



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX[®])[†] to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for the use of 21-gene RT-PCR assay (i.e., Oncotype DX) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with breast cancer will be considered when ALL of the following criteria are met:

- Unilateral tumor, AND
- Hormone receptor positive (i.e., estrogen receptor-positive [ER+] or progesterone receptor-positive [PR+]); AND
- Human epidermal growth factor receptor 2 (HER2)-negative; AND
- Tumor size 0.6–1 cm with moderate/poor differentiation or unfavorable features OR tumor size greater than 1 cm; AND
- Node negative (lymph nodes with micrometastases (less than 2 mm in size) are considered node negative for this policy statement); AND
- Who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors AND;
- When the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
- When ordered within 6 months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

The 21-gene RT-PCR assay Oncotype DX should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

Based on review of available data, the Company may consider the use of EndoPredict^{®‡}, the Breast Cancer Index (BCI)^{SM‡}, and Prosigna^{®‡} to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer with the same characteristics as considered medically necessary for Oncotype DX to be **eligible for coverage**.

Note: Only one assay of genetic expression per tumor tissue specimen will be eligible for coverage.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX), EndoPredict, the BCI, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease or to consider length of treatment with tamoxifen to be **investigational**.*

Based on review of available data, the Company considers use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (DCIS) (i.e., Oncotype DX DCIS) to inform treatment planning after excisional surgery to be **investigational**.*

Based on review of available data, the Company considers the use of 70-gene signature (MammaPrint^{®‡}) for any indication to be **investigational**.*

Based on review of available data, the Company considers the use of Blueprint^{®‡} in conjunction with MammaPrint or alone to be **investigational**.*

Based on review of available data, the Company considers the use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint^{®‡}) to be **investigational**.*
Based on review of available data, the Company considers the use of gene expression assays in men with breast cancer to be **investigational**.*

Background/Overview

NEWLY DIAGNOSED BREAST CANCER

Most women with newly diagnosed breast cancer in the United States present with early-stage or locally advanced (i.e., nonmetastatic) disease. However, almost a third of women who are disease-free after initial local and regional treatment develop distant recurrences during follow-up. Current breast cancer treatment

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

regimens involve systemic adjuvant chemotherapy, hormonal therapy, biologic therapy, or a combination, depending on patients' baseline level of recurrence risk, hormonal markers, and risk tolerance.

Women whose tumors are positive for *HER2* should receive adjuvant therapy with a *HER2*-directed therapy (trastuzumab with or without pertuzumab). Decision making about adjuvant biologic therapy for women with *HER2*-positive cancer is not discussed here. This review focuses on 3 decision points:

1. ***The decision to pursue adjuvant chemotherapy following locoregional therapy, with or without neoadjuvant chemotherapy, based on predicted risk of recurrence, for women who are hormone receptor-positive but HER2-negative.*** The use of adjuvant chemotherapy reduces the risk of breast cancer recurrence but carries risks of systemic toxicity. The risk:benefit ratio must be balanced for each patient, with a higher likelihood of net health benefits for patients with a greater baseline predicted the risk of recurrence (ROR). Some of the individual considerations are discussed below. *HER2* expression independently confers an unfavorable prognosis, but assessing the independent effects of *HER2* is complicated in the presence of targeted therapy; therefore, we focus specifically on patients without *HER2* expression.
2. ***The decision to pursue adjuvant endocrine therapy from 5 to 10 years for women who are hormone receptor-positive but HER2-negative and who have survived without recurrence to 5 years.*** For patients with hormone receptor-positive tumors, the use of adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years after an initial diagnosis has support in clinical practice. The 2017 guidelines from the National Comprehensive Cancer Network (NCCN) recommend extended endocrine therapy. The American Society for Clinical Oncology's (ASCO) 2014 focused update to its guidelines on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer have recommended 10 years of tamoxifen for pre- or perimenopausal women, and a total of 7-8 to 10 years of endocrine therapy, following 1 of 4 regimens that include tamoxifen with or without an aromatase inhibitor for postmenopausal women.
3. ***The decision to pursue adjuvant radiotherapy in women with ductal carcinoma in situ (DCIS).*** Adjuvant radiotherapy reduces the risk of local recurrences but has not been shown to change the risk of distant recurrence or mortality. There may be a group of patients for whom the reduction in risk for local recurrence may not be large enough to justify the risks of radiotherapy.

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 cytotoxic 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 cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of patients' baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline ROR. Women with the best prognosis have tumors that are small, early-stage, ER+, and lymph node to negative (Table 1 shows recurrence risk for ER+ cancers for patients followed in the International Breast Cancer Study Group). Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy.) These women have an

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

approximately 15% ten-year ROR with tamoxifen alone; approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic 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 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 women’s decision making, some of whom may prefer to avoid chemotherapy if assured their risk is low.

Table 1. Effect of Nodal Involvement, Tumor Size, and Grade on Annual Recurrence Hazard in Estrogen Receptor–Positive Breast Cancers (Colleoni et al, 2016)

| Nodes | Recurrence, Hazard ^a (SE), % | | | | |
|--------------|---|------------|-----------|-----------|-----------|
| | Years | | | | |
| | 0-5 | 5-10 | 10-15 | 15-20 | 20-25 |
| 0 | 5.8 (0.5) | 3.3 (0.4) | 2.0 (0.4) | 2.1 (0.4) | 1.1 (0.4) |
| 1 to 3 | 9.5 (0.6) | 5.8 (0.6) | 3.0 (0.5) | 3.5 (0.7) | 1.5 (0.6) |
| ≥4 | 17.2 (0.9) | 10.9 (1.2) | 5.9 (1.2) | 3.8 (1.2) | 1.3 (0.9) |
| Size | | | | | |
| ≤2 cm | 7.0 (0.4) | 4.8 (0.4) | 2.9 (0.4) | 2.7 (0.5) | 1.5 (0.5) |
| >2 cm | 12.9 (0.6) | 6.1 (0.6) | 2.9 (0.5) | 2.7 (0.5) | 1.1 (0.5) |
| Grade | | | | | |
| 1 | 5.8 (0.6) | 4.9 (0.7) | 3.6 (0.7) | 4.0 (0.9) | 0.7 (0.5) |
| 2 | 9.6 (0.5) | 6.3 (0.5) | 2.8 (0.4) | 2.7 (0.5) | 1.8 (0.5) |
| 3 | 14.1 (0.8) | 4.1 (0.6) | 2.5 (0.6) | 2.4 (0.7) | 0.4 (0.4) |

^a Number of events occurring within a time interval divided by the total years of follow-up during the interval accrued by patients at risk during the interval. Patients may have received no adjuvant treatment or have been treated with adjuvant tamoxifen and/or adjuvant chemotherapy.

SELECTION OF EXTENDED ENDOCRINE THERAPY

Randomized controlled trials (RCTs) have established that 5 years of tamoxifen improves mortality in women with hormone receptor–positive breast cancer. A 2011 individual patient data meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group, including 20 trials (total N=21,457 patients) found that 5 years of tamoxifen in ER+ disease reduced the RORs by almost 50% over 10 years on the relative scale; breast cancer mortality was decreased by 29% through 15 years.

For patients with early-stage, invasive breast cancer that is hormone receptor–positive, the use of endocrine therapy (tamoxifen and/or aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years following initial diagnosis has support in national guidelines. However, the regimens available and the evidence to support them vary.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

RCTs published recently have shown that extended endocrine therapy decreases the ROR. The ASCO and NCCN guidelines were informed primarily by results of the ATLAS trial, which compared 5 and 10 years of tamoxifen and the subsequent aTTom trial (reported in abstract form). In both trials, in women who were hormone receptor–positive and had completed 5 years of tamoxifen, 5 years of extended tamoxifen was associated with improvements in breast cancer–specific mortality; ATLAS showed improvements in OS (see Table 2).

Three previously reported randomized trials of extended tamoxifen treatment had mixed findings: Tormey et al (1996; total N=194 patients), the National Surgical Adjuvant Breast and Bowel Project (Fisher et al, 2001; total N=1172 patients), and the Scottish Cancer Trials Breast Group (Stewart et al, 2001; total N=342 patients) (see Table 2).

Overall, the available trial evidence would suggest that 10 years of tamoxifen in pre- or postmenopausal women can be linked with improved survival while trials of extended aromatase inhibitors in different populations of hormone receptor–positive patients have had more mixed results.

Table 2. Randomized Trials Evaluating Adjuvant Extended Endocrine Therapies for Hormone Receptor–Positive Breast Cancer

| Study | Population | Comparators | Breast Cancer–Specific Mortality | | Overall Mortality | |
|-------------------------------------|---|---|---|------|---|------|
| | | | Event RR (95% CI) | p | Event RR (95% CI) | p |
| Extended tamoxifen | | | | | | |
| ATLAS (2013) | 6846 women with ER-positive, early breast cancer, after 5 y of tamoxifen | Continue tamoxifen to 10 y (n=3428) vs stop tamoxifen at 5 y (n=3418) | 0.83 (0.72 to 0.96) (331/3428 vs 397/3418) | 0.01 | 0.87 (0.78 to 0.97) 722 (639/3428 vs 722/3418) | 0.01 |
| aTTom (2013) | 6953 women with ER-positive or untested breast cancer, after 5 y of tamoxifen | Continue tamoxifen to y (n=3468) vs stop tamoxifen at 5 y (n=3485) | 10 years 392/3468 intervention vs 442/3485 control Years 5-9 1.03 (0.84 to 1.27) After year 9 0.77 (0.64 to 0.92) | 0.05 | 10 years 849/3468 intervention vs 910/3485 control Years 5-9 1.05 (0.90 to 1.22) After year 9 0.86 (0.75 to 0.97) | 0.1 |
| Extended aromatase inhibitor | | | | | | |
| ABCSG (2007) | 856 post-menopausal women with ER- and/or PR-positive breast cancer, after 5 y of tamoxifen | Anastrozole for 3 y (n=386) vs no further therapy (n=466) | | | 5 years 10.3% anastrozole vs 11.7% control Event HR (95% CI) 0.89 (0.59 to 1.34) | 0.57 |
| | | | Breast Cancer–Specific Survival | | Overall Survival | |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
 Original Effective Date: 03/01/2007
 Current Effective Date: 01/17/2018

| Study | Population | Comparators | Breast Cancer– Specific Mortality | Overall Mortality |
|-----------------------------------|--|--|--|---|
| NCIC CTG MA.17 trial (2003, 2005) | 5187 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y tamoxifen | Continue letrozole to 10 y (n=2593) vs stop tamoxifen at 5 y (n=2594) | 48 Months 94.4% letrozole vs 89.8% placebo Event HR 0.58 (0.45 to 0.76) | 48 Months 96% letrozole vs 94% placebo Event HR 0.76 (0.48 to 0.21) 0.25 40 Months 95.4% letrozole vs 95% placebo Event HR 0.82 (0.57 to 1.19) 0.3 |
| NSABP (2008) | 1598 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y of tamoxifen | Planned comparison: 5 y exemestane vs 5 y placebo. Accrual stopped (n=1598 randomized) and crossover allowed after results of NCIC CTG available: <ul style="list-style-type: none"> Exemestane: 783 randomized, 560 continued after unblinding) Placebo: 779 randomized, 334 crossed over to exemestane after unblinding | 48 Months ITT: 91% exemestane vs 89% placebo | 0.07 |

ABCSG: Austrian Breast and Colorectal Cancer Study Group; CI: confidence interval; ER: estrogen receptor; HR: hazard ratio; ITT: intention to treat; NCIC CTG: National Cancer Institute Clinical Trials Group; NSABP: National Surgical Adjuvant Breast and Bowel Project; PR: progesterone receptor; RR: rate ratio.

In addition to the trials published in full-length form, 3 trials presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: 10 years vs 5 years of letrozole; DATA [NCT00301457]: 6 years vs 3 years of anastrozole; and IDEAL [NTR3077] 10 years vs 7.5 years of letrozole) did not meet their primary end points.

CLINICAL USES OF GENE EXPRESSION SIGNATURES FOR BREAST CANCER

In other clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. Recently, several groups have identified panels of gene expression markers (“signatures”) that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiotherapy, and endocrine therapy (for hormone receptor to positive tumors). Several gene expression tests commercially available in the United States are listed in Table 3. If these panels are more accurate risk predictors than current conventional classifiers, they could be used to aid decision making on adjuvant treatments without greatly affecting disease-free survival and overall survival (OS). This review

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

focuses on gene expression profiling panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known ER and PR and *HER2* status. The proposed clinical utility of these tests varies by the clinical context; these specific indications are discussed in this review:

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, *HER2*-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
2. Prognosis and/or prediction of treatment response in patients with node-positive (1-3 nodes), hormone receptor-positive, early-stage, *HER2*-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
3. Prognosis and/or prediction of treatment response in patients with DCIS for the purpose of determining whether patients can avoid radiotherapy.
4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, *HER2*-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to 5 years postdiagnosis, for the purpose of determining whether patients will continue adjuvant hormonal therapy.

For each of these indications, clinical trials have shown that there is some clinical benefit to receiving the additional therapy under consideration. However, each additional treatment has potential adverse effects. If a patient subgroup can be defined that has an extremely low risk of distant recurrence, or a subgroup can be defined that does not respond to the treatment, then the additional treatment can be forgone with little effect on cancer outcome due to the low risk of poor outcome or lack of response to treatment.

Table 3. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein

| Test | Manufacturer | Description |
|--|---|---|
| Oncotype DX® | Genomic Health (Redwood City, CA) | 21-gene RT-PCR |
| EndoPredict® | Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT] in 2016) | 12-gene real-time RT-PCR |
| Breast Cancer Index Prognostic SM | Biotheranostics (San Diego, CA) | Combines MGI and the HOXB13:IL17BR Index measured using RT-PCR |
| MammaPrint® | Agendia (Amsterdam, The Netherlands) | 70-gene DNA microarray |
| Prosigna® | NanoString Technologies (Seattle, WA) | Gene expression protein signature Predictive signature based on nCounter® digital analysis system based on PAM50 breast cancer intrinsic subtype classifier |

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50-gene set; RT-PCR: reverse transcriptase polymerase chain reaction.

Additional commercially available tests may provide some prognostic or predictive information for breast cancer. Tests intended to assess ER, PR, and *HER2* status, such as TargetPrint (Agendia; via quantitative

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

microarray), are outside the scope of this review. In addition, tests that do not provide a specific recurrence risk are outside the scope of this review.

Other commercially available biomarkers are designed to provide information about tumors' molecular subtypes (i.e., luminal A, luminal B, *HER2* type, and basal type). Prosigna was initially offered a molecular subtype test. The Blueprint 80-gene molecular subtyping assay is offered in combination with MammaPrint to augment predictive data about response to chemotherapy.

DECISION FRAMEWORK FOR EVALUATING BREAST CANCER BIOMARKERS

Simon et al Framework

Many studies have investigated individual biomarkers or combinations of biomarkers associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al (2009) have described a framework to evaluate prognostic biomarker evidence. Study designs such as prospective clinical trials or previously conducted clinical trials with archived tumor samples constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcomes in the patient group of interest that would result in a change in management (e.g., withholding of chemotherapy), and the study must have sufficient precision (narrow CIs). Results of the same test across studies should show the consistency of results and more than 1 study demonstrating the desired result should be available. Simon has proposed that at least 2 Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.

Breast Cancer–Specific Outcomes

The main outcome of interest for this review is 10-year distant recurrence-free survival. Distant recurrence is a hallmark of advanced breast cancer and thus more informative of OS than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis than distant disease. For the extended endocrine indications in this review, the main outcome of interest is 10-year distant recurrence-free survival conditional on recurrence-free survival for 5 years.

Decisions to undergo or forgo adjuvant therapy (chemotherapy or endocrine) depend on how a woman values the potential benefit of lower recurrence risk relative to the harms of treatment. The balance of benefits and harms determines the thresholds that inform decisions. Most women will accept substantial adverse events for even modest benefit. For example, Simes et al (2001) interviewed 104 Australian women with breast cancer treated with cytotoxic chemotherapy and elicited preferences to undergo chemotherapy according to probable gain in survival. With an expected survival of 5 years without

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

chemotherapy, 73% said they would accept chemotherapy for an increased survival of 6 months or less; with an expected survival of 15 years, 39% would accept treatment for a gain of 6 months. Duric et al (2005) found 64% to 84% of 97 women expressing a willingness to undergo chemotherapy for a 1-year improvement in life expectancy or 3% increase in survival rates. About half felt a single day would justify adjuvant chemotherapy. A major difference between the 2 studies was that the chemotherapy regimen in Duric et al was less toxic. Thewes et al (2005) adopted the same approach for adjuvant endocrine therapy preferences in 102 premenopausal women with early-stage breast cancers. Among women having a baseline life expectancy of 5 years, 61% said they would accept endocrine therapy for a 6-month increase in life expectancy and 79% for 1 year; rates were similar if the baseline life expectancy was 15 years. These proportions are close to those for adjuvant chemotherapy found by Duric.

How these estimates correspond to the distant recurrence rates reported in prognostic studies is imprecise, but Henderson (2015) has suggested that below a recurrence threshold of 10% many patients will not elect adjuvant chemotherapy owing to the small absolute benefit. He also noted that a majority of those patients are older with small node-negative tumors. That interpretation is consistent with a recent study of 81 women by Hamelinck et al (2016) who found that 78% of women ages 40 to 49 years, 88% ages 50 to 59, 59% ages 60 to 69, and 40% age 70 or older would accept adjuvant chemotherapy for a 0% to 10% absolute decrease in recurrence risk (see Table 4). There was a wide range of minimally required absolute benefits, with the majority accepting chemotherapy for an absolute benefit of 1% to 5%. At a given age range, fewer women expressed a willingness to accept adjuvant endocrine therapy than chemotherapy for a given mortality benefit.

Table 4. Patient Preferences for Undergoing Adjuvant Therapy for <10% Reduction in Recurrence Risk

| Age Range, y | Proportion That Would Accept for 1% to 10% Benefit | |
|--------------|--|--------------|
| | Chemotherapy, % | Endocrine, % |
| 40-49 | 78 | 78 |
| 50-59 | 88 | 44 |
| 60-69 | 59 | 63 |
| ≥70 | 40 | 46 |

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 and other tests listed herein 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. FDA has chosen not to require any regulatory review of this test.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

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

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

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, decisions are left to the discretion of local Medicare carriers.

In November 2014, Palmetto GBA issued a local coverage determination for the BCI. Effective October 1, 2015, the policy limits coverage of the BCI to patients who meet the following criteria:

- “Post-menopausal female with non-relapsed, ER+ breast cancer; and
- Is lymph node negative, and
- Is completing 5 years of tamoxifen therapy, and
- Patient must be eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines, and
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects, and
- The test results will be discussed with the patient (including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines)”

Rationale/Source

EARLY-STAGE NODE-NEGATIVE INVASIVE BREAST CANCER CONSIDERING ADJUVANT CHEMOTHERAPY

Oncotype DX (21-Gene Assay)

We identified 4 studies meeting selection criteria). The studies derive from 3 completed randomized trials and thus are all Simon category B studies. The study by Paik et al (2006) evaluated patients from a trial in which the subjects were part of the training set used to develop the Oncotype algorithm, so its results might be biased. The study by Tang et al (2011) represents the same results as Paik et al (2004), but categorized by the Adjuvant! Online clinical risk stratifier (see Table 5).

Across all 3 studies in which patients were solely classified by Recurrence Score (RS), the 10-year risk of distant recurrence was low in the RS low category. Ten-year distant recurrence rates were all below the 10% threshold suggested by Henderson (2015) and the upper limit of the 95% CIs were also below 10%. In the study by Tang et al (2011), which categorized patients by both clinical risk and RS category, the RS

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

provided further risk stratification within clinical risk categories. The recurrence rates for each clinical risk and RS group, although they showed that each characteristic provides some predictive capability, are somewhat arbitrary because the cutoffs used to categorize clinical risk were simply based on creating classes similar in size to RS categories. Different cutoffs for the clinical risk categories would render different recurrence rates.

A prospective trial of Oncotype DX evaluating prognosis was published by Sparano et al (2015). Although the trial only evaluated outcomes at 5 years, it is among the few Simon category A studies available. In it, women with node-negative, ER+, HER2-positive breast cancer were evaluated with Oncotype DX. Depending on the RS, women were assigned to endocrine therapy alone (low RS), randomized to adjuvant chemotherapy or no chemotherapy (middle category RS), or assigned to adjuvant chemotherapy (high RS). The published trial only reported the findings of the group at low ROR assigned to endocrine therapy. Of 10,253 subjects, 1629 patients had a RS of 0 to 10 and did not receive adjuvant chemotherapy. Note that the cutoff score of 10 is lower than that for other studies evaluating Oncotype DX and thus evaluates a group at lower predicted risk of distant recurrence than other Oncotype DX studies, which typically used a cutoff of 18. Consequently, only 15.9% of the study population was judged low risk, which is much lower than other studies. At 5 years, the distant recurrence rate was 0.7% (95% CI, 0.4% to 1.3%). Other outcomes at 5 years were rate of invasive disease-free survival (93.8%; 95% CI, 92.4% to 94.9%), rate of freedom from recurrence (98.7%; 95% CI, 97.9% to 99.2%), and (OS; 98%; 95% CI, 97.1% to 98.6%). Results from the randomized subjects in the trial are not available. The outcomes of these subjects, who were at higher predicted ROR, would demonstrate the risk of outcomes of subjects with higher scores and perhaps determine the magnitude of benefit of chemotherapy in these subjects.

Section Summary: Oncotype DX (21-Gene Assay)

Multiple studies derived from archived samples of previously conducted RCTs, have shown that a low RS is associated with a low absolute risk of 10-year distant recurrence with an upper 95% CI bound not exceeding 10% in any study. These low absolute risks would translate to small absolute benefit from adjuvant chemotherapy. In these studies, over half of patients were classified at low risk. The 2015 prospective study by Sparano et al, although reporting results only at 5 years and using a more stringent cutoff to define a low-risk score, showed very low distant recurrence rates and is consistent with the previously reported studies.

Table 5. Ten-Year Distance Recurrence by Oncotype DX Risk Score Group

| Study (Source of Patients) | N | Risk Score Group by % Patients in Risk Group | | | 10-Year Distant Recurrence (95% Confidence Interval), % | | |
|--|-----|--|-----|------|---|-----------------------|------------------------|
| | | Low | Int | High | Low | Int | High |
| Paik et al (2004) (TAM arm of NSABP B-14 trial) | 668 | 51 | 22 | 27 | 6.8 (4.0 to 9.6) | 14.3 (8.3 to 20.3) | 30.5 (23.6 to 37.4) |
| Paik et al (2006) (TAM arm of NSABP B-20 trial) | 227 | 59 | 20 | 21 | 3.2 (0.1 to 6.3) | 9.1 (0.6 to 17.5) | 39.5 (25.2 to 53.8) |
| Buus et al (2016) (ATAC trial) | 680 | 64 | 27 | 10 | 5.3 (3.5 to 8.2) | 14.3 (9.8 to 20.6) | 25.1 (15.8 to 38.3) |
| Tang et al (2011) | 668 | Clin low/RS low: 32 | | | 5.6 (2.5 to 9) | | |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

| | | |
|-------------------------------|-------------------------------|-----------------|
| (TAM arm of NSABP B-14 trial) | Clin low/RS int-high: 21 | 12.9 (7 to 19) |
| | Clin int-high/RS low: 18 | 8.9 (4 to 14) |
| | Clin int-high/RS int-high: 29 | 30.7 (24 to 38) |

ATAC: Arimidex, Tamoxifen, Alone or in Combination; Clin: Clinical; Int: intermediate; NSABP: National Surgical Adjuvant Breast and Bowel Project; RS: Recurrence Score; TAM: tamoxifen.

EndoPredict

We identified 2 studies with 3 sets of findings that met selection criteria (see Table 6). The study by Filipits et al (2011) assessed patients from two previously conducted clinical trials. We selected the study even though it included patients with positive nodes (32% of patients) because the expected effect of inclusion of these patients is to increase the recurrence rates and result in a conservative (biased to be high) estimate of distant recurrence. Buus et al (2016) studied patients from the ATAC trial, which evaluated the efficacy and safety of anastrozole vs tamoxifen in postmenopausal women with localized breast cancer. In both studies, risk scores were defined as high and low based on a predefined cut point corresponding to a 10% risk of distant recurrence. EndoPredict provides an expression profile (EP) score based solely on the gene expression assay; the EPclin score incorporates the EP score and clinical data on tumor size and nodal status. Results of node-negative patients in Buus et al were only reported in supplementary materials because the main report focused on combined node-positive and node-negative results. Node-negative patients constituted 73% of the subjects included in Buus et al.

All 3 sets of findings showed that a low EP score is associated with a low absolute risk of 10-year distant recurrence. In 1 study the CI exceeded 10%, but this was the smallest study (n=378 subjects). When the EP score incorporates tumor size and nodal status, a low EPclin score is also associated with a low absolute risk of 10-year distant recurrence. A higher proportion of subjects were classified as low risk (55%-73%) using EPclin, but the 10-year distant recurrence rates in the low-risk group were similar to rates in the EP low-risk group. This demonstrated that EPclin discriminates outcomes better than EP; it also suggests that using EPclin would result in fewer patients choosing chemotherapy than using EP alone. The inclusion of some node-positive patients in two of the studies should have resulted in conservative estimates of prognosis, in that outcomes in node-negative patients in the low-risk group might be even better than shown in these studies.

Section Summary: EndoPredict

Three sets of findings, derived from archived samples of previously conducted RCTs, have shown that a low EP or EPclin score is associated with a low absolute risk of 10-year distant recurrence with an upper 95% CI bound generally below 10%, except in a small study. These low absolute risks would translate to small absolute benefit of adjuvant chemotherapy. In these studies, over half of the patients were classified at low risk. The EPclin score classified a higher proportion of patients as low risk than the EP score.

Table 6. Ten-Year Distance Recurrence by EndoPredict Risk Group

| Study (Source of Patients) | N | Risk Score Group by % Patients in Risk Group | | | | 10-Year Distant Recurrence (95% Confidence Interval), % | | | |
|----------------------------|---|--|----|--------|--------|---|----|--------|--------|
| | | EP | EP | EPclin | EPclin | EP | EP | EPclin | EPclin |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

| | | Low | High | Low | High | Low | High | Low | High |
|--|------|-----|------|-----|------|-----------------|--------------------|-----------------|--------------------|
| Filipits et al (2011) (ABCSG-6 trial) | 378 | 51 | 49 | 55 | 45 | 8 (3 to 13) | 22 (15 to 29) | 4 (1 to 8) | 28 (20 to 36) |
| Filipits et al (2011) (ABCSG-8 trial) | 1324 | 48 | 52 | 65 | 35 | 6 (2 to 9) | 15 (11 to 20) | 4 (2 to 5) | 22 (15 to 29) |
| Buus et al (2016) (ATAC trial) | 680 | 43 | 57 | 73 | 27 | 3.0 (2 to 6) | 14.6 (11 to 19) | 5.9 (4 to 9) | 20.0 (15 to 27) |

ABCSG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; EP: EP score; EPclin: EPclin score.

^a ABCSG-6 and ABCSG-8 studies included a combined 32% node-positive patients.

Breast Cancer Index

We identified 2 studies with 3 sets of findings of the BCI that met selection criteria (see Table 7). Some *HER2*-positive patients were included in both studies, but these numbers were not stated. Sgroi et al (2013) analyzed patients receiving anastrozole or tamoxifen in the ATAC trial. This trial constitutes a Simon category B study. Two versions of the BCI score were generated in the study: (1) the BCI-C, based on cubic combinations of the variables, and (2) the BCI-L, based on linear combinations of the variables. The second study, by Zhang et al (2013), reported 2 sets of findings, one deriving from a clinical trial and another from patient registries. Patients from the registry were only included if tissue samples were available.

In all sets of findings, a BCI low-risk category classified more than half of the patients as low risk, and such patients had low risk of disease recurrence at 10 years. Sgroi et al found that the BCI-C and BCI-L showed a low risk of disease recurrence in the low-risk groups, with the CIs not exceeding 10%. In the study by Zhang et al, patients in BCI low-risk categories also showed a low risk of distant disease recurrence, with CIs not exceeding 10%.

Section Summary: Breast Cancer Index

Three sets of findings for the BCI have shown a low risk of 10-year distant recurrence among patients classified at low risk. Two sets of findings have been derived from clinical trials and are categorized as Simon category B. The findings from the multicenter registry are Simon category C.

Table 7. Ten-Year Distance Recurrence by Breast Cancer Index Risk Group

| Study (Source of Patients) | N | Risk Score Group by % Patients in Risk Group | | | 10-Year Distant Recurrence (95% Confidence Interval), % | | |
|--|-----|--|-----------|------------|---|------------------------|------------------------|
| | | BCI Low | BCI Int | BCI High | BCI Low | BCI Int | BCI High |
| Zhang et al (2013) (multicenter registry) | 358 | 55 | 22 | 23 | 6.6 (2.9 to 10) | 23.3 (12.3 to 33) | 35.8 (24.5 to 45.5) |
| Zhang et al (2013) (Stockholm trial) | 317 | 64 | 20 | 16 | 4.8 (1.7 to 7.8) | 11.7 (3.1 to 19.5) | 21.1 (8.5 to 32.0) |
| Sgroi et al (2013) (ATAC trial) | 665 | BCI-C Low | BCI-C Int | BCI-C High | BCI-C Low | BCI-C Int | BCI-C High |
| | | 58 | 25 | 17 | 6.8 (4.4 to 10) | 17.3 (12.0 to 24.7) | 22.2 (15.3 to 31.5) |
| | | BCI-L Low | BCI-L Int | BCI-L High | BCI-L Low | BCI-L Int | BCI-L High |
| | | 59 | 25 | 16 | 4.8 (3.0 to 7.6) | 18.3 (12.7 to 25.8) | 29.0 (21.1 to 39.1) |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

ATAC: Arimidex, Tamoxifen, Alone or in Combination; BCI-C: Breast Cancer Index using cubic form of variables; BCI-L: Breast Cancer Index using linear form of variables.

^a Subgroup not receiving chemotherapy.

MammaPrint (70-Gene Signature)

We identified 1 study of MammaPrint that met selection criteria (see Table 8). Studies not meeting selection criteria often had mixed populations, including node-positive patients, mixed node-positive and node-negative patients, or patients receiving chemotherapy. The selected study by Bueno-de-Mesquita et al (2011) also initially evaluated a mixed population, but it presented relevant subgroup results. This study sample derived from 3 separate cohorts in cancer registry studies, thus the study would be classified as Simon category C. For this evidence review, we present only the results for ER+ cancers. Risk groups were based on multiple clinical classification methods and the gene EP. Three clinical classification methods were used, and the results of any 2 clinical methods were classified as concordant low risk, discordant, and concordant high risk. Because the patterns were very similar across all 3 combinations of 2 clinical classification methods, only the results for combining Adjuvant! Online and Nottingham Prognostic Index are presented.

Only patients with both clinical risk scores (low risk and a MammaPrint low-risk score) had a 10-year distant recurrence risk below 10%. All other combinations of clinical risk and MammaPrint risk had 10-year recurrence risks greater than 10%. This pattern would suggest that a clinical strategy of using MammaPrint only in those with 2 clinical risk scores indicating low risk would identify patients with low absolute ROR.

Table 8. Ten-Year Distance Recurrence by MammaPrint Risk Group

| Study (Source of Patients) | N | Risk Score Group by % Patients in Risk Group | 10-Year Distant Recurrence (95% Confidence Interval), % |
|--|-----|--|---|
| Bueno-de-Mesquita et al (2011) (3 combined cohorts) | 139 | Clin low/low MP low: 24 | 3 (0 to 9) |
| | | Clin low/low MP high: 10 | 34 (9 to 59) |
| | | Clin discordant MP low: 22 | 11 (0 to 22) |
| | | Clin discordant MP high: 9 | 31 (6 to 56) |
| | | Clin high/high MP low: 9 | 23 (0 to 46) |
| | | Clin high/high MP high: 26 | 47 (31 to 63) |

Clin: clinical; MP: MammaPrint.

We also present results from the MINDACT trial (Cardoso et al, 2016), because it represents a prospectively designed trial evaluating MammaPrint, with additional randomized components. Currently, only 5-year results are available. In this trial, women with early-stage breast cancer were evaluated with both MammaPrint and a clinical risk estimator. Women at low risk with both methods did not receive chemotherapy. Women with discordant risks were randomized to chemotherapy or to no chemotherapy. Women at high risk with both methods received chemotherapy.

Although parts of the study are an RCT, the end point for this particular analysis was the distant recurrence rate among patients with high-risk clinical and low-risk genetic profile who did not receive chemotherapy. Investigators prespecified that the upper bound of the 95% CI for distant recurrence was 8%, which they

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
 Original Effective Date: 03/01/2007
 Current Effective Date: 01/17/2018

stated would be a sufficiently low risk that such patients could reasonably avoid chemotherapy. Declaring this to be the main end point implies a clinical strategy of using MammaPrint only in patients at high clinical risk, and deferring chemotherapy in those tested patients who have low genetic risk score. In this strategy, patients at low clinical risk are not tested with MammaPrint.

Trial entry criteria included patients with either node-positive, ER+, or *HER2*-positive breast cancer. However, these patients constituted a minority of those in the study. The main results included these patients. The authors conducted supplemental analyses of various subgroups, including the subset who were node-negative, ER+, or *HER2*-negative. To report results of patients most comparable to the other studies discussed herein, we abstracted the results of these supplemental analyses (see Table 9). The results are qualitatively similar to the published main results.

In the main article, the principal objective of the study was met. The group at high clinical risk and low genomic risk who did not receive chemotherapy had a distant recurrence rate of 5.3% (95% CI, 3.8% to 7.5%). In the node-negative, ER+, or *HER2*-negative subgroup analysis, this group had a distant recurrence rate of 4.5% (95% CI, 3.8% to 8.4%).

In the group with clinical low risk and high genomic risk, who were not considered in the main outcome, in both the main analysis and in the node-negative, ER+, or *HER2*-negative subgroup, the results would indicate that the risk of distant recurrence is not low enough to avoid chemotherapy (main analysis distant recurrence, 5% [95% CI, 3% to 8.2%]; hazard ratio subgroup distant recurrence, 6.1% [95% CI, 3.9% to 9.4%]). In the testing strategy implied in this study, by not testing for genomic risk in the low clinical risk group, these patients would not be identified.

The groups randomized to chemotherapy showed no significant difference in 5-year distant recurrence, but the CIs were wide and thus uninformative regarding whether chemotherapy is or is not beneficial in these patient groups. In the main study, the hazard ratio for chemotherapy in the high clinical risk/low genomic risk was 0.78 (95% CI, 0.5 to 1.21). The hazard ratio for chemotherapy in the low clinical risk/high genomic risk group was 1.17 (95% CI, 0.59 to 2.28).

Table 9. MINDACT Trial 5-Year Distant Recurrence for the Node-Negative, Estrogen Receptor-Positive, or *HER2*-Negative Subgroup

| Study (Trial) | N | Risk Score Group by % Patients in Risk Group | 5-Year Distant Recurrence (95% Confidence Interval), % |
|--------------------------------------|------|--|--|
| Cardoso et al (2016) (MINDACT trial) | 4225 | Clin low/MP low: 58 | 2.4 (1.8 to 3.1) |
| | | Clin low/MP high: 11 | 6.1 (3.9 to 9.4) |
| | | Clin high/MP low: 17 | 4.5 (2.4 to 8.4) |
| | | Clin high/MP high: 14 ^a | 9.1 (6.8 to 12) |

Clin: clinical; *HER2*: human epidermal growth factor receptor 2; MINDACT: Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy; MP: MammaPrint.

^a All clin high/MP high subjects received chemotherapy

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

Section Summary: MammaPrint (70-Gene Signature)

One Simon category C study has evaluated MammaPrint and provided 10-year distant recurrence outcomes. In that study, only subjects with both low clinical risk and low gene profiling risk have absolute rates of recurrence low enough to consider deferring chemotherapy. The sample size for this result was small, and the proportion of patients identified at low risk was a small proportion (24%) of the study sample. The Simon category A study of MammaPrint has currently only provided 5-year distant recurrence outcomes. The principal result of the clinical high-risk plus MammaPrint low-risk patients may not be a low enough risk to defer chemotherapy because these 5-year recurrence rates will probably be much higher at 10 years. A group that may ultimately be identified as having sufficiently low absolute risk (but was not highlighted in the published study) is the group at clinical low risk and MammaPrint low risk, which at 5 years had a low absolute risk of distant recurrence of 2.4%.

Prosigna

We identified 2 sets of findings that met selection criteria. Both studies are classed as Simon category B. However, the distant recurrence rates from the study by Dowsett et al (2013) were not directly reported in the published article, so rates cited in Table 10 are based on visual estimates of the graphic results. CIs are not available either. Both studies reported distant recurrence rates below 5%, with the CIs for the 2 studies reporting them not exceeding 8%. In the 2 studies reporting the proportion of patients classified as low risk, more than 47% of patients were classified at low risk.

Section Summary: Prosigna

Two category Simon B studies of Prosigna have shown absolute risks of 10-year distant recurrence that are sufficiently low for consideration of avoiding adjuvant chemotherapy. However, these results should be viewed cautiously because they may be due to variation in the tests used in these different studies.

Table 10. Ten-Year Distance Recurrence by Prosigna Recurrence Score Group

| Study (Trial) | N | Risk Score Group (% Patients in Risk Group) | | | 10-Year Distant Recurrence (95% Confidence Interval), % | | |
|------------------------------------|------|--|-----|------|--|-------------------|---------------------|
| | | Low | Int | High | Low | Int | High |
| Gnant et al (2014) (ABCSG-8 trial) | 1047 | 47 | 32 | 22 | 3.4 (2.1 to 5.6) | 9.6 (6.7 to 13.7) | 15.7 (11.4 to 21.6) |
| Dowsett et al (2013) (ATAC trial) | 739 | 59 | 33 | 8 | 4.8 (NR) | 13.8 (NR) | 30.2 (NR) |

ABCSG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; Int: intermediate; NR: not reported.

EARLY-STAGE NODE-POSITIVE INVASIVE BREAST CANCER CONSIDERING ADJUVANT CHEMOTHERAPY

We identified 5 studies that met selection criteria (see Appendix 1), all prospective-retrospective designs, examining the prognostic value of gene expression profiling tests in patients with early-stage node-positive breast cancer receiving only endocrine therapy. Oncotype DX RS (risk score) was evaluated in 2 studies, Prosigna ROR in 1 study, and EndoPredict in 2 studies. Albain et al (2010) also explored a possible role for

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

Oncotype DX in predicting chemotherapy benefit. We also include results from the MINDACT trial, because it represents a prospectively designed trial evaluating MammaPrint. Table 11 displays the characteristics of patients assessed across the prospective-retrospective analyses. Almost all cancers were ER+ and HER2-negative, most patients had three or fewer positive lymph nodes, and all women were postmenopausal.

Table 11. Characteristics of Patients Included in Node-Positive Prospective-Retrospective Studies

| Study | N | ER+ | HER2+ | Tumor Size, n (%) | | | Nodes, n (%) | | Adjuvant Chemo n (%) | Trial/ Study |
|--------------------|-----|-----------|-------------------------------|-------------------------------|----------|-------|--------------|---------|----------------------|----------------|
| | | | | ≤2 cm | 2-5 cm | >5 cm | 1-3 | ≥4 | | |
| Oncotype DX | | | | | | | | | | |
| Albain (2010) | 148 | 145 (98) | 13 (9) | 46 (31) | 94 (64) | 8 (5) | 94 (64) | 54 (36) | 0 (0) | SWOG- |
| Albain (2010) | 219 | 210 (96) | 30 (14) | 74 (34) | 136 (62) | 9 (4) | 133 (61) | 86 (39) | 219 (100) | 8814 |
| Dowsett (2010) | 306 | 306 (100) | NR for node-positive patients | | | | 243 (79) | 63 (21) | 0 (0) | Trans ATAC |
| EndoPredict | | | | | | | | | | |
| Filipits (2011) | 537 | 537 (100) | 0 (0) | NR for node-positive patients | | | 454 (85) | 83 (15) | 0 (0) | ABCSG6, ABCSG8 |
| Buus (2016) | 248 | 248 (100) | 0 (0) | NR for node-positive patients | | | 198 (80) | 50 (20) | 0 (0) | Trans ATAC |
| Prosigna | | | | | | | | | | |
| Gnant (2015) | 543 | | 28 (5) | 314 (58) | | | 229 (42) | 0 (0) | 543 (100) | 0 (0) |

ABCSG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; chemo: chemotherapy; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; NR: not reported.

^aTamoxifen.

^bCyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen

Table 12 displays 10-year event rates reported by risk categories. Distant recurrence rates were not reported by Albain et al, but the 60% ten-year disease-free survival in the low-risk group would suggest substantial event rates in patients not receiving adjuvant chemotherapy. CIs were not reported, but, given the small number of low-risk patients intervals, would likely include a large range of plausible estimates. Dowsett et al (2010) reported a 17% distant recurrence rate (death was considered a censoring event) in the low-risk category. Finally, Gnant et al (2015) reported 10-year distant recurrence rates in the Prosigna low-risk group with a single positive node of 6.6% (as much as 2-fold greater than for Prosigna-classified low-risk node-negative patients; see Table 11) with an upper bound of the 95% CI of 12.8%. None of the studies reported the ability of tests to reclassify after assigning risk based on clinical predictors.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
 Original Effective Date: 03/01/2007
 Current Effective Date: 01/17/2018

Table 12. 10-Year Event Rates According to Risk Categories in Identified Prospective-Retrospective Studies

| Test | Study | N | Endpoint | Risk Category | | | | | | | | | Simon |
|-------------|--------------------------------|-----|-----------------|---------------|--------|-------------|-----------------|--------|------------|---------|-------------|-------------|-------|
| | | | | Low | | | Intermediate | | | High | | | |
| | | | n | Outcome | 95% CI | n | Outcome | 95% CI | n | Outcome | 95% CI | | |
| Oncotype Dx | Albain 2010, Tamoxifen | 148 | DFS | 55 | 60% | NR | 46 | 49% | NR | 47 | 43% | NR | B |
| | | | OS | | 77% | NR | | 68% | NR | | 51% | NR | |
| | Dowsett 2010 (9-year outcomes) | 296 | DR ^a | 150 | 17% | (12–24) | 94 | 28% | (20–49) | 52 | 49.0% | (35–54) | B |
| | | | OS | | 74% | | | 69% | | | 54% | | |
| EndoPredict | Filipits 2011 (EP score) | 537 | DR | 240 | 15% | NR | | | 297 | 27% | NR | B | |
| | Buus 2016 (EP score) | 248 | DR ^a | 94 | 21.3% | (13.9–31.9) | | | 154 | 36.4% | (28.9–45.2) | B | |
| | (EPclin score) | 248 | DR ^a | 47 | 5.0% | (1.2–18.9) | | | 201 | 36.9% | (30.2–44.5) | B | |
| Prosigna | Gnant 2015, 1 N+ | 331 | DR ^b | 132 | 6.6% | (3.3–12.8) | 106 | 15.5% | (9.5–25.5) | 93 | 25.5% | (17.5–36.1) | B |
| | Gnant 2015, 2-3 N+ | 212 | DR ^b | | | | 83 ^c | 12.5% | (6.6–22.8) | 129 | 33.7% | (25.5–43.8) | B |

CI: confidence interval; DFS: disease-free survival; DR: distant recurrence; NR: not reported; OS: overall survival.

^a Death from any cause considered a censoring event.

^b Death from breast cancer included as a distant recurrence.

^c Combined low- and intermediate-risk categories.

Oncotype DX (21-Gene Assay)

Albain et al (2010) analyzed data from the Southwest Oncology Group Trial 8814, an RCT that enrolled ER+ postmenopausal women and compared cyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen (CAF-T) for 5 years with tamoxifen alone. Archived samples from 41% (n=148) and 39% (n=219) of the 2 trial arms, respectively, were available for analysis, and patients included in the analyses had fewer positive nodes and smaller tumors than those in the overall trial. Based on the RS results (includes *HER2* assay), about 1 in 10 patients had a *HER2*-positive tumor. The primary end point was disease-free survival (time from enrollment to locoregional or distant recurrence, new primary cancer, or any cause of death). Neither distant disease-free survival nor distant recurrence rates were available for analysis.

In addition to examining the prognostic value of the RS in node-positive patients, its potential predictive ability was also analyzed (see Table 13). While the hazard ratios appeared to vary with time, the magnitude differed by RS category, raising the possibility that adjuvant chemotherapy might not benefit those with low-risk scores. However, the CIs for the low-risk group include hazard ratios consistent with benefit, and the small number of patients studied precludes drawing conclusions.

Table 13. Hazard Ratios for Chemotherapy Benefit of Sequential CAF-T vs Tamoxifen Alone (Albain et al, 2010) by Oncotype DX RS

| Variables | OS, HR (95% CI) | | DFS, HR (95% CI) | |
|--------------|---------------------|---------------------|---------------------|---------------------|
| | 10 Years | 10 Years | ≤5 Years | ≥5 Years |
| Parent trial | 0.78 (0.63 to 0.97) | 0.69 (0.56 to 0.84) | 0.68 (0.53 to 0.86) | 0.72 (0.51 to 1.00) |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

| | | | | |
|-----------------|---------------------|---------------------|---------------------|---------------------|
| RS sample | 0.77 (0.52 to 1.14) | 0.72 (0.51 to 1.00) | 0.79 (0.53 to 0.86) | 0.63 (0.39 to 1.04) |
| Low RS | | | 1.34 (0.47 to 3.82) | 0.88 (0.38 to 1.92) |
| Intermediate RS | | | 0.95 (0.43 to 2.14) | 0.52 (0.20 to 1.52) |
| High RS | | | 0.59 (0.32 to 1.11) | 0.60 (0.22 to 1.62) |

CAF-T: cyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen; CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; RS: risk score; OS: overall survival.

^a Adjusted for number of positive nodes.

Oncotype DX risk score appears to be associated with 10-year distant recurrence-free survival in patients with node-positive disease, although, as expected, the recurrence rates for the node-positive disease are higher than for node-negative (i.e., 10-year distant recurrence-free survival in Albain et al). Overall, there is significant uncertainty in the estimates, and only 1 Simon category 1 study has reported on point-estimates for 10-year distant recurrence-free survival with CIs.

Dowsett et al (2010) examined a sample of node-negative and node-positive patients from the ATAC trial. Archived samples were available for 306 node-positive patients of whom 243 (80%) had 1 to 3 involved nodes. The 9-year distant recurrence rate (censoring for any cause of death) in low-risk node-positive patients was 17% (95% CI, 12% to 24%) compared with 4% (95% CI, 3% to 7%) for the low-risk node-negative group. OS rates by risk group were similar to those reported by Albain et al. Dowsett et al fitted a model to recurrence rates using a continuous risk score and number of nodes, which suggested considerably lower recurrence rates with 1 to 3 nodes compared with 4 or more. A potential predictive effect was not examined and OS not reported.

Although the RS appears to have some prognostic ability across the risk categories for node-positive disease, the absolute distant recurrence rates in the low-risk group were considerably higher than those proposed to be low enough to lead patients to forgo to adjuvant chemotherapy in low-risk node-negative patients. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed so that patients can make informed decisions. Given that patients would typically elect adjuvant chemotherapy for a modest improvement in survival (almost 50% reported that they would choose it for even a 1% gain) raises a question whether in practice the RS offers sufficient prognostic information to inform decisions.

Section Summary: Oncotype DX (21-Gene Assay)

Results from 2 prospective-retrospective Simon category B studies have suggested uncertainty in the estimates of the distant recurrence-free survival risk for patients in different Oncotype DX RS categories. One study does not report CIs for the estimates of survival and, in the other, the CIs are very wide. Although it is expected that the distant recurrence-free survival estimates will be lower than that are seen for patients with node-negative disease, more certain estimates of risk are needed before a reasonable discussion about whether patients would or should decline adjuvant chemotherapy can occur. Albain et al (2010) suggested the test might also be predictive, albeit based on a small sample. Although there has been substantial adoption of the RS to inform adjuvant chemotherapy choices in node-positive patients,

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

convincing evidence that decisions based on test results will improve outcomes is lacking, and guidelines do not offer support. The ongoing RxPONDER trial is randomizing patients with early-stage ER+, *HER2*-negative breast cancer and 1 to 3 positive nodes, stratified by RS (0 to 13, 14 to 25) to adjuvant chemotherapy or no adjuvant chemotherapy. Results of that trial will most likely define the clinical utility of the RS in node-positive patients.

EndoPredict

Filipits et al (2011) evaluated the potential prognostic value of the EndoPredict EP risk scores among node-positive patients in a combined analysis of ABCSG-6 and ABCSG-6 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 in the article supplement. The 10-year absence of distance recurrence estimate for node-positive patients appears to be about 85% in EP low-risk and 73% in EP high-risk patients based on visual inspection; recurrence estimates by EPclin risk categories were not provided. CIs were not provided.

Buus et al (2016) also reported on the prognostic value of EndoPredict among node-positive patients from ATAC in the article supplement. 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 survival 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.

Section Summary: EndoPredict

Two Simon category B studies meeting inclusion criteria were identified. The 10-year distant recurrence rate estimate for node-positive, EPclin low-risk patients was about 5% in one publication but the CIs were wide and the upper bound for the 95% CI was well above the range judged clinically informative in node-negative patients. The second publication did not report CIs for 10-year distant recurrence by risk categories.

Breast Cancer Index

We did not identify studies meeting inclusion criteria in node-positive study populations for the BCI test.

70-Gene Signature (MammaPrint)

The previously described MINDACT study (Simon category A) initially enrolled only patients with node-negative disease but began including women with one to three positive nodes in 2009. Subgroup results were reported from the randomized MINDACT comparison of adjuvant chemotherapy with no chemotherapy in node-positive patients who were classified as high-risk based on clinical criteria and low-risk based on genetic risk with MammaPrint. Overall, the study included 1404 node-positive patients; 296 (16%) with 1 positive node, 114 (6%) with 2 positive nodes, 65 (4%) with 3 positive nodes, and 2 (0.1%) with 4 or more positive nodes. In the high clinical risk and low genetic risk group, 353 node-positive patients

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

were randomized to chemotherapy, and 356 node-positive patients were randomized to no chemotherapy. The 5-year distant recurrence was 3.7% (95% CI, 1.9% to 6.9%) in the chemotherapy group and 4.4% (95% CI, 2.6% to 7.3%) in the no chemotherapy group (HR=0.88; 95% CI, 0.42 to 1.82; p=0.72). MINDACT has currently only provided 5-year distant recurrence outcomes; high clinical risk, low genetic risk patients may not be at low enough risk to defer chemotherapy because these 5-year recurrence rates will probably be higher at 10 years.

Prosigna

Gnant et al (2015) examined the potential prognostic value of the PAM50 ROR 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 to 3 positive nodes, distant recurrence rates were considerably higher with upper bounds for the 95% CIs of 25% or more. OS was not included in the report.

Section Summary: Prosigna

One Simon category B study meeting inclusion criteria was identified. The 10-year distant recurrence rate in patients with a single positive node and low-risk ROR scores is about 2-fold the rate in node-negative patients with low-risk ROR scores. The 10-year distant recurrence rate estimate for node-positive, low-risk patients had an upper bound for the 95% CI approaching the range judged clinically informative in node-negative patients. Additional studies are needed to confirm the magnitude and precision of the estimates.

DUCTAL CARCINOMA IN SITU CONSIDERING RADIOTHERAPY

Oncotype DX Breast DCIS Score

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, accounting for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. Recommended treatment is lumpectomy or mastectomy with or without radiotherapy (RT); postsurgical tamoxifen treatment is recommended for ER+ DCIS, especially if excision alone is used. Because the overall rate of ipsilateral tumor recurrence (DCIS or invasive carcinoma) is approximately 25% at 10 years, it is believed many women are overtreated with RT. Thus, accurate prediction of recurrence risk may identify those women who can safely avoid radiation. The Oncotype DX Breast DCIS Score uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer to predict 10-year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is to help guide treatment decision making in women with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.

In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, Solin et al (2013) compared the Oncotype DX Breast DCIS Score with 10-

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

year local recurrence risk in a subset of DCIS patients treated only with surgery or with tamoxifen (n=327). The Oncotype DX Breast DCIS Score was significantly associated with local recurrence outcomes (hazard ratio [HR], 2.31; 95% CI, 1.15 to 4.49; p=0.02) whether or not patients were treated with tamoxifen. The standard Oncotype DX score for early breast cancer was not associated with local recurrence. This study addressed the development of the Oncotype DX Breast DCIS Score and clinical validity (association of the test result with local recurrence outcomes). Whether women are better categorized as to their local recurrence risk by Oncotype DX Breast DCIS Score compared with standard clinical indicators of risk has not been addressed.

In another retrospective analysis, Rakovitch et al (2015) 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. Median follow-up for the 571 women was 9.6 years. There were 100 local recurrence events—43 were DCIS, and 57 were invasive cancer. The Oncotype DX Breast DCIS Score was significantly associated with local recurrence outcomes (HR=2.15; 95% CI, 1.43 to 3.22). Sixty-two percent of patients were classified as low risk, 17% as intermediate risk, and 21% as high risk. Corresponding 10-year local recurrence estimates were 13% (95% CI, 10% to 17%), 33% (95% CI, 24% to 45%), and 28% (95% CI, 20% to 38%), respectively. Corresponding 10-year estimates for DCIS recurrence (5% [95% CI, 3% to 9%]; 14% [95% CI, 8% to 24%]; 14% [95% CI, 9% to 22%], respectively) and for invasive breast cancer recurrence (8% [95% CI, 6% to 12%]; 21% [95% CI, 13% to 33%]; 16% [95% CI, 9% to 25%], respectively) were based on small numbers of events.

Section Summary: Oncotype DX Breast DCIS Score

Although the Oncotype DX Breast DCIS Score successfully stratified patients into groups with different outcomes, it is unclear whether estimated recurrence risks for patients classified as low risk are low enough or estimated with sufficient precision to meaningfully affect the decision to have or forgo RT.

EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna

We did not identify studies evaluating the EndoPredict, BCI, MammaPrint, or Prosigna tests for patients with DCIS.

EXTENDED ADJUVANT ENDOCRINE THERAPY BEYOND 5 YEARS

Multiple RCTs have demonstrated improvements in overall and breast cancer-specific survival outcomes with 5 to 10 years of tamoxifen for ER+ tumors. However, adjuvant endocrine therapy may be associated with serious adverse events, including pulmonary embolism, endometrial cancer, osteoporosis, and fractures. Common side effects—hot flashes, sexual dysfunction, and musculoskeletal symptoms—often lead to poor compliance; as many as 40% of patients discontinue treatment after 3 years. Accurately identifying low-risk patients who might obtain little benefit from extended endocrine therapy could allow patients to make treatment decisions consistent with how they value the potential benefits and harms.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
 Original Effective Date: 03/01/2007
 Current Effective Date: 01/17/2018

Six studies (see Table 14) meeting selection criteria (see Appendix 1) were identified that examined the prognostic value of a gene expression profiling test for late recurrences after 5 years of endocrine therapy. All were prospective-retrospective designs of patients with early-stage node-positive breast cancer receiving up to 5 years of endocrine therapy. One study (2013) examining prognosis and an additional nested case-control study (Sgroi et al, 2013) analyzed the potential predictive value of the HOXB13/IL17BR (H/I) index included in the BCI test. All but 1 cohort analyzed in Zhang et al (2013) included only postmenopausal women. In addition, samples overlapped across some studies, as shown in the table by the trials used for analysis. Table 15 displays results from studies of prognosis subsequently discussed.

Table 14. Characteristics of Patients in Extended Endocrine Therapy Studies of Prognosis or Predicting Treatment Benefit

| Study | Tumor Size, n (%) | | | Nodes, n (%) | | | Adjuvant Chemo, n (%) | Trial |
|------------------------------|-------------------|----------------|----------|--------------|----------|--------|-----------------------|------------------------------|
| | N | ≤2 cm | >2 cm | None | 1-3 | ≥4 | | |
| Oncotype DX | | | | | | | | |
| Sestak (2013) | 940 | | | 683 (73) | 257 (27) | | 0 (0) | Trans ATAC |
| EndoPredict | | | | | | | | |
| Dubsky (2013) | 1702 | 1136 (67) | 563 (33) | 1165 (68) | 454 (27) | 83 (5) | 0 (0) | ABCSG-6, ABCSG-8 |
| Breast Cancer Index | | | | | | | | |
| Zhang et al (2013) | 285 | 259 (82) | 55 (17) | 285 (100) | 0 (0) | 0 (0) | 0 (0) | Stockholm Trial TAM-treated |
| | 358 | 237 (66) | 121 (34) | 358 (100) | 0 (0) | 0 (0) | 115 (32) | |
| Sgroi (2013) | 597 | 442 (74) | 155 (26) | 597 (100) | 0 (0) | 0 (0) | 0 (0) | Trans ATAC |
| Sgroi (2013) | 249 | 110 (44) | 139 (56) | 94 (38) | 146 (59) | | 148 (59) | Nested case-control in MA.17 |
| Prosigna | | | | | | | | |
| Filipits (2014) | 1246 | NR (see below) | | 919 (74) | 327 (26) | | 0 (0) | ABCSG-8 |
| Sestak (2013) | 940 | | | 683 (73) | 257 (27) | | 0 (0) | TransATAC |
| Sestak (2015), all patients | 862 | 587 (68) | 275 (32) | 647 (75) | 180 (21) | 35 (4) | 0 (0) | TransATAC |
| Sestak (2015), node-negative | 1275 | 938 (74) | 337 (26) | 933 (73) | 307 (24) | 35 (3) | 0 (0) | ABCSG-8 |

ABCSG: Austrian Breast and Colorectal Cancer Study Group; Chemo: chemotherapy; NR: not reported; TAM: tamoxifen; TransATAC: translational substudy of the Arimidex, Tamoxifen, Alone or in Combination.

^a Sample size and characteristics represent patients at enrollment for Dubsky et al (2013).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
 Original Effective Date: 03/01/2007
 Current Effective Date: 01/17/2018

Table 15. Prognosis for Late Distant Recurrence Based on Gene Expression Profiling Test Results

| Test | Study | N | Distant Recurrence Years | Risk Category | | | | | | | | | Simon |
|-------------|----------------------------|------|--------------------------|---------------|------|-----------|--------------|-------|------------|------|-------|-------------|-------|
| | | | | Low | | | Intermediate | | | High | | | |
| | | | | n | DR | 95% CI | n | DR | 95% CI | n | DR | 95% CI | |
| EndoPredict | Dubsky 2013 (EP) | 998 | 5-10 | 503 | 3.7% | (0.9-6.5) | | | | 495 | 9.0% | NR | B |
| | Dubsky 2013 (EPclin) | | | 642 | 1.8% | (0.1-3.5) | | | | 356 | 13.0% | NR | |
| BCI | Zhang 2013 (Stockholm TAM) | 285 | 5-10 | 184 | 2.8% | (0.3-5.2) | 58 | 7.2% | (0.1-13.8) | 43 | 10.1% | (0.2-19.1) | B |
| | Zhang 2013 (Cohort study) | 312 | 5-10 | 181 | 2.5% | (0.0-5.0) | 70 | 16.9% | (6.5-26.2) | 61 | 15.0% | (5.5-23.6) | C |
| | Sgroi 2013 | 596 | 5-10 | 366 | 3.5% | (2.0-6.1) | 146 | 13.4% | (8.5-20.5) | 84 | 13.3% | (7.4-23.4) | B |
| Prosigna | Filipits 2014 | 1246 | 5-15 | 460 | 2.4% | (1.1-5.3) | 416 | 9.1% | (5.8-14.1) | 370 | 17.5% | (12.9-25.2) | B |
| | Sestak 2013 | 940 | 5-10 | NR | 4.1% | NR | | NR | | NR | 19.0% | NR | B |
| | Sestak 2015, all patients | 2137 | 5-10 | 1183 | 2.4% | (1.6-3.5) | 538 | 8.3% | (6.1-11.2) | 416 | 16.6% | (13.1-20.9) | B |
| | Sestak 2015, node negative | 1580 | 5-10 | 983 | 2.0% | (1.3-3.2) | 344 | 9.0% | (6.3-13.0) | 122 | 11.5% | (6.8-19.0) | B |
| Oncotype DX | Sestak 2013 | 940 | 5-10 | NR | 7.6% | NR | | | | NR | 17.6% | NR | B |

Simon refers to study category as discussed in the Background.

Sestak et al (2015) includes samples from Sestak et al (2013) and Filipits et al (2014).

Note that, except for Filipits et al (2014), recurrences are over 5-year periods, or shorter than reported for adjuvant chemotherapy.

BCI: Breast Cancer Index; CI: confidence interval; DR: distant recurrence; EP: EndoPredict; EPclin: EndoPredict with clinical factors; NR: not reported; TAM: tamoxifen.

Oncotype DX (21-Gene Assay)

Sestak et al (2013) (previously discussed with the TransATAC study) also displayed late distant recurrences for risk categories of Oncotype DX in a Kaplan-Meier curve without CIs. The cumulative distant recurrence rate in the low-risk group between 5 and 10 years was estimated at 7.6%, or considerably higher than for any of the other tests considered. That result was consistent with the higher annualized hazard found in those years compared with PAM50 ROR. These limited results do not suggest a role for Oncotype DX for predicting late recurrences.

EndoPredict

Dubsky et al (2013) analyzed late recurrences from patients in the ABCSG6 and ABCSG8 trials (see Table 14) treated with 5 years of endocrine therapy (tamoxifen for 5 years or tamoxifen for 2 years followed by anastrozole for 3 years). Although 32% of patients were node-positive, none received adjuvant chemotherapy. Of the 1702 enrolled patients with ER+ HER2-negative cancers, follow-up was analyzed for 998 patients free of recurrence over 5 years and untreated with extended endocrine therapy. Risk categories were assigned based gene EP alone and combined with a score that included nodal status and tumor size (EPclin). In the EP low-risk group, between 5 and 10 years the cumulative late distant recurrence rate was 3.7% (95% CI, 0.9% to 6.5%) (see Table 15). The distant recurrence rate in the EP high-risk group was 9% (CI not reported). Adding clinical predictors suggested fewer late distant recurrences in the low-risk group (see Table 15). The risk of late distant recurrence in the node-negative patients (from digitized supplemental figure) was 3.6% or comparable to the overall EP low-risk group (n=503).

EP and EPclin appear to be able to identify a group at low risk of distant recurrence from years 5 to 10 in this prospective-retrospective study (Simon category B) of patients untreated with adjuvant chemotherapy



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

enrolled in the ABCSG-6 and -8 trials. In the current environment, a significant proportion of high-risk patients would have been treated with adjuvant chemotherapy based on a gene expression profiling result. C statistics (area under the receiver operating characteristic curve) were reported to support incremental improvement with the EP or EPclin over Adjuvant! Online or nodal status, tumor size, or grade. However, they appeared to include EP and EPclin as continuous variables and not threshold cutoffs for those tests that would inform decisions.

Section Summary: EndoPredict

One Simon category B study with some limitations found EndoPredict (EP and EPclin) prognostic for late distant recurrences. At least 2 Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence.

Breast Cancer Index

Breast Cancer Index Prognosis

Incorporating the BCI as a continuous variable, Zhang et al (2013) developed an “optimized model” to predict early and late distant recurrences. Patient samples from 2 studies were used (see Table 16): the Stockholm trial, which compared 2 or 5 years of tamoxifen with no treatment in early-stage breast cancer; and a cohort of ER+ lymph node–negative patients retrospectively identified from a U.S. university medical center and from a hospital (treated between 1990 and 2000). Data from patients in the untreated arm of the Stockholm trial were used for model development; the tamoxifen arm of the trial and the 2-institution cohort were used for validation. The primary end point was distant recurrence-free survival (censoring for any cause of death). The Stockholm trial enrolled postmenopausal women who did not receive adjuvant chemotherapy; the 2-institution cohort included premenopausal and postmenopausal women of whom one-third received adjuvant chemotherapy (see Table 16). A median follow-up of 10 years was analyzed with distant recurrences occurring in 16% of all patients over 10 years. In the validation tamoxifen-treated arm of the Stockholm trial, there were 20 late distant recurrences and 65% of patients were classified as low risk; in the 2-institution cohort, there were 23 late distant recurrences, and 58% of patients were classified as low risk.

From years 5 to 10, distant recurrence rates were low in the low-risk groups of the validation samples (see Table 15). The results support the prognostic value of the BCI for late recurrences in node-negative patients. About one-third (32%) of the cohort received adjuvant chemotherapy, but whether any of those patients were at low BCI risk was not noted. However, the authors reported chemotherapy was not associated with a lower risk of late recurrence.

SgROI et al (2013) examined late distant recurrences among 597 ER+, *HER2*-negative, node-negative patients from the ATAC trial not treated with adjuvant chemotherapy. Patients who died were censored in the analysis of distant recurrences. In the analytic sample, distant recurrences occurred among 4% of patients in years 0 to 5 and among 7% in years 5 to 10. From years 5 to 10, in the BCI low-, intermediate-, and high-risk groups' distant recurrence rates were 3.5% (95% CI, 2.0% to 6.1%), 13.4% (95% CI, 8.5% to

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

20.5%), and 13.3% (95% CI, 7.4% to 23.4%), respectively. But when examined as a continuous predictor for late recurrence (using the model developed by Zhang et al), at a value of 5 (which is categorized as low risk), the predicted distant recurrence rate was 6.8% (95% CI, 2.5% to 17.6%) (obtained from Supplemental Figure 5), suggesting greater uncertainty in estimates of distant recurrence toward the upper range of “low risk” than the mean value over the entire range of “low risk” conveys.

The authors concluded: “...our results suggest that BCI might have the potential to influence two important decisions in the management of postmenopausal patients with oestrogen-receptor-positive, NO breast cancer: first at the time of diagnosis and second at 5-year disease-free follow-up.” These results would suggest that the BCI has prognostic value for late distant recurrences over a 5-year period, but the model suggests variability in the estimates for the upper end of the low-risk group. Among the higher risk patients, none received adjuvant chemotherapy or therapy not consistent with test results; the accuracy of late recurrence predictions in those patients is uncertain.

Breast Cancer Index Prediction

Sgroi et al (2013) conducted a prospective-retrospective, nested case-control study within the MA.17 trial that compared extended endocrine therapy (letrozole) with placebo in postmenopausal women with hormone receptor-positive cancers. The trial randomized 5157 women recurrence-free at 5 years to letrozole or placebo. A case-control design was adopted owing to challenges in obtaining archived tumor samples. An eligible case (319 of which 83 were examined) was one that experienced a local, regional, or distant recurrence and had an available tumor sample. Two controls free of recurrence longer than cases were matched to each case based on age, tumor size, node status, and prior chemotherapy. Any recurrence (locoregional or distant) was used as the end point; patients with contralateral or unknown recurrences were excluded. Using the 2-gene expression H/I ratio (HOXB13/IL17BR), which is obtained from the BCI, in the low-risk group there was a 42% relative risk reduction vs a 77% reduction in the high-risk group. Although statistical significance was lacking in the low-risk group, the CIs were wide and included values consistent with those observed in the high-risk group (see Table 16).

Zhang et al (2013) also reported a larger potential relative risk reduction in the high-risk group of the Stockholm trial, with similar uncertainty reflected in the CIs (see Table 16).

Table 16. Predictive Effect of the H/I Index in the BCI for Extended Endocrine Therapy Benefit

| Study | N | Comparators | Low Risk | | High Risk | | Note |
|--------------------|-----|----------------------|------------------------|--------|------------------------|--------|---|
| | | | HR (95% CI) | ARR, % | HR (95% CI) | ARR, % | |
| Sgroi et al (2013) | 249 | Letrozole vs placebo | 0.58 (0.25 to 1.36) | 4% | 0.33 (0.15 to 0.73) | 16.5% | Nested matched CC study; 83 recurrences in 166 controls; 5-y ARR reported |
| Zhang et al (2013) | 600 | Tamoxifen vs placebo | 0.67 (0.36 to 1.24) | 4.9% | 0.35 (0.19 to 0.65) | 19.6% | Stockholm trial, 15-y results |

ARR: absolute risk reduction; BCI: Breast Cancer Index; CC: case-control; CI: confidence interval; H/I test: HOXB13/IL17BR; HR: hazard ratio.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

MammaPrint (70-Gene Signature)

We did not identify studies examining MammaPrint for this indication.

Prosigna

Filipits et al (2014) analyzed data from patients in the ABCSG-8 trial (5 years of adjuvant tamoxifen vs tamoxifen for 2 years followed by anastrozole). Adjuvant chemotherapy was not administered. The PAM50 ROR predecessor test of Prosigna was obtained from archival samples using the NanoString nCounter device. At 5 years, 1246 patients free of recurrence were included in the analyses (74% node-negative). Almost all patients (97%) classified as low risk were node-negative. Between years 5 and 15, there were 7 distant recurrences in the low-risk group (n=460) and none recorded among the 12 low-risk node-positive patients. The cumulative risk of late distant recurrence was 2.4% (95% CI, 1.1% to 5.3%). However, as of year 11, 59% of the low-risk group was being followed and at risk, and at year 14 just 11%. The authors also evaluated a clinical linear predictor score (age, grade, nodal status, endocrine treatment) but did not present recurrence rates by clinical risk categories (e.g., low, intermediate, high).

Sestak et al (2013) reported limited results concerning late recurrences obtained from patients in the ATAC trial who received anastrozole with tamoxifen alone or in combination. From a subset of women in the monotherapy arms with archived tissue (a sample forming the TransATAC study), a total of 940 U.K. women from the study were analyzed. Distant recurrence was the primary end point (censored at death). The sample included patients with node-positive and node-negative cancers, but proportions were not reported. There were 83 distant recurrences from years 5 to 10. A clinical treatment score (CTS) derived from age, node status, treatment, stage, and grade was examined but its prognostic value not reported. Annualized hazards (distant recurrence rates) were consistent with a lower late recurrence risk for node-negative tumors 2 cm or smaller and among those with a low PAM50 ROR score. From a Kaplan-Meier plot, the late distant recurrence risk in the PAM50 ROR low-risk group was estimated at 4.1% (CIs were not displayed). The absence of CIs and comparison or reclassification of clinical predictors' prognosis limits any conclusions.

A subsequent publication by Sestak et al (2015) combined samples of women with hormone receptor-positive, *HER2*-negative cancers from the ABCSG-8 and TransATAC studies included in the 2 prior publications. Risk was determined using both a CTS (treatment received, positive nodes, tumor size, age, and grade) and the PAM50 ROR. As in the prior studies, death was considered a censoring event; women with recurrences through 5 years were excluded and the median follow-up was 10 years. Approximately 25% of patients had positive nodes. Both the ROR and CTS were prognostic, but cumulative event rates reported only for the ROR (see Table 17). In the ROR low-risk group, the distant recurrence rate was 2.4% (95% CI, 1.6% to 3.5%) in all women and 2.0% (95% CI, 1.3% to 3.2%) when only node-negative patients were examined. Finally, the authors compared the ability of the ROR to reclassify patients with the CTS. From a reclassification analysis (see Table 17), assuming a selective as opposed to a treat-all strategy and that only low-risk women would not be treated: (1) adding the ROR to the CTS would have resulted in 5 (3.4%) more of 148 patients experiencing distant recurrence being treated, and (2) 60 (3.0%) of 1989 additional patients not experiencing a recurrence would have been incorrectly treated. The

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

reclassification results would suggest caution when interpreting prognostic estimates without considering clinical predictors.

Table 17. Classification and Reclassification Achieved by Adding ROR Score to the CTS

| Distant Recurrence | | CTS | | | | CTS | | | | |
|-----------------------|--------------|------|-----|------|-------|-----------|------|-----|-----|------|
| | | Low | Int | High | Total | | | | | |
| ROR | Low | 18 | 14 | 0 | 32 | ROR + CTS | 25 | 3 | 0 | 28 |
| | Intermediate | 7 | 31 | 7 | 45 | | 8 | 53 | 0 | 61 |
| | High | 8 | 17 | 46 | 71 | | 0 | 6 | 53 | 59 |
| | Total | 33 | 62 | 53 | 148 | | 33 | 62 | 53 | 148 |
| No Distant Recurrence | | CTS | | | | CTS | | | | |
| | | Low | Int | High | Total | | | | | |
| ROR | Low | 837 | 273 | 41 | 1151 | ROR + CTS | 1030 | 136 | 0 | 1166 |
| | Intermediate | 209 | 221 | 63 | 493 | | 76 | 448 | 25 | 549 |
| | High | 60 | 137 | 148 | 345 | | 0 | 47 | 227 | 274 |
| | Total | 1106 | 631 | 252 | 1989 | | 1106 | 631 | 252 | 1989 |

CTS: Clinical Treatment Score; Int: intermediate; ROR: risk of recurrence.

Section Summary: Prosigna

Studies obtained from 2 completed trials analyzed in different publications (in effect, 2 Simon category B studies) have found that the PAM50 ROR can identify patients at low risk of late distant recurrence. However, a reclassification result suggested that the test may offer little improvement over clinical predictors alone.

Section Summary: Extended Endocrine Therapy Beyond 5 Years

Absent direct evidence that using a gene expression profiling test to decide whether to extend endocrine therapy improves outcomes, inferring benefit requires considering: (1) the expected magnitude and certainty of benefit from extended endocrine therapy, (2) how women value harms relative to benefit, and the range of thresholds in risk that a test is likely to change decisions, (3) whether a test accurately discriminates good from poor outcomes (i.e., prognostic value for recurrences) at those thresholds, and (4) whether the test provides incremental improvement over clinical risk prediction algorithms or tools.

At least 3 RCTs have demonstrated survival improvements with extended tamoxifen. While the evidence for extended aromatase inhibitor is more mixed, guidelines have recommended extended endocrine therapy with tamoxifen or an aromatase inhibitor in all hormone receptor-positive women. However, 3 trials completed and presented in 2017 but not yet published (described in the Background section) may challenge a “treat-all” approach. Results of these trials may affect the uncertainty in possible benefit and the impact on treatment strategies.

Compared with the choice of adjuvant chemotherapy depending on baseline recurrence risk, there is less empirical research on women’s threshold for decision making to forgo extended endocrine therapy based on recurrence risk. To be clinically useful, a test should be able to predict accurately a cumulative lifetime recurrence rate in a range that would be meaningful for decision making.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

Assuming, as suggested by the studies reviewed, the predicted 10-year or later distant recurrence rates would be sufficiently lower than 10%, according to the Simon levels of evidence, BCI and Prosigna have 2 category B studies appropriately reported to support their use. However, evidence demonstrating incremental reclassification improvement applying decision informative thresholds is lacking. The single reclassification result does not offer strong support for net incremental improvement, particularly if how women value benefits (net improvement in those recurrences) and harms (increased false positives in those without recurrences) are considered.

Moreover, how the test result informs decision making at the time results are available is not readily apparent.

TEST COMPARISON STUDIES

Sgroi et al (2013) compared BCI with Oncotype DX in 665 lymph node–negative women receiving endocrine therapy but not chemotherapy in the ATAC trial. The distribution of patients across risk groups was similar. For patients receiving tamoxifen alone or in combination with anastrozole, 10-year distant recurrence risk estimates for the 2 tests were similar within risk groups. In the anastrozole group, BCI was a better predictor of risk: 5% of BCI low-risk patients had distant recurrence compared with 9% of Oncotype DX low-risk patients, and 22% of BCI high-risk patients had distant recurrence compared with 13% of Oncotype DX high-risk patients. Importantly, these values were reported without 95% CIs; it is therefore not possible to assess the degree of overlap between risk groups.

Dowsett et al (2013) compared the PAM50 ROR score with the Oncotype DX 21-gene RS and IHC4 breast cancer algorithm. Patients had ER+, primary breast disease treated with anastrozole or tamoxifen in the ATAC trial (a double-blinded, phase 3 clinical trial designed to compare the ability of anastrozole, tamoxifen, and the 2 drugs in combination to prevent breast cancer recurrence in postmenopausal women with hormone receptor–positive tumors). Lymph node–negative and –positive patients were included. Messenger RNA (mRNA) from 1017 patients was assessed for ROR, and likelihood ratio tests and concordance indices were used to assess the prognostic information provided beyond that of a CTS. Statistical testing of these parameters was significant and favored the ROR score over the RS. More patients were classified as high risk and fewer as intermediate risk by the ROR than by RS. Prognostic information provided by the ROR score and IHC4 was similar.

Hornberger et al (2012) conducted a systematic review on the clinical validity, clinical utility, change in clinical practice, and economic implications of early-stage breast cancer stratifiers. Fifty-six articles published original evidence addressing the Oncotype DX RS (n=31), MammaPrint (n=14), Adjuvant! Online (n=12), 5-antibody immunohistochemical (IHC) panel (Mammostrat; n=3), and a14-gene signature (BreastOncPx; n=1). Oncotype DX RS satisfied level 1 evidence for estimating distant recurrence risk, OS, and response to adjuvant chemotherapy, and level 2 evidence for estimating local recurrence risk. Mammostrat and MammaPrint satisfied level 2 evidence for estimating distant recurrence risk and OS. Adjuvant! Online satisfied level 2 evidence for estimating distant recurrence risk, OS, and chemotherapy

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

response. BreastOncPx satisfied level 3 evidence for predicting distant recurrence risk and OS. Ten studies reported changes in clinical practice patterns using Oncotype DX; overall, Oncotype DX was associated with change in treatment recommendations and/or decisions in 21% to 74% of cases.

Fan et al (2006) used 5 gene expression classifiers to evaluate a single set of samples from 295 women with stage I or II breast cancer, variable node involvement, and variable endocrine or chemotherapy treatment. The classifiers included the 21-gene RS, the 70-gene signature, the H/I ratio, and the intrinsic subtype classifier (similar to the commercially available PAM50). Most highly correlated were the 21-gene RS and the 70-gene signature, with a Cramer V of 0.6 (scale 0-1, with 1 indicating perfect agreement). More specifically, 81 (79%) of 103 samples with an RS of low or intermediate risk were classified as having a low-risk 70-gene profile. Restricting the analysis to 225 ER+ samples slightly reduced the correlation. Analysis was not further restricted to node-negative patients, the present indication for both tests.

Espinosa et al (2005) compared Oncotype DX, MammaPrint, and the 2-gene ratio (H/I ratio) in 153 patients with ER+ breast cancer treated with adjuvant tamoxifen. Sixty-two percent of patients were node-negative, and 63% were additionally treated with chemotherapy. Estimated distant metastasis-free survival for RS risk groups was 98% for low-risk, 81% for intermediate-risk, and 69% for high-risk patients; for the 70-gene signature, estimates were 95% for good prognosis and 66% for poor prognosis patients; and for the 2-gene ratio, estimates were 86% for favorable and 70% for unfavorable prognosis. The correlation between the 21-gene RS and the 70-gene signature was good (Cramer V=0.6). Slightly more variation in distant metastasis-free survival was explained by the combination of the 21-gene RS plus either Adjuvant! Online (25.8, SD=1.4) or the Nottingham Prognostic Index (23.7, SD=1.5) than by the combination of the 70-gene signature plus Adjuvant! Online (23.1, SD=1.2) or the Nottingham Prognostic Index (22.4, SD=1.3), but differences were small and any combination was significantly better than any test or clinicopathologic classifier alone.

Two studies have compared Oncotype DX with other gene EPs. Kelly et al (2012) evaluated Oncotype DX and PAM50 in 108 cases and found good agreement between the 2 assays for high- and low-prognostic risk assignment; PAM50 assigned about half of Oncotype DX intermediate-risk patients to the PAM50 luminal A (low-risk) category. Prat et al (2012) evaluated several gene expression tests, including Oncotype DX, PAM50, and MammaPrint, in 594 cases; they found all predictors were significantly correlated (Pearson *r* range, 0.36-0.79; *p*<0.001 for each comparison).

ADDITIONAL APPLICATIONS AND OTHER TESTS

Based on a 2008 study that compared Oncotype DX ER and PR results with traditional IHC results, Genomic Health now includes quantitative estrogen and PR component results in Oncotype DX 21-gene profile reports. The study reported 90% or better concordance between the 2 assays, but the quantitative ER by Oncotype DX was more strongly associated with disease recurrence than the IHC results. However, estrogen and PR analysis is traditionally conducted during pathology examination of all breast cancer biopsies, whereas Oncotype DX is indicated only for known ER+ tumors, after the pathology examination is complete, the patient meets specific criteria, and patient and physician are considering preferences for risk and chemotherapy. Thus, Oncotype DX should not be ordered as a substitute for estrogen and PR IHC.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

Additionally, accepted guidelines for estrogen and PR testing outline standards for high-quality IHC testing and do not recommend confirmatory testing; thus the 21-gene RS should not be ordered to confirm estrogen and PR IHC results. A subsequent study by Khoury et al (2015) reported better correlation (for overall data) between the IHC and Oncotype DX for PR status (Spearman $\rho=0.91$) than for ER status (Spearman $\rho=0.65$), but worse concordance (at various cut points) for PR status (99%) than for ER status (88).

Investigators have examined the ability of gene expression tests to provide risk information for locoregional recurrence. The reason for analyzing these tests in relation to locoregional recurrence is that they may have implications for the type and extent of initial local treatment. Drukker et al (2014) used MammaPrint to assess 1053 tumor specimens from 1848 patients enrolled in 8 previous MammaPrint studies. Most patients had ER+, *HER2*-negative disease; approximately half of patients had positive axillary lymph nodes. Most patients received RT and did not receive adjuvant chemotherapy; approximately half received adjuvant endocrine therapy. At a median follow-up of 9 years, estimated 10-year locoregional recurrence risk was 13% (95% CI, 10% to 16%) for 492 patients categorized as MammaPrint high-risk vs 6% (95% CI, 4% to 9%) for 561 MammaPrint low-risk patients. This association was observed during the first 5 years after diagnosis, but not during years 5 to 10. Recurrence stratified by MammaPrint risk class was not associated with primary locoregional treatment (i.e., not predictive of treatment response).

Fitzal et al (2015) evaluated local recurrence using EndoPredict in breast tumor samples from 1324 patients who had participated in the ABCSG-8 trial (29% of enrolled patients), which compared adjuvant endocrine therapy regimens. Most patients had node-negative, ER+ disease and received breast-conserving surgery and RT; approximately half of patients received adjuvant endocrine therapy. At a median follow-up of 6 years, the Kaplan-Meier estimate for 10-year risk of local recurrence-free survival was 96% (91% reported in the article abstract) among 683 patients classified by EndoPredict as high risk vs 99% among 641 patients classified by EndoPredict as low risk. EndoPredict risk groups were not associated with treatment outcomes.

Although the 3 gene expression tests are associated with risk of local recurrence, how these results would be used to change management, either by providing more aggressive treatment to high-risk patients or by providing less aggressive treatment to low-risk patients, is not clear.

SUMMARY OF EVIDENCE

For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.

Early-Stage Node-Negative Invasive Breast Cancer

For the evaluation of breast cancer-related gene expression profiling tests for the management of all early-stage breast cancer populations, study populations considered had positive hormone receptor status, and negative *HER2* status. Only studies presenting 10-year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

Oncotype DX (21-Gene Assay)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low risk with Oncotype DX have a low ROR in which avoidance of adjuvant chemotherapy is reasonable (average risk at 10 years, 7% to 9%; upper bound of the 95% CIs, 11% to 15%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 3 prospective-retrospective studies and observational studies. The studies revealed that a low score was associated with a low absolute risk of 10-year distant recurrence. Over half of patients in the studies were classified at low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the BCI, the evidence includes findings from 2 prospective-retrospective studies and a registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk BCI score is associated with low 10-year distant recurrence rates. The findings from the registry-based observational study also showed low 10-year distant recurrence rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

MammaPrint (70-Gene Signature)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes 1 study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence, it did not derive from high-quality data sources. A recently reported study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes 2 prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low-risk scores. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

Early-Stage Node-Positive Invasive Breast Cancer

For decisions on management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated.

Oncotype DX (21-Gene Assay)

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 2 prospective-retrospective studies. Studies showed that Oncotype DX stratifies node-positive patients into high and low risk for distant recurrence-free survival. However, only one of the studies reported CIs for estimates and those are very wide. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed to inform patient decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 2 prospective-retrospective analyses. The 10-year distant recurrence rate in low-risk EPclin patients was estimated to be 5% in one study, but the upper bound of the 95% CI was close to 20%. The estimate of 10-year distant recurrence in EP low-risk patients in a second publication was approximately 15%, and no CIs were provided. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

MammaPrint (70-Gene Signature)

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a clinical utility study. The study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna ROR score, the evidence includes a prospective-retrospective study. The 10-year distant recurrence rate in low-risk ROR patients with a single positive node is roughly two-fold the rate in low-risk ROR node-negative patients. However in the single available study, the upper bound of the 95% CI for 10-year distant recurrence in node-positive patients classified as ROR low-risk was about 13%, which approaches the range judged clinically informative in node-negative patients. The predicted recurrence rates require replication. To establish that the test has

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/17/2018

potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ductal Carcinoma In Situ

The Oncotype DX Breast DCIS Score is the only assay investigated for patients with DCIS.

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS Score, the evidence includes prospective-retrospective studies and prospective trials. Although 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Extended Endocrine Therapy

For this indication, Oncotype DX, EndoPredict, BCI, and Prosigna were evaluated.

Oncotype DX (21-Gene Assay)

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes a study from a previously conducted clinical trial. The study did not show low distant recurrence rates in patients classified as low risk with the test, and no CIs were presented. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes a study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified as low risk with the test. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Additional prospective trials or retrospective-prospective studies of archived samples reporting on the association between risk score and survival are needed. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

Breast Cancer Index

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with the BCI, the evidence includes 2 studies of archived tissue samples from previously conducted clinical trials and a retrospective cohort study. The 3 studies showed low distant recurrence rates in patients classified as low risk with the test. Two studies suggested that, in addition to having a more favorable prognosis, low-risk

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

patients may receive lesser benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with Prosigna, the evidence includes 2 studies from previously conducted clinical trials examined in 3 publications. The studies showed low distant recurrence rates in patients classified as low risk with the test. A reclassification result would suggest that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients with Breast Cancer", Policy 2.04.36, 08:2017.
2. Colleoni M, Sun Z, Price KN, et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the International Breast Cancer Study Group Trials I to V. *J Clin Oncol*. Mar 20 2016;34(9):927-935. PMID 26786933
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2017. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed May 12, 2017.
4. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol*. Aug 10 2010;28(23):3784-3796. PMID 20625130
5. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol*. Jul 20 2014;32(21):2255-2269. PMID 24868023
6. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. Nov 1 2013;31(31):3997-4013. PMID 24101045
7. Early Breast Cancer Trialists' Collaborative Group, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. Aug 27 2011;378(9793):771-784. PMID 21802721
8. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. *J Clin Oncol*. May 10 2016;34(14):1689-1701. PMID 26884586
9. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. Mar 09 2013;381(9869):805-816. PMID 23219286
10. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [abstract]. *J Clin Oncol*. 2013;31(18 Suppl):5-5. PMID
11. Tormey DC, Gray R, Falkson HC. Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. *J Natl Cancer Inst*. Dec 18 1996;88(24):1828-1833. PMID 8961972
12. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. May 02 2001;93(9):684-690. PMID 11333290

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

13. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. *J Natl Cancer Inst.* Mar 21 2001;93(6):456-462. PMID 11259471
14. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst.* Dec 19 2007;99(24):1845-1853. PMID 18073378
15. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* Sep 07 2005;97(17):1262-1271. PMID 16145047
16. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med.* Nov 06 2003;349(19):1793-1802. PMID 14551341
17. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol.* Apr 20 2008;26(12):1965-1971. PMID 18332472
18. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst.* Nov 4 2009;101(21):1446-1452. PMID 19815849
19. Pauker SG, Kassirer JP. Therapeutic decision making: a cost-benefit analysis. *N Engl J Med.* Jul 31 1975;293(5):229-234. PMID 1143303
20. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med.* May 15 1980;302(20):1109-1117. PMID 7366635
21. Simes RJ, Coates AS. Patient preferences for adjuvant chemotherapy of early breast cancer: how much benefit is needed? *J Natl Cancer Inst Monogr.* 2001(30):146-152. PMID 11773309
22. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? *Ann Oncol.* Nov 2005;16(11):1786-1794. PMID 16126738
23. Thewes B, Meiser B, Duric VM, et al. What survival benefits do premenopausal patients with early breast cancer need to make endocrine therapy worthwhile? *Lancet Oncol.* Aug 2005;6(8):581-588. PMID 16054569
24. Henderson IC. *Breast cancer: fundamentals of evidence-based disease management.* New York: Oxford University Press; 2015.
25. Hamelinck VC, Bastiaannet E, Pieterse AH, et al. A prospective comparison of younger and older patients' preferences for adjuvant chemotherapy and hormonal therapy in early breast cancer. *Clin Breast Cancer.* Oct 2016;16(5):379-388. PMID 27212474
26. Buus R, Sestak I, Kronenwett R, et al. Comparison of EndoPredict and EPclin with Oncotype DX Recurrence Score for prediction of risk of distant recurrence after endocrine therapy. *J Natl Cancer Inst.* Nov 2016;108(11). PMID 27400969
27. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* Dec 30 2004;351(27):2817-2826. PMID 15591335
28. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* Aug 10 2006;24(23):3726-3734. PMID 16720680
29. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. *Breast Cancer Res Treat.* May 2011;127(1):133-142. PMID 21221771
30. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med.* Nov 19 2015;373(21):2005-2014. PMID 26412349
31. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res.* Sep 15 2011;17(18):6012-6020. PMID 21807638
32. Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol.* Oct 2013;14(11):1067-1076. PMID 24035531
33. Zhang Y, Schnabel CA, Schroeder BE, et al. Breast cancer index identifies early-stage estrogen receptor-positive breast cancer patients at risk for early- and late-distant recurrence. *Clin Cancer Res.* Aug 1 2013;19(15):4196-4205. PMID 23757354
34. Bueno-de-Mesquita JM, Sonke GS, van de Vijver MJ, et al. Additional value and potential use of the 70-gene prognosis signature in node-negative breast cancer in daily clinical practice. *Ann Oncol.* Sep 2011;22(9):2021-2030. PMID 19955335

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

35. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med.* Aug 25 2016;375(8):717-729. PMID 27557300
36. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol.* Aug 1 2013;31(22):2783-2790. PMID 23816962
37. Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Ann Oncol.* Feb 2014;25(2):339-345. PMID 24347518
38. 3Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol.* Jan 2010;11(1):55-65. PMID 20005174
39. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol.* Apr 10 2010;28(11):1829-1834. PMID 20212256
40. Gnant M, Sestak I, Filipits M, et al. Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive hormone receptor-positive early-stage breast cancer treated with endocrine therapy: a combined analysis of ABCSG-8 and ATAC using the PAM50 risk of recurrence score and intrinsic subtype. *Ann Oncol.* Aug 2015;26(8):1685-1691. PMID 25935792
41. Jasem J, Fisher CM, Amini A, et al. The 21-Gene Recurrence Score assay for node-positive, early-stage breast cancer and impact of RxPONDER Trial on chemotherapy decision-making: have clinicians already decided? *J Natl Compr Canc Netw.* Apr 2017;15(4):494-503. PMID 28404760
42. Roberts MC, Miller DP, Shak S, et al. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. *Breast Cancer Res Treat.* Jun 2017;163(2):303-310. PMID 28243896
43. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* Apr 1 2016;34(10):1134-1150. PMID 26858339
44. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* May 15 2013;105(10):701-710. PMID 23641039
45. Rakovitch E, Nofech-Mozes S, Hanna W, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. *Breast Cancer Res Treat.* Jul 2015;152(2):389-398. PMID 26119102
46. Esserman L, Gallant E, Alvarado M. Less is more: The evolving surgical approach to breast cancer. *Am Soc Clin Oncol Educ Book.* 2016;35:e5-e10. PMID 27249759
47. Dubsy P, Brase JC, Jakesz R, et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. *Br J Cancer.* Dec 10 2013;109(12):2959-2964. PMID 24157828
48. Filipits M, Nielsen TO, Rudas M, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clin Cancer Res.* Mar 1 2014;20(5):1298-1305. PMID 24520097
49. Sestak I, Cuzick J, Dowsett M, et al. Prediction of late distant recurrence after 5 years of endocrine treatment: a combined analysis of patients from the Austrian Breast and Colorectal Cancer Study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. *J Clin Oncol.* Mar 10 2015;33(8):916-922. PMID 25332252
50. Sestak I, Dowsett M, Zabaglo L, et al. Factors predicting late recurrence for estrogen receptor-positive breast cancer. *J Natl Cancer Inst.* Oct 2 2013;105(19):1504-1511. PMID 24029245
51. Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst.* Jul 17 2013;105(14):1036-1042. PMID 23812955
52. Hornberger J, Alvarado MD, Rebecca C, et al. Clinical validity/utility, change in practice patterns, and economic implications of risk stratifiers to predict outcomes for early-stage breast cancer: a systematic review. *J Natl Cancer Inst.* Jul 18 2012;104(14):1068-1079. PMID 22767204
53. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med.* Aug 10 2006;355(6):560-569. PMID 16899776

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

54. Espinosa E, Vara JA, Redondo A, et al. Breast cancer prognosis determined by gene expression profiling: a quantitative reverse transcriptase polymerase chain reaction study. *J Clin Oncol.* Oct 10 2005;23(29):7278-7285. PMID 16129846
55. Kelly CM, Bernard PS, Krishnamurthy S, et al. Agreement in risk prediction between the 21-gene recurrence score assay (Oncotype DX(R)) and the PAM50 Breast Cancer Intrinsic Classifier in early-stage estrogen receptor-positive breast cancer. *Oncologist.* 2012;17(4):492-498. PMID 22418568
56. Prat A, Parker JS, Fan C, et al. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. *Ann Oncol.* Nov 2012;23(11):2866-2873. PMID 22532584
57. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. *J Clin Oncol.* May 20 2008;26(15):2473-2481. PMID 18487567
58. Khoury T, Yan L, Liu S, et al. Oncotype DX RT-qPCR assay for ER and PR correlation with IHC: a study of 3 different clones. *Appl Immunohistochem Mol Morphol.* Mar 2015;23(3):178-187. PMID 24992175
59. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. *Breast Cancer Res Treat.* Dec 2014;148(3):599-613. PMID 25414025
60. Fitzal F, Filipits M, Rudas M, et al. The genomic expression test EndoPredict is a prognostic tool for identifying risk of local recurrence in postmenopausal endocrine receptor-positive, her2neu-negative breast cancer patients randomised within the prospective ABCSG 8 trial. *Br J Cancer.* Apr 14 2015;112(8):1405-1410. PMID 25867274
61. Krop I, Ismaila N, Stearns V. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice focused update guideline summary. *J Oncol Pract.* Jul 11 2017;JOP2017024646. PMID 28696818
62. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* Aug 2015;26(8):1533-1546. PMID 25939896
63. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): MoIDX: Breast Cancer IndexSM Genetic Assay (L35631). 2015; <https://med.noridianmedicare.com/documents/10546/6990983/MoIDX+Breast+Cancer+Index+Genetic+Assay+LCD/a9495a31-0ba2-4c7b-81e4-8d424689d2c7>. Accessed August 8, 2017.
64. Zujewski JA, Kamin L. Trial assessing individualized options for treatment for breast cancer: the TAILORx trial. *Future Oncol.* Oct 2008;4(5):603-610. PMID 18922117

Policy History

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

- | | |
|------------|---|
| 09/06/2006 | Medical Director review |
| 09/20/2006 | Medical Policy Committee approval |
| 10/03/2007 | Medical Director review |
| 10/17/2007 | Medical Policy Committee approval. Policy Statements Changed. Oncotype DX eligible for coverage. Not medically necessary statement added. |
| 02/13/2008 | Medical Director review |
| 02/20/2008 | Medical Policy Committee approval. Policy statement changed to include patient selection criteria. Added 21-gene RT-pcr assay Oncotype DX . |
| 02/04/2009 | Medical Director review |
| 02/19/2009 | Medical Policy Committee approval. Clarified 6th and 7th criteria bullets. No change to coverage eligibility. |
| 02/04/2010 | Medical Policy Committee review |
| 02/17/2010 | Medical Policy Implementation Committee approval. No change to coverage. |
| 02/03/2011 | Medical Policy Committee review |
| 02/16/2011 | Medical Policy Implementation Committee approval. New criteria added. |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

| | |
|-----------------------------|---|
| 02/02/2012 | Medical Policy Committee review |
| 02/15/2012 | Medical Policy Implementation Committee approval. Rationale extensively revised. Coverage eligibility unchanged. |
| 02/07/2013 | Medical Policy Committee review |
| 02/20/2013 | Medical Policy Implementation Committee approval. Added the BreastOncPx and the PAM50 Breast Cancer Intrinsic Classifier as examples of investigational gene expression assays. |
| 04/02/2015 | Medical Policy Committee review |
| 04/20/2015 | Medical Policy Implementation Committee approval. Added investigational statements to include newer assays (prosignia, BluePrint, TargetPrint, EndoPredict, MammaPrint, Mammostrat, NexCourse, Oncotype DCIS) and use of gene assays in men. Updated FDA, rationale and references. |
| 10/08/2015 | Medical Policy Committee review |
| 10/21/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2016 | Coding update |
| 10/06/2016 | Medical Policy Committee review |
| 10/19/2016 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 01/05/2017 | Medical Policy Committee review |
| 01/18/2017 | Medical Policy Implementation Committee approval. EndoPredict, Breast Cancer Index and Prosigna removed from investigational statement. Coverage statement added that these tests are medically necessary for same indication as Oncotype. Coverage statement clarified with "primary, invasive" and investigational statement clarified with "length of treatment with tamoxifen." |
| 01/04/2018 | Medical Policy Committee review |
| 01/17/2018 | Medical Policy Implementation Committee approval. Added a "Note" after the eligible for coverage section that only one assay of genetic expression per tumor tissue specimen will be eligible for coverage. Coverage eligibility unchanged. |
| 07/01/2018 | Coding update |
| Next Scheduled Review Date: | 01/2019 |

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211
 Original Effective Date: 03/01/2007
 Current Effective Date: 01/17/2018

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code | | | | | | | | | | | | | | | | | | | | | | | | |
|------------------|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|---------------|---------------|---------------|---------------|--|--|
| CPT | 0008M, 81519, 84999 Codes added eff 1/1/18: 81520, 81521 Code added eff 7/1/18: 0045U | | | | | | | | | | | | | | | | | | | | | | | | |
| HCPCS | S3854 | | | | | | | | | | | | | | | | | | | | | | | | |
| ICD-10 Diagnosis | <table border="0"> <tr> <td>C50.011-C50.019</td> <td>C50.111-C50.119</td> <td>C50.211-C50.219</td> <td>C50.311-C50.319</td> </tr> <tr> <td>C50.411-C50.419</td> <td>C50.511-C50.519</td> <td>C50.611-C50.619</td> <td>C50.811-C50.819</td> </tr> <tr> <td>C50.911-C50.919</td> <td>C50.021-C50.029</td> <td>C50.121-C50.129</td> <td>C50.221-C50.229</td> </tr> <tr> <td>C50.321-C50.329</td> <td>C50.421-C50.429</td> <td>C50.521-C50.529</td> <td>C50.621-C50.629</td> </tr> <tr> <td>C50.821-C50.829</td> <td>C50.921-C50.929</td> <td>D05.00-D05.02</td> <td>D05.10-D05.12</td> </tr> <tr> <td>D05.80-D05.82</td> <td>D05.90-D05.92</td> <td></td> <td></td> </tr> </table> | C50.011-C50.019 | C50.111-C50.119 | C50.211-C50.219 | C50.311-C50.319 | C50.411-C50.419 | C50.511-C50.519 | C50.611-C50.619 | C50.811-C50.819 | C50.911-C50.919 | C50.021-C50.029 | C50.121-C50.129 | C50.221-C50.229 | C50.321-C50.329 | C50.421-C50.429 | C50.521-C50.529 | C50.621-C50.629 | C50.821-C50.829 | C50.921-C50.929 | D05.00-D05.02 | D05.10-D05.12 | D05.80-D05.82 | D05.90-D05.92 | | |
| C50.011-C50.019 | C50.111-C50.119 | C50.211-C50.219 | C50.311-C50.319 | | | | | | | | | | | | | | | | | | | | | | |
| C50.411-C50.419 | C50.511-C50.519 | C50.611-C50.619 | C50.811-C50.819 | | | | | | | | | | | | | | | | | | | | | | |
| C50.911-C50.919 | C50.021-C50.029 | C50.121-C50.129 | C50.221-C50.229 | | | | | | | | | | | | | | | | | | | | | | |
| C50.321-C50.329 | C50.421-C50.429 | C50.521-C50.529 | C50.621-C50.629 | | | | | | | | | | | | | | | | | | | | | | |
| C50.821-C50.829 | C50.921-C50.929 | D05.00-D05.02 | D05.10-D05.12 | | | | | | | | | | | | | | | | | | | | | | |
| D05.80-D05.82 | D05.90-D05.92 | | | | | | | | | | | | | | | | | | | | | | | | |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer

Policy # 00211

Original Effective Date: 03/01/2007

Current Effective Date: 01/17/2018

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.