Local Coverage Determination (LCD):
MolDX: Breast Cancer IndexTM (BCI) Gene Expression Test (L37822)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
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LCD Information

Document Information

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MolDX: Breast Cancer IndexTM (BCI) Gene Expression Test

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AMA CPT / ADA CDT / AHA NUBC Copyright Statement

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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This Medicare contractor will provide limited coverage for the Breast Cancer Index™ (BCI) gene expression test (Biotheranostics, Inc., San Diego, CA) for the management of postmenopausal women diagnosed with early-stage (TNM stage T1-3, pN0, M0), node-negative, non-relapsed, ER and/or PR-positive, HER2-negative breast cancer, who are being or will be treated with primary adjuvant endocrine therapy. The BCI test is used by physicians to provide a genomic-based estimate of 10y distant recurrence risk when considering addition of chemotherapy, and/or late distant recurrence risk and endocrine responsiveness when considering extension of endocrine therapy, depending upon when in the continuum of care testing is requested.

Summary of Evidence

Adjuvant therapy decisions initially and at 5 years in ER+ HR- node negative breast cancer

In 2017, approximately 253,000 patients were expected to be diagnosed with invasive breast cancer in the United States,[1] of which approximately 90% are diagnosed with early-stage disease. Hormone-receptor positive (HR+) breast cancer is the most common subtype of breast cancer (~80% of cases[1]) and has the most favorable prognosis overall.[1] Standard-of-care treatment for HR+ disease includes primary adjuvant anti-estrogen therapy with tamoxifen, an aromatase inhibitor (AI), or a sequence of these. In addition to anti-estrogen therapy, two key treatment decisions are priorities in the management of early stage breast cancer. The first decision is whether the patient is of sufficient risk of recurrence to recommend systemic adjuvant chemotherapy. In addition, while HR+ early-stage breast cancer patients have a favorable prognosis overall, there is an ongoing risk of distant recurrence (DR) beyond year 5 (late recurrence), and 75% of deaths occur more than 5 years post-diagnosis. As such, the second key decision is whether to recommend extension of endocrine therapy beyond the initial primary adjuvant therapy. For each treatment decision, physicians and patients must weigh whether the potential benefit from the additional treatment regimen is likely to outweigh the risks of serious toxicities and side effects.

Improving Patient Stratification for Addition of Adjuvant Chemotherapy

Adjuvant chemotherapy has been shown to improve outcomes in patients with early stage HR+ breast cancer. In a meta-analysis of 100,000 women across 123 randomized trials,[2] the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that patients with early-stage breast cancer experience an approximately 30% reduction in DR rate or benefit from adjuvant chemotherapy. Notably, this analysis also showed that proportional risk reduction was not affected by traditional clinical and pathologic factors (e.g.,

nodal status, tumor size, tumor grade). Patients therefore with a limited underlying risk of DR will have a lower absolute benefit from chemotherapy, compared to patients with a high underlying risk of DR. For each patient, the expected absolute benefit of chemotherapy needs to be weighed against the 2-3% chance of fatal, life-threatening, or life-changing toxicities.[3]

Standard clinical and pathologic factors (e.g., tumor size, grade, and nodal status) are commonly used for assessment of a patient's risk of DR to make decisions about the addition of chemotherapy to endocrine therapy. However, molecular tests have been shown to improve prognostic accuracy compared to standard clinical and pathologic features and have become increasingly important for patients with early-stage HR+/HER2- breast cancer to identify patients who have a low risk of DR such that chemotherapy would not provide an overall benefit. In determining the cutoff to identify low risk patients, breast cancer prognostic tests commonly use a threshold of a 10% risk of DR at 10 years. Identification of a group of patients with a risk of DR<10% is a well-accepted standard used by many currently available breast prognostic tests and accepted by the American Society of Clinical Oncology (ASCO). [3, 4, 5]

Additional Genomic Tools to Weigh Risk-Benefit with Extended Endocrine Therapy

In studies of HR+ patients treated with primary adjuvant endocrine therapy, patients who were DR-free after 5 years had an approximately 10% risk of recurrence during years 5-10.[5-7] The critical question of whether longer durations of endocrine therapy would provide additional clinical benefit led to a series of randomized trials that compared the benefit of extended endocrine therapy (EET; 10 years total) versus the 5-year standard of care. The results of these trials demonstrated that EET led to a modest clinical benefit, with statistically significant increases in disease-free survival (3-4% absolute benefit; 10-40% relative risk reduction) in most trials.[8-14] Analyses of the numbers needed to treat (NNT) from these trials demonstrate that approximately 70-100 patients need to be treated to prevent one DR. While only a small percentage of patients benefit from EET, all patients are at risk of experiencing side effects, which include several serious toxicities such as endometrial cancer, pulmonary embolism, ischemic heart disease and even death in some trials for tamoxifen, and higher rates of osteoporosis, bone fractures, thrombotic events with AIs. In addition to serious safety concerns, prolonged endocrine therapy has numerous lower grade side effects and tolerability challenges that can have a substantial impact on quality of life such as arthralgia, joint pain, and musculoskeletal symptoms with AIs, and hot flashes, fatigue, vaginal dryness, and mood swings with tamoxifen.[9, 13, 15-17] Side effects and tolerability issues commonly lead to treatment nonadherence or discontinuation of endocrine therapy or EET, causing worse patient outcomes.[18]

The large randomized trials have demonstrated that EET is associated with a 10-40% relative reduction in risk of DR.[8-11, 13, 14, 19] The risk of serious toxicities (e.g., spinal fractures, thrombotic events, and endometrial cancers that lead to deaths) have been reported in ~1-2% of patients treated with EET. If the 28% relative risk reduction from NSABP B-42 is applied to a group of patients with a 7% risk of late DR, the absolute benefit of treatment is at most 2%, which is approximately equivalent to the risk of serious treatment-related toxicities. Therefore, a 7% cutoff for assessing risk versus benefit may be applied, such that if a biomarker identifies patients with a 7% or lower risk of late DR, the likelihood of benefit from EET is unlikely to outweigh the risks of serious toxicities.

Test Description and Intended Use

The Breast Cancer Index (BCI) is a molecular assay that evaluates the differential expression (qRT-PCR) of 11 genes: 7 informational genes that interrogate multiple cell-signaling pathways associated with breast cancer recurrence [proliferative (Molecular Grade Index or MGI) and estrogen signaling (HoxB13/IL17BR or H/I)], and 4 RNA normalization (reference) genes. The test provides both prognostic and predictive results reported as 1) individualized risk of DR as a percentage based on a BCI Score. Specific risk estimates are generated for the risk of overall DR (0-10 years after diagnosis) and late DR (5-10 years after diagnosis) in

patients who are recurrence-free at year 5, and 2) the test separately reports a categorical output of H/I High versus Low for likelihood of endocrine response, with a High H/I ratio associated with endocrine responsive disease.

BCI is used for the management of postmenopausal women diagnosed with early-stage (TNM stage T1-3, pN0, M0), node-negative, non-relapsed, ER and/or PR-positive , HER2-negative breast cancer, who are being treated with primary adjuvant endocrine therapy. The test is used by physicians to provide a genomic-based estimate of distant recurrence risk and endocrine responsiveness to identify patients:

- who have sufficiently low risk of distant recurrence over 10 years, wherein the absolute benefit of adjuvant chemotherapy is unlikely to outweigh the risks of serious toxicities; and/or
- who are distant recurrence-free and have a sufficiently low residual risk of late distant recurrence (post- 5 years from diagnosis) wherein the absolute benefit of extension of endocrine therapy is unlikely to outweigh the risks of complications and nonadherence to therapy

BCI is tested once per patient lifetime on FFPE tissue from the primary tumor specimen obtained prior to adjuvant treatment.

Clinical Validation

Evidence supporting the clinical validity of risk assessment for newly-diagnosed patients considering adjuvant chemotherapy

The prognostic ability of BCI for identifying patients at low risk of both early (0-5y) and cumulative overall DR (0-10 years) in the absence of adjuvant chemotherapy was validated in prospective-retrospective studies in randomized trial cohorts that included ER+ and/or PR+, LN- patients who were treated with adjuvant tamoxifen or AI therapy (Tables 1 and 2).

Table 1: Risk of early DR (years 0-5), by BCI risk group in clinical validation studies

| Cohort | Patient subset | No. of Pts | BCI Low Risk | | BCI Intermediate Risk | | BCI High Risk | | Hazard ratio (96% CI) | | |
			% of Pts	Risk of DR between 0-5y (95% CI)	% of Pts	Risk of DR between 0-5y (95% CI)	% of Pts	Risk of DR between 0-5y (95% CI)	Intermediate vs Low risk groups	High vs Low risk groups	P value
Stockholm RCT*	Node negative	317	64%	2.0% (0.0-4.0%)	20%	4.8% (0.0-9.9%)	16%	12.2% (2.6-21.0%)	2.31 (0.52-10.3)	6.19 (1.75-21.92)	P=0.0063
TransATAC RCT*	Node negative	665	59%	1.3% (0.5-3.1%)	25%	5.6% (2.9-10.5%)	16%	18.1% (12.0-27.0%)	3.13 (1.03-24.30)	8.59 (3.03-24.30)	P<0.0001
Multi-institutional*	Node negative	358	55%	4.1% (1.3-6.9%)	22%	7.7% (1.6-13.5%)	23%	24.5% (14.6-33.3%)	6.55 (2.89-14.88)	6.55 (2.89-14.88)	P<0.0001

* Distant recurrence-free survival data were converted to distant recurrence rates to allow for comparison between studies.
** Hazard ratios in the Stockholm randomized study were based on 0-15yr analysis
Pts, patients.

Table 2: Risk of overall DR (years 0-10), by BCI risk group in clinical validation studies

Cohort	Patient subset	No. of Pts	BCI Low Risk		BCI Intermediate Risk		BCI High Risk		Hazard ratio (96% CI)		
			% of Pts	Risk of DR between 0-10y (95% CI)	% of Pts	Risk of DR between 0-5y (95% CI)	% of Pts	Risk of DR between 0-10y (95% CI)	Intermediate vs Low risk groups	High vs Low risk groups	P value
Stockholm RCT*	Node negative	317	64%	4.8% (1.7-7.8%)	20%	11.7% (3.1-19.5%)	16%	21.1% (8.5-32.0%)	2.23 (0.91-5.45)	4.79 (2.18-10.5)**	P=0.0063
TransATAC RCT*	Node negative	665	59%	4.8% (3.0-7.6%)	25%	18.3% (12.7-25.8%)	16%	29.0% (21.1-39.1%)	2.89 (1.55-5.40)	4.86 (2.58-9.17)	P<0.0001
Multi-institutional*	Node negative	358	55%	6.6% (2.9-10.0%)	22%	23.3% (12.3-33.0%)	23%	35.8% (24.5-45.5%)	3.54 (1.67-7.48)	6.81 (3.47-13.34)	P<0.0001

* Distant recurrence-free survival data were converted to distant recurrence rates to allow for comparison between studies.

** Hazard ratios in the Stockholm randomized study were based on 0-15yr analysis

Pts, patients.

Development of the 11-gene BCI assay was based on a combination of H/I and MGI using patients from the untreated arm of the Stockholm prospective trial as the training set (n=283). Scores and pre-specified risk groups were then validated in a prospective-retrospective study including 317 ER+, LN- patients treated with primary adjuvant tamoxifen from the Stockholm trial.[20] The BCI Low Risk group had only a 6% risk of death due to breast cancer over a 20 year follow-up (years 0-20). Multivariate analyses adjusted for clinicopathologic factors (e.g., patient age, tumor size, tumor grade) showed that BCI was the only significant predictor of DR during years 0-10 (hazard ratio, 5.44; 95% CI, 21.3–13.88; P=0.0004). Further independent validations were performed on a well-annotated multi-institutional cohort of 358 ER+, LN- patients[20], and in a prospective-retrospective study evaluating 665 ER+, LN- patients from the translational cohort of the prospective, randomized, controlled ATAC trial.[20,22] In a multivariate analysis, BCI was a significant prognostic factor for risk of DR from years 0-10 (HR, 2.30; 95% CI, 1.62–3.27; P<0.0001) that included the CTS (a prognostic algorithm based on classic clinical and pathologic factors of tumor size/grade, LN status, patient age, and treatment).[22] These studies collectively demonstrate the ability of BCI to significantly stratify patients based on risk of DR, and to identify a low risk group (55-64% of patients across studies) with excellent 10 year outcomes (4.8-6.6% DR rate) when treated with a regimen of 5 years of endocrine therapy only. BCI was also determined to provide independent prognostic information compared to clinical and pathologic features alone.

Evidence supporting the clinical validity of risk assessment for patients who are distant recurrence-free at year 5 considering extended endocrine therapy.

Evaluation of BCI prognostic performance for late DR was performed in ER+ and/or PR+, LN- patients who were treated with no more than 5 years of adjuvant tamoxifen or AI therapy and were DR-free at 5 years (Table 3).

Table 3: Risk of late DR (years 5-10) in patients who were disease free following 5 years of adjuvant endocrine therapy, by BCI risk group in validation studies

| Cohort | Patient subset | No. of Pts | BCI Low Risk | | BCI Intermediate Risk | | BCI High Risk | | Hazard ratio (95% CI) | | |
			% of Pts	Risk of DR between 0-10y (95% CI)	% of Pts	Risk of DR between 0-5y (95% CI)	% of Pts	Risk of DR between 0-10y (95% CI)	Intermediate vs Low risk groups	High vs Low risk groups	P value
Stockholm RCT*	Node negative	285	65%	2.8% (0.3-5.2%)	20%	7.2% (0.1-13.8%)	15%	10.1% (0.2-19.1%)	2.2 (0.72-6.73)**	4.04 (1.46-11.14)**	P=0.0152
TransATAC RCT*	Node negative	596	61%	3.5% (2.0-6.1%)	25%	13.4% (8.5-20.5%)	14%	13.3% (7.4-23.4%)	2.93 (1.37-6.29)	2.97 (1.23-7.13)	P<0.0001
Multi-institutional*	Node negative	312	58%	2.5% (0-5.0%)	22%	16.9% (6.5-26.2%)	20%	15.0% (5.5-23.6%)	6.9 (2.17-22.02)	7.03 (2.17-22.84)	P<0.0002

* DR-free survival was converted to DR rates to allow for comparison between studies.
** Hazard ratios in the Stockholm randomized study were based on 5-15yr analysis
Pts, patients

Validation studies for prediction of late DR included 285 ER+, LN- patients that were DR-free following treatment with primary adjuvant tamoxifen, 312 patients that were DR-free following treatment with primary adjuvant treatment, and 596 patients that were DR-free following treatment with primary adjuvant treatment.[20], These studies collectively demonstrate the ability of BCI to significantly stratify patients based on risk of late DR, and to identify a low risk group (58-65% of patients across studies) with excellent outcomes in the extended timeframe (<3.5% DR rate from years 5-10 in all studies) when treated with a regimen of 5 years of endocrine therapy only, with a risk of DR that is sufficiently low that the likelihood of benefit from 5 additional years of endocrine therapy is outweighed by the probability of complications and treatment nonadherence.

Evidence supporting the clinical validity of prediction of benefit from endocrine therapy

In addition to stratification of patients based on risk of DR, the BCI assay also reports results from the estrogen signaling biomarker component of BCI—the HoxB13/IL17BR gene expression ratio (H/I). The H/I ratio has been shown to be predictive of benefit from endocrine therapies in 3 prospective randomized study cohorts (N=1514; Table 4).[20, 26, 27] In each of these studies, a statistically significant interaction between H/I and endocrine treatment was demonstrated. Thus, in all three studies, H/I had statistically significant ability to identify patients likely to benefit from endocrine therapy versus those patients not likely to benefit.

Table 4: Summary of predictive treatment benefit by H/I categorization

Study Cohort	Endocrine Treatment	Relative Risk Reduction by Endocrine Treatment	Interaction P Value
Stockholm (n=600)	Adjuvant tamoxifen vs. untreated	H/I-High HR: 0.35 (0.19-0.65); p=0.0005 H/I-Low HR: 0.67 (0.36-1.24), p=0.2	0.003
TransATAC (n=665)	Adjuvant anastrozole vs. tamoxifen	H/I-High HR: 0.51 (0.27-0.97);	0.004

		p=0.04 H/I-Low HR: 1.33 (0.65-2.71), p=0.4	
MA.17 (n=249)	Extended letrozole vs. placebo	H/I-High OR: 0.33 (0.15-0.73); p=0.006 H/I-Low OR: 0.58 (0.25-1.36), p=0.21	0.03

H/I was validated in the extended (> 5 years) treatment setting in a cohort of patients from the MA.17 trial.[27] H/I predicted which patients benefited from treatment with an AI between years 5-10 post-diagnosis. The reduction in risk of recurrence with extended letrozole (an AI) was 16.5% for patients with High H/I (p=0.007), while patients with a Low H/I did not statistically benefit from the extended AI therapy (p=0.35).

Analysis of Evidence
(Rationale for Determination)

<u>Level of Evidence</u>

Quality of Evidence – Moderate
Strength – High
Weight - Moderate

The BCI test is covered for postmenopausal women with invasive breast cancer when the following criteria are met:

- Pathology reveals invasive carcinoma of the breast that is ER+ and/or PR+ and HER2-; and
- Patient has early-stage disease (T1-3, pN0, M0); and
- Patient is lymph node negative
- Patient has no evidence of distant breast cancer metastasis (i.e., non-relapsed); and
- Test results will be used in determining treatment management of the patient for chemotherapy and/or extension of endocrine therapy.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
01/01/2020	R2	The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)
01/01/2020	R1	As required by CR 10901, all billing and coding information has been moved to the companion article,	• Revisions Due To Code Removal

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		this article is linked to the LCD. Several CMS National Coverage Policy references were moved to the article. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all of the fields included on the LCD are applicable as noted in this policy.	

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57773 - Billing and Coding: MolDX: Breast Cancer IndexTM (BCI) Gene Expression Test
A56356 - Response to Comments: MolDX: Breast Cancer IndexTM (BCI) Gene Expression Test
LCD(s)
DL37822 - MolDX: Breast Cancer IndexTM (BCI) Gene Expression Test

Related National Coverage Documents

N/A

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- HER2
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- neoplasm