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Clinical UM Guideline

Subject:	**Gene Expression Profiling for Managing Breast Cancer Treatment**		
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Description

This document addresses the use of genetic profiling of breast tumors to predict breast cancer recurrence and response to therapy.

Clinical Indications

Medically Necessary:

Gene expression profiling with the Oncotype DX® Breast Recurrence Score, EndoPredict®, Prosigna® Breast Cancer Prognostic Gene Signature Assay, the Breast Cancer Index℠ or MammaPrint® as a technique for managing the treatment of breast cancer is considered medically necessary when *all* of the following criteria are met:

- **A. Individual has had surgery and full pathological evaluation of the specimen has been completed; and**
- **B. Histology is ductal, lobular, mixed, or metaplastic; and**
- **C. Estrogen receptor positive (ER+), or progesterone receptor positive (PR+), or both; and**
- **D. HER2 (human epidermal growth factor receptor-2) receptor negative; and**
- **E. pN0 (node negative) or pN1mi with axillary lymph node micrometastasis less than or equal to 2 mm; and**
- **F. Any of the following:**
  1. **Tumor size 0.6-1.0 cm moderate/poorly differentiated; or**
  2. **Tumor size 0.6-1.0 cm and well-differentiated with any of the following unfavorable features: angiolymphatic invasion, or high nuclear grade, or high histologic grade; or**

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3. **Tumor greater than 1.0 cm and less than or equal to 5.0 cm; and**

G. **Chemotherapy is a therapeutic option being considered by the individual and their provider; and**

H. **No other breast cancer gene expression profiling assay has been conducted for the same tumor (for example a metastatic focus) or from more than one site when the primary tumor is multifocal.**

Use of gene expression profiling with EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, or the Breast Cancer Index as a genetic index used to assist in decisions of extending adjuvant hormonal therapy beyond 5 years of treatment is considered medically necessary when *all* of the following criteria are met:

A. **When criteria A through F above have been met; and**

B. **When the Oncotype DX Breast Recurrence Score was the initial gene expression profiling test used, and**

C. **The individual is a candidate for additional hormonal or chemotherapy.**

Not Medically Necessary:

Gene expression profiling with the Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, the Breast Cancer Index or MammaPrint as a technique of managing the treatment of breast cancer is considered not medically necessary when the criteria above have not been met.

~~**Investigational and Not Medically Necessary:**~~

Gene expression profiling as a technique of managing the treatment of ductal carcinoma in situ (DCIS) (when DCIS is the sole breast cancer histology) is considered ~~investigational and~~ not medically necessary under all circumstances.

Repeat gene expression profiling with the Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, the Breast Cancer Index, or MammaPrint for the same

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tumor (for example a metastatic focus) or from more than one site when the primary tumor is multifocal is considered ~~investigational and~~ not medically necessary.

Gene expression profiling as a technique of managing the treatment of breast cancer is considered ~~investigational and~~ not medically necessary when a gene profiling test other than the Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, the Breast Cancer Index or MammaPrint is being used, including but not limited to:

1. **BluePrint™ (also referred to as "80-gene profile")**
2. **BreastOncPX™**
3. **BreastPRS**
4. ~~**Insight® DX Breast Cancer Profile**~~
4. **Insight TNBCtype™**
5. **Mammostrat**
6. **MammaTyper®**
7. **NexCourse® Breast IHC4**
8. **NuvoSelect™ eRx 200-Gene Assay**
9. **Oncotype DX® Breast DCIS Score**
10. **PAM50 Breast Cancer Intrinsic Classifier™**
11. **SYMPHONY™ Genomic Breast Cancer Profile**
12. **TargetPrint®**
13. **TheraPrint ™**
14. **The 41-gene signature assay**
15. **The 76-gene "Rotterdam signature" assay**

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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When services may be Medically Necessary when criteria are met for Breast Cancer Index, EndoPredict, MammaPrint, Oncotype DX, or Prosigna Breast Cancer Prognostic Gene Signature Assay:

CPT	
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy Breast Cancer Index, Biotheranostics, Inc
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score Oncotype DX®, Genomic Health
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score Prosigna® Breast Cancer Assay, NanoString Technologies, Inc
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis MammaPrint®, Agendia, Inc
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score EndoPredict®, Myriad Genetic Laboratories, Inc

ICD-10 Diagnosis	
C50.011-C50.929	Malignant neoplasm of breast
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.02	Lobular carcinoma in situ of breast

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D05.80-D05.92	**Other and unspecified type of carcinoma in situ of breast**
Z17.0	**Estrogen receptor positive status [ER+]**
Z85.3	**Personal history of malignant neoplasm of breast**

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, for all other diagnoses not listed, or when the code describes a procedure or situation designated in the Clinical Indications section as not medically necessary.

~~**When services are Investigational and Not Medically Necessary:**~~
~~**For the procedure codes listed above for all other diagnoses or for situations indicated in the Position Statement section as investigational and not medically necessary.**~~

~~**CPT**~~	
~~**0045U**~~	~~**Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score The Oncotype DX® Breast DCIS Score™ Test, Genomic Health, Inc, Genomic Health, Inc**~~
~~**0153U**~~	~~**Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple-negative breast cancer clinical subtype(s) with information on immune cell involvement Insight TNBCtype™, Insight Molecular Labs**~~
~~**ICD-10 Diagnosis**~~	
	~~**All diagnoses**~~

When services are also ~~Investigational and~~ Not Medically Necessary:

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For any other type of gene expression testing for breast cancer, or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.~~indicated in the Position Statement section as investigational and not medically necessary.~~

CPT	
81599	**Unlisted multianalyte assay with algorithmic analysis [when specified as a breast cancer gene expression profile other than Oncotype DX, Prosigna, EndoPredict, MammaPrint or the Breast Cancer Index]**
84999	**Unlisted chemistry procedure [when specified as a breast cancer gene expression profile other than Oncotype DX, Prosigna, EndoPredict, MammaPrint or the Breast Cancer Index]**
0045U	**Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score** **The Oncotype DX® Breast DCIS Score™ Test, Genomic Health, Inc, Genomic Health, Inc**
0153U	**Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement** **Insight TNBCtype™, Insight Molecular Labs**
HCPCS	
S3854	**Gene expression profiling panel for use in the management of breast cancer treatment [when specified as a breast cancer gene expression profile other than Oncotype DX, Prosigna, EndoPredict, MammaPrint or the Breast Cancer Index]**
ICD-10 Diagnosis	
	All diagnoses

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Discussion/General Information

There is a continuum of disease recurrence risk among individuals with breast cancer. The continuum is based on many factors including age, the presence of various hormone receptors in tumor samples, tumor size, whether or not the cancer has spread outside the breast, and others. Clinicians have, for practical use, divided this continuum up into three risk categories: (1) low-risk, (2) intermediate-risk, and (3) high-risk. These risk categories have been used as a method of helping to determine what treatment methods to use for specific individuals.

In individuals deemed at high risk for disease recurrence, medical evidence has shown that the use of chemotherapy in addition to other treatment may provide a significant survival benefit. In low-risk individuals, the data have shown that chemotherapy, in addition to other treatment, does not provide any significant benefits. However, the available information regarding whether or not intermediate-risk individuals benefit from chemotherapy is unclear. Traditionally, treating clinicians have to balance each individual's risk of disease recurrence with the risks of chemotherapy, which include hair loss, nausea, vomiting, weakness, infection, and others.

Gene expression profiling assays have been developed to help clinicians determine which populations of intermediate-risk individuals would benefit from chemotherapy. Gene expression profiling assays measure the presence of a variety of genes which have been associated with the recurrence of breast cancer. Using these tests, in conjunction with other traditional risk assessment methods, clinicians may be able to more accurately determine which intermediate-risk individuals would benefit from chemotherapy, and which individuals would not. In this way individuals most likely to benefit from chemotherapy are identified and receive needed care, and those individuals who would not benefit are spared the unnecessary treatment and risks associated with chemotherapy without adversely affecting disease-free and overall survival outcomes.

There is a wide array of gene expression profiling assays either available or in various stages of development. These tests are intended for use in identifying those individuals at low risk of recurrence for whom adjuvant chemotherapy can be avoided. Several assays have been developed and validated using a variety of different

genes and biomarkers. However, the combined use of such assays has not been studied and it is unclear if such combined use provides additional clinical utility.

The Oncotype DX panel was developed using the candidate gene method in which a relatively small number of genes known to be involved in breast cancer progression were selected. By analyzing expression of these genes in tumor specimens, a 21-gene signature predicting recurrence was developed. Other gene profiling assays were developed by analyzing gene expression of tumor specimens on large scale microarrays with thousands of gene transcripts, followed by pattern or cluster analysis to identify a much smaller gene signature that correlated with disease recurrence. Two assays which have been compared, a 70-gene panel (MammaPrint or "Amsterdam signature") and a 76-gene panel ("Rotterdam signature"), overlap by only 3 genes, due partly to the use of different microarray platforms in developing the panels. More recent studies indicate that the two panels share 21 biological pathways, if not the same genes.

These panels were developed using banked specimens from clinical trials or cohorts for which long-term outcomes were already known. This is an efficient method for defining and establishing the clinical validity of the gene expression signatures. Clinical validity for this application is defined as evidence supporting the ability of the panel to accurately predict outcomes such as disease recurrence, disease-free survival (DFS), or overall survival (OS).

In terms of agreement among tests, Bartlett (2016) compared the results of Oncotype DX, Prosigna, MammaPrint, NexCourse Breast, and conventional IHC4 assays in 313 individuals. Additionally, subtype classification by Blueprint, MammaTyper, and Prosigna were compared. The authors reported that the five tests used showed "only modest agreement when dichotomizing results between high vs low/intermediate risk were compared. Concordant classification as either low/intermediate-risk or high-risk was noted in 119 (39.4%) tumors, and 183 (60.6%) were assigned to different risk categories by different tests. Agreement between four of five tests was seen in 94 subjects (31.1%). The subtype tests (BluePrint, MammaTyper, and Prosigna) assigned 59.5% to 62.4% of tumors to luminal A subtype. However, only 121 (40.1%) were classified as luminal A by all three tests and only 58 (19.2%) were uniformly assigned as nonluminal A. Discordant subtyping was observed in 123 (40.7%) tumors. This study highlights significant variations in tumor risk and tumor sub-type results.

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Information on specific commercially available tests is described below:

Oncotype DX

Several retrospective studies have been published that support the clinical utility of Oncotype DX in individuals with node-negative breast cancer. Paik (2006) used available, banked specimens from the randomized tamoxifen-positive chemotherapy-treated arms of National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-20 compared to the tamoxifen-only arm (samples also used as the test set to develop the assay) and correlated gene expression signatures to chemotherapy benefit. The 424 selected subjects with high recurrence score (RS ≥ 31) had an absolute increase in distant recurrence-free survival (DRFS) at 10 years of 27.6 ± 8% (mean ± standard error [SE]; p=0.01) compared to the tamoxifen-only group. Subjects with low RS (< 18) had little benefit from chemotherapy (absolute DRFS increase at 10 years, -1.1 ± 2.2%). Interaction between chemotherapy and RS was significant at p<0.05. These results suggest that the Oncotype DX RS is closely associated with the magnitude of the benefit from chemotherapy.

Also in 2006, Habel and colleagues described a retrospective case control study of 4964 subjects with node-negative invasive breast cancer. In this study, cases (n=220) were defined as subjects who died of breast cancer and controls (n=570) were described as individually matched breast cancer subjects who were alive at the time of the study. The results of the study found that the RS from Oncotype DX assay was associated with the risk of breast cancer-related death in estrogen receptor (ER) positive, tamoxifen-treated subjects. At 10 years, the risk for death in this population was found to be 2.8% in low RS individuals, 10.7% in intermediate RS individuals and 15.5% in high RS individuals. Individuals who were ER positive but not treated with tamoxifen had a risk of death of 6.2% in low RS individuals, 17.8% in intermediate RS individuals and 19.9% in high RS individuals.

In 2015, Sparano and colleagues published the results of a prospective cohort study involving 10,253 women age 18 to 75 years old. Inclusion criteria were hormone receptor positive, HER2 negative (HER2-), node-negative breast cancer with tumor size between 1.1 and 5.0 cm of any grade or 0.6 to 1.0 for intermediate to nuclear grade (or both). Using the Oncotype DX on this population, 1626 women had an RS result of 0-10,

indicating a very low risk of recurrence. This low-risk cohort prospectively received hormone therapy without chemotherapy. The authors reported that invasive disease-free 5-year survival was 93.8% (95% confidence interval [CI], 92.4-94.9), freedom from recurrence of breast cancer at a distant site at 5 years was 99.3% (95% CI, 98.7-99.6), freedom from recurrence at 5 years was 98.7% (95% CI, 97.9-99.2) and OS at 5 years was 98.0% (95% CI, 97.1-98.6). Overall recurrence rates were not significantly different when stratified by histological grade or age at diagnosis. The authors concluded that their findings supported the use of the Oncotype DX test to spare the use of chemotherapy in subjects who would otherwise receive it on the basis of clinicopathologic features.

This same group (Sparano, 2018) published the results of a prospective study involving 6711 subjects aged 18 to 75 years old with receptor and HER2 negative, node negative breast cancer with an RS of 11 to 25. Subjects were randomly assigned to treatment with either chemoendocrine therapy (n=3312) or endocrine therapy alone (n=3399). The purpose of the study was to demonstrate noninferiority of endocrine therapy alone for invasive disease-free survival. The median duration of follow-up was 90 months for disease-free survival and 96 months for overall survival. The median duration of endocrine therapy was 5.4 years, with similar durations distributions in the combined chemoendocrine therapy and endocrine therapy alone groups. The rate on non-adherence to the assigned treatment group differed significantly, with 18.4% of combined therapy subjects and 5.4% endocrine therapy alone subjects not adhering to assigned treatments.

In the intention-to-treat (ITT) population, endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive DFS (hazard ratio [HR] for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; p=0.26). Endocrine therapy was likewise noninferior to chemoendocrine therapy in the analyses of other end points, including freedom from recurrence of breast cancer at a distant site (HR for recurrence, 1.10; p=0.48), freedom from recurrence of breast cancer at a distant or local-regional site (HR for recurrence, 1.11; p=0.33), and OS (HR for death, 0.99; p=0.89). Results of the as-treated analyses were consistent with those of the ITT analysis. At 9 years in the ITT population, the rate of invasive disease-free survival was 83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group. The corresponding rates were 94.5% and 95.0% for freedom from recurrence of breast cancer at a distant site, 92.2% and 92.9% for freedom from recurrence of breast cancer at a distant or local-regional site, and 93.9% and 93.8% for overall survival. Exploratory analysis revealed

that there were significant interactions between chemotherapy treatment and age (≤ 50 vs. 51 to 65 vs. > 65 years) for invasive DFS (p=0.03) and for freedom from recurrence of breast cancer at a distant or local-regional site (p=0.02) but not at a distant site (p=0.12). The authors concluded that, among women in the study with a midrange Oncotype score (11 to 25), endocrine therapy was found to be non-inferior to chemoendocrine therapy, indicating that adjuvant chemotherapy did not provide added value. Additionally, they noted that chemotherapy was associated with some benefit for women 50 years of age or younger who had a recurrence score of 16 to 25.

Gluz (2016) reported the 3-year results from the PlanB trial, in which Oncotype DX was prospectively used to define a subset of subjects to receive endocrine-only therapy. The study enrolled 2568 subjects with node-positive or high-risk node and HER2- early breast cancer following surgical intervention. No subjects had distant metastases detected. The objective of the study was to compare the use of independent prospective central pathology review and assessment of immunohistochemistry markers vs. use of the Oncotype DX RS and local pathology. The central laboratory pathologists were blinded. In the overall study population, 18% were classified as low RS, 60.4% were intermediate RS, and 21.6% were high RS. Based on their low RS status, 348 subjects had chemotherapy omitted from their treatment regimen. There were 135 events reported during the reported trial period, with 73 (55.3%) occurring in the HER2 positive (HER2+) population, including 54 distant recurrences, 11 secondary neoplasms and local relapses, and 8 deaths without relapse. Three year DFS was significantly poorer in the high-risk RS group vs. both the low- and intermediate-risk groups (91.9% vs. 97.8% and 97.4%, respectively, p<0.001). Nodal status, central and local grade, the Ki-67 protein encoded by the MKI67 gene, estrogen receptor, progesterone receptor, tumor size, and RS were univariate prognostic factors for DFS; only nodal status, both central and local grade, and RS were independent multivariate factors.

Petkov and colleagues (2016) published the results of a large study involving 45,287 subjects with hormone receptor positive non-metastatic primary invasive breast cancer with available RS identified in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database. Node negative status was reported for 40,134 subjects, 4691 had micrometastases or up to three positive nodes, and 642 had four or more positive nodes. The Oncotype DX test was completed for 99.5% of all subjects with fewer than four positive nodes. In subjects with 4-9 positive nodes, only 1% of subjects had Oncotype DX results. The mean

follow-up for the group with node-negative disease was 39 months vs. 30 months for those with node-positive disease.

A total of 38,568 subjects were included in the primary analysis of subjects with hormone receptor positive, HER2, node-negative, non-metastatic disease who had RS results. In this group, 21,023 subjects (55%) had RS results < 18, 14,494 subjects (38%) had RS results 18-30, and 3051 subjects (8%) had RS results ≥ 31. The authors reported that breast cancer specific mortality (BCSM) was significantly associated with RS (p<0.001), with unadjusted 5-year estimates of 0.4%, 1.4%, and 4.4%, respectively. A total of 4691 subjects with positive lymph nodes had RS results; 57% had RS < 18, 36% had RS results 18-30, and 7% had RS results ≥ 31. Among this population, the 5-year BCSM was significantly different for the three RS groups (1.0%, 2.3%, and 14.3%, respectively; p<0.001).

In the analysis, RS was found to be significantly prognostic (p<0.001) for 5-year BCSM, regardless of node status. Five-year BCSM was 1.3% or lower for subjects with RS results < 18, regardless of nodal status and age group. Low BCSM was also observed for subjects > 70 years of age with RS results 18-30. However, for subjects with RS results ≥ 31, 5-year BCSM was substantially higher. Subjects with node-positive disease with RS ≥ 31 had 5-year BCSM greater than 9.5%, regardless of age. Higher RS was also associated with higher 5-year BCSM regardless of node status, race, or socioeconomic status. Multiple linear regression modeling, controlling for a variety of factors, demonstrated that the 18-30 and ≥ 31 RS groups remain at significantly higher risk of BCSM (p<0.001). RS results continued to be prognostic regardless of chemotherapy use (p=0.03). These results support the conclusions that use of the Oncotype Dx RS is a reliable prognostic tool for predicting 5-year BCSM.

The prognostic use of RS in genomically low-risk individuals who were clinically high-risk was reported by Nitz (2017). The WSG-PlanB study involved 2642 subjects with unilateral primary invasive HER2-, node-positive or negative breast cancer randomized to receive treatment with either chemotherapy (n=1970) or endocrine-only therapy (n=348). Mean follow-up was 55 months. Compliance with treatment recommendations was 95.2% for the node-negative subjects and 75.2% in the node-positive subjects. In hormone receptor positive subjects, 5-year DFS was higher in the RS < 11 and RS 12-25 groups vs. RS > 25 (93.6%, 94.3%, and 84.2% respectively; p<0.001 for comparisons with RS > 25). In subjects with RS < 11

and treated with endocrine therapy alone, 5-year DFS was 94.2%, with no significant difference between node status groups. In subjects with RS > 25, 5-year DFS was 61.7%. The 5-year OS was 99% in endocrine-treated subjects with RS < 11 vs. 97% in those with RS 12-14, and 93% for those with RS > 25 (p<0.001). The authors concluded that, "The excellent five-year outcomes in clinically high-risk, genomically low-risk (RS ≤ 11) pN0-1 patients without adjuvant chemotherapy support using RS with standardized pathology for treatment decisions in HR+ HER2 negative EBC."

Stemmer (2017a and 2017b) published two studies reporting the outcomes of subjects, both node-negative and node-positive, who underwent RS-guided treatment for ER+ HER2- breast cancer. The first report (2017a) involved 1801 ER+, HER2-, node-negative subjects with a mean follow-up of 6.2 years. The authors reported that 48.9% of subjects had RS < 18, 40.7% had RS 18-30, and 10.4% had RS ≥ 31. The lower RS groups has a higher proportion of grade 1 tumors and a lower proportion of grade 3 tumors compared to the higher RS groups. Subjects judged to be at very low risk based on clinicopathologic characteristics were reported in all RS groups. Adjuvant chemotherapy use was consistent with RS results with 1.4%, 23.7%, and 87.2% of subjects receiving chemotherapy in the < 18, 18-30 and the ≥ 31 groups, respectively. The 5-year distant recurrence rates were significantly different between groups, with 0.8%, 3.0% and 8.6% reported, respectively. In the RS ≥ 18 group, risk of distant recurrence increased with increasing tumor size. The risk of 5-year breast cancer-related death was also significantly associated with RS group, with the risk reported to be 0.0%, 0.9% and 6.2%, respectively. Multivariable regression modeling showed a significant association with RS and distant recurrence.

The second Stemmer report (2017b) involved 709 subjects with ER+, HER2- subjects with 1-3 positive nodes with a mean follow-up of 5.9 years. RS distribution was reported to be as follows: 53.4% of subjects had RS < 18; 36.4% had RS 18-30; and 10.2% had RS ≥ 31. Adjuvant chemotherapy use was consistent with RS results with 7.1%, 39.5%, and 86.1% of subjects receiving chemotherapy in the < 18, 18-30 and the ≥ 31 groups, respectively. The 5-year distant recurrence rates were significantly different between groups, with 3.2%, 6.3% and 16.9% reported, respectively. Stratified by nodal status, 5-year distant recurrence rates were 1.2% for subjects with N1mi, 4.4 for those with 1 positive node, and 5.4% for 2-3 positive nodes. The risk of 5-year breast cancer-related death was also significantly associated with RS group, with the risk reported to be 0.5%, 3.4% and 5.7%, respectively (p<0.001 between groups). In the endocrine therapy only

subjects (90.2% of subjects with RS < 18 and 59.3% with RS 18-30), the 5-year distant recurrence rates were 2.7% and 9.9%, respectively (p<0.001), and corresponding BCSM was 0.6% and 5.1% (p=0.002). The 5-year distant recurrence rate in subjects with RS ≤ 31 was stratified by adjuvant chemotherapy use. In subjects with RS < 18, the recurrence rate was 7.7% for subjects who received chemotherapy (n=27) vs. 2.9% in those who did not (n=352; p=0.245). In subjects whose RS was 18-30, the recurrence rate in the chemotherapy-treated subjects (n=102) was significantly lower than untreated subjects patients (n=156; 1.0% vs. 9.7%, p=0.019). The authors surmised that this difference was due to the subgroup of RS 26-30 and not from the 18-25 subgroup (p=0.017 and 0.058, respectively). As with the study in node-negative subjects, a multivariable regression modeling showed a significant association with RS and distant recurrence.

The use of the Oncotype DX test for individuals with node-positive breast cancer has been evaluated in several studies. Eiermann and colleagues (2012) study involved 379 subjects, 244 who were node-negative (N0) and 122 who were node-positive (N+), and evaluated how the Oncotype DX test influenced treatment decisions. The results showed that treatment recommendations changed in 33% of all subjects (N0 30%; N+ 39%). In 39% of N0 and 37% of N+ subjects with an initial recommendation for chemoendocrine therapy, the post-RS recommendation changed to endocrine therapy. In 22% of N0 and 39% of N+ subjects with an initial recommendation for endocrine therapy only, treatment recommendations changed to combined chemoendocrine therapy. Overall, 33% (N0 29%; N+ 38%) fewer subjects actually received chemotherapy as compared with subjects recommended for chemotherapy pre-test. This study indicates that there was a positive result from the use of the Oncotype DX test in impacting treatment recommendations in individuals with node-positive breast cancer. However, no data has yet been presented regarding health outcomes of Oncotype DX-directed treatment decisions for node-positive individuals. Prognosis in node-positive individuals who are classified as low-risk remains poor with 10-year DFS of 60% and OS of 77%, respectively.

Albain and colleagues (2010) published an analysis of the Southwest Oncology Group (SWOG) S8813 study which included women with node-positive, ER-positive breast cancer. The study randomized women to receive tamoxifen only, chemotherapy followed by tamoxifen or concurrent chemotherapy and tamoxifen. This analysis, which included samples from 367 participants, examined the association between Oncotype Dx and DFS. Adjusting for the number of positive nodes, Oncotype Dx was found to be prognostic in the

tamoxifen arm. In the chemotherapy arm, there was improvement in DFS in the group with a high score on Oncotype Dx but not in the group with a low score on Oncotype Dx.

Another analysis of the SWOG S8813 study was published in 2020 by Woodward and colleagues. The analysis, which excluded individuals who underwent mastectomy and radiotherapy, had breast conserving surgery without radiotherapy or had an unknown surgical type, consisted of 316 of the 367 (87%) participants in the parent trial. The focus of the analysis was the association between the Oncotype Dx recurrence score and locoregional recurrence (LRR). There were 7 LRR events (5.8%) among the 121 individuals with a low Oncotype Dx recurrence score and 27 LRR events (13.8%) among the 195 individuals with a high recurrence score. In a multivariate analysis, a higher Oncotype Dx recurrence score was found to be prognostic for LRR (HR, 2.36; 95% CI, 1.02 to 5.45; p=0.04). A subgroup analysis was conducted among individuals who had a mastectomy, between 1 and 3 positive nodes and did not undergo radiotherapy. In this subgroup, those with a low recurrence score had a 1.5% rate of LRR and the group with an intermediate or high recurrence score had an 11.1% LRR; the difference in LRR rates was marginally significant, p=0.051. Further studies are needed before concluding that women with ER-positive breast cancer, 1 to 3 positive nodes and a low Oncotype Dx recurrence score can forego radiotherapy.

The National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology: Breast Cancer (V.6 2020) notes that the 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for node negative breast cancer.

Review of the literature indicates that data addressing the use of the Oncotype DX test for tumors greater than 4.0 cm is sparse. In the major trials available to date, including the NSABP B-14 and B-20 studies used in development of the Oncotype DX algorithm as reported, more than 95% of all participants had tumors less than or equal to 4.0 cm (Fisher, 1994; Fisher, 1997; Habel, 2006; Paik 2004; Paik 2006).

Repeat testing of either a single sample or of a new sample from the same individual using the Oncotype DX test has not been evaluated in the scientific literature. Additionally, Oncotype DX testing of multiple tumor sites in a single individual has not been addressed in published studies. Further evidence is needed to fully address the impact of repeat testing or the testing of multiple sites. It is not unknown for an individual to

experience two separate and unrelated cases of breast cancer in their lifetime. Under such circumstances, use of the Oncotype DX test to evaluate each separate case would not be deemed a repeat test, but separate tests.

Roberts and colleagues (2017) performed a population-based study to determine the 5-year breast cancer specific survival (BCSS) in lymph node positive (LN+) individuals with recurrence score (RS) results in surveillance, epidemiology and end results (SEER) databases. The primary analysis included individuals (n=6768) diagnosed between 2004 and 2012 with LN+ (including micrometastases), hormone receptor positive (per SEER), and HER2-negative (per RT-PCR) primary invasive breast cancer. The researchers used the actuarial method to calculate BCSS. They found that the proportion of individuals with RS results and LN+ disease (n=8782) increased over time and decreased with increasing lymph node involvement from micrometastases to ≥ 4 lymph nodes. The 5-year BCSS for individuals with RS < 18 ranged from 98.9% with micrometastases to 92.8% with ≥ 4 lymph nodes. For micrometastases or up to three positive lymph nodes, the RS group was strongly predictive of BCSS (p<0.001). They concluded that "5-year BCSS is excellent for patients with RS < 18 and micrometastases, one or two positive lymph nodes, and worsens with additionally involved lymph nodes." They recommended further longitudinal updates.

EndoPredict

The EndoPredict assay is based on the quantification of eight cancer-related genes and three normalization genes resulting in an EndoPredict Risk Score (EP). When the EP is combined with the clinical risk factors of nodal status and tumor size, an EndoPredict Clinical Risk Score (EPclin) is derived. The results of this test stratify individuals into low and high-risk categories for distant metastases at 5 and 10 years.

In 2013, Filipits and colleagues reported on a retrospective validation study using 964 tumor samples from ER+, HER2- subjects treated with tamoxifen only, who were enrolled in the ABCSG-6 and ABCSG-8 studies. The results of a multivariate analysis indicated that EP was an independent predictor of distant recurrence in both ABCSG-6 and ABCSG-8 cohorts. At 10 years, the distant recurrence rates for the low-EP and high-EP groups were 8% vs. 22% in the ABCSG-6 cohort and 6% and 15% in the ABCSG-8 cohort (p<0.0010 for both). Similar findings were reported for EPclin, with the distant recurrence rates for the low-EP and high-EP groups at 4% vs. 28% in the ABCSG-6 cohort and 4% vs 22% in the ABCSG-8 cohort

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(p<0.0001 for both). The concordance index, (c-index) was calculated for the addition of the EP to both clinicopathologic markers as well as Adjuvant! Online score. For the clinicopathologic markers, the addition of EP resulted in a significantly improved prognostic power (c-index=0.727 in the ABCSG-6 cohort and 0.728 in the ABCSG-8 cohort). Similar results were reported for the addition of EP to the Adjuvant! Online score (c-index=0.785 in the ABCSG-6 cohort and 0.733 in the ABCSG-8 cohort). The EPclin had a higher c-index than any combination of EP and clinicopathologic variables (c-index=0.788 in the ABCSG-6 cohort and 0.732 in the ABCSG-8 cohort).

The same group published additional data from 1702 subjects in the ABCSG-6 and ABCSG-8 studies (Dubsky, 2013a). In this study, all subjects were assigned to a risk category based on cut-off values from the German S3, NCCN, and St. Gallen treatment recommendations. Low-risk categorization was assigned to 15% of subjects with German S3, 6% with the NCCN, 19% with the St. Gallen recommendations and 63% with EPclin. Absolute freedom of distant recurrence (AFDR) at 10 years was reported to be 94.7%, 94.5%, 96.6% and 95.3%, respectively. Using EPclin, AFDR was reported as 95.3%. The authors compared the distant metastasis-free survival (DMFS) for the low-risk group vs. the intermediate and high-risk groups for each guideline. For the German S3, DMFS was significantly better than the other two risk groups (p=0.014, HR-2.2 and absolute risk reduction [ARR] of 7.9%). No significant differences were reported for NCCN (p=0.12, HR=2.16, and ARR=6.9%). St. Gallen resulted in a significant association with decreased 10-year DMFS (p<0.001, HR=2.78, and ARR=11.2%). Use of the EPclin resulted in the best separation between the low, and high-risk groups (p<0.001, HR=5.11 and ARR=18.7%).

A third study from this group (Dubsky, 2013b), used the same dataset. Overall, 49% of subjects (n=832) were classified as low-risk by EP. Analysis indicated that this cohort had significantly improved clinical outcomes in the first 5 years (p<0.001), and beyond 5 years (p=0.002). This group also found a freedom from distant recurrence of 96.29% between 5 and 10 years. As with their earlier study, c-indices were reported. The addition of clinical parameters to the EP value (EPclin) increased the c-index from 0.644 to 0.716 (p<0.001). The addition of the EP to the Adjuvant! Online score resulted in the c-index improving from 0.674 to 0.756 (no p-value provided). At 10 years, the absolute freedom from distant recurrence in the EPclin low-risk and EPclin high-risk groups was reported to be 98.2% and 87.69%, respectively.

In 2015, Fitzal reported the results of a retrospective cohort study that used tumor blocks from 1324 subjects who participated in the ABCSG 8 trial to predict local recurrence-free survival (LRFS) following surgery for breast cancer in post-menopausal women. Median follow-up was 72.3 months and the cumulative incidence of local recurrence was 2.6% (0.4% per year). The risk of local recurrence over a 10 year period among subjects with lesions identified as high-risk by the EndoPredict test (n=683) was significantly higher (10 year LRFS=91%) when compared to subjects identified with low-risk lesions (n=641; 10 year LRFS=97.5%) (HR=1.31; p<0.005). The groups that received breast conservation surgery and mastectomy had similar local recurrence rates (p=0.879). RT after breast conservation surgery significantly improved LRFS in the cohorts predicted by EndoPredict to be low-risk for LR (p<0.005). The authors concluded that among post-menopausal, low-risk individuals, use of the EndoPredict test does not appear to be useful for tailoring local therapy.

Martin and others (2014) reported the results of a validation study involving 555 ER+, HER2-, lymph node+ subjects enrolled in the chemotherapy-treated arm of the GEICAM 9906 study. In this study, the estimated DMFS at 10 years was 93% for the low-risk EP group and 70% in the high-risk EP group. The ARR was calculated at 23% (HR=4.8, p<0.0001). As with the previously described studies, c-index values were reported. The authors reported that the c-index for clinicopathologic parameters alone was 0.065 and increased to 0.67 when EP was added (p<0.0018). For EPclin, 10-year estimates of DMFS were 100% in the low-risk group and 72% in the high-risk group with an ARR of 28% (p<0.001). When stratified for menopausal status, the data indicated that EP was prognostic for distant metastases in pre-menopausal subjects (HR=6.7, p<0.0001) as well as post-menopausal subjects (HR=3.3, p<0.0069). The results for EPclin were similar (p=0.0006 and 0.0023, respectively).

In 2016, Buus and colleagues published the results of a retrospective study involving 928 samples from the TransATAC trial for women with localized primary ER+, HER2- breast cancer, who had not received chemotherapy and who had sufficient material for EndoPredict (EP) and EndoPredict Clinical analysis. TransATAC also served as a validation study for Oncotype DX and allowed comparisons between EP and the Oncotype Risk Score (RS). Comparisons were made for distant recurrences between 0-5 years and 5-10 years. Distant recurrence occurred in 128 subjects within 10 years (59/680 node-negative and 69/248 node-positive subjects). Both EP and EPclin were highly prognostic across 10 years, with EPclin being

significantly more prognostic than EP alone (LRχ^2: EP=49.3; LRχ^2: EPclin=139.3). Both were more prognostic than the Oncotype DX RS over 10 years in the total subject pool (LRχ^2: RS=29.1). Both EP and EPclin provided significant prognostic value vs. RS with later recurrences, 5-10 years, for all subjects (LRχ2: EPclin=59.3, p<0.001; LRχ2: EP=23.6, p<0.001; LRχ2: RS=5.6 p=0.02) and for node-positive subjects (LRχ2: EPclin=48.3, p<0.001; LRχ2: EP=14.5, p<0.001; LRχ2: RS=8.0, p=0.005). EPclin was particularly good at stratifying node-positive subjects with an absolute separation at 10 years for distant recurrence of 31.9% vs. 14.1% in node-negative subjects. The HR between high- and low-risk groups was marginally greater for EP (HR=2.98, p<0.001) than for RS (HR=2.73, p<0.001) and substantially greater than for EPclin (HR=5.99, p<0.001). In the majority of cases, EPclin and RS were in agreement (K=0.40), but 117 cases (12.6%) were classified as EPclin high-risk and RS non-low-risk. Additionally, 144 cases (15.5%) were EPclin high-risk and RS low-risk. The authors concluded that EP and EPclin were highly prognostic for distant recurrence in endocrine-treated subject with ER+, HER2- breast cancer, and that EPclin provided more prognostic information than the Oncotype DX RS.

The above studies demonstrate that both the EndoPredict and the EPclin assays can assist in the prognosis of select individuals with breast cancer, both as an initial test prior to treatment and after 5 years of treatment to determine whether or not additional endocrine therapy is warranted.

Prosigna Breast Cancer Prognostic Gene Signature Assay

The Prosigna Breast Cancer Prognostic Gene Signature Assay uses the NanoString nCounter® device to assess the PAM50 gene subtype data. In addition to the PAM50 data, an additional algorithm using clinical information is used to derive an overall Risk of Recurrence (ROR) Score. The ROR scores range from 0 to 100 and further stratify individuals into 1 of 3 risk categories, with scores of 0 to 40 assigned "low" risk, scores of 41 to 60 "intermediate" risk, and scores of 61 to 100 "high" risk.

Dowsett and colleagues (2013) reported the results of an analysis of banked samples from 1017 subjects involved in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) study. The prognostic power of the Oncotype DX RS, ROR, or IHC4 (immunohistochemical prognostic model) was compared to that of a clinical treatment score derived from immunohistochemical assessment of ER, progesterone receptor, HER2,

and Ki67. The authors reported that ROR added significant prognostic information beyond clinical treatment score (CTS) in all subjects (p<0.001) and in all four subgroups: node-negative, node-positive, HER2 negative, and HER2 negative/node negative. More subjects were scored as high-risk and fewer as intermediate-risk by ROR than by RS. Relatively similar prognostic information was added by ROR and IHC4 in all subjects, but more by ROR in the HER2 negative/node negative group. They concluded that ROR provides more prognostic information in endocrine treated subjects with ER positive, node-negative disease than RS, with better differentiation of intermediate and higher-risk groups.

Sestak (2013) described the results of a retrospective study involving 940 samples from the ATAC and TransATAC (Translational Substudy of Anastrozole, Tamoxifen, Alone or in Combination) studies. The study was limited to subjects from the UK who had not previously received chemotherapy, and for whom results from the Oncotype DX, the IHC4, and Prosigna assay (without tumor size) were available. Median follow-up time was 10 years. It was reported that the Prosigna derived risk of recurrence (ROR) score was the strongest molecular prognostic factor in the late follow-up period (5-10 years) (χ^2=16.29; p<0.001), whereas IHC4 (χ^2=7.41) and RS (χ^2=5.55) were only weakly prognostic in this period. Similar results were seen for all subgroups and for all recurrences. The authors concluded that, except for nodal status and tumor size, none of the IHC4 markers provided statistically significant prognostic information in years 5 to 10. However, the ROR gave the strong prognostic information for the 5- to 10-year period. The ATAC and TransATAC studies were designed to evaluate the effect of treatment on women with breast cancer and were not designed to prospectively compare outcomes in individuals managed with or without the Prosigna or other GEP tests.

In a 2018 publication, Sestak and colleagues analyzed 774 samples from the TransATAC study from individuals with hormone-receptor positive early-stage breast cancer treated with 5 years of tamoxifen or anastrozole in the ATAC trial. This analysis included subjects for whom data on all gene expression-based signatures were available. A total of 591 subjects had node-negative disease and experienced 58 (9.8%) distant recurrences over 10 years. The other 183 subjects had 1 to 3 positive nodes and experienced 40 (21.9%) distant recurrences. In individuals with node-negative disease, all of the 6 GEP tests provided statistically significant prognostic information. The most value (largest hazard ratios) were for the Prosigna ROR (HR, 2.56, 95% CI: 1.06 to 3.35), BCI (HR, 2.46, 95% CI, 1.88 to 3.23) and Endopredict (EPclin) (HR,

2.14, 95% CI, 1.71 to 2.68) tests. For individuals with 1 to 3 positive nodes, the Prosigna ROR (HR, 1.58, 95% CI, 1.16 to 2.15), Endopredict (HR, 1.69, 95% CI, 1.29 to 2.22) and Clinical Treatment Score (CTS) (HR, 1.63, 95% CI, 1.20 to 2.21) provided statistically significant prognostic information. The CTS is a score developed in the TRANSATAC study.

In 2015, Sestak published a using combined data from 862 subjects from the ATAC study and 1275 subjects from the Austrian Breast & Colorectal Cancer Study Group (ABCSG-8) study. All subjects had hormone receptor positive breast cancer treated with endocrine therapy and were free from recurrence 5 years after diagnosis. Mean follow-up was 10 years. The authors stated that the mean ROR for individuals excluded from this trial due to recurrence within 5 years was significantly higher than the included subjects (ROR=53.57 vs. 20.4, p<0.001). In the overall population, when compared to the low-risk ROR group, subjects in the high-risk group had a 6.9 fold higher risk of distant recurrence and those in the intermediate-risk ROR group had a 3.3 fold higher risk. The CTS added more prognostic information for distant recurrence 5 years following diagnosis than the ROR in the overall population (univariate likelihood ratio (LR) χ^2=67.94, bivariate LR χ^2=35.25). However, in the node-negative subjects, the ROR score added more prognostic information in both the univariate and bivariate analyses (univariate ROR LR χ^2=30.95 and LR χ^2=21.48; bivariate CTS LR χ^2=17.25 and LR χ^2=7.79). In this subpopulation, subjects in the low-risk ROR group had a 2% risk of distant recurrence by 10 years compared to 9% for the intermediate-risk group and 11.5% for the high-risk group. In node-positive subjects, the CTS provided the most prognostic information (LR χ^2=35.60). The correlation of CTS and ROR was weak (r=0.36). Agreement between the two scores was similar for the low-risk groups, but the CTS categorized more subjects into the intermediate-risk group (32.4% vs. 25.2%) and the ROR categorized more subjects into the high-risk group (19.5% vs. 14.3%). When the classification using ROR was compared to classification using the CTS alone, net reclassification was 7.4%. When classification using the ROR plus the CTS was compared to the CTS alone, the net reclassification was also 7.4%.

In 2014, Gnant and others described the findings of a retrospective study using banked samples from 1478 post-menopausal subjects who participated in the ABCSG-8 trial. Both PAM50 intrinsic subtypes and ROR score were calculated for each sample. The authors reported that in all tested subgroups, ROR score significantly added prognostic information to the clinical predictor (p<0.0001). PAM50 assigned an intrinsic

subtype to all cases, and the Luminal A cohort had a significantly lower ROR at 10 years compared with Luminal B (p<0.0001). The authors reported significant and clinically relevant discrimination between low- and high-risk groups occurred also within all tested subgroups.

Gnant (2015) used data from 543 evaluable tissue samples from subjects involved in the TransATAC and ABCSG-8 studies with one to three positive nodes. Mean follow-up was 9.6 years. Overall, 97 distant recurrence-free survival events were reported. In the subjects with one positive node, absolute 10-year risk of distant recurrence was 6.6% in the low-risk ROR group vs. 15.5% in the intermediate group, 25.5% in the high-risk group (p=0.0002 for intermediate and high-risk groups combined), 8.4% in the luminal A subgroup, and 25.3% in the luminal B subgroup (p=0.0001 for the luminal A and luminal B subgroup combined). The predictive power of CTS with regard to 10-year risk of distant recurrence was significantly improved by the addition of the ROR when stratified by the number of nodes with metastases (p<0.0001, for 1, 2, and 3 nodes). When subjects in each nodal subgroup were further stratified by ROR risk category, there were no significant differences between the low and intermediate groups. However, the probability of distant recurrence was significantly increased in the high-risk group vs. the low-risk group (HR=3.56; p=0.0016).

Filipits and colleagues (2014) described the findings on 1246 subjects enrolled in the ABCSG-8 study whose banked samples underwent PAM50 ROR testing. They reported that PAM50 ROR score and ROR-based risk groups provided significant additional prognostic information with respect to late DRFS compared with a combined score of clinical factors alone (ROR score, p<0.001; ROR-based risk groups, p<0.001). Looking at clinical outcomes between years 5 and 15, the absolute risk of distant recurrence was found to be 2.4% in the low ROR-based risk group, vs. 17.5% in the high ROR-based risk group. The DRFS differences according to the PAM50 ROR score were observed for both node-positive and node-negative disease.

Laenkholm and colleagues published two analyses of data from the Danish Breast Cancer group database on the association between Prosigna-PAM50 score and distant recurrence (DR) of breast cancer. Both studies included individuals diagnosed with ER-positive HER2-normal breast cancer from 2000-2003 who were treated with 5 years of endocrine therapy and followed for a median of 9.2 years for DR and 15.2 years for OS. Laenkholm, 2018a included 2,558 individuals with carcinomas >20mm (any histological subtype) and/or

1-3 positive lymph nodes. Over 10 years of follow-up, 228 (8.9%) developed a distance breast cancer recurrence and 46 (1.5%) died of breast cancer. In individuals with node-negative disease or 1-3 positive nodes, Prosigna, using the continuous ROR score, was significantly associated (p<0.001) with the risk of DR at 10 years. In the study population as a whole, the risk of DR was significantly lower in the intermediate ROR and low-risk groups compared with the high ROR risk group. Using the commercial product cutoff for node-positive disease (ROR ≤40), Prosigna identified a low-risk population (absolute risk of DR at 10 years=4.8%) and a high-risk group (absolute risk of DR at 10 years=21.9%).

In Laenkholm 2018b, the analysis was limited to individuals with carcinomas >20mm and/or 1-3 positive lymph nodes and with either rare subtypes other than (invasive lobular carcinoma) or invasive ductal carcinoma. The study included 1570 individuals with invasive ductal carcinoma and 89 individuals with special histological subtypes. The overall 10-year DR rate for the special subtypes was 9.2% (95% CI, 4.0% to 17.2%) compared to 13.7% (95% CI, 11.9% to 15.7%) for invasive ductal carcinoma. The 10-year OS was 74.2% (95% CI, 63.7% to 82.0%) for the special subtypes and 75.4% (95% CI, 73.2% to 77.4%) for invasive ductal carcinoma. Prosigna had a statistically significant association of the continuous ROR score with risk of DR for both invasive ductal carcinoma and the special subtypes. The Danish Breast Cancer group database contains observational data and did not compare outcomes in individuals managed with and without use of the Prosigna GEP test.

Breast Cancer Index

The Breast Cancer Index (BCI) is a test that combines a two-gene ratio HOXB13:IL17BR (H:I) with a five-gene molecular grade index. It has been proposed as an aid in the prediction of recurrence of breast cancer in individuals with ER+, lymph node-negative tumors. A blind, retrospective analysis of data from a prospective RCT evaluating tamoxifen treatment (Stockholm trial) was published by Jerevall and others (2011). The Jerevall study involved 588 samples from 314 subjects who were ER+ and received tamoxifen therapy, and 274 subjects who were ER- and did not receive endocrine therapy. All subjects were considered at low-risk of recurrence, were node-negative and had tumors < 3 cm. The authors report that in a multivariate Cox linear regression model of tamoxifen-treated subjects, the BCI was a prognostic factor of breast cancer specific death, independent of tumor size, grade, HER2 status, and PR status (p=0.05). In

untreated subjects, the BCI was prognostic for distant recurrence and breast cancer specific death independent of tumor size, grade, HER2 status and PR status (p=0.003). The authors note that the data for this study was derived from a study conducted from 1976 to 1990 and acknowledge that significant changes in practice patterns have occurred. They conclude that, "Further studies are warranted to determine whether these findings will extend to current standard of care of ER positive patients receiving 5-10 years of aromatase inhibitors."

Jankowitz and others (2011) described the results of a study involving tumor samples from 265 subjects with ER+, lymph node-negative breast cancer who had received adjuvant tamoxifen. Samples were assessed with the BCI and compared to Adjuvant!Online (AOL) results. The authors built a proportional hazard model using known prognostic clinical variables (age, tumor size, tumor grade, and treatment). When BCI was included in the model, it was highly significant and associated with recurrence risk (p=0.0002), all-cause mortality (p<0.0001), and breast cancer specific mortality (p<0.0001). A combined multivariate analysis with only BCI and AOL showed that both remained independently and significantly associated with risk of recurrence (p=0.0004 and p=0.0007, respectively), all-cause mortality (p=0.009 and p<0.0001, respectively), and breast cancer specific mortality (p=0.009 and p=0.0001, respectively). To assess accuracy, the concordance between BCI and AOL were compared to survival times gathered from subject records over a period of 10 years (iAUC). For time to distant recurrence for all subjects, iAUC values were 0.642 for models with AOL only and 0.717 for models combining AOL and BCI. For the subjects treated with tamoxifen alone, these probability values increased to an iAUC of 0.671 and 0.750 for models, respectively. Further analysis indicates that for a time period less than 4 years, the addition of BCI to predictive models provided no significant benefits. For time periods between 4 and 10 years, the minimum predictive accuracy was 61.4% to 66.2% for AOL only and 71.1% to 75.7% for AOL plus BCI. For subjects receiving tamoxifen alone, the ranges for this time period were 54.6% to 65.0% for AOL and 73.4% to 80.7% for AOL plus BCI. The findings of this study are limited by its retrospective nature, as well as having come from a single institution that is a tertiary care center, which may introduce selection bias. Additionally, limitations in sample availability also may have introduced confounding factors.

Zhang and colleagues (2013) reported the results of a study testing the prognostic performance of the BCI in a population of 675 subjects who were enrolled in two separate trials. The first, referred to as the Stockholm

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study, enrolled 317 post-menopausal women with node-negative early-stage invasive breast cancer treated with either tamoxifen or no additional treatment. Subjects were followed for a mean of 17 years in this study. The second study, referred to as the multi-institutional study is described above (Jankowitz, 2011) and involved tumor samples from 265 subjects with ER+, lymph node-negative breast cancer who had received adjuvant tamoxifen. Subjects were followed for a mean of 10 years. Using data from a trial set of 283 subjects from the Stockholm trial data, an optimized BCI was developed for subjects with ER+, lymph node -negative breast cancer. In this population, 156 subjects were classified as low-risk, 75 as intermediate-risk, and 52 as high-risk. The 10-year rates of distant recurrence were reported to be 11.2%, 21.0% and 34.4%, respectively. Data from the Stockholm and multi-institutional study were used to validate the performance of the BCI. In the Stockholm study population (n=317), early 5-year DMFS was reported to be 98% in the low-risk group, 95.2% in the intermediate-risk group, and 87.8% in the high-risk group (p=0.0063). For late recurrence (greater than 5 years) 285 subjects were included for analysis. In this population, 10-year DMFS was reported to be 97.2%, 92.8% and 89.9% in the low, intermediate, and high-risk classification groups, respectively (p=0.0152). Using data from the multi-institutional study (n=358), 5-year DMFS was 95.5%, 92.3% and 75.5% % in the low, intermediate, and high-risk classification groups, respectively (p<0.0001), and 10-year DMFS was 97.5%, 83.1% and 85.0% in the low, intermediate, and high-risk classification groups, respectively (p=0.0002).

Mathieu and colleagues (2012) reported on the results of a blinded retrospective analysis of 150 subjects previously treated with surgery for breast cancer and treated with chemotherapy and/or tamoxifen. Ninety-seven percent of subjects had T1-T3 tumors, and 68% were ER+. Using the BCI assay, 64 subjects (42%) were classified as low-risk, 52 (35%) subjects were classified as intermediate-risk, and 34 subjects (23%) as high-risk. BCI risk categories were significantly associated with tumor grade (p<0.0001) and ER/PR status (p=0.0013). BCI was also associated with an 18-fold increased likelihood of pathological complete response between high-risk (n=10/34, 29%) vs. low-risk subjects (n=1/64, 1.6%; p=0.0001). Within a multivariate analysis which included age, ER/PR, grade, size and HER2 status, BCI remained significantly associated with pathological complete response, both as a continuous score (p=0.0013) and as categorized risk groups with an odds ratio of 34 for high vs. low-risk (p=0.0055). The authors stratified BCS eligibility BCI, and reported a more than threefold increase in the percentage of subjects undergoing conservative surgery within intermediate-risk or high vs. low-risk groups (p=0.0002). In multivariate analysis, tumor size and BCI

risk group remained significantly associated with BCS with an odds ratio of 5.78 for high vs. low-risk groups (p<0.0001 and p=0.0022, respectively). The authors acknowledge that the study design may have increased the predictive power of the BCI due to subjects not being selected based on ER or HER2 expression for the indications of neoadjuvant chemotherapy. Additionally, the retrospective nature of the trial also impacts the generalizability of the findings.

In 2013, Sgroi reported the results of a prospective comparative study investigating the prognostic value of the BCI, Oncotype DX, and an immunohistochemical prognostic model (IHC4). This study used archival tumor blocks from the TransATAC tissue bank from all post-menopausal individuals with estrogen receptor positive breast cancer from whom the 21-gene recurrence score and IHC4 values had already been derived. BCI testing was conducted on all samples with sufficient residual RNA using two BCI models, cubic (BCI-C) and linear (BCI-L). The prognostic ability of BCI for distant recurrence over 10 years was compared with that of results from the Oncotype DX test and the IHC4. The ability to predict early (0-5 years) and late (5-10 years) distant recurrence was also evaluated. Testing was successfully done in 665 samples. No significant difference in risk of distant recurrence over 10 years was noted using the BCI-C test compared to the other tests (p<0.0001). However, the BCI-L test was a much stronger predictor for overall (0-10 year) distant recurrence compared with BCI-C (p<0.0001). Compared with BCI-L, the Oncotype DX test was less predictive (HR=1.4, p=0.0002) and IHC4 was similar (HR=1.69, p<0.0001). In a multivariate analysis, all assays had significant prognostic ability for early distant recurrence (BCI-L: HR=2.77, p<0.0001; Oncotype DX: HR=1.80, p<0.0001; IHC4: HR=2.90, p<0.0001). However, only BCI-L was significant for late distant recurrence (p=0.0048). This study only included post-menopausal women, limiting the generalizability of these results. Additionally, the main conclusions are made based upon a secondary linear combination analysis, not on primary analysis.

MammaPrint

In an early study on the MammaPrint test, Van de Vijver (2002) reported on samples from 295 subjects with primary stage I or II breast carcinoma. The 70-gene assay was used to predict poor or good prognosis. A total of 180 subjects had a poor prognostic signature and 115 had a good prognostic signature. The mean overall 10 year survival rate was 54.6 ± 4.4% and 94.5 ± 2.6%, respectively. At 10 years, the probability of

remaining free of distant metastases was 50.6 ± 4.5% in the group with a poor prognosis signature and 85.2 ± 4.3% in the group with a good prognosis signature. The estimated HR for distant metastases in the group with a poor prognosis signature, versus the good prognosis signature group was 5.1 (p<0.001). This ratio remained statistically significant when the groups were analyzed according to lymph node status. A multivariate analysis showed that the prognosis profile was a strong independent factor in predicting disease outcome. In 2014, Drukker and colleagues published follow-up data on this population. The median follow-up for this series was extended to 18.5 years. A statistically significant difference was reported in long-term DMFS for the subjects with a low, and a high-risk 70-gene signature (DMFS p<0.0001), as well as separately for node-negative (DMFS p<0.0001) and node-positive subjects (DMFS p=0.0004). The 25-year HRs for all subjects for DMFS and OS were 3.1 (95% CI, 2.02-4.86) and 2.9 (95% CI, 1.90-4.28), respectively. The HRs for DMFS and OS were largest in the first 5 years after diagnosis: 9.6 (95% CI, 4.2-22.1) and 11.3 (95% CI, 3.5-36.4), respectively. The 25-year HRs in the subgroup of node-negative subjects for DMFS and OS were 4.57 (95% CI, 2.31-9.04) and 4.73 (95% CI, 2.46-9.07), respectively, and for node-positive subjects for DMFS and OS were 2.24 (95% CI, 1.25-4.00) and 1.83 (95% CI, 1.07-3.11), respectively. Subsequently, the translational research network of the Breast International Group (TRANS-BIG) published validation studies on the MammaPrint test (Buyse, 2006; Desmet, 2007; Rutgers, 2011).

In 2016, Cardoso and colleagues published the results of the Microarray for Node Negative Disease may Avoid Chemotherapy Trial (MINDACT). This study was designed to examine the clinical utility of the MammaPrint test in addition to standard clinical–pathological criteria in selecting subjects for adjuvant chemotherapy. In a prospective, randomized study, 6693 women with early-stage breast cancer had their genomic risk and clinical risk determined using the MammaPrint and a modified version of Adjuvant! Online, respectively. Women at low clinical and genomic risk did not receive chemotherapy (2745 subjects, 41.0%), whereas those at high clinical and high genomic risk did receive chemotherapy (1806 subjects, 27.0%). Subjects with discordant risk results were randomized to determine the use of chemotherapy using either the clinical or genomic risk. This was a non-inferiority study, with non-inferiority defined as a lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis of 92% or higher in subjects with high clinical risk and a low-risk gene expression profile who did not receive chemotherapy. A total of 1550 subjects (23.2%) were determined to be at high clinical risk and low genomic risk. At 5 years, the rate of survival without distant metastasis in this group was 94.7% (95% CI, 92.5 to

96.2) among those not receiving chemotherapy, higher than the non-inferiority boundary of 92% and therefore establishing non-inferiority. In a secondary analysis of the data, there was no significant advantage in directing therapy on the basis of genomic risk among subjects at low clinical risk and high genomic risk, since these subjects had no benefit from the use of adjuvant chemotherapy [those receiving chemotherapy, 5-year rate of survival without distant metastasis of 95.8% (95% CI, 92.9 to 97.6), compared to those without chemotherapy with a rate of 95.0% (95% CI, 91.8 to 97.0%), adjusted HR of 1.17 (95% CI, 0.59 to 2.28; p=0.66)], and there was no significant difference between the chemotherapy group and the no-chemotherapy group with respect to DFS and OS. The authors concluded that for women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, avoiding chemotherapy on the basis of MammaPrint testing led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy and that given these findings, when using MammaPrint results, approximately 46% of women might not require chemotherapy.

A number of studies have evaluated the prognostic ability of the MammaPrint test. Mook and colleagues (2009) was a retrospective analysis of tumor samples in individuals with node-positive breast cancer and found that the 10-year DMFS and BCSS probabilities were reported to be 91% and 96% respectively for the good prognosis group and 76% for both DMFS and BCSS for the poor prognosis group. Mook (2010), also a retrospective analysis of tumor samples, found that the BCSS at 5 years was 99% for the good prognosis signature group versus 80% for the poor prognosis signature group (p=0.036). Bueno-de-Mesquita and colleagues evaluated the use of the MammaPrint test in subjects with node-negative disease (Bueno-de-Mesquita, 2007, 2009). In both of these studies, MammaPrint prognostic index results were compared to other commonly used clinicopathologic risk indexes, and both reported favorable results. None of these studies evaluated the impact of the MammaPrint test on overall survival, nor on the avoidance of unnecessary treatment with chemotherapy. Saghatchian (2012) evaluated the prognostic value of the MammaPrint test in individuals with breast cancer and 4-9 positive nodes. Seventy (40%) of the samples were classified as low risk and 103 (60%) as high risk. In the low-risk category, the 5-year OS was 97% vs. 76% for the high-risk group (p<0.01). Distant metastasis-free survival at 5 years was reported to be 87% for low-risk subjects and 63% for high-risk subjects (p<0.01). Kok and colleagues (2012) found that, in subjects treated with tamoxifen for metastatic disease, MammaPrint results were associated with outcomes but there was additional value when these findings were combined with ER and PR status (p=0.013).

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Drukker and others provided data from a prospective evaluation of the MammaPrint test in the microarRAy-prognoSTics-in-breast-cancER (RASTER) study (2013). This study involved 427 subjects with unilateral, unifocal, primary operable invasive adenocarcinoma of the breast with no positive nodes. ER status was positive in 342 (80%) of subjects and negative in 85 (20%). PR status was positive in 293 (69%) subjects and HER2 status was, negative in 358 (84%) subjects. When comparing the results of the MammaPrint test to AOL risk prediction, there was 38% (161/427) discordance. Most were seen in the signature-identified low-risk group and in the AOL high-risk identified group (124/427, 29%). The rest were in the signature-identified high-risk group and in the AOL low-risk identified group (37/427, 9%). Five-year distant recurrence-free survival was 98.4% in subjects with signature-identified low-risk / AOL high-risk (n=124), of which 76% (n=94) had not received adjuvant chemotherapy. The group that had not received adjuvant chemotherapy had a 5-year distant recurrence-free survival of 98.9%. The group that did not receive any systemic therapy (chemotherapy nor endocrine therapy) (n=70) had a 5-year distant recurrence-free survival of 100%. No significant difference (p=0.29) was seen between systemically untreated subjects with a concordant low-risk assessment and subjects with a 70-gene signature low-risk result even with a high-risk assessment by AOL. The authors concluded that 5-year distant recurrence-free survival probabilities demonstrated significant additional prognostic value of MammaPrint results to clinicopathological risk estimations such as AOL.

In 2017, Esserman and others reported on a study evaluating the "ultralow-risk threshold" of the MammaPrint test to determine 20-year risk of recurrence in 652 subjects enrolled in the STO-3 trial who have not has any breast cancer-related deaths within 15 years of initial treatment. All subjects were postmenopausal with node-negative breast cancer and tumors ≤ 3 cm who had received either treatment with tamoxifen (n=313) or no endocrine therapy (n=339). Another 15% (n=98) were classified as ultralow-risk. Additionally, 538 were ER+, 369 were PR+, 8 were HER2+, and 178 has Ki67 ≥ 15%. Tumor grade 1 was reported in 19% of subjects, grade 2 in 58%, and grade 3 in 23%. MammaPrint scored 42% (n=275) of subjects as high-risk and 58% (n=377) as low-risk. A statistically significant difference was reported between groups (p<0.001), with low-risk subjects having > 95% 5-year breast cancer survival. At 20 years, women with 70-gene high-risk and low-risk tumors, but not ultralow-risk tumors, had a significantly higher risk of disease-specific death compared with ultralow-risk subjects (HR=4.73 and 4.54, respectively). No deaths

were reported for the ultralow-risk subjects treated with tamoxifen at 15 years, and the 20-year disease-specific survival rate was 97%. Untreated ultralow-risk subjects had a survival rate was 94%. All ultralow risk tumors were HE+, HER2-, luminal subtype.

Several studies published in 2017 examined the impact of MammaPrint test results on physician decision-making. Kuijer and colleagues (2017) reported on a prospective study evaluating physician decisions regarding adjuvant chemotherapy for women who underwent MammaPrint testing as part of routine clinical practice in the Netherlands. Dutch guidelines recommend a validated gene expression profiling test for women with ER+ ductal carcinoma for whom there is uncertainty about the benefit of chemotherapy. The study included 698 individuals with ER+ early-stage breast cancer. Prior to learning Mammaprint test results, physicians recommended chemotherapy in 41% of cases and recommended against chemotherapy for 16% of cases. For the remaining cases, physicians preferred to wait until test results were available. Among individuals initially recommended chemotherapy by physicians, 41% were assigned by Mammaprint to the high-risk category and 56% were assigned by Mammaprint to the low-risk category. Among individuals who were not initially recommended chemotherapy, 59% were categorized by Mammaprint as low risk and 41% as high risk. Among individuals for whom an initial recommendation regarding chemotherapy had been made, physicians changed their recommendation for 51% of the cases after receiving MammaPrint results. The actually administered chemotherapy differed from the preliminary recommendation in 52% of cases and was consistent with MammaPrint results in 91% of cases.

Tsai and colleagues (2017) reported on the Prospective Study of MammaPrint in Breast Cancer Patients with an Intermediate Score (PROMIS) trial, which was conducted at multiple sites in the United States. A total of 876 individuals with breast cancer and an intermediate Oncotype DX result (recurrence score,18 to 30) were enrolled in the study. Eighteen individuals were later considered ineligible for inclusion because they did not pass the MammaPrint quality check and 18 other individuals were removed from the analysis for various reasons, leaving 840 individuals in the analysis. As part of the study, physicians provided recommendations regarding adjuvant chemotherapy before and after receiving MammaPrint results. Before MammaPrint testing (but following Oncotype DX testing), 382 individuals (45.5%) were recommended to have adjuvant chemotherapy and 458 (54.5%) were recommended not to have adjuvant chemotherapy. MammaPrint reclassified the 840 individuals as low risk in 374 cases (44.5%) and high risk in 466 cases (55.5%).

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MammaPrint classification was significantly associated with a change in chemotherapy treatment recommendations (p<0.001). For a total of 368 individuals, the original physician recommendation conflicted with the MammaPrint test results. In this subgroup, 279 individuals (75.8%) had their treatment recommendation changed. That is, 108 of 142 (76%) individuals categorized as low risk by MammaPrint had their recommendation change from receiving chemotherapy to not receiving chemotherapy, and 171 of 226 (76%) individuals categorized as high risk by MammaPrint who were not originally recommended chemotherapy had it added to their treatment regimen.

Soliman (2020) reported on a prospective study examining physician treatment recommendations before and after receiving results of the MammaPrint test in a sample of 358 individuals. According to clinical risk criteria, 227 (63%) were classified as low risk and 131 (36.6%) were classified as high risk. In their initial recommendations, physicians recommended that 176 (77.5%) of the low-risk individuals not receive chemotherapy and 82 (62.6%) of the high-risk individuals receive chemotherapy. MammaPrint classified 224 individuals (62.5%) as low risk and 134 (37.5%) as high risk. After receiving MammaPrint test results, physicians changed their recommendations regarding chemotherapy in 86 (24%) of cases. For the individuals considered clinically high risk and MammaPrint low risk, the primary population of interest in this analysis, physicians removed chemotherapy from the treatment recommendations for 21 of the 35 individuals (60%) for whom they recommended chemotherapy based on clinical classification alone.

Oncotype DX DCIS

The use of a modified version of the Oncotype DX test (discussed above) has been proposed for guiding treatment decisions in individuals with ductal carcinoma in situ (DCIS). The DCIS variation of the Oncotype DX test, named the Oncotype DX DCIS test, relies on the expression of fewer genes than the original Oncotype DX test (12 vs 21), and the modifications are based on proprietary algorithms. This test is scaled as a continuous variable from 1 to 100, with low risk defined as Oncotype DX DCIS Score (DS) less than 39, intermediate risk defined as DS from 39-54, and high risk defined as greater than or equal to 55.

The prospective use of this test was addressed by Solin (2013). This study involved 327 tissue samples from subjects who participated in the ECOG E5194 study, which was a nonrandomized prospective trial designed

to evaluate the use of surgical excision without radiation for women with DCIS. The authors reported that the DCIS Score was significantly associated with the development of an ipsilateral breast event (IBE), defined as local recurrence of DCIS or invasive carcinoma in the ipsilateral breast, when adjusted for tamoxifen use (HR, 2.31; p=0.02). This risk remained almost unchanged when the adjustment for tamoxifen use was removed (HR=2.38; p=0.01). For invasive carcinoma alone, the HR was 3.68 (p=0.01). In a multivariate analysis, DCIS Score, tumor size, and menopausal status were all independently and significantly associated with developing an IBE (p≤0.02 for all). Using the DCIS Score to stratify risk into three pre-specified risk groups (low, intermediate, and high), the 10-year risk of an IBE was 10.6%, 26.7%, and 25.9%, respectively (log rank p=0.006). The corresponding 10-year rates for developing invasive cancer alone were 3.7%, 12.3%, and 19.2%, respectively (log rank p=0.003). No significant association was found between the DCIS Score and the risk of developing a DCIS or invasive cancer in the contralateral breast. No association was reported for the standard Oncotype DX Recurrence Score and the risk of developing a DCIS or invasive cancer in either breast. The results of this study demonstrate that while the use of the DCIS Score may help predict the risk of ipsilateral IBE in women with DCIS, this study was small and retrospective, and did not demonstrate any change in clinical outcomes as a result of care guided by the Oncotype DX DCIS test.

A prospective case series study (Alvarado, 2015) involving 115 subjects with DCIS who were eligible for breast-conserving therapy was conducted to study the impact of Oncotype DX DCIS scoring on treatment recommendations for radiation therapy following breast conserving surgery (BCS). Subjects with invasive carcinoma and planned mastectomy were excluded. The median size of DCIS was 8 mm (range 1-115 mm). Pre-assay median physician estimate of 10-year local recurrence risk was 20% (range: 6-60%) for any DCIS or invasive cancer and 10% for invasive cancer only (range: 3-25%). Post-assay estimates were 16% (range: 5-25%) for any DCIS or invasive cancer and 7% (range: 2-25%) for invasive cancer only. Pre-assay, 73% of subjects had radiotherapy (RT) recommendations vs. 59.1% post-assay (p=0.008). This study demonstrated that the DCIS Score led to statistically significant changes in physician treatment choice. This study was not an assessment of whether the decision was made appropriately, as no data was presented relating to the impact on health outcomes as a result of treatment guided by the results of the Oncotype DX DCIS test.

Rakovitch and others (2015) published the results of a retrospective study involving tumor block samples from 718 subjects with DCIS treated with BCS, 571 (79.5%) of whom had negative margins. Median follow-up was 9.6 years. In the primary pre-specified analysis, the DCIS Score was associated with any local recurrence (DCIS or invasive cancer) in ER+ individuals (HR=2.26; p<0.001) and in all subjects regardless of ER status (HR=2.15; p<0.001). The DCIS Score provided independent information on local recurrence risk beyond clinical and pathologic variables including size, age, grade, necrosis, multifocality, and subtype (adjusted HR=1.68; p=0.02). The DCIS score was associated with invasive local recurrence (HR=1.78; p=0.04) and DCIS local recurrence (HR=2.43; p=0.005). The authors concluded that the DCIS Score independently predicts and quantifies individualized recurrence risk in a population of individuals with pure DCIS treated by BCS alone. This report does not provide any data related to the impact on health outcomes as a result of treatment guided by the results of the Oncotype DX DCIS test.

The same group reported another study involving tumor blocks from 1260 subjects with DCIS treated with BCS; 571 treated with BCS alone and 689 treated with BCS plus RT (Rakovitch, 2017). All samples came from tumor samples greater than 2 mm. Median follow-up for subjects from whom the samples were available was 9.4 years. At baseline the BCS+RT group had significantly more adverse features vs. the BCS alone group including age less than 50, high nuclear grade and presence of comedo-necrosis (p<0.001 for all). The 10-year cumulative risk of local recurrence in the BCS alone group was 19.2% vs. 12.7% in the BCS+RT group. In the BCS alone group, the factors associated with local recurrence included DS, multifocality, age at diagnosis and subtype. In the BCS+RT group subjects with clear margins, the factors associated with local recurrence included multifocality and tumor size greater than 1 cm. DS was associated with local recurrence in this group when adjusting for these factors (p<0.001). The HR for subjects with high-risk DS was 2.53 when compared to subjects with low-risk DS (p<0.001). For subjects with intermediate-risk DS, the HR was 1.62 vs. the low-risk DS group (p=0.11). The 10-year risk of local recurrence was 20.5% in the high-risk group, 13.6% in the intermediate group and 7.5% in the low-risk group (p<0.001). When the BCS alone and BCS+RT groups were pooled for analysis, the authors reported that age at diagnosis less than 50, tumor size greater than 1 cm, multifocality, and the administration of RT were associated with local recurrence. When adjusting for these factors, DS was still a significant predictor of local recurrence (HR=1.97, p<0.001). Furthermore, the HR for the high-risk and intermediate groups was significantly higher than the low-risk group (1.77 and 1.73, respectively). No interactions were found

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between DS and RT (p=0.44). When adjusted for propensity score, subjects with low-risk DS had a 10-year risk of local recurrence of 16% after BCS alone and 9.5% after BCS+RT. The 10-year risk of invasive local recurrence was 9.7% and 6.8%, respectively. For the high-risk DS group, when adjusted for propensity score, the 10-year risk of local recurrence was 32.7% in the BCS alone group and 20.0% in the BCS+RT group. The risk of invasive local recurrence was 17% and 11/9%, respectively.

BluePrint

The BluePrint test is intended as an adjunctive test to the MammaPrint test. It is proposed to further stratify Luminal-type cancers and improve recurrence risk stratification. Currently, the only peer-reviewed published study addressing the use of the BluePrint test is a retrospective study by Glück (2013). The study involved 437 tissue samples from subjects from four different studies evaluating pathologic complete response (pCR) after neoadjuvant chemotherapy in individuals with early stage breast cancer using BluePrint and MammaPrint tests vs. clinical subtyping with immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) for the determination of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2) status. It was reported that pCR rate differed substantially among BluePrint molecular subgroups: 6% in Luminal A-type, 10% in Luminal B-type, 47% in HER2-type, and 37% in Basal-type samples. The results indicated that for samples stratified as Luminal A-type samples by the BluePrint test, the pCR rate provided no prognostic information, suggesting these subjects may not benefit from chemotherapy. This study is hampered by several methodological flaws, including differences in the definition of positive HER2 results, different treatment regimens and different testing methodologies between study sites. Further data are needed from well conducted, prospective studies that address the clinical utility of the BluePrint test.

Breast Cancer Gene Expression Ratio

In 2006, Goetz and colleagues published a retrospective study addressing the Breast Cancer Gene Expression Ratio test. Tumor blocks from 206 women with breast cancer were examined for HOXB13/IL-17BR expression ratio (H:I ratio). They found that in lymph node-positive subjects (n=86) the H:I ratio was not

associated with relapse or survival. However, in node-negative subjects (n=103) a high H:I ratio was associated with significantly worse disease-free survival, relapse-free survival, and overall survival.

Rotterdam 76-gene assay and 41-gene assay

There is a lack of studies on use of the Rotterdam 76-gene assay, as well as the 41-gene assay. Further data on these tests are required to properly assess their clinical utility.

Insight TNBCtype

No published studies were identified that evaluated the accuracy or clinical utility of the Insight TNBCtype test.

Mammostrat

In 2012, Bartlett and others published the results of a study evaluating the Mammostrat test in the Tamoxifen versus Exemestane Adjuvant Multicenter (TEAM) trial. The authors tested 4598 pathology blocks from TEAM participants, who were node-positive in 47% of subjects and in whom 36% were treated with adjuvant chemotherapy, and reported on 3837 that were successfully scored. In the 1226 (31.9%) subjects that were both node-negative and did not receive chemotherapy, the Mammostrat test was a significant prognostic factor for distant relapse-free survival (p=0.004). Subjects with moderate or high scores were reported to be 58% and 159% more likely to experience distant relapse that those with low Mammostrat scores. Similarly, Mammostrat results were an independent factor in multivariate analysis for DFS in these populations (p=0.038). In the sample of subjects treated without chemotherapy (n=2559), multivariate analysis found that Mammostrat score remained an independent predictor of distant relapse-free survival risk (p<0.001), with a 45% and 75% increase in recurrence risk for medium and high-risk scores, respectively, compared with subjects with low-risk scores. However, for DFS, no significant benefit from Mammostrat was seen (p=0.085). When a multivariate analysis was conducted in the total study population, the Mammostrat score remained an independent predictor of distant relapse-free survival risk (P for trend <0.001) with a 50% and 91% increase in risk of recurrence for medium and high-risk scores,

respectively compared with subjects with low-risk scores. In a similar analysis for DFS, significant additional prognostic value of the Mammostrat score alongside conventional markers was found (P for trend <0.001). The results from this trial are promising, but further studies addressing the clinical utility of this test are warranted.

PAM50 Breast Cancer Intrinsic Classifier

The PAM50 Breast Cancer Intrinsic Classifier involves the analysis of a set of 50 genes to classify individuals into four separate subtypes based on gene expression profiles: Luminal A, Luminal B, HER2-enriched, and Basal-type. These subgroups, in addition to clinicopathologic data, have been proposed as a way to predict clinical outcomes in individuals with breast cancer.

A small comparative study by Kelly and colleagues in 2012 described the agreement between the Oncotype DX test and the PAM50 Breast Cancer Intrinsic Classifier. The PAM50 assay classifies four tumor types: Luminal A, Luminal B, HER2 enriched, and Basal-type. The study utilized archived tumor block samples from 108 subjects who had previously received Oncotype DX testing and treatment. Samples from the tumor blocks were evaluated with the PAM50 assay and compared with the Oncotype DX RS for each subject. All subjects were ER+ and HER-; 96% had node-negative disease (n=102). Most subjects (71%) did not receive chemotherapy but did receive adjuvant hormone therapy (94%). The authors reported that 103 (95%) were classified as Luminal A (n=76) or Luminal B (n=27). Ninety-two percent (n=98) had a low (n=59) or intermediate (n=39) RS. Among Luminal A cancers, 70% had low RS (n=53) and the remainder (n=23) had an intermediate RS. Among Luminal B cancers, 9 were high (33%) and 13 were intermediate (48%) by the RS. Almost all cancers with a high RS were classified as Luminal B (90%, n=9). One high RS cancer was identified as Basal-type and had low estrogen receptor/estrogen receptor gene 1 (ER/ESR1) and low human epidermal growth factor receptor (HER2) expression by quantitative polymerase chain reaction in both assays. The majority of low RS cases were Luminal A (83%, n=53). Importantly, half of the intermediate RS cancers were re-categorized as low-risk Luminal A subtype by PAM50. The authors conclude that "There is good agreement between the two assays for high (i.e., Luminal B or RS > 31) and low (i.e., Luminal B or RS < 18) prognostic risk assignment but PAM50 assigns more individuals to the low risk category." Additional data are required to fully evaluate the clinical utility of the PAM50 assay.

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BreastPRS

D'Alfonso and others (2013) described a validation study using samples of 246 subjects with invasive breast carcinoma and known Oncotype DX results. They applied the BreastPRS test and a 120-gene Oncotype DX approximation algorithm to a series of untreated, node-negative, estrogen receptor positive (ER+) subjects from previously published studies with known clinical outcomes. Correlation of recurrence score and risk group between Oncotype DX and BreastPRS was statistically significant (p<0.0001). Out of 260 subjects, 59 (23%) from four previously published studies were classified as intermediate risk when the 120-gene Oncotype DX approximation algorithm was applied. The BreastPRS test reclassified the 59 subjects into binary risk groups (high vs. low risk), with 23 (39%) subjects classified as low risk, and 36 (61%) as high risk. At 10-years from diagnosis, the low-risk group had a 90% recurrence-free survival (RFS) rate compared to 60% for the high-risk group. The authors concluded that "BreastPRS recurrence score is comparable with Oncotype DX and can reclassify Oncotype DX intermediate risk subjects into two groups with significant differences in RFS. Further studies are needed to validate these findings." A limitation of this study is the use of the "120-gene Oncotype DX approximation algorithm" which, was developed by the authors, instead of the actual Oncotype DX test. The methodology used undermines the comparison, since the results of the algorithm may or may not reflect the actual Oncotype DX results.

Practice Guidelines

Recommendations from the 14th St. Gallen International Breast Cancer Conference (2015), in reviewing therapies for the management of early breast cancer, noted the increasing evidence for the prognostic value of multiparametric molecular markers, stating, "Oncotype DX®, MammaPrint®, PAM-50 ROR® score, EndoPredict®, and the Breast Cancer Index® were all considered usefully prognostic for years 1-5." Beyond 5 years, only the PAM50 ROR score was agreed to be clearly prognostic. The panel further states, "Only Oncotype DX® commanded a majority in favor of its value in predicting the usefulness of chemotherapy."

The ASCO recommendations (Harris, 2016) addressing the appropriate use of breast tumor biomarker assay results to guide decisions on adjuvant systemic therapy in early-stage invasive breast cancer, notes that

the panel found sufficient evidence of clinical utility for the biomarker assays Oncotype DX, EndoPredict, PAM50 ROR, and Breast Cancer Index. Stating further that, "No biomarker except for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was found to guide choices of specific treatment regimens." The panel supported their statement on the clinical utility of assays in guiding decisions on adjuvant systemic chemotherapy by rating the type of evidence as "evidence based", the quality at "high" and strength of recommendation as "strong" for Oncotype DX and the PAM50 ROR; and for the EndoPredict and Breast Cancer Index assays as type of evidence "evidence based", quality "intermediate" and strength of recommendation "moderate."

It should be noted that in making these statements, ASCO utilized the following definition of clinical utility (Harris, 2016, supplemental material): "The use of test results to guide clinical decisions improved measurable outcomes of patient management, compared to decisions independent of test results." With regard to their recommendations for the PAM50 test, this standard is not met.

In 2017, ASCO published an update to the 2016 recommendations, specifically addressing the MammaPrint assay (Krop, 2017). Their 2017 strong recommendations, based primarily on the results of the MINDACT study published by Cardoso (2016), support the use of MammaPrint for patients with high clinical risk per the MINDACT categorization, but do not support use in patients with low clinical risk. ASCO notes that the MammaPrint assay:

> **May be used in patients with one to three positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit from chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.**

The NCCN Practice Guidelines in Oncology: Breast Cancer (V.6 2020) rates the 21-gene (Oncotype Dx) for pN0 or node negative as preferred category 1, noting that, "Other prognostic multigene assays can provide additional prognostic information in patients with 1-3 positive lymph nodes but are unknown if predictive of chemotherapy benefit in 1-3 positive lymph nodes." The NCCN guidelines (V.6 2020) also states that there

are limited data to make chemotherapy recommendations for those over 70 years old. Thus, the use of the gene expression profiling in this population may not be warranted.

Definitions

Ductal carcinoma in situ (DCIS): An early, non-invasive form of breast cancer, where abnormal cells grow inside a milk duct in the breast.

Estrogen receptor status: A laboratory finding related to the presence or absence of cellular receptors for the hormone estrogen.

HER2 receptor status: A laboratory finding related to the presence or absence of cellular receptors for HER2/neu (also known as ErbB-2, ERBB2) protein family. HER2 is notable for its role in the pathogenesis of breast cancer and as a target of treatment. There are two different methods by which HER2 receptor status can be discovered; the first is immunohistochemistry (IHC) and the other is in situ hybridization (ISH).

Histology: A method of categorizing tissues by evaluating cells and tissues at the cellular level with microscopic examination; the following are several histological categories of breast cancer:

- **Colloid**
- **Ductal**
- **Lobular**
- **Metaplastic**
- **Mixed**
- **Tubular**

Progesterone receptor status: A laboratory finding related to the presence or absence of cellular receptors for the hormone progesterone.

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TNM (tumor size, nodal involvement, and metastasis) classification: A staging system for breast cancer developed by the American Joint Committee on Cancer. The system was most recently updated in 2018 (Eighth Edition) and is available at: https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx.

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Websites for Additional Information

1. **American Cancer Society. Breast cancer? Available at: https://www.cancer.org/cancer/breast-cancer.html. Accessed on December 1, 2020.**
2. **National Cancer Institute. Breast Cancer Treatment. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/breast/Patient/page1. Accessed on December 1, 2020.**
3. **National Library of Medicine. Medical Encyclopedia: Breast Cancer. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000913.htm. Accessed on December 1, 2020.**

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This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Breast Cancer Index
Breast Cancer Risk Testing Network
EndoPredict
Insight TNBCtype
MammaPrint
MammaTyper
Oncotype DX
Oncotype DX DCIS
Prosigna
Rotterdam signature

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
New	02/11/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development. Moved content of GENE.00011 to new clinical utilization management guideline document with the same title. In 'Not Medically Necessary' statement, added Insight TNBCtype™ and removed Insight® DX Breast Cancer Profile.

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