The 12-gene DCIS Score Assay and Quantitative Gene Expression for ER, PR, and HER2: Experience with 3,947 Patients

Alvarado M,1 Tan V,2 Bailey H,2 Anderson J,2 Rothney M,2 Baehner FL,1,2 Sing AP3
1University of California, San Francisco, CA; 2Genomic Health, Inc., Redwood City, CA;

Background

- The incidence of ductal carcinoma in situ (DCIS) has increased in recent decades, largely because of increases in mammography screening.1
- Women diagnosed with DCIS are at risk for local recurrence (LR), which is typically 50% DCIS and 50% invasive carcinoma.2
- Management of DCIS remains controversial.2
- Randomized studies have demonstrated that radiotherapy after excisional surgery reduces local invasive and non-invasive recurrence rates by approximately 50%, but it has not been demonstrated to prolong survival.1,2
- However, some experts argue that DCIS is over-treated without any benefit in patient overall survival.

Objective

- To examine the quantitative expression of the estrogen receptor (ER), progesterone receptor (PR), Her-2/neu receptor (HER2), and DCIS Score result across clinico-pathologic variables (patient age, specimen type, DCIS subtypes) from submitted patient samples tested in the Genomic Health laboratory.

Methods

- A total of 3,947 patient samples from December 2011 through June 2014 that passed pathology review and RT-PCR quality measures were included.
- Descriptive statistics for the DCIS Score, ER, PR, and HER2 values were obtained.
  - Low, intermediate, and high risk categories are defined as DCIS Scores of <39, 39–54, and ≥55, respectively
  - ER: ≥25 is positive
  - PR: ≥5 is positive
  - HER2: 11.5 is positive, 8.7–11.4 is equivocal, <8.7 is negative
  - DCIS Score ≥55 (High)
  - DCIS Score <39 (Low)

Results

- The DCIS Score™ result was clinically validated in a cohort of patients from the ECOG 5194 study.
- The incidence of ductal carcinoma in situ (DCIS) has increased in recent decades, largely because of increases in mammography screening.
- The majority of samples were ER/PR-positive and HER2-negative.

Table 1. Mean DCIS Score Result, ER, PR and HER2 by Age Category

<table>
<thead>
<tr>
<th>Age Category</th>
<th>N (%)</th>
<th>DCIS Score Result</th>
<th>ER (≥25 positive)</th>
<th>PR (≥5 positive)</th>
<th>HER2 (equivocal or negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ages</td>
<td>1,346 (100%)</td>
<td>39 (≥39)</td>
<td>8.7 (≥25)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>40-49</td>
<td>513 (38%)</td>
<td>39 (39–54)</td>
<td>8.2 (11.5)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>50-59</td>
<td>514 (38%)</td>
<td>39 (39–54)</td>
<td>8.2 (11.5)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>≥60</td>
<td>319 (24%)</td>
<td>39 (≥39)</td>
<td>8.7 (≥25)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
</tbody>
</table>

- A wide range of DCIS Score results, ER, PR, and HER2 was noted.
- The DCIS Score distribution was similar across age groups (p=0.40).
- The median age of all patients is 60 years with a range of 21 to 94.

Table 2. Mean DCIS Score Result, ER, PR and HER2 by Tumor and Surgery Types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>N (%)</th>
<th>DCIS Score Result</th>
<th>ER (≥25 positive)</th>
<th>PR (≥5 positive)</th>
<th>HER2 (equivocal or negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>394 (10%)</td>
<td>39 (≥39)</td>
<td>8.7 (≥25)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>Comedonecrosis</td>
<td>547 (14%)</td>
<td>39 (39–54)</td>
<td>8.2 (11.5)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>218 (6%)</td>
<td>39 (39–54)</td>
<td>8.2 (11.5)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>Papillary</td>
<td>297 (8%)</td>
<td>39 (≥39)</td>
<td>8.7 (≥25)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
<tr>
<td>Other</td>
<td>1,931 (51%)</td>
<td>39 (≥39)</td>
<td>8.7 (≥25)</td>
<td>7.0 (≥5)</td>
<td>9.9 (equivocal or negative)</td>
</tr>
</tbody>
</table>

- A wide range of DCIS Score results, ER, PR, and HER2 was noted.
- The majority of samples (81.2%) were ER-positive and PR-positive.
- Very few (approximately 1%) of DCIS cases were PR-positive.
- The majority of samples (78.4%) were ER-positive and HER2-negative.
- Approximately 8.9% of samples were ER-negative and HER2-negative.
- A total of 8.4% of DCIS cases were ER-positive with concurrent elevated levels of HER2 expression.

Conclusion

- The majority of samples submitted were ER/PR-positive and HER2-negative. A wide distribution of DCIS Score results, quantitative ER and PR was noted.
  - Similar results were observed in the DCIS Score result, ER and PR gene expression between excisions and cores.
  - DCIS with comedonecrosis (>50% comedonecrosis) had a higher average DCIS Score results than the other DCIS subtypes.
  - Papillary DCIS had lower average DCIS Score results than the other histologic subtypes.
  - There is no significant difference in DCIS Score results within age groups.
  - Strengths: Approximately 4,000 cases of DCIS were analyzed using quantitative RT-PCR from formalin fixed tissue, all cases were reviewed histologically by board-certified surgical pathologists, RT-PCR is reproducible with a wide dynamic range.
  - Limitations: No long term follow-up for patient outcomes, only one slide per case reviewed, other genes not assessed using the DCIS Score assay may be biologically important.
  - HER2 status in DCIS is an area of controversy. While the HER2 gene group is not included in the DCIS Score algorithm, the single gene expression is available. Of the ~4,000 samples processed, the estimated rate of HER2 positivity is ~13% based on the single gene expression by RT-PCR.
  - In the first two years of availability, there have been almost 4,000 samples sent for a DCIS Score assay. The distribution of scores is consistent with the clinical validation study (ECOG 5194). With the majority of patients at low risk for local recurrence. These observations reinforce the utility of the DCIS Score result and underscore the importance of the underlying biology of the disease.

References