Gene Expression Profiling for the Management of Breast Cancer

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DESCRIPTION

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society has estimated that 290,560 Americans will be diagnosed with breast cancer and 43,780 will die of disease in the United States in 2022.

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies is based on several prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node (ALN) status, tumor ER/PR content, tumor HER2 status, multi-gene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. One percent of breast cancers occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the

use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis. Patient's preference is a major component of the decision-making process, especially in situations in which survival rates are equivalent among available treatment options.

After surgical treatment, adjuvant systemic therapy should be considered. In patients with early- stage breast cancer, systemic adjuvant therapy is administered to reduce the risk of cancer recurrence. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (e.g.. ER/PR and HER2 status). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy, and comorbidity. The decision-making process requires collaboration between the health care team and patient.

There are many laboratory tests developed to detect genetic variation in breast tumor tissue, particularly gene expression tests. These results may be used to predict distant recurrent risk for individuals with early- stage breast cancer. In turn, this may help with the decision of whether to include adjuvant chemotherapy or extend endocrine therapy. Several gene expression tests commercially available in the United States are listed in the below table.

Test	**Manufacturer**
BluePrint	Agendia
Breast Cancer Index	bioTheranostics (San Diego, CA)
EndoPredict	Myriad (Salt Lake City, UT)
InsightTNBCtype	Insight Genetics
MammaPrint (70-Gene Signature)	Agendia (Irvine, CA)
Mammostrat Breast Cancer Test	Clarient Diagnostic Services
Oncotype DX Breast (21-Gene Assay)	Genomic Health (Redwood City, CA)
Oncotype DX Breast DCIS Score	Genomic Health (Redwood City, CA)
Prosigna	NanoString Technologies (Seattle, WA)
TargetPrint	Agendia

Selection of Adjuvant Chemotherapy Based on Risk of Recurrence
An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant chemotherapy. For example, for women with early-stage invasive breast cancer (i.e., cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of patient's baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline risk of recurrence. Women with the best prognosis have tumors that are small, early-stage, estrogen receptor-positive, and lymph node-negative. Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy. These women have an approximately 15%, 10-year risk of recurrence with tamoxifen alone, which means that approximately 85% of these patients could avoid the toxicity of adjuvant chemotherapy if they could be accurately identified. Conventional risk classifiers (e.g., Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and the number of affected lymph nodes. Consensus guidelines for defining receptor status exist; however, no single classifier is considered a criterion standard. As a result, a substantial number of patients are treated with chemotherapy who fail to benefit. Better predictors of recurrence risk could help decision-making, some individuals may prefer to avoid chemotherapy if assured their risk is low.

Clinical Context and Test Purpose
Professional society guidelines recommend that women with estrogen receptor (ER) positive, HER2-negative breast cancer receive adjuvant endocrine therapy. Initial treatment may also include adjuvant chemotherapy. Decisions regarding the addition of chemotherapy are based on the risk of distant recurrence, as many women with low -risk disease can safely avoid chemotherapy. The purpose of gene expression assays of tumor tissue in patients with early- stage node-negative or node-positive invasive breast cancer is to predict the 10-year risk of distant recurrence to assist with the initial treatment decisions regarding adjuvant chemotherapy and in patients with ductal carcinoma in situ (DCIS) for guiding treatment decisions such as those considering radiotherapy as an initial treatment.

Patients
The population of interest include:

- Individuals with early-stage node-negative or node-positive, hormone receptor-positive but HER2-negative, invasive breast cancer considering adjuvant chemotherapy.
- Individuals with DCIS considering initial treatment decisions.

Interventions
The interventions of interest are assays of genetic expression in tumor tissue: BluePrint, Breast Cancer Index, EndoPredict, MammaPrint, Mammostrat Breast Cancer Test, Oncotype DX Breast, Oncotype DX DCIS, Prosigna and TargetPrint.

- For individuals with early-stage invasive breast cancer, the assays would be performed following the diagnoses of early-stage node-negative or node-positive invasive breast cancer, when patients are considering adjuvant chemotherapy.
- For individuals with DCIS, the assay would be performed following the diagnosis of DCIS, when patients are considering initial treatment decisions.

Gene Expression Assay	Description
Blue Print	Is an 80 gene expression assay that classifies breast cancer into basal type, luminal type, or HER2 type. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint. This assists the physician in determining a patient's individual risk for metastasis and/or recurrence and which patients can safely forego chemotherapy.
Breast Cancer Index (BCI)	Risk of Recurrence is intended for use in patients diagnosed with estrogen receptor positive (ER+), lymph node negative early-stage invasive breast cancer. BCI provides the individualized risk of late distant recurrence of breast cancer years 5-10. Breast Cancer Index is a quantitative molecular assessment of estrogen signaling pathways HoxB13/IL17BR with a five gene molecular grade index (MGI) (BUB1B, CENPA, NEK2, RACGAP1, RRM2, H/I). This information may be used by the treating physician to guide therapy decisions by identifying which patients are sufficiently low risk of recurrence so that they can safely forgo chemotherapy. A numerical result is reported on a continuous curve delineated by high/low risk categories.
EndoPredict	Combines a breast tumor 12 gene expression signature (eight disease-relevant genes: BIRC5, UBE2C, DHCR7, RBBP8, IL6ST, AZGP1, MGP, and STC2 are compared to three RNA normalization genes CALM2, OAZ1 and RPL37A, and to one DNA reference gene HBB) with clinical features of the tumor (tumor size and nodal status) to predict the 10- year distant recurrence rate. This information may be used by the treating physician to guide therapy decisions by

	identifying which patients are sufficiently low risk of recurrence so that they can safely forgo chemotherapy.
Insight TNBCtype Test	Uses next-generation sequencing of 101 genes to generate 5 molecular subtypes, as well as a complementary immunomodulatory classifier to help predict response to immuno-oncology therapies. This may include directing selection and combination of chemotherapies, as well as to support development of novel TNBC targeted therapeutics and diagnostics.
MammaPrint **(70-Gene Signature)**	Is a 70 gene breast cancer recurrence assay that utilizes FFPE (formalin-fixed paraffin-embedded) breast tumor tissue to analyze and predict whether existing cancer has the ability to metastasize. Breast cancer recurrence and/or metastasis is partly dependent on the activation and suppression of certain genes located within the primary breast tumor. This information may be used by the treating physician to guide therapy decisions by identifying which patients are sufficiently low risk of recurrence so that they can safely forgo chemotherapy. ▪ MammaPrint provides a numerical index with a range of -1 to +1, that is overlayed with a binary low risk/high risk clinical classification system. ○ Low Risk Results: 10% chance of cancer recurrence within 10-years without any additional adjuvant treatment, either hormonal therapy or chemotherapy. ○ High Risk Results: 29% chance of cancer recurrence within 10-years without any additional adjuvant treatment, either hormonal therapy or chemotherapy.

Mammostrat Breast Cancer Test	Uses five immunohistochemical markers (SLC7A5, HTF9C, P53, NDRG1 and CEACAM5) to stratify patients regarding recurrence risk and may inform treatment decisions. The Mammostrat test measures the levels of the five immunohistochemical markers into a risk index score and the individual is assigned to a risk category high, moderate or low
Oncotype DX Breast **(21-Gene Assay)**	Is an assay that measures the expression of 21 genes (16 cancer genes and 5 reference genes) in RNA extracted from samples of tissue from a primary breast tumor. The initial indications for the 21-gene expression profile (Oncotype DX Breast) was for patients newly diagnosed with stage I or II disease that is node negative and estrogen receptor (ER) positive, invasive breast cancer who would be treated with tamoxifen. Primary validation studies enrolled node-negative women. More recently, Genomic Health has expanded their indication to include all stage II disease and IIIa (tumor ≤2 cm with spread to axillary lymph nodes or 2-5 cm without lymph node involvement) and ductal carcinoma in situ (DCIS). Results from the Oncotype DX 21-gene expression profile are combined into a Recurrence Score (RS) which is reported as a number between 0 and 100. A lower score means the cancer has a lower chance of returning, and a higher score means that there is a higher chance of the cancer returning. The score also provides patients and doctors with important information regarding the potential benefit of adding chemotherapy to hormonal therapy. A low score indicates that the patient will receive minimal benefit from chemotherapy, whereas a patient with a high score may have significant benefit from chemotherapy. Oncotype DX Breast cancer test provides information in addition to standard measurements (such as tumor size, tumor grade and lymph node status) that doctors have traditionally used to estimate how likely a patient's cancer is to return, and to help

	make treatment decisions. Each report also includes quantitative, single gene scores for ER, PR and HER2 expression. The report can guide more informed treatment decisions with information to answer critical questions in early- stage breast cancer: ▪ Quantifies a patient's 10- year risk of distant recurrence, assuming 5- years of hormonal therapy. ▪ Predicts the likelihood of chemotherapy benefit across the range of Recurrence Score results, with higher scores indicating a greater likelihood of chemotherapy benefit. ▪ Provides an individualized, quantitative risk assessment that reflects the patient's unique tumor biology, rather than just a high or low binary result. ▪ Personalized treatment decision that goes beyond clinical and pathological factors such as age, tumor size and tumor grade.
Oncotype DX Breast DCIS Score	Uses information from 12 (7 cancer related and 5 reference genes) of the 21 genes assayed in the standard Oncotype DX Breast test (21-gene expression profile) for early breast cancer to predict 10 -year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is help guide treatment decision making in women with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.
Prosigna	Is based on PAM50, the 50 gene classifier algorithm that is performed on the NanoString nCounter DX Analysis System using RNA extracted FFPE (formalin-fixed paraffin-embedded) breast tumor tissue previously diagnosed as invasive breast carcinoma. The algorithm uses a 50 gene expression profile to assign breast cancer to one of four PAM50 molecular subtypes determined by the tumors molecular profile. This qualitative assay utilizes gene expression data, weighted together with clinical variables to generate a numerical value on a 0 to 100 scale that

	correlates with the probability of distant recurrence within 10- years. This information may be used by the treating physician to guide therapy decisions by identifying which patients are sufficiently low risk of recurrence so that they can safely forgo chemotherapy. The Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated in women with hormone receptor positive and lymph node negative invasive breast cancer.
TargetPrint	Is a microarray based gene expression test that offers a quantitative assessment of ER, PR and HER2 overexpression in breast cancer. The test is marketed to be used in conjunction with MammaPrint and BluePrint. This assists the physician in determining a patient's individual risk for metastasis and/or recurrence and which patients can safely forego chemotherapy.

Comparators
The comparators of interest for all assays are clinical risk prediction algorithms. For adjuvant therapy, a conventional risk classifier (e.g., Adjuvant! Online) estimates recurrence risk by considering criteria such as tumor size, type, grade and histologic characteristics; hormone receptor status; and lymph node status. No single classifier is considered a criterion standard. Several common criteria have qualitative or subjective components that add variability for risk estimates.

Outcomes
Outcomes of interest for all assays are disease specific survival and change in disease status.

- Individuals with early- stage invasive breast cancer are classified as low risk for distance recurrence, patients may be able to forgo adjuvant chemotherapy safely.
- Individuals with DCIS are classified as low risk for distant recurrence, they may be able to safely forgo radiotherapy.

Timing

- Individuals with early- stage invasive breast cancer, the assays would be performed following the diagnosis of early stage node negative or node positive invasive breast cancer, when patients are considering adjuvant chemotherapy.
- For patients with DCIS, the assay would be performed following the diagnosis of DCIS for patients considering radiotherapy (RT).

Early- Stage Node-Negative Invasive Breast Cancer Considering Adjuvant Chemotherapy

Oncotype DX Breast (21 Gene Assay)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2011, Tang et. al. compared the prognostic and predictive utility of two tools (Oncotype DX Recurrence Score (RS) and Adjuvant! [developed using SEER registry data and results from the Early Breast Cancer Clinical Trialists' overview analyses to estimate outcome and benefit from adjuvant hormonal therapy and chemotherapy]) in node-negative, ER-positive breast cancer. RS and Adjuvant! results were available from 668 tamoxifen-treated NSABP B-14 patients: 227 tamoxifen-treated NSABP B-20 patients, and 424 chemotherapy-plus-tamoxifen-treated B-20 patients. Adjuvant! results were also available from 1952 B-20 patients. The primary endpoint was distant recurrence-free interval (DRFI). Cox proportional hazards models were used to compare the prognostic and predictive utility of RS and Adjuvant!. Both RS ($p<0.001$) and Adjuvant! ($p=0.002$) provided strong independent prognostic information in tamoxifen-treated patients. Combining RS and individual clinicopathologic characteristics provided greater prognostic discrimination than combining RS and the composite Adjuvant!. In the B-20 cohort with RS results (n=651), RS was significantly predictive of chemotherapy benefit (interaction $p=0.031$ for DRFI, $p=0.011$ for overall survival [OS], $p=0.082$ for disease-free survival [DFS]), but Adjuvant! was not (interaction $p=0.99$, $p=0.311$ and $p=0.357$, respectively). However, in the larger B-20 sub-cohort (n=1952), Adjuvant! was significantly predictive of chemotherapy benefit for OS (interaction $p=0.009$) but not for DRFI ($p=0.219$) or DFS ($p=0.099$). Prognostic estimates can be optimized by combining RS and clinicopathologic information instead of simply combining RS and Adjuvant!. The authors concluded RS should be used for estimating relative chemotherapy benefit.

Sparano et. al. (2015), performed a prospective trial involving women with hormone-receptor-positive, human epidermal growth factor receptor type 2 (HER2)-negative, axillary node-negative breast cancer with tumors of 1.1 to 5.0 cm in the greatest dimension (or 0.6 to 1.0 cm in the greatest dimension and intermediate or high tumor grade) who met established guidelines for the consideration of adjuvant chemotherapy on the basis of clinicopathologic features. A reverse-transcriptase-polymerase-chain-reaction assay of 21 genes was performed on the paraffin-embedded tumor tissue, and the results were used to calculate a score indicating the risk of breast-cancer recurrence; patients were assigned to receive endocrine therapy without chemotherapy if they had a recurrence score of 0 to 10, indicating a very low risk of recurrence (on a scale of 0 to 100, with higher scores indicating a greater risk of recurrence). Of the 10,253 eligible women enrolled, 1626 women (15.9%) who had a recurrence score of 0 to 10 were

assigned to receive endocrine therapy alone without chemotherapy. At 5- years, in this patient population, the rate of invasive disease-free survival was 93.8% (95% confidence interval [CI], 92.4 to 94.9), the rate of freedom from recurrence of breast cancer at a distant site was 99.3% (95% CI, 98.7 to 99.6), the rate of freedom from recurrence of breast cancer at a distant or local-regional site was 98.7% (95% CI, 97.9 to 99.2), and the rate of overall survival was 98.0% (95% CI, 97.1 to 98.6). The authors concluded, among patients with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who met established guidelines for the recommendation of adjuvant chemotherapy on the basis of clinicopathologic features, those with tumors that had a favorable gene-expression profile had very low rates of recurrence at 5- years with endocrine therapy alone.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Low-Risk Threshold (Recurrence Score $\leq$ 10)
Evidence for clinical validity has shown that patients within the low risk threshold for Oncotype DX may consider safely forgoing adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Intermediate-Risk Threshold (Recurrence Scores 11-25)
Sparano et. al. (2018) performed a prospective trial involving 10,273 women with hormone-receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, axillary node-negative breast cancer. Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score (21 gene expression assay) of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The trial (TAILORx) was designed to show non-inferiority of endocrine therapy alone for invasive disease-free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death). Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease-free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine versus chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease-free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local-regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease-free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women

50 years of age or younger with a recurrence score of 16 to 25. The authors concluded, adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50- years of age or younger.

High Risk (Recurrence Score ≥31)
Patient with lymph node-negative, HR-positive, HER2-negative cancers with high recurrence score (RS) (≥31) have a higher risk of distant recurrence and secondary analysis of prospective studies demonstrate a clear benefit from adjuvant chemotherapy. (NCCN Brest Cancer Version 7.2021)

Summary of Evidence
Individuals with HR- positive, HER2 negative, and node-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence and those deemed at high risk for distance recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. Systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit, and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, and gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. For individuals who have HR-positive, HER2-negative, node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21 gene assay), the recurrence score (RS) is helpful in determining the prognosis of these individuals being treated with endocrine therapy alone by predicting locoregional and distant recurrence. This assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for individuals with HR-positive, HER2-negative, node-negative invasive breast cancer. Based on the evidence which includes multiple prospective clinical trials and prospective-retrospective studies. Among patients with T1b/c lymph node negative, HR-positive, HER2 negative tumors with RS between 0-10, the risk of distant recurrence is low, and these patients derive no incremental benefit from the addition of adjuvant chemotherapy to endocrine therapy. The absolute benefit of adjuvant chemotherapy in those with intermediate RS 11-25 the recently reported TAILORx trial of postmenopausal women (n=6711) with lymph node-negative, HR-positive, HER2 negative breast cancer showed similar disease -free survival rates at 9 years in those who received adjuvant chemotherapy followed by endocrine therapy compared with endocrine therapy alone. However, in a subset analysis women 50 years of age or younger with RS 16-25 had significantly lower rates of distance recurrence with the addition of adjuvant chemotherapy to endocrine therapy. Patients with lymph node-negative, HR-positive, HER2 negative cancers with high RS ≥ 31 have a higher risk of distant recurrence and secondary analyses of prospective studies

demonstrate a clear benefit from adjuvant chemotherapy. NCCN Breast Cancer guideline (Version 7.2021) states the following: “for patients with invasive ductal or lobular tumors greater than 0.5cm in diameter and no lymph node involvement (lymph node node-negative) the NCCN panel recommends strongly considering the 21-gene RT-PCR assay to help estimate likelihood of recurrence and benefit from chemotherapy (category 1).” The evidence is sufficient to determine that the technology results in meaningful improvement in the net health outcome.

EndoPredict

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2011, Filipits et. al. assessed patients from two previously large- randomized phase III trials. According to current guidelines, molecular tests predicting the outcome of breast cancer patients can be used to assist in making treatment decisions after consideration of conventional markers. We developed and validated a gene expression signature predicting the likelihood of distant recurrence in patients with estrogen receptor (ER)–positive, HER2-negative breast cancer treated with adjuvant endocrine therapy. RNA levels were assessed by quantitative reverse transcriptase PCR in formalin fixed, paraffin-embedded tumor tissue was utilized to calculate a risk score (Endopredict, EP) consisting of eight cancer-related and three reference genes. EP was combined with nodal status and tumor size into a comprehensive risk score, EPclin. Both prespecified risk scores including cutoff values to determine a risk group for each patient (low and high) were validated independently in patients from two large- randomized phase III trials [Austrian Breast and Colorectal Cancer Study Group (ABCSG)-6: n = 378, ABCSG-8: n = 1,324]. In both validation cohorts, continuous EP was an independent predictor of distant recurrence in multivariate analysis (ABCSG-6: P = 0.010, ABCSG-8: P < 0.001). Combining Adjuvant!Online, quantitative ER, Ki67, and treatment with EP yielded a prognostic power significantly superior to the clinicopathologic factors alone [c-indices: 0.764 versus 0.750, P = 0.024 (ABCSG-6) and 0.726 versus 0.701, P = 0.003 (ABCSG-8)]. EPclin had c-indices of 0.788 and 0.732 and resulted in 10-year distant recurrence rates of 4% and 4% in EPclin low-risk and 28% and 22% in EPclin high-risk patients in ABCSG-6 (P < 0.001) and ABCSG-8 (P < 0.001), respectively. The authors concluded, the multigene EP risk score provided additional prognostic information to the risk of distant recurrence of breast cancer patients, independent from clinicopathologic parameters. The EPclin score outperformed all conventional clinicopathologic risk factors.

Buus et. al. (2016), compared the prognostic information provided by Oncotype DX recurrence score (RS) and EndoPredict (EPclin) for 10- year distant recurrence risk (DR). They used likelihood ratio χ^2 and Kaplan-Meier survival analyses to compare prognostic information provided by EP, EPclin, RS, and the clinical treatment score (CTS) of clinicopathologic parameters in 928 patients with ER+ disease treated with five years'

anastrozole or tamoxifen. Comparisons were made for early (0-5 years) and late (5-10 years) DR according to nodal status. All statistical tests were two-sided. In the overall population, EP and EPclin provided substantially more prognostic information than RS (LRχ(2): EP = 49.3; LRχ(2): EPclin = 139.3; LRχ(2): RS = 29.1), with greater differences in late DR and in node-positive patients. EP and EPclin remained statistically significantly prognostic when adjusted for RS (LRχ(2): EP+RS vs RS = 20.2; LRχ(2): EPclin+RS vs RS = 113.8). Using predefined cut-offs, EPclin and RS identified 58.8% and 61.7% patients as low risk, with hazard ratios for non-low vs low risk of 5.99 (95% confidence interval [CI] = 3.94 to 9.11) and 2.73 (95% CI = 1.91 to 3.89), respectively. The authors concluded, this study has confirmed the independent prognostic ability of EP and EPclin in postmenopausal women with ER positive/HER2 negative primary disease. EPclin provided more prognostic information than RS partly because of its integration with node and tumor size information but also because of a superior molecular component able to predict late events better than RS.

In 2018, Sestak et. al. conducted a within-patient comparison of the prognostic value of 6 multigene signatures in women with early ER-positive breast cancer who received endocrine therapy for 5- years. This retrospective biomarker analysis included 774 postmenopausal women with ER-positive ERBB2 (formerly HER2)-negative breast cancer. This analysis was performed as a preplanned secondary study of data from the Anastrozole or Tamoxifen Alone or Combined randomized clinical trial comparing 5-year treatment with anastrozole vs tamoxifen with 10-year follow-up data. The signatures included the Oncotype Dx recurrence score, PAM50-based Prosigna risk of recurrence (ROR), Breast Cancer Index (BCI), EndoPredict (EPclin), Clinical Treatment Score, and 4-marker immunohistochemical score. Data were collected from January 2009, through April 2015. The primary objective was to compare the prognostic value of these signatures in addition to the Clinical Treatment Score (nodal status, tumor size, grade, age, and endocrine treatment) for distant recurrence for 0 to 10 years and 5 to 10 years after diagnosis. Likelihood ratio (LR) statistics were used with the χ2 test and C indexes to assess the prognostic value of each signature. In this study of 774 postmenopausal women with ER-positive, ERBB2-negative disease (mean [SD] age, 64.1 [8.1] years), 591 (mean [SD] age, 63.4 [7.9] years) had node-negative disease. The signatures providing the most prognostic information were the ROR (hazard ratio [HR], 2.56; 95% CI, 1.96-3.35), followed by the BCI (HR, 2.46; 95% CI, 1.88-3.23) and EPclin (HR, 2.14; 95% CI, 1.71-2.68). Each provided significantly more information than the Clinical Treatment Score (HR, 1.99; 95% CI, 1.58-2.50), the recurrence score (HR, 1.69; 95% CI, 1.40-2.03), and the 4-marker immunohistochemical score (HR, 1.95; 95% CI, 1.55-2.45). Substantially less information was provided by all 6 molecular tests for the 183 patients with 1 to 3 positive nodes, but the BCI (LR χ2 = 9.2) and EPclin (LR χ2 = 7.4) provided more additional prognostic information than the other signatures. The authors concluded, women with node-negative disease, the ROR, BCI and EPclin were significantly more prognostic for overall and late distant recurrence. For women with 1-3 positive nodes, limited independent information was available from any test. These data might help oncologists and patients to choose the most appropriate test when considering chemotherapy use and/or extended endocrine therapy.

Clinically Useful
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Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

NCCN Breast Cancer Guideline Version 4.2022
Based on results of two Austrian Breast Cancer Study Group Trials ABCSG-6 and ABCSG-8, patients with HR-positive, HER2 negative and lymph node-negative disease with a low- risk score by the 12-gene assay had risk of distant recurrence of 4% at 10 years. The prognostic values of the risk score from the 12-gene assay was found to be independent of conventional clinicopathologic factors. Patients with T1 and T2 HR-positive, HER2-negative, and lymph node-negative tumors, a 12-gene low risk score, regardless of T size, places the tumor into same prognostic category as T1a-T1b, N0, M0.

NCCN summarizes the evidence for EndoPredict as level 2A (based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative and node negative disease.

Summary of Evidence
Individuals with HR- positive, HER2 negative, and node-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence and those deemed at high risk for distance recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. Systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. Based on the evidence the EndoPredict (12-gene assay) utilizes 12-genes to calculate a prognostic score. This assay appears to be useful in identifying a subgroup of patients with ER-positive, HER2-negative, node-negative tumors, with very low risk of recurrence without adjuvant chemotherapy and helpful in identifying patients at low risk for a late recurrence. Based on results of two Austrian Breast Cancer Study Group Trials ABCSG-6 and ABCSG-8, patients with HR-positive, HER2 negative and lymph node-negative disease with a low -risk score by the 12-gene assay had risk of distant recurrence of 4% at 10 years. The prognostic values of the risk score from the 12-gene assay was

found to be independent of conventional clinicopathologic factors. Patients with T1 and T2 HR-positive, HER2-negative, and lymph node-negative tumors, a 12-gene low risk score, regardless of T size, places the tumor into same prognostic category as T1a-T1b, N0, M0. NCCN Breast Cancer guideline (Version 4.2022) states the following: "The panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence." NCCN summarizes the evidence for EndoPredict as level 2A (based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative and node negative disease." The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2013, Sgori et. al. reported on a prospective comparison study using archival tumor blocks from the TransATAC tissue bank from all postmenopausal patients with estrogen-receptor-positive breast cancer from whom the 21-gene recurrence score and IHC4 values had already been derived. Breast cancer index (BCI) analysis was performed in matched samples with sufficient residual RNA using two BCI models-cubic (BCI-C) and linear (BCI-L)-using previously validated cutoffs. They assessed prognostic ability of BCI for distant recurrence over 10- years (the primary endpoint) and compared it with that of the 21-gene recurrence score and IHC4. We also tested the ability of the assays to predict early (0-5 years) and late (5-10 years) distant recurrence. To assess the ability of the biomarkers to predict recurrence beyond standard clinicopathological variables, we calculated the change in the likelihood-ratio $\chi(2)$ (LR-$\chi(2)$) from Cox proportional hazards models. Suitable tissue was available from 665 patients with estrogen-receptor-positive, N0 breast cancer for BCI analysis. The primary analysis showed significant differences in risk of distant recurrence over 10 -years in the categorical BCI-C risk groups ($p<0{\cdot}0001$) with 6·8% (95% CI 4·4-10·0) of patients in the low-risk group, 17·3% (12·0-24·7) in the intermediate group, and 22·2% (15·3-31·5) in the high-risk group having distant recurrence. The secondary analysis showed that BCI-L was a much stronger predictor for overall (0-10 year) distant recurrence compared with BCI-C (interquartile HR 2·30 [95% CI 1·62-3·27]; LR-$\chi(2)=22{\cdot}69$; $p<0{\cdot}0001$). When compared with BCI-L, the 21-gene recurrence score was less predictive (HR 1·48 [95% CI 1·22-1·78]; LR-$\chi(2)=13{\cdot}68$; $p=0{\cdot}0002$) and IHC4 was similar (HR 1·69 [95% CI 1·51-2·56]; LR-$\chi(2)=22{\cdot}83$; $p<0{\cdot}0001$). All further analyses were done with the BCI-L model. In a multivariable analysis, all assays had significant prognostic ability for early distant recurrence (BCI-L HR 2·77 [95% CI 1·63-4·70], LR-$\chi(2)=15{\cdot}42$, $p<0{\cdot}0001$; 21-gene recurrence score HR 1·80 [1·42-2·29], LR-$\chi(2)=18{\cdot}48$, $p<0{\cdot}0001$; IHC4 HR 2·90 [2·01-4·18], LR-$\chi(2)=29{\cdot}14$, $p<0{\cdot}0001$); however, only BCI-L was significant for late distant recurrence (BCI-L HR 1·95 [95% CI 1·22-3·14], LR-$\chi(2)=7{\cdot}97$, $p=0{\cdot}0048$; 21-gene recurrence score HR 1·13 [0·82-1·56], LR-$\chi(2)=0{\cdot}48$, $p=0{\cdot}47$; IHC4 HR 1·30 [0·88-

1·94], LR-χ(2)=1·59, p=0·20). The authors concluded BCI-L was the only significant prognostic test for risk of both early and late distant recurrence and identified two risk population for each timeframe. It could help to identify patients at high- risk for late distant recurrence who might benefit from extended endocrine or other therapy.

Zhang et. al. (2013) examined the prognostic performance of an optimized model of Breast Cancer Index (BCI), an algorithmic gene expression-based signature, for prediction of early (0-5 years) and late (>5 years) risk of distant recurrence in patients with estrogen receptor-positive (ER (+)), lymph node-negative (LN (-)) tumors. The BCI model was validated by retrospective analyses of tumor samples from tamoxifen-treated patients from a randomized, prospective trial (Stockholm TAM, n = 317) and a multi-institutional cohort (n = 358). Within the Stockholm TAM cohort, BCI risk groups stratified the majority (65%) of patients as low risk with less than 3% distant recurrence rate for 0 to 5 years and 5 to 10 years. In the multi-institutional cohort, which had larger tumors, 55% of patients were classified as BCI low risk with less than 5% distant recurrence rate for 0 to 5 years and 5 to 10 years. For both cohorts, continuous BCI was the most significant prognostic factor beyond standard clinicopathologic factors for 0 to 5 years and more than five years. The authors concluded, the prognostic sustainability of BCI to assess early and late distant recurrence risk at diagnosis has clinical use for decisions of chemotherapy at diagnosis and for decisions for extended adjuvant endocrine therapy beyond five -year.

Sestak et. al. (2018) See information above under EndoPredict.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because there are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

NCCN Breast Cancer Guideline Version 4.2022
In a secondary analysis of the ATAC trial BCI was prognostic in node-negative breast cancer for both early years 0-5 and late years 5-10 distant recurrence. For patients with T1 and T2 HR-positive, HER2 negative and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0.

NCCN summarizes the evidence for Breast Cancer Index (BCI) as level 2A (based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative and node negative disease.

Summary of Evidence
Individuals with HR- positive, HER2 negative, and node-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence and those deemed at high risk for distance recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. Systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. The Breast Cancer Index (BCI) is a combination of two profiles, the HOXB13-to-IL17BR expression ratio (H:1) ratio and the Molecular Guide Index *MGI). Compared with clinical prognostic factors (i.e., age, tumor size, tumor grade and lymph node status), the H:I ratio has been shown to be prognostic in the setting of adjuvant tamoxifen monotherapy. The addition of MGI to H:I as determined to provide additional prognostic discrimination leading the BCI assay. In a secondary analysis of the ATAC trial BCI was prognostic in node-negative breast cancer for both early years 0-5 and late years 5-10 distant recurrence. For patients with T1 and T2 HR-positive, HER2 negative and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. NCCN Breast Cancer guideline (Version 4.2022) states the following: "The panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence. NCCN summarizes the evidence for Breast Cancer Index (BCI) as level 2A (based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative and node negative disease." The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

MammaPrint (70-Gene Signature)

Clinically Valid
A test must detect the presence of absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Bueno-de-Mesquita et. al. (2011), the 70 gene prognosis signature has strong prognostic value in node-negative breast cancer, independent of established prognostic factors, and is unclear whether all node-negative patients should receive a signature result. They evaluated its additional prognostic information to a combination of established prognostic guidelines. Seven hundred and one (701) patients were evaluated in whom signature results were available. Clinical risk was on the basis of Adjuvant! Online (AO), St Gallen guidelines (St G) and Nottingham Prognostic Index (NPI). Overall survival (OS) analyses

were carried out in patients treated at the Netherlands Cancer Institute (Amsterdam) who did not receive adjuvant systemic treatment (AST). Only 6% (10 of 156) of estrogen receptor (ER)-negative tumors had a good prognosis signature. The signature was not useful for ER-positive tumors and concordant high AO, high St G and/or high NPI clinical risks (N = 139). The 10-year OS estimate for good signature tumors with these characteristics was <80% and AST would therefore be appropriate irrespective of the signature result. In contrast, for patients with a concordant low AO, low St G and/or low NPI risk and in discordant clinical risk patients, the signature identified low-risk patients in whom AST could be safely withheld (10-year OS > 90%).The authors concluded, the 70-gene prognosis signature provides additional prognostic information especially in ER-positive lymph node-negative breast cancer patients with a predominant low or discordant clinical risk on the basis of AO, St G and/or NPI.

In 2017, van 't Veer et. al., their study analyses was conducted on the Stockholm tamoxifen (STO-3) trial which randomized postmenopausal node-negative patients to 2-year tamoxifen (followed by an optional randomization for an additional 3-year tamoxifen versus nil), versus no adjuvant treatment, provides a unique opportunity to evaluate long-term 20-year benefit of endocrine therapy within prognostic risk classes of the 70-gene prognosis signature that was developed on adjunctively untreated patients. This was assessed by the Kaplan-Meier analysis 20-year breast cancer-specific survival (BCSS) and 10-year distant metastasis-free survival (DMFS) for 538 estrogen receptor (ER)-positive, STO-3 trial patients with retrospectively ascertained 70-gene prognosis classification. Multivariable analysis of long-term (20- years) BCSS by STO-3 trial arm in the 70-gene high-risk and low-risk subgroups was performed using Cox proportional hazard modeling adjusting for classical patient and tumor characteristics. Tamoxifen-treated, 70-gene low- and high-risk patients had 20-year BCSS of 90 and 83%, as compared to 80 and 65% for untreated patients, respectively (log-rank $p < 0.0001$). Notably, there is equivalent tamoxifen benefit in both high (HR 0.42 (0.21-0.86), $p = 0.018$) and low (HR 0.46 (0.25-0.85), $p = 0.013$) 70-gene risk categories even after adjusting for clinicopathological factors for BCSS. Limited tamoxifen exposure as given in the STO-3 trial provides persistent benefit for 10-15 years after diagnosis in a time-varying analysis. 10-year DMFS was 93 and 85% for low- and high-risk tamoxifen-treated, versus 83 and 70% for low- and high-risk untreated patients, respectively (log-rank $p < 0.0001$). The authors concluded, patients with ER-positive breast cancer, regardless of high or low 70-gene risk classification, receive significant survival benefit lasting over 10 years from adjuvant tamoxifen therapy, even when given for a relatively short duration.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because there are intervention studies, the preferred evidence would be from the randomized controlled trials (RCTs).

The MIDACT trail (Cardosa et. al. 2016) an international, prospective, randomized, phase 3 study sought to provide evidence on clinical utility of the addition of the 70-gene signature to standard clinical-pathologic criteria in selecting patients for adjuvant chemotherapy. They reported five- year outcomes and the results of the treatment randomization for groups with discordance in risk. From 2007 and 2011 patients were enrolled at 112 institutions in nine European countries. Eligible patients were women between the ages of 18 and 70 years with histologically confirmed primary invasive breast cancer (stage T1 or T2 or operable T3). In the initial study design all patients had to have lymph-node negative disease as described in the protocol. In August 2009, the protocol was revised to allow the enrollment of women with up to three positive axillary nodes. The study design called for following all the patients according to local standards for at least 10- years; those receiving endocrine therapy will be followed for a minimum of 15 -years. The study enrolled 6693 women with early-stage breast cancer and determined their genomic risk (using the 70-gene signature) and their clinical risk (using a modified version of Adjuvant! Online). Women at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did receive such therapy. In patients with discordant risk results, either the genomic risk or the clinical risk was used to determine the use of chemotherapy. The primary goal was to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be 92% (i.e., the noninferiority boundary) or higher. A total of 1550 patients (23.2%) were deemed 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% confidence interval, 92.5 to 96.2) among those not receiving chemotherapy. The absolute difference in this survival rate between these patients and those who received chemotherapy was 1.5 percentage points, with the rate being lower without chemotherapy. Similar rates of survival without distant metastasis were reported in the subgroup of patients who had estrogen-receptor-positive, human epidermal growth factor receptor 2-negative, and either node-negative or node-positive disease. The authors concluded, in a large group of patients at high clinical risk for breast cancer recurrence, the addition of the 70-gene signature to the traditional clinical and pathological factors provided valuable information for considering which patients might benefit from adjuvant chemotherapy. Chemotherapy with its attendant toxic effects could be avoided in these patients at high clinical risk but low genomic risk at a cost of a risk of distant metastasis at 5- years that is 1.5 percentage points higher. Follow-up is ongoing to determine whether these conclusions remain valid for longer-term outcome.

Indirect evidence on clinical utility rests on clinical validity, if the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. However, evidence for clinical validity has shown that MammaPrint is able to identify

women who can safely forgo adjuvant chemotherapy and thereby avoid effects of the therapy.

Summary of Evidence

Individuals with HR- positive, HER2 negative, and node-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence and those deemed at high risk for distance recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. Systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. MammaPrint (70-gene assay) utilizes FFPE (formalin-fixed paraffin-embedded) breast tumor tissue to analyze and predict whether existing cancer has the ability to metastasize. Breast cancer recurrence and/or metastasis is partly dependent on the activation and suppression of certain genes located within the primary breast tumor. This information may be used by the treating physician to guide therapy decisions by identifying which patients are sufficiently low risk of recurrence so that they can safely forgo chemotherapy. MammaPrint provides a numerical index with a range of -1 to +1, that is overlaid with a binary low risk/high risk clinical classification system: Low Risk Result: 10% chance of cancer recurrence within 10- years without any additional adjuvant treatment, either hormonal therapy or chemotherapy; High Risk Results: 29% chance of cancer recurrence within 10 years without any additional adjuvant treatment, either hormonal therapy or chemotherapy. Results from the randomized-MINDACT trials, demonstrated that the 70-gene assay can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade, nodal status). In this trial 79% had lymph node negative disease and 21% and 1-3 positive lymph nodes and all patients underwent risk assessment by clinical criteria (using Adjuvant! Online) and genomic risk assessment by the 70-gene assay. Patients with low-risk disease according to both clinical criteria and genomic assay results did not receive adjuvant chemotherapy, whereas patients categorized as high-risk by both assessments received chemotherapy. Patients with discordant results (e.g., either high clinical risk/low genomic risk) were randomized to the chemotherapy group or the no-chemotherapy group, on the basis of either the clinical result or the genomic result. The primary outcome of the study was met with the demonstration that among those with high clinical risk/low genomic risk, the 5-year rate of survival without distant metastasis in those who did not receive adjuvant chemotherapy was 94.7% (95% CI, 92.5 to 96.2). NCCN Breast Cancer guideline (Version 4.2022) states the following: “The panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence. Also, amongst the other assays, the panel has listed the 70-gene assay as a category 1 option based on the results of the prospective MINDACT trial demonstrating

the ability of the 70-gene assay to identify a good genomic risk population despite a high clinical risk, in who chemotherapy may be omitted with a detrimental effect." The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Prosigna (PAM50)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2013, Dowsett et. al. compared PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. mRNA from 1,017 patients with ER-positive primary breast cancer treated with anastrozole or tamoxifen in the ATAC trial was assessed for risk of recurrence (ROR) using the NanoString nCounter. Likelihood ratio (LR) tests and concordance indices (c indices) were used to assess the prognostic information provided beyond that of a clinical treatment score (CTS) by RS (recurrence score), ROR (risk of recurrence), or IHC4, an index of DR (distant recurrence) risk derived from immunohistochemical assessment of ER, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and Ki67. ROR added significant prognostic information beyond CTS in all patients (LR-$\chi(2) = 33.9$; $P < .001$) and in all four subgroups: node negative, node positive, HER2 negative, and HER2 negative/node negative; more information was added by ROR than by RS. C indices in the HER2-negative/node-negative subgroup was 0.73, 0.76, and 0.78 for CTS, CTS plus RS, and CTS plus ROR, respectively. More patients 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 patients but more by ROR in the HER2-negative/node-negative group. The authors concluded, ROR provides more prognostic information to endocrine treated patients with ER positive, node-negative disease than RS, with better differentiation of intermediate and higher risk groups.

Gnant et. al. (2014) reported on 1478 postmenopausal women with estrogen receptor (ER) positive early breast cancer (EBC) treated with tamoxifen or tamoxifen followed by anastrozole from the prospective randomized ABCSG-8 trial were entered into this study. Patients did not receive adjuvant chemotherapy. RNA was extracted from paraffin blocks and analyzed using the PAM50 test. Both intrinsic subtype (luminal A/B, HER2-enriched, basal-like) and risk of recurrence (ROR) score were calculated. The primary analysis was designed to test whether the continuous ROR score adds prognostic value in predicting distant recurrence (DR) over and above standard clinical variables. In all tested subgroups, ROR score significantly adds prognostic information to the clinical predictor ($P<0.0001$). PAM50 assigns an intrinsic subtype to all cases, and the luminal A cohort had a significantly lower ROR at 10 years compared with Luminal B ($P<0.0001$). Significant and clinically relevant discrimination between low- and high-risk groups occurred also within all tested subgroups. The authors concluded, the results of the primary analysis, in combination with recently published results from the ATAC trial,

constitute Level 1 evidence for clinical validity of the PAM50 test for predicting the risk of DR in postmenopausal women with ER positive EBC. A 10-year metastasis risk of <3.5% in the ROR low category makes it unlikely that additional chemotherapy would improve this outcome-this finding could help to avoid unwarranted overtreatment.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary treating.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

NCCN Breast Cancer Guideline Version 4.2022
In a study from the Danish Breast Cancer Cooperative Group database, patients with lymph node-negative tumors and low ROR had a distant recurrence risk of 5.0% (95% CI, 2.9% to 8.0%) whereas tumors with high ROR had a distant recurrence risk of 17.8% (95% CI, 140% to 22.0%). Based on this analysis, patients with T1 and T2, HR, positive, HER2-negative, lymph node-negative tumors, a ROR score in the low range, regardless of tumor size, places the individual into the same prognostic category as those with T1a-T1b, N0, M0 tumors.

NCCN summarizes the evidence for Prosigna (Pam50) as level 2A (based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative and node negative disease.

Summary of Evidence
Individuals with HR- positive, HER2 negative, and node-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence and those deemed at high risk for distance recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. Systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. The Prosigna assay (50-gene assay, PAM50) risk of recurrence (ROR) score stratifies patients into high, medium and low risk groups. Several studies have demonstrated the prognostic value of ROR score in estimating risk of disease recurrence. In a study from

the Danish Breast Cancer Cooperative Group database, patients with lymph node-negative tumors and low ROR had a distant recurrence risk of 5.0% (95% CI, 2.9% to 8.0%) whereas tumors with high ROR had a distant recurrence risk of 17.8% (95% CI, 140% to 22.0%). Based on this analysis, patients with T1 and T2, HR, positive, HER2-negative, lymph node-negative tumors, a ROR score in the low range, regardless of tumor size, places the individual into the same prognostic category as those with T1a-T1b, N0, M0 tumors. NCCN Breast Cancer guideline (Version 4.2022) states the following: "The panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence. NCCN summarizes the evidence for Prosigna (Pam50) as level 2A (based upon lower level of evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative and node negative disease." The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Early- Stage HR-Positive, Her2-Negative, Node-Positive Invasive Breast Cancer Considering Adjuvant Chemotherapy

NCCN Breast Cancer Guideline Version 4.2022
For patients with four or more involved nodes the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Oncotype DX Breast (21 Gene Assay)

Clinically valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Albain et. al. (2010) performed a retrospective analysis on the prognostic and predictive value of the 21 gene recurrence score assay in postmenopausal women with node-positive, estrogen-receptor positive breast cancer on chemotherapy. The phase 3 trial SWOG-8814 for postmenopausal women with node-positive, estrogen-receptor-positive breast cancer showed that chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil (CAF) before tamoxifen (CAF-T) added survival benefit to treatment with tamoxifen alone. Optional tumor banking yielded specimens for determination of recurrence score by RT-PCR. In this retrospective analysis, they assessed the effect of recurrence score on disease-free survival by treatment group (tamoxifen vs CAF-T) using Cox regression, adjusting for number of positive nodes. There were 367 specimens (40% of the 927 patients in the tamoxifen and CAF-T groups) with sufficient RNA for analysis (tamoxifen, n=148; CAF-T, n=219). The recurrence score was prognostic in the tamoxifen-alone group (p=0.006; hazard ratio [HR] 2.64, 95% CI 1.33-5.27, for a 50-point difference in recurrence score). There was no benefit of CAF in patients with a low recurrence score (score <18; log-rank p=0.97; HR 1.02, 0.54-1.93), but an improvement in disease-free survival for those with a high recurrence score (score > or =31; log-rank p=0.033; HR 0.59, 0.35-1.01), after adjustment for number of positive nodes. The recurrence score by treatment interaction was significant in the first 5- years (p=0.029),

with no additional prediction beyond 5 years (p=0.58), although the cumulative benefit remained at 10- years. Results were similar for overall survival and breast-cancer-specific survival. The authors concluded, the recurrence score using the 21-gene recurrence score assay is prognostic for tamoxifen-treated patients with positive nodes and predicts significant benefit of CAF in tumors with a high recurrence score. A low recurrence identifies women who might not benefit from anthracyline-based chemotherapy, despite positive nodes.

Dowsett et. al. (2010) examined a sample of node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen to predict the risk of distant recurrence using the 21-gene recurrence score from the TransATAC study (tamoxifen alone or in combination). RNA was extracted from 1,372 tumor blocks from postmenopausal patients with hormone receptor-positive primary breast cancer in the monotherapy arms of ATAC. Twenty-one genes were assessed by quantitative reverse transcriptase polymerase chain reaction, and the RS was calculated. Cox proportional hazards models assessed the value of adding RS (recurrence score) to a model with clinical variables (age, tumor size, grade, and treatment) in node-negative (N0) and node-positive (N+) women. Reportable scores were available from 1,231 evaluable patients (N0, n = 872; N+, n = 306; and node status unknown, n = 53); 72, 74, and six DRs (distant recurrence) occurred in N0, N+, and node status unknown patients, respectively. For both N0 and N+ patients, RS was significantly associated with time to DR in multivariate analyses (P < .001 for N0 and P = .002 for N+). RS also showed significant prognostic value beyond that provided by Adjuvant! Online (P < .001). Nine-year DR rates in low (RS < 18), intermediate (RS = 18 to 30), and high RS (RS > or = 31) groups were 4%, 12%, and 25%, respectively, in N0 patients and 17%, 28%, and 49%, respectively, in N+ patients. The prognostic value of RS was similar in anastrozole- and tamoxifen-treated patients. The authors concluded, this study confirmed the performance of RS (recurrence score) in postmenopausal HR positive patients treated with tamoxifen in a large contemporary population and demonstrated that RS is an independent predictor of DRA in No and N + (positive) hormone receptor positive patients treated with anastrozole, adding value to estimates with standard clinicopathologic features.

In 2017, Nitz et. al. a prospective randomized phase 3 PlanB trial used the Oncotype DX Recurrence Score (RS) to define a genomically low-risk subset of clinically high-risk pN0-1 early breast cancer (EBC) patients for treatment with adjuvant endocrine therapy (ET) alone. They reported on five-year data evaluating the prognostic value of RS, Ki-67, and other traditional clinicopathological parameters. A central tumor bank was prospectively established within PlanB. Following an early amendment, hormone receptor (HR)+, pN0-1 RS ≤ 11 patients were recommended to omit chemotherapy. Patients with RS ≥ 12, pN2-3, or HR-negative/HER2-negative disease was randomized to anthracycline-containing or anthracycline-free chemotherapy. Primary endpoint: disease-free survival (DFS). From 2009 to 2011, PlanB enrolled 3198 patients (central tumor bank, n = 3073) with the median age of 56 years, 41.1% pN+, and 32.5% grade 3 EBC. Chemotherapy was omitted in 348/404 (86.1%) eligible RS ≤ 11 patients. After

55 months of median follow-up, five-year DFS in ET-treated RS ≤ 11 patients were 94% (in both pN0 and pN1) versus 94% (RS 12-25) and 84% (RS > 25) in chemotherapy-treated patients ($p < 0.001$); five-year overall survival (OS) was 99 versus 97% and 93%, respectively ($p < 0.001$). Nodal status, central/local grade, tumor size, continuous Ki-67, progesterone receptor (PR), IHC4, and RS were univariate prognostic factors for DFS. In a multivariate analysis including all univariate prognostic markers, only pN2-3, central and local grade 3, tumor size >2 cm, and RS, but not IHC4 or Ki-67 were independent adverse factors. If RS was excluded, IHC4 or both Ki-67 and PR entered the model. The impact of RS was particularly pronounced in patients with intermediate Ki-67 (>10%, <40%) tumors. The authors concluded, 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-positive HER2-negative EBC. Ki-67 has the potential to support patient selection for genomic testing.

Wang et al. (2018) examined the value of Oncotype Dx when determining the prognosis in female breast cancer patients with tumor stage 1-2 (tumor is 20-55mm), positive in 1-3 lymph nodes and no evidence of metastasis (T1-2 N1M0). The study reviewed 4059 cases to categorize them to prognostic stages IA and IIB and used data derived from the National Cancer Institute's limited use Surveillance, Epidemiology, and End Results (SEER) 18 registry databases, released in November 2017. Cases in the SEER database were linked to recurrence score (RS) results from assays performed by Genomic Health. All cases with RS had negative HER2, and the authors selected female ER-positive invasive ductal carcinoma cases in T1-2N1M0 stage with Oncotype RS results diagnosed between 2004 and 2012. Patients were categorized into low-risk (RS<11), intermediate-risk (RS 11–25), and high-risk (RS >25) groups. The median patient age was 59 years. Of these patients, 2898 (71.4%) had stage T1 cancer, 1854 (45.7%) had stage N1mic cancer, 743 (18.3%) had grade 3 cancer, and 3746 (92.3%) had positive PR status. They were stratified into the RS low-risk group (794, 19.6%), the RS intermediate-risk group (2667, 65.7%), and 598 (14.7%) were in the RS high-risk group. The high-risk group tended to have younger patients, larger tumors, a higher percentage of grade 3 disease, negative PR, and more advanced cancer staging. They also had more frequent use of chemotherapy. Otherwise, the RS groups did not differ much in race, N stage, surgery, or radiation. In terms of pathological prognostic stages, there were 2781 patients (68.5%) in stage IA, 829 (20.4%) in stage IB, 360 (8.9%) in IIA, and 89 (2.2%) in IIB. The distributions of clinical and pathological characteristics, including breast cancer specific survival (BCSS) and overall survival (OS), were compared between RS and pathological staging groups using a variety of statistical analysis. The median follow-up period was 57 months. The results showed a statistically significant correlation ($p<.001$) between the RS groups and pathological stage results. In the low and high-risk RS groups, the BCSS and OS were similar between RS and pathological staging groups. In the intermediate RS group, however, survival rates differed significantly between RS staging and pathological staging. The survival rates were inversely correlated with the escalation of prognostic stages. Similar trends were seen in the high-risk group but were not statistically significant. In this retrospective study, RS was an independent prognosticator for BCSS,

and with pathological stage for OS. The authors concluded that Oncotype Dx could complement the prognostic staging system in node positive patients.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

NCCN Breast Cancer guideline version 4.2022 states the following regarding Oncotype DX in node positive, HR-positive, HER-2 negative tumors:

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene (Oncotype DX) for pN1 (1-3 positive nodes)	Yes	Yes	Postmenopause Preferred Premenopausal: Other	1 2A

Use of Multigene Assays in Axillary Lymph-Node-Positive HR-Positive, HER2-Negative Tumors
For patients with four or more involved nodes the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Patients with less than four involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis, are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant chemotherapy be based on elements of clinical risk stratification such as clinical characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision making.

The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. While a secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillar lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS ($\geq$ 31) from the 21-gene assay. At this time the optimal RS cut-off (<11 versus <18) to withhold chemotherapy for HR-positive, HER2-negative, 1-3 lymph node-positive tumors is still unknown. The results of the Rx-PONDER rial, are expected to determine the benefit (if any) of chemotherapy. In the MINDACT trial, among patients with 1-3 positive nodes who had high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group. Other multigene assays have not proven to be predictive of benefit from chemotherapy.

Summary of Evidence

The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. Results from prospective and retrospective studies have suggested using Oncotype DX recurrence risk score for treatment decisions in early- stage node positive breast cancer may identify those women who can safely forgo adjuvant chemotherapy and thereby avoid negative effects of therapy. NCCN Breast Cancer guideline version 4.2022 for invasive breast cancer for the use of multigene assays in axillary lymph-node-positive HR-positive, HER2-negative tumors states: “The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. A secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillar lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS ($\geq$ 31) from the 21-gene assay. The ongoing RxPonder trial is randomizing patients with early- stage estrogen receptor-positive, HER2-negative breast cancer and 1 to 3 positive nodes, stratified by RS (recurrence score) (0 to 13, 14 to 25) to adjuvant chemotherapy or no adjuvant chemotherapy. Results of the trial will most likely define utility of the RS in node-positive patients. Oncotype Dx for breast cancer is considered a preferred test by NCCN for pN0 or node-negative patients (Level 1 based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate)

and is considered prognostic for pN+ or node positive with an evidence level of 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate). NCCN noted that they were waiting on the results of the Rxponder study to comment on Oncotype Dx to be predictive." The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2011, Filipits et. al. evaluated the potential prognostic value of EndoPredict EP and EPclin risk scores among node-positive patients in a combined analysis of ABCSG-6 and ABCSG-8 trial samples. Of the 537 node-positive patients, 85% had a single positive node, 240 were classified as EP low risk and 297 were classified as EP high risk. The 10-year absence of distant recurrence for node-positive patients was shown in a Kaplan-Meier curve. The 10- year absence of distant recurrence estimate for node-positive patients appears to be about 85% in EP low risk and 73% in high- risk patients. CIs were not provided. The 10- year absence of distance recurrence estimates for the EPclin low - risk group and EPclin high- risk group were 94.9% (95% CI, 90.8% to 99.0%) and 72.2% (95% CI, 65.6% and 78.8%), respectively.

Buus et. al. (2016) reported on the prognostic value of EndoPredict among node-positive patients from ATAC trial. Of the 248 node-positive patients, 80% had a single positive node, 94 were classified as EP low risk, and 154 were classified as EP high risk; 47 were classified as EPclin low risk and 201 were classified as EPclin high- risk. The 10- year distant recurrence-free survival for EP low and high risk were 21.3% (95% CI, 13.9% to 31.9%) and 36.4% (95% CI, 28.9% to 45.2%), respectively. The 10- year distant recurrence-free rate for EPclin low and high- risk were 5.0% (95% CI, 1.2% to 18.9%) and 36.9% (95% CI, 30.2% to 44.5%), respectively.

In 2019, Filipits et.al. reevaluated the prognostic value of the 12-gene expression assay EndoPredict in the combined ABCSG-6/8 cohorts with longer clinical follow-up. EndoPredict was evaluated with ER-positive, HER2-negative node positive and node negative breast cancer who received 5 -years of endocrine therapy only (median follow-up, 9.6 years; N=1,702). Distant recurrence-free rate (DRFR; 95% confidence interval) was assessed 10 and 15- years after diagnosis. Overall, 62.6% of patients had low-risk EndoPredict clinical scores with significant improved DRFR relative to high-risk patients (HR, 4.77; 95% CI, 3.37-6.67; P < 0.0001). Ten- year DRFR (0-10 years) was improved among patients with low risk versus high risk EndoPredict clinical scores in the full cohort (95.5% [94.1%-97.0%) versus 80.3% [76.9%-83.9%]) as well as for patients with node negative disease (95.5% [94.0%-97.1%] versus 87.0% [82.6%-91.7%]) or with 1 to 3 positive nodes (95.6% [92.2%-99.1%) versus 80.3% [76.9%-83.9%]). The molecular and EndoPredict clinical scores were significant predictors of DRFR after adjusting for

clinical variables, regardless of nodal status. Similar results were observed for late recurrence (5-15 years; HR, 4.52; 95% CI, 2.65-7.72; P < 0.0001). The EndoPredict clinical score significantly added prognostic information to the late metastasis nomogram (CTS5 score; P < 0.001). A limitation of this study is the number of patients with follow-up data beyond 12 -years. Although the maximum follow-up time was over 15- years, there were very few evaluable patients at the 15-year time point. As such, Kaplan–Meier survival analysis was limited in power for some patient subgroups. For example, the 5 to 15-year DRFR for patients with node-positive disease was similar for low-risk (87.0%) and high-risk patients (84.0%). This is driven by the limited power at 15- years for this subgroup. However, DRFR curves for high- and low-risk patients with node-positive disease are significantly different at earlier time points. This is consistent with existing data on late-recurrence from 5 to 10 -years and may still support different treatment decisions for high- and low-risk patients. In addition, the longer-term follow-up data presented here was sufficiently powered to assess the value of a prognostic assay in the 5 to 15-year time frame for the first time in the whole cohort of patients. The authors concluded the data presented demonstrated the prognostic value of the EndoPredict clinical score in predicting early and late distant recurrence among women ER-positive, HER2-negative breast cancer. The EndoPredict score was a significant predictor of DRFR among women with newly diagnosed disease, which may aid in identifying patients having most likely no additional benefit from adjuvant chemotherapy. This is of particular importance for women with 1 to 3 positive nodes who have low-risk disease and would likely receive chemotherapy without the added prognostic information obtained from EndoPredict clinical score. In addition, there is significant prognostic value in predicting 15-year distant recurrence among women who are distant recurrence-free at 5 years and are faced with the decision of whether or not to extend endocrine therapy. Collectively, this demonstrates the prognostic value of the 12-gene molecular assay in making treatment decisions for women with ER-positive, HER2-negative breast cancer.

Clinically Useful
A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

NCCN Breast Cancer Guideline Version 4.2022

12 gene-assay (EndoPredict): In TransTAC study, patients with 1-3 positive nodes in the low- risk group and a 5.6% risk of distant recurrence at 10- years, suggesting that chemotherapy would be of limited benefit in these women.

Use of Multigene Assays in Axillary Lymph-Node-Positive HR-Positive, HER2-Negative Tumors

Patients with less than four involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis, are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant chemotherapy be based on elements of clinical risk stratification such as clinical characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision making. The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. While a secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillar lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS ($\geq$ 31) from the 21-gene assay. At this time the optimal RS cut-off (<11 versus <18) to withhold chemotherapy for HR-positive, HER2-negative, 1-3 lymph node-positive tumors is still unknown. The results of the Rx-PONDER rial, are expected to determine the benefit (if any) of chemotherapy. In the MINDACT trial, among patients with 1-3 positive nodes who had high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group. Other multigene assays have not proven to be predictive of benefit from chemotherapy.

Summary of Evidence

The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. For individuals who have early-stage HR-positive, HER2-negative, node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 2 prospective-retrospective analyses. In the TransTAC study, patients with 1-3 positive nodes in the low- risk group had a 5.6% risk of distant recurrence at 10 years. Suggesting that chemotherapy would be of limited benefit in these individuals. NCCN Breast Cancer Guideline Version 4.2022 summarizes

the evidence as level 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2-negative, and node negative or 1-3 node positive. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index (BCI)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2017, Zhang et al. examined the predictive ability of Breast Cancer Index (BCI) results, when integrated with tumor size and grade (BCIN), to accurately identify outcomes in a well annotated retrospective series of node positive patients. A total of 402 patients with 1-3 positive nodes who were treated with adjuvant endocrine therapy with or without chemotherapy using a prespecified model. The primary endpoint was time-to-distant recurrence (DR). BCIN classified 20% of patients as low- risk with a 15-year DR rate of 1.3% and 321 patients as high risk with a DR risk of 29%. When the results were unblinded and compared to participant outcome, BCI alone was significantly prognostic ($p<.0001$), and when tumor size was added the prognostic ability was even further improved ($p<.0003$) but only incrementally with adding tumor grade ($p=.01$). Overall, BCIN identified 20% of node positive patients with a limited risk of recurrence over 15 years that could avoid extended endocrine treatment. Further studies on combined genomic and clinical algorithmic predictions are needed on node positive patients.

Clinically Useful
A test is clinically useful if the use of the result informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

NCCN Breast Cancer Guideline Version 4.2022 states the following regarding Breast Cancer Index (BCI), “there are limited data as the role of BCI in HR-positive, HER2-negative, and lymph node-positive breast cancer.”

Summary of Evidence
The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of

recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. A study by Zhang et. al. in 2017 examined the predictive ability of Breast Cancer Index (BCI) results, when integrated with tumor size and grade (BCIN), to accurately identify outcomes in a well annotated retrospective series of node positive patients. A total of 402 patients with 1-3 positive nodes who were treated with adjuvant endocrine therapy with or without chemotherapy using a prespecified model. The primary endpoint was time-to-distant recurrence (DR). The authors of this study concluded further studies on combined genomic and clinical algorithmic predictions are needed on node positive patients. NCCN Breast Cancer Guideline Version 7.2021 states the following regarding Breast Cancer Index (BCI), "there are limited data as the role of BCI in HR-positive, HER2-negative, and lymph node-positive breast cancer." The evidence is insufficient to determine the effects of this testing on net health outcomes.

MammaPrint (70 Gene Signature)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The previously described MINDACT trials (Cardosa et. al. 2016) initially enrolled only patients with node-negative disease but began including women with 1 to 3 positive nodes in 2009. The MINDACT trials demonstrated that the 70-gene assay (MammaPrint)can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade, nodal status). In this trial 79% had lymph node negative disease and 21% and 1-3 positive lymph nodes and all patients underwent risk assessment by clinical criteria (using Adjuvant! Online) and genomic risk assessment by the 70-gene assay. Patients with low-risk disease according to both clinical criteria and genomic assay results did not receive adjuvant chemotherapy, whereas patients categorized as high-risk by both assessments received chemotherapy. Patients with discordant results (e.g.. either high clinical risk/low genomic risk) were randomized to the chemotherapy group or the no-chemotherapy group on the basis of either the clinical result or the genomic result. The primary outcome of the study was met with the demonstration that among those with high clinical risk/low genomic risk, the 5-year rate of survival without distant metastasis in those who did not receive adjuvant chemotherapy was 94.7% (95% CI, 92.5 to 96.2).

Clinically Useful
NCCN Breast Cancer Guideline Version 7.2021: Use of Multigene Assays in Axillary Lymph-Node-Positive HR-Positive, HER2-Negative Tumors
Patients with less than four involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis, are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant

chemotherapy be based on elements of clinical risk stratification such as clinical characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision making. The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. While a secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillar lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS ($\geq$ 31) from the 21-gene assay. At this time the optimal RS cut-off (<11 versus <18) to withhold chemotherapy for HR-positive, HER2-negative, 1-3 lymph node-positive tumors is still unknown. The results of the Rx-PONDER rial, are expected to determine the benefit (if any) of chemotherapy. In the MINDACT trial, among patients with 1-3 positive nodes who had high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group. Other multigene assays have not proven to be predictive of benefit from chemotherapy.

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The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. Based on the evidence from the MINDACT trial among patients with 1-3 positive nodes who had high clinical risk or recurrence but low risk by the 70-gene assay (MammaPrint), the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group. NCCN Breast Cancer Guideline version 7.2021 summarizes the evidence for MammaPrint as level 1 (based upon high level evidence, there is uniform NCCN consensus that the intervention is appropriate) for use in patients with node negative or 1-3 node positive breast cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Prosigna (PAM 50)

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Grant et. al. (2015) examined the potential prognostic value of the PAM50 ROR (risk of recurrence) score, including clinical predictors, among node-positive patients in a combined analysis of the ABCSG-8 and ATAC trial samples. Samples from 543 patients treated with endocrine therapy alone were included, and 10-year distant recurrence (the primary end point) analyzed. Among patients with a single positive node and a low- risk score, a 10-year distant recurrence occurred in 6.6% (95% CI, 3.3% to 12.8%). In all other risk categories or with 2 or 3 positive nodes, distant recurrence rates were considerably higher with upper bounds for the 95% CIs of 25% or more. Overall survival (OS) was not included in the report.

In 2018, Laenkholm et. al. evaluated PAM50 Risk of Recurrence Score predicting 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. The PAM50-based Prosigna risk of recurrence (ROR) score has been validated in randomized clinical trials to predict 10-year distant recurrence (DR). The value of Prosigna for predicting DR was examined in a comprehensive nationwide Danish cohort consisting of postmenopausal women with hormone receptor-positive early breast cancer treated with 5 -years of endocrine therapy alone. Patients and Methods Using the population-based Danish Breast Cancer Cooperative Group database, follow-up data were collected on all patients diagnosed from 2000 through 2003 who, by nationwide guidelines, were treated with endocrine therapy for 5- years. Primary tumor blocks from 2,740 patients were tested with Prosigna and, after determination of human epidermal growth factor receptor 2 (HER2) status, data from 2,558 hormone receptor-positive/HER2-negative samples were analyzed, including 1,395 node-positive patients. Fine and Gray models were applied to determine the prognostic value of ROR for DR. Results Median follow-up for recurrence was 9.2 years. Twenty-six percent of the node-positive patients were classified as low ROR (n = 359) with a DR risk of 3.5% (95% confidence interval [CI], 1.9% to 6.1%) versus a DR risk of 22.1% (95% CI, 18.6% to 25.8%) at 10- years for patients classified as high ROR (n = 648). Node-negative patients classified as low and high ROR had a risk of DR of 5.0% (95% CI, 2.9% to 8.0%) and 17.8% (95% CI, 14.0% to 22.0%), respectively. Luminal B tumors (n = 947; DR risk, 18.4% [95% CI: 15.7% to 21.3%]) had a significantly worse outcome than luminal A tumors (n = 1,474;DR risk, 7.6% [95% CI: 6.1% to 9.2%]; P < .001). Conclusion Prosigna ROR score improved the prediction of outcome in this nationwide Danish population. In a real-world setting, Prosigna can reliably identify node-negative patients and a significant proportion of patients with one to three positive nodes who can be spared treatment with adjuvant chemotherapy.

Clinically Useful
A test is clinically useful if the use of the result informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

NCCN Breast Cancer Guideline Version 7.2021: Use of Multigene Assays in Axillary Lymph-Node-Positive HR-Positive, HER2-Negative Tumors
Patients with less than four involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis, are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant chemotherapy be based on elements of clinical risk stratification such as clinical characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision making. The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. While a secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillar lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS ($\geq$ 31) from the 21-gene assay. At this time the optimal RS cut-off (<11 versus <18) to withhold chemotherapy for HR-positive, HER2-negative, 1-3 lymph node-positive tumors is still unknown. The results of the Rx-PONDER rial, are expected to determine the benefit (if any) of chemotherapy. In the MINDACT trial, among patients with 1-3 positive nodes who had high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group. Other multigene assays have not proven to be predictive of benefit from chemotherapy.

Summary of Evidence
The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see benefit and a better predictor of

recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. Based on review of the peer reviewed medical literature and NCCN Breast Cancer guideline version 4.2022 summarizes the evidence for Prosgina (PAM50) as level 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) for breast cancer patients with hormone receptor positive, HER2 -negative, and node negative or 1-3 positive. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Additional Gene Expression Assays in Breast Cancer

BluePrint and TargetPrint

Gene expression patterns have led to the identification of molecular subtypes of breast cancer, which have different prognoses and responses to treatment regimens. These molecular subtypes are largely distinguished by differential expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) in the tumor, and are classified as luminal basal, or HER2 type. Luminal type breast cancers are ER-positive; basal type breast cancers correlate best with ER-, PR- and HER2- negative (triple negative) tumors, and HER2 type, with high expression of HER2.

At present, methodology for molecular subtyping is not standardized, and breast cancer subtyping is routinely assessed by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH).

BluePrint is an 80- gene expression assay that classifies breast cancer into basal type, luminal type, or HER2 type. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint. This assists the physician in determining a patient’s individual risk for metastasis and/or recurrence and which patients can safely forego chemotherapy.

In 2018, van Steenhoven et al. evaluated the ability of 70-GS ("Mammaprint") and 80-GS ("BluePrint") molecular subtyping to surrogate pathological subtyping (PS) for determining treatment options and prognosis. Between 2013 and 2015, 595 intermediate risk ER+ early-stage breast cancer patients were studied. HER2 receptor status was determine through routine immunohistochemisty and fluorescent in situ hybridization. The overall concordance between molecular sub-typing and PS for luminal cancers type A and B together was 98%. Individually it was poor, at 64%. The ability of the 80-GS assay to differentiate between luminal, HER2-type and basal-like cancers was limited, and furthermore the concordance between PS and the 70-GS approach was low. The authors concluded that two classification methods had significant disparity in outcomes, resulting in the risk of inadequate treatment. More studies are needed to demonstrate the efficacy of this test.

TargetPrint is a microarray- based gene expression test that offers a quantitative assessment of ER, PR and HER2 overexpression in breast cancer. The test is marketed to be used in conjunction with MammaPrint and BluePrint. This assists the physician in determining a patient's individual risk for metastasis and/or recurrence and which patients can safely forego chemotherapy.

Summary of Evidence
The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. Based on review of the peer reviewed medical literature. The 80-gene expression assay BluePrint discriminates among three breast cancer molecular subtypes, and TargetPrint is a method to measure ER, PR, and HER2 as an alternative to immunohistochemistry and FISH. Clinical utility of BluePrint is unknown, as it is unclear how this test will add to treatment decision making using currently available, accepted methods (i.e., clinical and pathologic parameters). The incremental benefit of using TargetPrint as an alternative to current standard methods of measuring ER, PR and HER2 has not been demonstrated, nor is it included in recommendations for testing issued by the American Society of Clinical Oncology (ASCO) or NCCN. Additional studies are needed related to both of these assays to demonstrate their efficacy. The evidence is insufficient to determine the effects of this testing on net health outcomes.

Mammostrat
Patients with early- stage breast cancer, treated with endocrine therapy, have approximately 90% 5-year disease free survival. However, some postmenopausal patients with hormone sensitive early breast cancer remain at high- risk of relapse despite endocrine therapy and, in addition, might benefit from adjuvant chemotherapy. The challenge is to prospectively identify such patients. The Mammostrat test uses five immunohistochemical markers (SLC7A5, HTF9C, P53, NDRG1 and CEACAM5) to stratify patients regarding recurrence risk and may inform treatment decisions. The Mammostrat test measures the levels of the five immunohistochemical markers into a risk index score and the individual is assigned to a risk category high, moderate, or low.

The existing studies include a single validation study and randomized clinical trials. Bartlett and others published the results of a study evaluating the efficacy of Mammostrat in a multinational randomized open label phase III trial (TEAM trial) in postmenopausal women with hormone receptor positive early breast cancer testing the efficacy of 5- years of exemestane (25 mg once per day) versus tamoxifen (20 mg once per day for 2.5 to 3- years) followed by exemestane (for another 2.5 to 2- years). 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 disease-free survival 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 disease-free survival, no significant benefit from Mammostrat was seen (p=0.085). When a multivariate analysis was conducted in the total study population, analyses adjusted for conventional prognostic factors (i.e., nodal status, grade, size, age, treatment, HER2, and quantitative PR and ER), 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 disease-free survival, 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 this is only an initial report of the use of the Mammostrat test.

Summary of Evidence

The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of therapy and comorbidity. A substantial number of patients are treated with adjuvant chemotherapy who fail to see a benefit and a better predictor of recurrence risk could help with decision making as some individuals may prefer to avoid adjuvant chemotherapy if assured their risk is low for recurrence, gene expression test results are being utilized in these individuals to predict distant recurrence risk and assist with decision making regarding their treatment management. Further studies seeking evidence addressing the clinical utility of this test are warranted. Additionally, per the American Society of Clinical Oncology guidelines (see below) Mammostrat is not recommended to guide decisions in adjuvant systemic chemotherapy in patients with breast cancer. Also, The NCCN Breast Cancer guideline Version 4.2022 does not include or indicate the use of this assay in the management of breast cancer. The evidence is insufficient to determine the effects of this testing on net health outcomes.

Ductal Carcinoma in Situ (DCIS)

DCIS is breast cancer located in the lining of the mammary ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated. The incidence of DCIS diagnosis in the United States has increased in tandem with the widespread use of screening mammography, account for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. The goal of primary therapy for DCIS is to prevent progression to invasive breast carcinoma. Management strategies for DCIS treatment

include surgery (lumpectomy or mastectomy), radiation therapy and adjuvant endocrine therapy to reduce risk of recurrence.

The use of a modified version of the Oncotype DX test 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.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2013, Solin et. al. in a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, they compared the Oncotype DX Breast DCIS Score with 10- year local recurrence risk in a subset of DCIS patients (N=327) treated only with surgery or with tamoxifen. The continuous Oncotype DX Breast DCIS Score was significantly associated with developing either a local recurrence or invasive carcinoma (HR=2.31; 95% CI, 1.15 to 4.49; p=0.02) whether or not patients were treated with tamoxifen. However, whether women are better categorized as to their local recurrence risk by Oncotype DX Breast DCIS Score compared with standard clinical indicators of risk was not addressed.

In 2015, Rakovitch et. al. in a retrospective analysis evaluated 571 tumor specimens with negative margins from a convenience cohort of patients with DCIS treated by breast-conserving surgery (lumpectomy) alone. Patients were drawn from a registry of 5752 women in Ontario Canada, who were diagnosed with DCIS between 1994 and 2003 with validation of treatment and outcomes. Central pathology assessment excluded cases with invasive cancer, DCIS < 2 mm or positive margins. Cox model was used to determine the relationship between independent covariates, the DS (DCIS Score) (hazard ratio (HR)/50 Cp units (U)) and LR (local recurrence). Tumor blocks were collected for 828 patients. Final evaluable population includes 718 cases, of whom 571 had negative margins. Median follow-up was 9.6 years. 100 cases developed LR following BCS (breast conserving surgery) alone (DCIS, N = 44; invasive, N = 57). In the primary pre-specified analysis, the DS was associated with any LR (DCIS or invasive) in ER positive patients (HR 2.26; P < 0.001) and in all patients regardless of ER status (HR 2.15; P < 0.001). DCIS Score provided independent information on LR risk beyond clinical and pathologic variables including size, age, grade, necrosis, multifocality, and subtype (adjusted HR 1.68; P = 0.02). DCIS was associated with invasive LR (HR 1.78; P = 0.04) and DCIS LR (HR 2.43; P = 0.005). This study had several limitations: patients were not randomized and were selected for treatment by BCS alone based on clinic-pathologic features and patient preference; during the time interval of this study many pathology

reports lacked tumor size and resection margin width information, therefore, margin width and tumor size data were incomplete; in addition data on clinical presentation or family history of breast cancer which may predict LR were not available; tamoxifen utilization during the time period of this study was limited and 95% of cases treated with BCS alone had ER-positive DCIS and therefore slightly lower event rates might be expected with tamoxifen administration.

In 2017, Gorringe et. al. discussed the available studies and value of the 12 gene expression assay. The two primary studies to date both demonstrated that the test had some prognostic value, but the low- risk group still had a chance of recurrence over 10-years of 10-13%, and there was no difference in outcome between intermediate and high-risk groups. The authors noted that on 50% of patients in each study the clinicopathological data was incomplete, which could have been important to understanding outcome. In addition, the cases were taken from a prolonged timeframe, nearly a decade, in which advances in surgical and other treatments vastly improved and could have confounded the results.

Rakovitch et. al. (2018) combined the population from the 2 studies described above in Solin (2013) and Rakovitch (2015) and calculated 10-year local recurrence (LR) rates by DCIS category (low, intermediate, and high), age, tumor size, and year of diagnosis. The combined cohort included 773 patients. The DS and age at diagnosis, tumor size and year of diagnosis provided independent prognostic information on the 10-year LR risk ($p \leq 0.009$). Hazard ratios from E5194 and ODC cohorts were similar for the DS (2.48, 1.95 per 50 units), tumor size ≤ 1 versus > 1-2.5 cm (1.45, 1.47), age ≥ 50 versus < 50 year (0.61, 0.84) and year ≥ 2000 (0.67, 0.49). Utilization of DS combined with tumor size and age at diagnosis predicted more women with very low ($\leq 8\%$) or higher (> 15%) 10-year LR risk after BCS alone compared to utilization of DS alone or clinicopathological factors alone. This analysis has several limitations: the study population includes few women (N=37) with tumors > 2.5 cm treated by breast conserving surgery (BCS) alone (6% of Ontario cohort); therefore, risk estimates in women with DCIS lesions > 2.5 cm should be interpreted with caution; and the analysis does not account for the impact of tamoxifen. Approximately one-third of the E5194 and 17% of those > 65 -years in Ontario cohort received tamoxifen. Tamoxifen was used more frequency by patients diagnosed in 2000 or later (48.9%) than patients diagnosed before 2000 (15.0%). A sensitivity analysis E5194 data was conducted to assess the effect of tamoxifen regression parameter estimates. The values of the HRs (hazard rations) are similar to those in the main analysis, indicating that tamoxifen use did not greatly influence the estimates in this study.

Lin et al. (2018) reported on the retrospective review of 37 patients who used Oncotype DX DCIS within the past four years. These patients had histological data, management decisions and outcomes on file. High Oncotype Dx DCIS recurrence scores were associated with necrosis, high nuclear grade, biopsy site change, estrogen receptor positive, progesterone receptor positive, and a Van Nuys Prognostic Index score of eight or more. Low Oncotype Dx DCIS recurrence scores were associated with low nuclear

grade and a lower rate of radiation therapy. In seven cases (19%) the Oncotype DX DCIS score was not correlated as expected with histological findings, such as a high nuclear grad with comedonecrosis and a low Oncotype score, or the inverse. These were unexpected results, and the authors noted that this could confound individual recommendations.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

NCCN Recommendations for Management of DCIS after Primary Treatment
According to the NCCN Panel (Breast Cancer Guideline Version 4.2022), endocrine therapy with tamoxifen (for premenopausal and postmenopausal women) or an aromatase inhibitor (for postmenopausal women especially those under 60 years of age or in those with concerns of embolism), may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with ER-positive DCIS treated with breast conserving therapy (category 1 for those undergoing breast conserving surgery followed by radiation therapy, category 2A for those undergoing excision alone). The benefit of endocrine therapy for ER negative DCIS is unknown.

Multigene assays such as gene expression profiling assays in the management of DCIS to include Oncotype DX DCIS is not discussed or included in this NCCN guideline.

Summary of Evidence
For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with a Breast DCIS Score is low enough to consider changing the management of DCIS. Overall, there is limited evidence available on the clinical efficacy of Oncotype DX DCIS and more studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Gene Expression Profiling for Triple Negative Breast Cancer (TNBC)
Historically, TNBC has been defined as tumors that are negative for ER, PR, and HER2 expression, and comprises up to 15-20 percent of all breast cancers. TNBC is an aggressive disease with a higher- risk of both local and distant recurrence compared to

patients with other types of breast cancer. Triple negative breast cancer has long been a challenge because few proven treatment options.

The Insight TNBCtype test is based on a proprietary algorithm that uses gene expression data from next-generation sequencing to generate five molecular subtypes (BL1, BL2, LAR, MSL and M), as well as a complementary immunomodulatory (IM) classifier that may help predict response to immuno-oncology therapies.

In 2015, Prat et. al. (2015) that predicting treatment benefit and/or outcome before any therapeutic intervention has taken place would be clinically very useful. These researchers examined the ability of the intrinsic subtypes and the risk of relapse score at diagnosis to predict survival and response following neoadjuvant chemotherapy. In addition, they evaluated the ability of the Claudin-low and 7-TNBCtype classifications to predict response within triple-negative breast cancer (TNBC). Gene expression and clinical-pathological data were evaluated in a combined dataset of 957 breast cancer patients, including 350 with TNBC, treated with sequential anthracycline and anti-microtubule-based neoadjuvant regimens. Intrinsic subtype, risk of relapse score based on subtype and proliferation (ROR-P), the Claudin-low subtype and the 7-TNBCtype subtype classification were evaluated. Logistic regression models for pathological complete response (pCR) and Cox models for distant RFS (DRFS) were used. Basal-like, Luminal A, Luminal B, and HER2-enriched subtypes represented 32.7 %, 30.6 %, 18.2 %, and 10.3 % of cases, respectively. Intrinsic subtype was independently associated with pCR in all patients, in hormone receptor-positive/HER2-negative disease, in HER2-positive disease, and in TNBC. The pCR rate of Basal-like disease was greater than 35 % across all clinical cohorts. Neither the Claudin-low nor the 7-TNBCtype subtype classifications predicted pCR within TNBCs after accounting for intrinsic subtype. Finally, intrinsic subtype and ROR-P provided independent prognostic information beyond clinicopathological variables and type of pathological response. A 5-year DRFS of 97.5 % (92.8 to 100.0 %) was observed in these neoadjuvant-treated and clinically node-negative patients predicted to be low- risk by ROR-P (i.e., 57.4 % of Luminal A tumors with clinically node-negative disease). The authors concluded that intrinsic subtyping at diagnosis provided prognostic and predictive information for patients receiving neoadjuvant chemotherapy. Although these researchers could not exclude a survival benefit of neoadjuvant chemotherapy in patients with early breast cancer with clinically node-negative and ROR-low disease at diagnosis, the absolute benefit of cytotoxic therapy in this group might be rather small (if any). These researchers stated that further studies are needed to determine the role of intrinsic subtyping in treatment decision-making at diagnosis of breast cancer.

Ring et al (2016) noted that recently, a gene expression algorithm, TNBCtype, was developed that can divide TNBC) into molecularly-defined subtypes. The algorithm has potential to provide predictive value for TNBC subtype-specific response to various treatments. TNBCtype used in a retrospective analysis of neoadjuvant clinical trial data of TNBC patients demonstrated that TNBC subtype and pathological complete response to neoadjuvant chemotherapy were significantly associated. These researchers described

an expression algorithm reduced to 101 genes with the power to subtype TNBC tumors similar to the original 2,188-gene expression algorithm and predicted patient outcomes. The new classification model was built using the same expression data sets used for the original TNBCtype algorithm. Gene set enrichment followed by shrunken centroid analysis were used for feature reduction, then elastic-net regularized linear modeling was used to identify genes for a centroid model classifying all subtypes, comprised of 101 genes. The predictive capability of both this new "lean" algorithm and the original 2,188-gene model were applied to an independent clinical trial cohort of 139 TNBC patients treated initially with neoadjuvant doxorubicin/cyclophosphamide and then randomized to receive either paclitaxel or ixabepilone to determine association of pathologic complete response within the subtypes. The new 101-gene expression model reproduced the classification provided by the 2,188-gene algorithm and was highly concordant in the same set of 7 TNBC cohorts used to generate the TNBCtype algorithm (87 %), as well as in the independent clinical trial cohort (88 %), when cases with significant correlations to multiple subtypes were excluded. Clinical responses to both neoadjuvant treatment arms, found BL2 to be significantly associated with poor response (OR = 0.12, p = 0.03 for the 2,188-gene model; OR = 0.23, p < 0.03 for the 101-gene model). Additionally, while the BL1 subtype trended towards significance in the 2,188-gene model (OR = 1.91, p = 0.14), the 101-gene model demonstrated significant association with improved response in patients with the BL1 subtype (OR = 3.59, p = 0.02). The authors concluded that these findings demonstrated that a model using small gene sets could recapitulate the TNBC subtypes identified by the original 2,188-gene model and in the case of standard chemotherapy, the ability to predict therapeutic response. Moreover, the researchers stated that additional studies are planned comparing both models on randomized clinical trial samples to fully explore the utility of models to identify responsive patient populations.

In 2016, Lehmann et. al. stated that TNBC is a heterogeneous disease that can be classified into distinct molecular subtypes by gene expression profiling. Considered a difficult-to-treat cancer, a fraction of TNBC patients benefit significantly from neoadjuvant chemotherapy and have far better OS. Outside of BRCA1/2 mutation status, biomarkers do not exist to identify patients most likely to respond to current chemotherapy; and, to-date, no FDA-approved targeted therapies are available for TNBC patients. Previously, these researchers developed an approach to identify 6molecular subtypes TNBC (TNBCtype), with each subtype displaying unique ontologies and differential response to standard-of-care chemotherapy. Given the complexity of the varying histological landscape of tumor specimens, these investigators used histopathological quantification and laser-capture microdissection to determine that transcripts in the previously described immunomodulatory (IM) and mesenchymal stem-like (MSL) subtypes were contributed from infiltrating lymphocytes and tumor-associated stromal cells, respectively. Thus, these researchers refined TNBC molecular subtypes from 6 (TNBCtype) into 4 (TNBCtype-4) tumor-specific subtypes (BL1, BL2, M and LAR) and demonstrated differences in diagnosis age, grade, local and distant disease progression and histopathology. Using 5 publicly available, neoadjuvant chemotherapy breast cancer gene expression data sets, these investigators retrospectively

evaluated chemotherapy response of over 300 TNBC patients from pre-treatment biopsies subtyped using either the intrinsic (PAM50) or TNBCtype approaches. Combined analysis of TNBC patients demonstrated that TNBC subtypes significantly differed in response to similar neoadjuvant chemotherapy with 41 % of BL1 patients achieving a pCR compared to 18 % for BL2 and 29 % for LAR with 95 % CIs ([33 to 51], [9 to 28], [17 to 41], respectively). The authors provided pre-clinical data that could inform clinical trials designed to test the hypothesis that improved outcomes can be achieved for TNBC patients, if selection and combination of existing chemotherapies was directed by knowledge of molecular TNBC subtypes.

In 2018, Guo et. al. stated that triple negative breast cancer (TNBC) is an operational term for breast cancers lacking targetable estrogen receptor expression and HER2 amplifications. Thus, TNBC is inherently heterogeneous, and is associated with worse prognosis, greater rates of metastasis, and earlier onset. TNBC displays mutational and transcriptional diversity, and distinct mRNA transcriptional subtypes exhibiting unique biology. High-throughput sequencing has extended cancer research far beyond protein coding regions that include non-coding small RNAs, such as miRNA, isomiR, tRNA, snoRNAs, snRNA, yRNA, 7SL, and 7SK. These researchers performed small RNA profiling of 26 TNBC cell lines and compared the abundance of non-coding RNAs among the transcriptional subtypes of TNBC. They also examined their co-expression pattern with corresponding mRNAs. The authors provided a detailed description of small RNA expression in TNBC cell lines that could aid in the development of future biomarker and novel targeted therapies.

In 2019, Funakoshi et. al. stated that inflammatory breast cancer (IBC) is an aggressive form of breast cancer. The triple-negative subtype of IBC (TN-IBC) is particularly aggressive. Identification of molecular differences between TN-IBC and TN-non-IBC may help clarify the unique clinical behaviors of TN-IBC. However, the authors' previous study comparing gene expression between TN-IBC and TN-non-IBC did not identify any TN-IBC-specific molecular signature. Lehmann et al (2016) recently reported that the mesenchymal stem-like (MSL) TNBC subtype consisted of infiltrating tumor-associated stromal cells but not cancer cells. Thus, these investigators compared the gene expression profiles between TN-IBC and TN-non-IBC patient samples not of the MSL subtype. They classified 88 TNBC samples from the World IBC Consortium into subtypes according to the Vanderbilt classification and Insight TNBCtype, removed samples of MSL and unstable subtype, and compared gene expression profiles between the remaining TN-IBC and TN-non-IBC samples. In the Vanderbilt analysis, these researchers identified 75 genes significantly differentially expressed between TN-IBC and TN-non-IBC at an FDR of 0.2. In the Insight TNBCtype analysis, they identified 81 genes significantly differentially expressed between TN-IBC and TN-non-IBC at an FDR of 0.4. In both analyses, the top canonical pathway was "Fc Receptor-mediated Phagocytosis in Macrophages and Monocytes", and the top 10 differentially regulated genes included PADI3 and MCTP1, which were up-regulated, and CDC42EP3, SSR1, RSBN1, and ZC3H13, which were down-regulated. The authors concluded that these findings suggested that the activity of macrophages might be enhanced in TN-IBC

compared with TN-non-IBC. Moreover, these researchers stated that further pre-clinical and clinical studies are needed to determine the cross talk between macrophages and IBC cells.

Summary of Evidence
Based on review of the peer reviewed medical literature regarding gene expression profiling for triple negative breast cancer (TNBC) and the use of Insight TNBCtype test further studies are needed to determine the role of this testing to help predict response to immuno-oncology therapies. NCCN Breast Cancer Guideline Version 4.2022 does not include or indicate the use of this assay in the management of breast cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Society of Clinical Oncology (ASCO)
In 2020, the American Society of Clinical Oncology (ASCO) issued a guideline for management of male breast cancer which included the following recommendations: Many of the management approaches used for men with breast cancer are like those used for women. Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy should be offered tamoxifen for an initial duration of five years; those with a contraindication to tamoxifen may be offered a gonadotropin-releasing hormone agonist/antagonist plus aromatase inhibitor. Men who have completed five years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence may be offered an additional five years of therapy. Men with early-stage disease should not be treated with bone-modifying agents to prevent recurrence but could still receive these agents to prevent or treat osteoporosis. Men with advanced or metastatic disease should be offered endocrine therapy as first-line therapy, except in cases of visceral crisis or rapidly progressive disease. Targeted systemic therapy may be used to treat advanced or metastatic cancer using the same indications and combinations offered to women. Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy regardless of genetic predisposition; contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation. Breast magnetic resonance imaging is not recommended routinely. Genetic counseling and germline genetic testing of cancer predisposition genes should be offered to all men with breast cancer.

In 2019, the American Society of Clinical Oncology (ASCO) issued an update on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer, integration of results from TAILORx which included the following recommendation:

Oncotype DX
- If a patient has ER/PgR positive, HER2 negative (node-negative) breast cancer, the clinician may use the 21-gene recurrence score (RS; Oncotype DX; Genomic Health) to guide decisions on adjuvant systemic chemotherapy.

Type of recommendation: evidence based
Evidence quality: high
Strength of recommendation: strong

- For patients older than 50 -years whose tumors have Oncotype DX recurrence scores (RSs) < 26 and for patients age 50- years and younger whose tumors have Onctoype DX recurrence scores (RSs) < 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone.

  Type of recommendation: evidence based
  Evidence quality: high
  Strength of recommendation: strong
- For patients 50- years of age or younger with Oncotype DX recurrence scores (RSs) of 16 to 25, clinicians may offer chemoendocrine therapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

- Patients with Oncotype DX recurrence scores (RSs) > 30 should be considered candidates for chemoendocrine therapy.

  Type of recommendation: evidence based
  Evidence quality: high
  Strength of recommendation: strong

- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores 26 to 30.

  Type of recommendation: Informal consensus
  Evidence quality: insufficient
  Strength of recommendation: moderate

- If a patient has ER/PgR positive, HER2 negative (node-positive) breast cancer, the clinician should not use the 21 gene RS (Oncotype DX; Genomic Health) to guide decisions on adjuvant systemic chemotherapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

- If a patient has HER2-positive breast cancer or triple negative (TN) breast cancer, the clinician should not use the 21-gene RS (Oncotype DX; Genomic Health) to guide decisions on adjuvant systemic therapy.

Type of recommendation**:** informal consensus
Evidence quality: insufficient
Strength of recommendation: strong

EndoPredict

- If a patient has ER/PgR positive, HER2-negative (node negative) breast cancer, the clinician may use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

- If a patient has ER/PgR positive, HER2-negative (node positive) breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy.

  Type of recommendation: evidence based
  Evidence quality: insufficient
  Strength of recommendation: moderate

- If a patient has HER-2 positive breast cancer or triple negative (TN) breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic therapy.

  Type of recommendation**:** informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

MammaPrint

- If a patient has ER/PgR positive, HER-2 negative, node-negative, breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit.

  Type of recommendation: evidence based
  Evidence quality: high
  Strength of recommendation: strong

- If a patient has ER/PgR positive, HER2-negative, node negative, breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in low clinical risk category had excellent

outcomes and did not appear to benefit from chemotherapy even with genomic high-risk cancer.

Type of recommendation: evidence based
Evidence quality: high
Strength of recommendation: strong

- If a patient has ER/PgR positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.

  Type of recommendation: evidence based
  Evidence quality: high
  Strength of recommendation: strong

- If a patient has ER/PgR positive, HER2-negative, node positive, breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population.

  Type of recommendation: evidence based
  Evidence quality: high
  Strength of recommendation: moderate

- If patient has HER-2 positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER-2 targeted therapy.

  Type of recommendation: informal consensus
  Evidence quality: low
  Strength of recommendation: moderate

- If a patient has ER-PgR negative and HER2-negative breast cancer, triple negative (TN), the clinician should not use MammaPrint assay to guide decisions on adjuvant systemic chemotherapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

Note: MINDACT categorization is based on age, tumor size, tumor grade, lymph node status, hormone receptor status, HER2 status and clinical pathologic subtype)

Prosigna (PAM50) Risk of Recurrence Score

- If a patient has ER/PgR-positive, HER-2-negative (node negative) breast cancer, the clinician may use the PAM50 risk of recurrence (ROR) score (Prosigna Breast Cancer Prognostic Gene Signature Assay), in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy.

  Type of recommendation: evidence based
  Evidence quality: high
  Strength of recommendation: strong

- If a patient has ER/PgR positive, HER-2 negative (node positive) breast cancer, the clinician should not sure the PAM50-ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay) to guide decisions on adjuvant systemic therapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

- If a patient has HER-2 positive breast cancer, the clinician should not sure the PAM50-ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay) to guide decisions on adjuvant systemic therapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

- If a patient has triple negative (TN) breast cancer, the clinician should not use the PAM50-ROR (Prosigna Breast Cancer Prognostic Gene Signature Assay) to guide decisions on adjuvant systemic therapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

Breast Cancer Index

- If a patient has ER/PgR positive, HER2-negative, node negative breast cancer, the clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy.

  Type of recommendation: evidence based

Evidence quality: intermediate
Strength of recommendation: moderate

- If a patient has ER/PgR positive, HER2-negative, node positive breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

- If a patient has HER2-positive breast cancer or triple negative (TN) breast cancer, the clinician should not sure the Breast Cancer Index to guide decisions on adjuvant systemic therapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

Mammostrat

- If a patient has ER/PgR-positive, HER2-negative (node-positive or node negative) breast cancer, the clinician should not use the five-protein assay Mammostrat to guide decisions on adjuvant systemic therapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

- If a patient has HER-2 positive breast cancer or triple negative (TN) breast cancer, the clinician should not use the five- protein assay Mammostrat to guide decisions on adjuvant systemic therapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

Immunohistochemistry 4 (IHC-4)

- If a patient has ER/PgR positive, HER2-negative (node positive or node negative) breast cancer, the clinician should not use immunohistochemistry 4 (IHC-4) to guide decisions on adjuvant systemic chemotherapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

- If a patient has HER2-positive breast cancer or triple negative (TN) breast cancer, the clinician should not use IHC-4 to guide decisions on adjuvant systemic therapy.

  Type of recommendation: informal consensus
  Evidence quality: insufficient
  Strength of recommendation: strong

Extended Endocrine Therapy

- If a patient has ER/PgR positive, HER2-negative (node negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use multi-parameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50 (Prosigna Breast Cancer Prognostic Gene Signature Assay), Breast Cancer Index, or IHC4) to guide decisions on extended endocrine therapy.

  Type of recommendation: evidence based
  Evidence quality: intermediate
  Strength of recommendation: moderate

Recommendation 1.1.1. For patients older than 50- years and whose tumors have Oncotype DX recurrence scores of less than 26 and for patients age 50- years or younger whose tumors have Oncotype DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone (Type: evidence- based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.2. For patients 50-years of age or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.1.3. Patients with Oncotype DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy (Type: evidence- based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.4. Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30 (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)**.**

National Comprehensive Cancer Network (NCCN)

Breast Cancer Version 4.2022

Ductal Carcinoma in Situ (DCIS)

Primary Treatment for DCIS

The goal of primary therapy for DCIS is to prevent progression to invasive breast carcinoma. Management strategies for DCIS treatment include surgery (mastectomy and lumpectomy), radiation therapy, and adjuvant endocrine therapy to reduce risk of recurrence.

NCCN Recommendations for Management of DCIS after Primary Treatment

According to the NCCN Panel, endocrine therapy, with tamoxifen (for premenopausal and postmenopausal women) or an aromatase inhibitor (for postmenopausal women especially those under 60- years of age or in those with concerns of embolism), may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with ER-positive DCIS treated with breast conserving therapy (category 1 for those undergoing breast conserving surgery followed by radiation therapy, category 2A for those undergoing excision alone). The benefit of endocrine therapy for ER negative DCIS is unknown.

Multigene assays such as gene expression profiling assays in the management of DCIS to include Oncotype DX DCIS is not discussed or included in this NCCN guideline.

Invasive Breast Cancer

Adjuvant System Therapy

After surgical treatment, adjuvant systemic therapy should be considered. In patients with early- stage breast cancer, systemic therapy is administered to reduce risk of cancer recurrence. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (i.e., ER/PR and HER2 status). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy and comorbidity. The decision-making process requires collaboration between the health care team and patient.

Adjuvant Systemic Therapy for Hormone Receptor-Positive, HER2 Negative Tumors

Women with HR positive, HER2 negative tumors, receive adjuvant endocrine therapy to reduce the risk of recurrent and those deemed at high risk for distant recurrence despite adjuvant endocrine therapy, receive adjuvant chemotherapy. The incremental benefit of adding adjuvant chemotherapy to endocrine therapy in patients with low clinical risk of recurrence such as those with very small, low grade lymph node-negative tumors is relatively small. The decision whether or not, to administer adjuvant chemotherapy in patients with HR-positive, HER2-negative tumors is based on many factors including lymph node status, size, grade, lymphovascular invasion, age, comorbid conditions and/or the results of gene expression profile testing using multigene assays.

Multigene Assays
Several commercially available gene-based assays are useful in determining prognosis by predicting distance recurrence, local recurrence, or survival. Of these, only one the 21-gene assay (Oncotype DX) has been clinically validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence.

21-gene assay (Oncotype DX) in Node-negative, HR-positive, HER2-negative disease: The 21-gene recurrence score (RS) is one of the most validated multigene assays. The RS is helpful in determining the prognosis in women with HR-positive, HER2-negative tumors treated with endocrine therapy alone by predicting locoregional and distant recurrence. The assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for women with HR-positive, HER2-negative, node negative breast cancer.

Among patients with T1b/c and T2, lymph node-negative, HR-positive, HER2-negative tumors with RS between 0-10, the risk of distant recurrence is low, and these patients derive no incremental benefit from the addition of adjuvant chemotherapy to endocrine therapy. At the other end of the spectrum patients with node-negative, HR-positive, HER2-negative cancers with RS ($\geq$ 31) have a higher risk of distance recurrent and secondary analysis of prospective studies demonstrate a clear benefit from adjuvant chemotherapy.

For those with intermediate RS (11-25) the recently reported TAILORx trial of postmenopausal women (n=6711) with lymph node-negative, HR-positive, HER2-negaive breast cancer, showed similar disease-fee survival rates at 9 -years in those who received adjuvant chemotherapy followed by endocrine therapy compared with endocrine therapy alone. However, in a subset analysis, women 50- years of age or younger with RS 16-25 had significantly lower rates of distance recurrence with the additional adjuvant chemotherapy to endocrine therapy. The cutoff for low, intermediate and high RS was different in the TAILORx versus NSABP B-20. The NSABP-B20 was the first trial to validate the 21-gene assays both as a prognostic as well as a predictive tool and identified RS cut-offs to predict the magnitude of chemotherapy benefit in patients with node-negative, HR-positive breast cancer.

21-gene assay (Oncotype DX) in node-positive, HR positive, HER2-negative disease in the West German Plan B Study, women (n-110) with lymph node positive, HER2-negative tumors, and RS of $\leq$ 11, were found to have a 5-year disease free survival was 94.4% when treated with endocrine therapy alone. In a secondary analysis of prospective registry of women with HR-positive, HER2-negative, lymph node-positive tumors, the 5-year risk of distant recurrence in patients with a RS of < 18, treated with endocrine therapy alone was 2.7%. These results suggest that in patients with limited nodal disease (1-3 positive lymph nodes) and a low RS, the absolute benefit from chemotherapy is likely to be very small.

There is a clear benefit from adjuvant chemotherapy in patients with node positive, HR-positive, HER2-negative tumors, if the RS is high (≥ 31). In a secondary analysis of the SWOG 8814 trial of women with HR-positive, lymph node-positive tumors, high RS (≥ 31) was predictive of chemotherapy benefit. This study evaluated breast cancer specimens from node-positive, HER-positive postmenopausal women (n=367) randomized to endocrine therapy with tamoxifen alone or chemotherapy with CAF followed ty tamoxifen. Compared with tamoxifen alone, treatment with CAF among women with a high RS (≥ 31) resulted in improved 10 -year DFS (55% versus 43%; HR 0.59, 95% CI 0.35-1.01) and OS (73% versus 54%; HR 0.56, 95% CI 0.31-1.02).

The absolute benefit of chemotherapy in patients with limited lymph node involvement and a RS ≤ 25 remains to be determined. The ongoing Southwest Oncology Group (SWOG) S1007 RxPONDER trial, assigned women with 1-3 lymph node-positive nodes, HR-positive, HER2-negative breast cancer and a RS ≤ 25 to standard endocrine therapy with or without adjuvant chemotherapy. The results of this trial are expected to determine the benefit (if any) for chemotherapy in this group of patients.

70-gene assay (MammaPrint): Results from the randomized MINDACT trial, demonstrated that the 70- gene assay can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade and nodal status).

50-gene assay (PAM50): The 50-gene assay (Pam-50) risk of recurrence (ROR) score stratifies patients with HR-positive disease into high, medium, and low risk groups. Several studies have demonstrated the prognostic value or ROR score in estimative risk of disease recurrence.

12-gene assay (EndoPredict): The assay utilizes 12-genes to calculate a prognostic score. This assay appears to be useful in identifying a subgroup of patients with ER-positive, HER2-negative tumors with very low risk of recurrence without adjuvant chemotherapy and helpful in identify patients at low risk for late recurrence.

Breast Cancer Index: The Breast Cancer Index (BCI) is a combination of two profiles, the HOXB13-to-17BR expression ratio (H:I ratio) and the Molecular Grade Index (MGI). Compared with the clinical prognostic factors (i.e., age, tumor size, tumor grade and lymph node status), the H:I ratio has been shown to be prognostic in the setting of adjuvant tamoxifen monotherapy. The addition of MGI to H:I was determined to provide additional prognostic discrimination, leading to the BCI assay.

NCCN Recommendations for Use of Multigene Assay: Considering the ability of the multigene assays to predict benefit of adjuvant systemic chemotherapy and ability to determine prognosis by predicting risk of distant recurrence, the NCCN Panel has summarized the treatment implications based on risk scores and nodal status. The Panel notes that multigene assays provide prognostic and therapy-predictive information that complements TNM and biomarker information.

Use of Multigene Assays in Axillary Lymph-Node Negative HR Positive, HER2 Negative Tumors

Small tumors (up to 0.5 cm in greatest diameters) that do not have involve the lymph nodes have a favorable prognosis, so adjuvant chemotherapy is not recommended. According to the NCCN Panel, adjuvant endocrine therapy may be considered in this group of patients to reduce the risk for a second contralateral breast cancer, as well as the small benefit in reducing the risk of local/regional and distant recurrence (Category 2B).

For patients with invasive ductal or lobular tumors greater than 0.5 cm in diameter and no lymph node involvement (lymph node node-negative), the NCN panel recommends strongly considering the 21-gene RT-PCR assay to help estimate likelihood of recurrence and benefit from chemotherapy (category 1). The panel has noted that an exploratory analysis from the TAILORx study, adjuvant chemotherapy may be considered in women 50 years of age or younger with a 21-gene RS of 16-25. Also, patients with T1b tumors with low grade histology should be considered for endocrine monotherapy, as the TAILORx study did not include patients with such tumors.

The Panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence, but these assays have not been validated to predict the benefit of systemic chemotherapy. Also, amongst the other assays, the panel has listed the 70-gene assay as a category 1 option based on the results of the prospective MINDACT trial demonstrating the ability of the 70-gene assay to identify a good genomic risk population despite a high clinical risk, in whom chemotherapy may be omitted without a detrimental effect. High clinical risk in the MINDACT trial was defined for grade 1 tumors as > 30 cm N0 or T2N1, for grade 2 tumors T2N0-1, and for grade 3 tumors T1c-2N0-1.

Furthermore, given no difference in outcomes with or without chemotherapy in the discordant low clinical risk/high genomic risk group, the MINDACT study suggest that the 70-gene panel is not useful guiding systemic chemotherapy decisions in this subgroup of patients.

Since results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor.

Use of Multigene Assays in Axillary Lymph-Node-Positive HR-Positive, HER2-Negative Tumors

For patients with four or more involved nodes the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Patients with less than four involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis, are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant chemotherapy be based on elements of clinical risk stratification such as clinical

characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology the panel recommends considering multigene assays to assess prognosis as a tool to assist with treatment decision making. The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. While a secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillar lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS ($\geq$ 31) from the 21-gene assay. At this time the optimal RS cut-off (<11 versus <18) to withhold chemotherapy for HR-positive, HER2-negative, 1-3 lymph node-positive tumors is still unknown. The results of the Rx-PONDER rial, are expected to determine the benefit (if any) of chemotherapy. In the MINDACT trial, among patients with 1-3 positive nodes who had high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group. Other multigene assays have not proven to be predictive of benefit from chemotherapy.

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, if multigene assay is not available, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy. (category-1)

Table 1. Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy[a,c]

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene (Oncotype DX) for pN0	Yes	Yes	Preferred	1

21-gene (Oncotype DX) for pN1 (1-3 positive nodes)	Yes	Yes	Postmenopause Preferred Premenopausal: Other	1 2A
70-gene (MammaPrint) for pN0 and pN1 (1-3 positive nodes)	Not determined	Yes	Other	1
50-gene (Prosigna) for pN0 and pN1 (1-3 positive nodes)	Not determined	Yes	Other	2A
12-gene (Endo-Predict) for pN0 and pN1 (1-3 positive nodes)	Not determined	Yes	Other	2A
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A

[a]Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype DX) is preferred by the NCCN Breast Cancer Panel for node negative breast cancer. Other prognostic gene expression 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.

[c]In the overall study population of the RxPONDER trial, 10.3% had high grade disease and 9.2% had 3 involved nodes.

Table 2. Gene Expression Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy[a]

Assay	Recurrence Risk	Treatment Implications

21-gene (Oncotype DX) for postmenopausal patients with pN0 and PN1 (1-3 positive nodes)		
	<26	Patients with T1b/c-2, pN0, HER2-negative tumors with risk scores (RS) between 0-10 have a risk of distant recurrence of <4% and those with RS 11-25 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study. Postmenopausal patients with pT1-3, HR-positive, HER-2 negative, with RS <26 derived no benefit from the additional of chemotherapy to endocrine therapy in the prospective RxPONDER study.
	≥ 26	In postmenopausal patients with pT1-3, HR-positive, HERT2-negative and pN0 and pN1 (1-3 positive nodes) tumors and an RS ≥ 26, the addition of chemotherapy to endocrine therapy is recommended.
21- gene (Oncotype DX) for premenopausal patients: pN0		
	≤15	Premenopausal patients with T1b/c-2, pN0, HR-positive, HER-2 negative tumors with RS <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study
	16-25	In premenopausal patients with RS between 16-25, a

		small benefit from the addition of chemotherapy could not be ruled out, but it is unclear if the benefit was due to the ovarian suppression effect promoted by chemotherapy in premenopausal patients. For this group, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either Tamoxifen or an AI.
	≥ 26	In premenopausal patients with HR-positive, HER-2 negative and pN0 tumors and an RS ≥ 26, the addition of chemotherapy to endocrine therapy is recommended
21-gene (Oncotype DX) for premenopausal patients with 1-3 positive nodes		
	<26	In premenopausal patients with pT1-3 and pN1 (1-3 positive nodes) tumors and an RS < 26 the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy. For this group of patients consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.

	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1-3 and pN1 (1-3 positive nodes) tumors and RS ≥26 the addition of chemotherapy to endocrine therapy is recommended.
70-Gene (MammaPrint) (for node negative and 1-3 positive nodes)		
	Low	With a median follow-up of 5 years, among patients at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% confidence interval (CI), 92.5% to 96.2%) among those who did not receive adjuvant chemotherapy. Among patients with 1-3 positive nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1 to 98.1) in those who received adjuvant chemotherapy versus 95.6% (95% CI, 92.7 to 97.4) in those who did not receive adjuvant chemotherapy. Therefore, the additional benefit of adjuvant chemotherapy may be small in this group. In a subset analysis the benefit of chemotherapy was mostly seen in patients under 50 - years of age. The absolute difference in distant metastatic-free survival at 8-years in those receiving chemotherapy for patients ≤50 years was 5.4% ±2.8%

		versus 0.2% ± 2.3% for those >50 years. It is not known whether the benefit of chemotherapy observed in women ≤50 years is related to chemotherapy – induced ovarian function suppression.
	High	With a median follow-up of 5- years, among patients at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% confidence interval (CI), 92.5% to 96.2%) among those who did not receive adjuvant chemotherapy. Among patients with 1-3 positive nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1 to 98.1) in those who received adjuvant chemotherapy versus 95.6% (95% CI, 92.7 to 97.4) in those who did not receive adjuvant chemotherapy. Therefore, the additional benefit of adjuvant chemotherapy may be small in this group. In a subset analysis the benefit of chemotherapy was mostly seen in patients under 50-years of age. The absolute difference in distant metastatic-free survival at 8-years in those receiving chemotherapy for patients ≤50 years was 5.4% ±2.8% versus 0.2% ± 2.3% for those >50 years. It is not

		known whether the benefit of chemotherapy observed in women ≤50 years is related to chemotherapy – induced ovarian function suppression.
50-gene (Prosigna) for pN0 and 1-3 positive nodes		
	Node negative low (0-40	For patients with T1 and T2, HER2- negative, pN0 tumors, a risk of recurrence score in the low range regardless of T size places the tumor into the same prognostic category as T1a-T1b, N0, M0.
	Node negative intermediate (41-60)	For patients with T1 and T2, HER2- negative, pN0 tumors, a risk of recurrence score in the low range regardless of T size places the tumor into the same prognostic category as T1a-T1b, N0, M0.
	Node negative high (61-100)	For patients with T1 and T2, HER2 negative, pN0 tumors, a risk of recurrence score in the low range regardless of T size places the tumor into the same prognostic category as T1a-T1b, N0, M0.
	Node positive low (0-40)	In patients with HR-positive, HER2-negative, pN+ tumors (1-3 positive lymph nodes) with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10- years and no distant recurrence was seen at 10 -years in TransATAC study in similar group.
	Node positive high (41-100)	In patients with HR-positive, HER2 -negative, pN+ tumors (1-3 positive lymph

		nodes) with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10- years and no distant recurrence was seen at 10 -years in TransATAC study in similar group.
12-gene (Endo-Predict) pN0 and 1-3 positive nodes		
	Low (≤3.33)	For patients with T1 and T2 HR-positive, HER2 negative, pN0 tumors, a 12 gene low risk score regardless of T size places the tumor into the same prognostic category as T1a-T1b, N0, M0. In ABCSG 6/8 patients in low- risk group has risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1-3 positive nodes in the low -risk group had a 5.6% risk of distance recurrence at 10 -years. This assay is prognostic in endocrine and chemo-endocrine treated patients.
	High (>3.33)	For patients with T1 and T2 HR- positive, HER2 negative, pN0 tumors, a 12 gene low risk score regardless of T size places the tumor into the same prognostic category as T1a-T1b, N0, M0. In ABCSG 6/8 patients in low- risk group has risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1-3 positive nodes in the low- risk group had a 5.6% risk of distance

		recurrence at 10- years. This assay is prognostic in endocrine and chemo-endocrine treated patients.
Breast Cancer Index (BCI)		
	BCI (H/I) Low	For patients with T1 and T2 HR-positive, HER2 negative and pN0 tumors, a BCI (H/I) in the low-risk range regardless of T size places the tumor into the same prognostic category as T1a-T1b, N0, M0. Patients with BCI (HI) low demonstrated lower- risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in DFS or OS compared to the control in arm in terms of extending endocrine therapy duration.
	BCI (H/I) High	For patients with T1 HR-positive, HER2 negative and pN0 tumors, a BCI (H/I) in high (5.1-10) demonstrated significant rates of late distance recurrence. In a secondary analysis of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1-T3, pN0 or pN+ who had a BCI (H/I) demonstrated significant improvements in DFS with adjuvant endocrine therapy was extended, compared to the control arm.

		In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy.

[a]Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype DX) is preferred by the NCCN Breast Cancer Panel for node negative breast cancer. Other prognostic gene expression 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.

Special Considerations for Breast Cancer in Men
Few men have been included in breast cancer trials. Therefore, recommendations regarding management of breast cancer in men are generally extrapolated from findings of clinical trials focusing on breast cancer in women.

Although there are some biologic and clinical differences between breast cancer in men and women, management of breast cancer in men is similar overall to management of breast cancer in women, with the following special considerations pertinent to male patients.

- Use of molecular assays: Data are limited regarding the use of molecular assays to assess prognosis and to predict benefit from chemotherapy in men with breast cancer. Available data suggest the 21-gene assay recurrence score provides prognostic information in men with breast cancer.
- Preoperative/adjuvant systemic therapy: Chemotherapy with/without HER2-targeted therapy should be recommended for men with breast cancer according to guideline for women with breast cancer. Options for adjuvant endocrine therapy for men with breast cancer include tamoxifen for 5-10 years or, if tamoxifen is contraindicated, a GnRH analog plus an aromatase inhibitor. In men, single-agent adjuvant treatment with an aromatase inhibitor has been associated with inferior outcomes compared to tamoxifen alone, likely due to inadequate estradiol suppression and is not recommended.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Oncotype DX Breast and other tests listed are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

December 2018 Insight TNBCtype (Insight Genetics, Inc) is a CLIA-validated assay The test is based on a proprietary algorithm that uses gene expression data from next-generation sequencing to generate five molecular subtypes (BL1, BL2, LAR, MSL and M), as well as a complementary immunomodulatory (IM) classifier that may help predict response to immuno-oncology therapies.

February 2007, MammaPrint (Agendia) was cleared for marketing by the FDA through the 501(k) process for the prediction of breast cancer metastasis. In January 2015, MammPrint was cleared for marketing by the FDA thorugh the 510(k) process for use in fresh-frozen, paraffin-embedded breast cancer tissue.

September 2013, Prosigna was cleared for marketing by the FDA through the 510(k) process. Moreover, the FDA determined that Prosigna was substantially equivalent to MammaPrint.

Currently the Breast Cancer Index (Biotheranostics) and EndoPredict (distributed by Myriad) are not FDA approved.

PRIOR APPROVAL

Not applicable.

POLICY

Oncotype DX Breast, MammaPrint, Prosigna (PAM50), EndoPredict
The use of one of the following gene expression profiling assays: OncoType DX Breast, MammaPrint, Prosigna (PAM50) or EndoPredict is proven and **medically necessary** for managing the treatment of localized invasive breast cancer in females or males in the following situation:

- Newly diagnosed within the last 6 months when **ALL** of the following criteria are met:
    - Unilateral tumor; **AND**
    - Node-negative (lymph nodes with micrometastases not greater than 2 mm are considered negative for purposes of this policy statement) **OR** with 1-3 positive axillary lymph nodes; **AND**
    - Breast tumor is hormone-receptor-positive (estrogen-receptor positive [ER-positive] or progesterone-receptor positive [PR-positive] or both [ER/PR positive]); **AND**
    - Breast tumor is HER2 receptor negative; **AND**
    - Tumor size 0.6 to 1.0 cm with moderate/poor differentiation or unfavorable features, **OR** tumor size > 1 cm; **AND**
    - The patient will be treated with adjuvant endocrine therapy (i.e., tamoxifen or aromatase inhibitors); **AND**

- Adjuvant chemotherapy is being considered by the individual and treating physician and is not precluded due to any other factor (i.e., advanced age and/or significant co-morbidities); **AND**
- The individual and treating physician have had a discussion prior to testing regarding the potential results of the test and determined to use the results to guide therapy regarding adjuvant chemotherapy.

For patients who otherwise meet the above medical necessity criteria but who have multiple ipsilateral primary tumors, the use of one of the following gene expression profiling assays: OncoType DX Breast, MammaPrint, Prosigna (PAM50) or EndoPredict may be considered **medically necessary** for the tumor with the most aggressive histologic characteristics. It is not necessary to conduct testing on each tumor as treatment is based on the most aggressive lesion.

The use of more than one gene expression profiling assay for the same tumor in an individual with invasive breast cancer is considered **not medically necessary**. Results of the different assays may not be concordant with each other, and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor. (NCCN Breast Cancer Version 7.2021)

Gene expression profiling with OncoType DX Breast, MammaPrint, Prosigna (PAM50) or EndoPredict as a technique of managing the treatment of invasive breast cancer is considered **not medically necessary** when the criteria above is not met.

Breast Cancer Index (BCI)
The use of the gene expression profiling assay Breast Cancer Index (BCI) is proven and **medically necessary** for managing the treatment of localized invasive breast cancer in females or males in the following situation:

- Newly diagnosed within the last 6 months when **ALL** of the following criteria are met:
  - Unilateral tumor; **AND**
  - Node-negative (lymph nodes with micrometastases not greater than 2 mm are considered negative for purposes of this policy statement); **AND**
  - Breast tumor is hormone-receptor-positive (estrogen-receptor positive [ER-positive] or progesterone-receptor positive [PR-positive] or both [ER/PR positive]); **AND**
  - Breast tumor is HER2 receptor negative; **AND**
  - Tumor size 0.6 to 1.0 cm with moderate/poor differentiation or unfavorable features, **OR** tumor size > 1 cm; **AND**
  - The patient will be treated with adjuvant endocrine therapy (i.e., tamoxifen or aromatase inhibitors); **AND**
  - Adjuvant chemotherapy is being considered by the individual and treating physician and is not precluded due to any other factor (i.e., advanced age and/or significant co-morbidities); **AND**

- The individual and treating physician have had a discussion prior to testing regarding the potential results of the test and determined to use the results to guide therapy regarding adjuvant chemotherapy.

For patients who otherwise meet the above medical necessity criteria but who have multiple ipsilateral primary tumors, the use of one Breast Cancer Index (BCI) may be considered medically necessary for the tumor with the most aggressive histologic characteristics. It is not necessary to conduct testing on each tumor as treatment is based on the most aggressive lesion.

The use of more than one gene expression profiling assay for the same tumor in an individual with invasive breast cancer is considered not medically necessary. Results of the different assays may not be concordant with each other, and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor. (NCCN Breast Cancer Version 7.2021)

Gene expression profiling with Breast Cancer Index (BCI) as a technique of managing the treatment of invasive breast cancer is considered not medically necessary when the criteria above is not met.

Oncotype DX Breast DCIS Score
Gene expression profiling using Oncotype DX Breast DCIS Score as a technique of managing the treatment of ductal carcinoma in situ (DCIS) is considered investigational for all indications as there is limited evidence to support a conclusion on the clinical efficacy concerning net health outcomes and additional studies are needed.

Gene expression profiling assays including but not limited to the following as a technique of managing the treatment of breast cancer is considered investigational for all indications:

- BluePrint (also referred to as “80 gene profile”)
- Insight TNBCtype
- TargetPrint

Based on the peer reviewed medical literature further studies seeking evidence addressing clinical utility of these tests are warranted. Additionally, society guidelines including NCCN do not include or indicate the use of these tests to guide decisions regarding adjuvant therapy in the management of breast cancer. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Definitions
Adjuvant Chemotherapy: Adjuvant means additional. Adjuvant chemotherapy is given to patients after primary treatment (i.e., chemotherapy and radiation, or chemotherapy and surgery), when the doctor thinks there is a high risk the cancer will return. Adjuvant chemotherapy aims to destroy hidden cancer cells that remain but are undetectable.

Adjuvant Endocrine Therapy: Adjuvant means additional. Adjuvant endocrine therapy provides benefit by reducing breast cancer recurrences and improving associated mortality in early-stage endocrine-responsive breast cancers (estrogen receptor and/or progesterone receptor positive).

Neoadjuvant Chemotherapy: Is the administration of chemotherapeutic agents before surgery or radiation therapy. The reduction in the size of larger tumors, or to prevent metastatic cancer from spreading is the goal of neoadjuvant chemotherapy.

Ipsilateral: On the same side.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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 [BCI])
- 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 Breast)
- 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 recurrence risk score (Prosigna Breast Cancer Prognostic Gene Signature Assay)
- 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)
- 81522 Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorith reported as recurrence risk score (EndoPredict)
- 81479 Unlisted molecular pathology procedure (may be used to represent Mammostrat, BluePrint, TargetPrint)
- 81599 Unlisted multianalyte assay with algorithmic analysis (may be used to represent Mammostrat, BluePrint, TargetPrint)
- 84999 Unlisted chemistry procedure (may be used to represent Mammostrat, BluePrint, TargetPrint)

- 0008M Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin embedded (FFPE) tissue, prognostic algorithm reported as a risk score (Prosigna Breast Cancer Prognostic Gene Signature Assay)
- 0045U Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score (Oncotype DX Breast DCIS Score Test)
- 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)
- S3854 Gene expression profiling panel for use in the management of breast cancer treatment (may be used to represent Mammostrat, BluePrint, TargetPrint)

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POLICY HISTORY

Date	Reason	Action
August 2022	Annual Review	Policy Renewed
August 2021	Annual Review	Policy Renewed
August 2020	Annual Review	Policy Revised
November 2019	Interim Review	Policy Revised
August 2019	Annual Review	Policy Renewed
December 2018	Interim Review	Policy Revised
August 2018	Annual Review	Policy Revised
August 2017	Annual Review	Policy Revised
March 2017	Interim Review	Policy Revised
August 2016		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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