was observed between BRCAm or BRCAwt patients \((p \geq 0.21)\), however, there were non-significant numerical differences. BRCAm patients were younger with a median age at diagnosis 45 compared to 48 years, had more diverse race, and more family members with ovarian cancer. Similarly, tumor characteristics were not significantly different \((p \geq 0.066)\). More patients with BRCA mutations had PR-negative cancers, 18% versus 10%, and higher nuclear grade. Only 1 BRCAm cancer was nuclear grade 1. Conversely, treatment differed significantly among the two groups. Over half of the BRCAm patients received chemotherapy, compared to approximately 1/3 of BRCAwt patients \((p = 0.009)\). BRCAm patients were less likely to receive adjuvant endocrine therapy \((82\% \text{ vs. } 92\%, p = 0.0049)\) or radiation therapy \((24\% \text{ vs. } 49\%, p = 0.0065)\). See Table 3.

### Recurrence Score® results

The impact of patient and tumor characteristics on the RS was evaluated (Table 4). BRCAm patients had significantly higher RS than those without mutation. The median RS was 29 with BRCAm and 16 with BRCAwt, \(p < 0.0001\). Cancers that were PR negative or with higher nuclear grade also had higher RS \((p < 0.0001)\).

### Patient outcomes

Patients in the study were followed for median of 5.9 years. RFS was inferior in BRCAm patients with RFS events in 6/33 (18.18%) compared to BRCAwt patients who had 63/712 (8.85%) events (Figure 1). However, in
| BRCA          | Negative | Positive | p-value |
|--------------|----------|----------|---------|
| Age at diagnosis |          |          |         |
| ≤50          | 401 (56.3%) | 22 (66.7%) | 0.24   |
| >50          | 311 (43.7%) | 11 (33.3%)  |         |
| Race         |          |          |         |
| White        | 500 (70.2%) | 19 (57.6%) | 0.22   |
| Hispanic     | 120 (16.9%) | 6 (18.2%)  |         |
| Black        | 33 (4.6%)  | 3 (9.1%)   |         |
| Asian        | 48 (6.7%)  | 4 (12.1%)  |         |
| Other        | 11 (1.5%)  | 1 (3%)     |         |
| Breast cancer, 1st degree relative |          |          |         |
| 0            | 471 (71.1%) | 15 (65.2%) | 0.54   |
| ≥1           | 191 (28.9%) | 8 (34.8%)  |         |
| Breast Cancer Family Hx |          |          |         |
| 0            | 174 (26.4%) | 8 (34.8%)  | 0.34   |
| ≥1           | 486 (73.6%) | 15 (65.2%) |         |
| Ovarian cancer, 1st degree relative |          |          |         |
| 0            | 628 (94.9%) | 21 (91.3%) | 0.27   |
| ≥1           | 34 (5.1%)  | 2 (8.7%)   |         |
| Ovarian Cancer Family Hx |          |          |         |
| 0            | 547 (82.9%) | 17 (73.9%) | 0.2651 |
| ≥1           | 113 (17.1%) | 6 (26.1%)  |         |
| Progesterone receptor |          |          |         |
| POS          | 641 (90.2%) | 27 (81.8%) | 0.12   |
| NEG          | 70 (9.8%)  | 6 (18.2%)  |         |
| Stage        |          |          |         |
| I            | 468 (66.3%) | 24 (72.7%) | 0.40   |
| II           | 226 (32.0%) | 8 (24.2%)  |         |
| III          | 12 (1.7%)  | 1 (3%)     |         |
| T stage      |          |          |         |
| T0           | 0 (0%)    | 1 (3%)    | 0.24\(^b\) |
| T1           | 515 (72.9%) | 27 (81.8%) |         |
| T2           | 172 (24.4%) | 4 (12.1%)  |         |
| T3           | 18 (2.5%)  | 1 (3%)     |         |
| T4b          | 1 (0.1%)  | 0 (0%)     |         |
| N stage      |          |          |         |
| N0           | 597 (84.6%) | 27 (81.8%) | 0.33\(^c\) |
| N1           | 103 (14.6%) | 4 (12.1%)  |         |
| N2           | 5 (0.7%)   | 1 (3%)     |         |
| NX           | 1 (0.1%)   | 1 (3%)     |         |
| Nuclear grade|          |          |         |
| I            | 89 (13.0%) | 1 (3.1%)  | 0.066  |
| II           | 444 (64.8%) | 19 (59.4%) |         |
| III          | 152 (22.2%) | 12 (37.5%) |         |
| Lymphatic invasion |        |          |         |
| NEG          | 573 (84.1%) | 26 (83.9%) | 1.00   |
| POS          | 108 (15.9%) | 5 (16.1%)  |         |
| Vascular invasion |       |          |         |
| NEG          | 574 (84.3%) | 26 (83.9%) | 1.00   |
| POS          | 107 (15.7%) | 5 (16.1%)  |         |
| Adjuvant Chemo |       |          |         |
| Y            | 232 (32.6%) | 18 (54.5%) | 0.0090 |
| N            | 480 (67.4%) | 15 (45.5%) |         |
| Adjuvant Endocrine Tx |     |          |         |
| Y            | 653 (91.7%) | 27 (81.8%) | 0.0489 |
| N            | 59 (8.3%)  | 6 (18.2%)  |         |
| Radiation Tx |       |          |         |
| Y            | 345 (48.5%) | 8 (24.2%)  | 0.0065 |
| N            | 367 (51.5%) | 25 (75.8%) |         |

The bold values indicate statistically significant.

Abbreviations: Chemo, chemotherapy; Hx, history; NEG, negative; POS: positive; Tx, treatment.

\(^a\)Missing or unknown data was excluded from this analysis.

\(^b\)The patients with T0 or T4b tumor were not included in the comparison between the BRCA positive and BRCA negative patients.

\(^c\)The two patients with NX tumor were not included in the comparison between the BRCA positive and BRCA negative patients.
**Table 4** Association between patient characteristics and Oncotype DX Breast Recurrence Score<sup>a</sup>

| Characteristic                  | n   | Range | Mean (SD) | Median | p-value  |
|---------------------------------|-----|-------|-----------|--------|----------|
| **BRCA**                        |     |       |           |        |          |
| NEG                             | 712 | 0–71  | 18.2 (10.6) | 16.0   | <0.0001  |
| POS                             | 33  | 10–60 | 28.0 (12.0) | 29.0   |          |
| **Lymphatic invasion**          |     |       |           |        |          |
| NEG                             | 599 | 0–71  | 18.8 (11.0) | 16.0   | 0.46     |
| POS                             | 113 | 0–47  | 17.2 (8.4)  | 16.0   |          |
| **Vascular invasion**           |     |       |           |        |          |
| NEG                             | 600 | 0–71  | 18.8 (11.0) | 16.0   | 0.53     |
| POS                             | 112 | 0–47  | 17.3 (8.4)  | 16.5   |          |
| **Nuclear grade**               |     |       |           |        |          |
| I                               | 90  | 0–35  | 14.7 (6.5)  | 13.5   | <0.0001  |
| II                              | 463 | 0–52  | 16.0 (7.7)  | 16.0   |          |
| III                             | 164 | 5–71  | 28.0 (14.0) | 26.0   |          |
| **Pathologic stage**            |     |       |           |        |          |
| I                               | 492 | 0–56  | 18.5 (10.1) | 16.0   | 0.54     |
| II                              | 234 | 0–71  | 18.8 (11.9) | 16.0   |          |
| III                             | 13  | 13–44 | 20.7 (9.0)  | 18.0   |          |
| **T stage**                     |     |       |           |        |          |
| T0<sup>b</sup>                  | 1   | 26–26 | 26.0 (NA)  | 26.0   | 0.8<sup>a</sup> |
| T1                              | 542 | 0–56  | 18.4 (9.9)  | 16.0   |          |
| T2                              | 176 | 0–71  | 19.6 (13.0) | 16.0   |          |
| T3                              | 19  | 0–32  | 15.9 (8.4)  | 17.0   |          |
| T4b<sup>b</sup>                 | 1   | 16–16 | 16.0 (NA)  | 16.0   |          |
| **N stage**                     |     |       |           |        |          |
| N0                              | 624 | 0–71  | 18.8 (11.0) | 16.0   | 0.35<sup>b</sup> |
| N1                              | 107 | 0–38  | 17.0 (8.4)  | 17.0   |          |
| N2                              | 6   | 13–44 | 23.5 (11.3) | 22.0   |          |
| NX<sup>c</sup>                  | 2   | 17–20 | 18.5 (2.1)  | 18.5   |          |
| **Progesterone receptor**       |     |       |           |        |          |
| NEG                             | 76  | 11–67 | 33.3 (13.9) | 31.0   | <0.0001  |
| POS                             | 668 | 0–71  | 17.0 (9.0)  | 16.0   |          |
| **Age at diagnosis**            |     |       |           |        |          |
| ≤50                             | 423 | 0–67  | 18.2 (10.2) | 16.0   | 0.28     |
| >50                             | 322 | 0–71  | 19.2 (11.5) | 17.0   |          |
| **Race**                        |     |       |           |        |          |
| White                           | 519 | 0–67  | 18.3 (10.5) | 16.0   | 0.097    |
| Hispanic                        | 126 | 0–71  | 19.1 (12.0) | 17.0   |          |
| Black                           | 36  | 1–56  | 22.9 (12.2) | 22.0   |          |
| Asian                           | 52  | 0–40  | 18.4 (9.0)  | 16.5   |          |
| Other                           | 12  | 1–42  | 18.2 (12.1) | 16.5   |          |
| **Breast cancer, 1st degree relative** |     |       |           |        |          |
| 0                               | 486 | 0–67  | 18.8 (10.6) | 17.0   | 0.37     |
| ≥1                              | 199 | 0–71  | 18.5 (11.8) | 16.0   |          |
| **Breast cancer Family Hx**     |     |       |           |        |          |
| 0                               | 182 | 0–67  | 18.3 (10.3) | 16.5   | 0.76     |
| ≥1                              | 501 | 0–71  | 18.9 (11.2) | 16.0   |          |
| **Ovarian cancer, 1st degree relative** |     |       |           |        |          |
| 0                               | 649 | 0–71  | 18.7 (10.9) | 16.0   | 0.78     |
| ≥1                              | 36  | 1–60  | 18.9 (11.1) | 17.0   |          |
| **Ovarian cancer Family Hx**    |     |       |           |        |          |
| 0                               | 564 | 0–71  | 18.7 (10.9) | 16.0   | 0.41     |
| ≥1                              | 119 | 0–60  | 19.1 (11.1) | 17.0   |          |

The bold values indicate statistically significant.

**Abbreviations:** Hx, history; NEG, negative; POS, positive; SD, standard deviation.

<sup>a</sup>The patients with T0 or T4b tumor were not included in the comparison between the BRCA positive and BRCA negative patients.

<sup>b</sup>The two patients with NX tumor were not included in the comparison between the BRCA positive and BRCA negative patients.

<sup>c</sup>Missing or unknown data was excluded from this analysis.
multivariate analysis, adjusting for RS and receipt of endocrine therapy, RFS by BRCA status was not statistically significant with HR 1.52 (95% confidence interval [CI] 0.64–3.58; p = 0.3401). Lower RS was associated with improved RFS (Figure 2).

BRCAm patients had a small improvement in OS with 1/33 (3.03%) deaths compared to BRCAwt patients who had 29/712 (4.07%) deaths (Figure 3). On univariate analysis, only RS had a statistically significant impact on OS. After adjusting for RS, the difference in OS by BRCA status was not statistically significant with HR 0.448 (95% CI 0.06–3.34, p = 0.4333). However, lower RS was again associated with improved OS (Figure 4).

5 | DISCUSSION

This study evaluated differences between early-stage HR+, HER2-negative breast cancers among patients with and without germline BRCA mutations. We demonstrated that BRCAm breast cancers are associated with higher Oncotype DX Breast Recurrence Scores®, which is consistent with other reports.17–19 To our knowledge, this is the first report that also includes survival data. In the overall population, lower RS is associated with improved OS. Of interest, BRCAm patients had a small numerical improvement in OS compared to BRCAwt patients. However, the improved OS was not statistically significant

**FIGURE 1** Recurrence-free survival by BRCA mutation status legend: Kaplan–Meier curve displaying recurrence-free survival (RFS) by the presence or absence of a germline BRCA1 or BRCA2 mutation. E/N, number of events/total number of patients

**FIGURE 2** Recurrence-free survival by Oncotype DX recurrence score. Kaplan–Meier curve displaying recurrence-free survival (RFS) by high or low Oncotype DX Breast Recurrence Score® with median of 16 used as the cutoff. E/N, number of events/total number of patients
after adjusting for RS, demonstrating an HR of 0.448 but a wide confidence interval. The small number of BRCAm patients may have affected the results.

Use of RS to aid in clinical decision making is part of routine clinical care and has been validated as both a prognostic and predictive tool for early-stage HR+ breast cancer.11,12 The positive association of higher RS in BRCAm cancers provides further evidence that BRCAm breast cancers have distinct characteristics compared to BRCAwt. Cancers with BRCA1 and BRCA2 mutations have homologous recombination deficiency resulting in error-prone repair of double-strand DNA breaks and overall genetic instability.20 Accordingly, BRCA-associated breast cancers are more sensitive to DNA-damaging agents21 and may be biologically primed to receive greater benefit from adjuvant chemotherapy. Also, genetic instability may render the cancers more likely to develop resistance mechanisms to endocrine therapy. Better understanding of the biology of BRCAm cancers is crucial to optimizing management and thereby improving outcomes.

The data suggest that HR+ BRCAm cancers are more likely to be PR negative and have a higher nuclear grade, properties that may suggest more aggressive cancers that are less responsive to endocrine therapy. Similarly, in the entire study population, PR negative and higher nuclear grade cancers had higher RS. Our study demonstrated that lower RS is associated with significantly better outcomes, including RFS and OS. Since patients
with high RS breast cancers benefit from chemotherapy, it is possible that BRCAm cancers may be more likely to benefit from chemotherapy. If this finding is confirmed, it would have important implications for adjuvant treatment decision making for BRCAm patients. Treating physicians may be more inclined to order Oncotype DX Breast Recurrence Score® testing before making the decision to omit chemotherapy for BRCAm breast cancers. To our knowledge, analysis of the utilization of RS in BRCAm patients is not available, however, such data would be of interest.

The study included patients with early-stage HR+ breast cancer who had genetic testing. Of the 745 patients included in the patient cohort, only 33 had a BRCA1 or BRCA2 mutation. Given the propensity for triple-negative breast cancer with BRCA1 mutations, as anticipated, most of the identified mutations were in BRCA2; therefore, the findings may be less applicable to BRCA1-associated breast cancers. The treatments administered differed significantly in patients with BRCA mutations compared to those without. Chemotherapy was administered more frequently in BRCAm patients, which is consistent with higher observed RS. However, endocrine therapy was given less often. It is possible that BRCAm breast cancers, especially those that are BRCA1, had lower levels of ER expression impacting the decision to proceed with endocrine therapy, however, this data is not available. BRCAm patients also received less radiation. While the surgical procedure performed for each patient is not known, it is likely that BRCAm patients were more inclined to choose mastectomy over breast conservation given the higher risk for second primary breast cancer. Most of the breast cancers were lymph node-negative stage I or stage II, which would not require radiation if mastectomy was performed.

Despite the large study cohort, the study results are limited by the small number of patients with BRCA mutations. The study population is composed of patients who underwent a genetics evaluation, and as such, the patients are young with more than half under the age of 50, and most patients had a family history of breast cancer. While the results may not be applicable to the average woman with HR+ breast cancer, the BRCAwt population in our study is likely to be better matched to the BRCAm patients than the general early-stage HR+ population. Additionally, intensified screening, such as breast MRI, is recommended for BRCAm patients per NCCN guidelines,22 and it is possible that this additional screening could have confounded the results. The small number of BRCAm patients may have limited the ability to detect differences in some of the variables evaluated as many were numerically different but not statistically significant.

Even with the limitations of a small BRCAm cohort, a statistically significant and clinically relevant increase in RS was detected in patients with BRCA1/BRCA2 mutations compared to those without and is substantiated by other reports.17–19 This consequential finding should be further evaluated in larger studies. Given the biological differences between BRCAm and BRCAwt breast cancers, there is also concern that BRCAm patients may have a worse prognosis without chemotherapy even with a low RS, but currently, available data do not clearly validate this theory.17,23 Larger studies to evaluate if RS in BRCAm patients provides prognostic and predictive value similar to that observed in the general population are needed to further optimize therapy.

CONFLICT OF INTEREST
Rachel M. Layman: Research support paid to the institution from Eli Lilly, Novartis, Pfizer, GlaxoSmithKline, Puma, Zentalis, and Celcuity. Consulting fees from Eli Lilly, Novartis, Pfizer and Celcuity, Heather Lin: nothing to disclose, Angelica M. Gutierrez Barrera: nothing to disclose, Meghan Sri Karuturi: Consulting fees from Eli Lilly and Pfizer, Clinton Yam: Research support paid to the institution from Astra Zeneca, AbbVie, Invitae. Nonpaid steering committee member for AbbVie.

AUTHOR CONTRIBUTIONS
Rachel M. Layman: Data analysis and interpretation, writing – original draft, and writing—review and editing. Heather Lin: Data acquisition, statistical analysis, data interpretation, writing—original draft, and writing—review and editing. Angelica M. Gutierrez Barrera: Design, data acquisition, data interpretation, writing—review and editing. Meghan Sri Karuturi: Data interpretation, writing—review and editing. Clinton Yam: Data interpretation, writing—review and editing. Banu K. Arun: Conception and design, data acquisition, data analysis and interpretation, writing—review and editing.

PRECIS FOR USE IN THE TABLE OF CONTENTS
This study demonstrates that early-stage BRCA-associated hormone receptor-positive breast cancers have higher Oncotype DX Breast Recurrence Score® results, less progesterone receptor expression and higher nuclear grade compared to those without BRCA mutations, however, relapse-free survival and overall survival were not significantly different when adjusting for Recurrence Score®. Further studies are warranted to further understand the impact of germline BRCA mutations on tumor characteristics and outcomes to further guide optimal selection of adjuvant systemic therapy in this patient population.
DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID
Rachel M. Layman https://orcid.org/0000-0002-8663-0331
Angelica M. Gutierrez Barrera https://orcid.org/0000-0002-8582-8186
Meghan S. Karuturi https://orcid.org/0000-0001-8795-3901

REFERENCES
1. Arun BK, Strong LC. Breast cancer genetic syndromes. In: Singletary SER GL, Hortobagyi GN, eds. Advanced Therapy of Breast Disease. BC Decker, Inc; 2004:75-83.
2. Stoppa-Lyonnet D, Ansquer Y, Dreyfus H, et al. Familial invasive breast cancers: worse outcome related to BRCA1 mutations. J Clin Oncol. 2000;18:4053-4059.
3. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317:2402-2416.
4. Chappuis PO, Nethercot V, Foulkes WD. Clinico-pathological characteristics of BRCA1- and BRCA2-related breast cancer. Semin Surg Oncol. 2000;18:287-295.
5. Atchley DP, Albharracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol. 2008;26:4282-4288.
6. Lakhani SR, Jacquemier J, Sloane JP, et al. Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst. 1998;90:1138-1145.
7. Da Silva L, Lakhani SR. Pathology of hereditary breast cancer. Mod Pathol. 2010;23(Suppl 2):S46-S51.
8. Armes JE, Trute L, White D, et al. Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2 mutation carriers: a population-based study. Cancer Res. 1999;59:2011-2017.
9. Yadav S, Hu C, Nathanson KL, et al. Germline pathogenic variants in cancer predisposition genes among women with invasive lobular carcinoma of the breast. J Clin Oncol. 2021;39:3918-3926.
10. Bordeleau L, Panchal S, Goodwin P. Prognosis of BRCA-associated breast cancer: a summary of evidence. Breast Cancer Res Treat. 2010;119:13-24.
11. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24:3726-3734.
12. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.
13. Woolson RF, Clarke WR. Statistical Methods for the Analysis of Biomedical Data. 2nd ed. John Wiley & Sons; 2002.
14. Kaplan EL, Meier P. Nonparametric estimator from incomplete observations. J Am Stat Assoc. 1958;53:457-481.
15. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966;50:163-170.
16. Cox DR. Regression models and life tables (with discussion). J R Statist Soc B. 1972;34:187-220.
17. Blanter J, Zimmerman B, Tharakan S, Ru M, Cascetta K, Tiersten A. BRCA mutation association with recurrence score and discordance in a large oncoType database. Oncology. 2020;98:248-251.
18. Halpern N, Sonnenblick A, Uziely B, et al. Oncotype DX recurrence score among BRCA1/2 germline mutation carriers with hormone receptors positive breast cancer. Int J Cancer. 2017;140:2145-2149.
19. Shah PD, Patil S, Dickler MN, Offit K, Hudis CA, Robson ME. Twenty-one-gene recurrence score assay in BRCA-associated versus sporadic breast cancers: differences based on germline mutation status. Cancer. 2016;122:1178-1184.
20. Turner N, Tutt A, Ashworth A. Hallmarks of ‘BRCAness’ in sporadic cancers. Nat Rev Cancer. 2004;4:814-819.
21. Kennedy RD, Quinn JE, Mullan PB, Johnston PG, Harkin DP. The role of BRCA1 in the cellular response to chemotherapy. J Natl Cancer Inst. 2004;96:1659-1668.
22. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2021;19:77-102.
23. Narod SA, Metcalfe K, Lynch HT, et al. Should all BRCA1 mutation carriers with stage I breast cancer receive chemotherapy? Breast Cancer Res Treat. 2013;138:273-279.

How to cite this article: Layman RM, Lin H, Gutierrez Barrera AM, Karuturi MS, Yam C & Arun BK. Clinical outcomes and Oncotype DX Breast Recurrence Score® in early-stage BRCA-associated hormone receptor-positive breast cancer. Cancer Med. 2022;11:1474–1483. doi: 10.1002/cam4.4566