Test Specific Guidelines

Prosigna Breast Cancer Prognostic Gene Signature Assay

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Introduction

The Prosigna breast cancer prognostic gene signature assay is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
Prosigna Breast Cancer Prognostic Gene Signature Assay	81520

What Is Prosigna?

Definition

Prosigna is a gene expression test designed to predict the chance of 10 year recurrence of breast cancer.

Prosigna is indicated in post-menopausal women with hormone receptor positive, node negative (Stage I or II) or 1-3 node positive (Stage II), early stage breast cancer.[1,2]

This assay is intended to be a prognostic indicator for distant recurrence-free survival at 10-years in women to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. [1,2]

Test Information

Introduction

Prosigna is based on the 50 gene expression signature called PAM50. This assay uses RNA from formalin fixed paraffin embedded (FFPE) samples to calculate a risk score.[1,2]

The algorithm used for the Prosigna score uses the 50-gene expression profile in combination with clinical variables to classify breast cancer into one of the following four types: Luminal A, Luminal B, HER2-enriched, and Basal-like.[1,2]

A risk of recurrence (ROR) score is also calculated using gene expression and clinical variables (such as tumor size and degree of proliferation). This ROR score is reported as 0-100 and reflects the probability of disease recurrence at 10 years.[1,2]

A ROR score of 1-10 corresponds to a 10 year distant recurrence of 0%. This risk increases to approximately 15% and then 33.3% when the ROR score reaches 61-70 and 91-100, respectively.[2]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Prosigna.

American Society of Clinical Oncology

The most recent evidence-based guideline from the American Society of Clinical Oncology (ASCO, 2022) stated:[3]

"If a patient is postmenopausal and has breast cancer that is node-negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

"If a patient is premenopausal and has node-negative or node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)."

"If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."

"If a patient has node-positive breast cancer with 4 or more positive nodes, evidence on the clinical utility of routine use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong)."

"If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use

Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."

"If a patient has HER2-positive breast cancer or TNBC [triple negative breast cancer], the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong)."

European Society of Medical Oncology

The European Society of Medical Oncology (ESMO, 2015) stated the following regarding gene expression profiles:[4]

"Gene expression profiles, such as MammaPrint (Agendia, Amsterdam, the Netherlands), Oncotype DX Recurrence Score (Genomic Health, Redwood City, CA), Prosigna (Nanostring Technologies, Seattle, WA) and EndoPredict (Myriad Genetics), may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant chemotherapy. The three latter tests are designed for patients with ER-positive early breast cancer only."

"In cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays, such as MammaPrint, Oncotype DX, Prosigna and EndoPredict, may be used, where available."

"In cases when decisions might be challenging, such as luminal B HER2-negative and node-negative breast cancer, commercially available molecular signatures for ER-positive breast cancer, such Oncotype DX, EndoPredict, Prosigna, and for all types of breast cancer (pN0–1), such as MammaPrint and Genomic Grade Index, may be used in conjunction with all clinicopathological factors, to help in treatment decision making."

In 2019 they stated: “Validated gene expression profiles may be used to gain additional prognostic and/or predictive information to complement pathology assessment and help in adjuvant ChT [chemotherapy] decision making."[5]

Food and Drug Administration

The US Food and Drug Administration (FDA) cleared Prosigna for clinical use in 2013.[6,7]

Molecular Oncology Advisory Committee

The Molecular Oncology Advisory Committee (2013) published a comparison of Oncotype DX with MammaPrint, PAM50, Adjuvant! Online, Ki-67, and IHC. Their recommendation is as follows:[8]

"In cases of breast carcinoma where Oncotype DX is indicated for clinical prognosis and treatment decisions, other assays should not currently be considered equivalent with respect to data generated or risk stratification."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) Clinical Practice Guidelines for Breast Cancer considered the 50-gene PAM50 assay suitable for prognostic purposes (with evidence category 2A) as follows:[9]

"For patients with T1 and T2, HR [hormone receptor]-positive, HER2-negative, pN0 [lymph node-negative] tumors, a risk of recurrence score in the low range, regardless of tumor size, places the individual into the same prognostic category as those with T1a–T1b, N0, M0 tumors."

"In patients with HR-positive, HER2-negative, pN+ (1-3 positive lymph nodes) with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10 years and no distant recurrence was seen at 10 years in the TransATAC study in a similar group."

These guidelines consider the therapeutic predictive value of this assay to be "not determined".

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE, 2018) stated:[10]

"EndoPredict (EPClin score), Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (RE)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease; see section 5.4) early breast cancer, only if:

they have intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic index

information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference"

Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care

The Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care (PEBC, 2022) conducted a systematic review of the literature to serve as the basis of their clinical practice guideline. The clinical practice guideline for the clinical utility of multigene profiling assays in early-stage invasive breast cancer stated the following regarding Prosigna:[11]

"In patients with early-stage estrogen receptor (ER)-positive/human epidermal growth factor 2 (HER2)-negative breast cancer, clinicians should consider using multigene profiling assays (i.e., Oncotype DX, MammaPrint, Prosigna, EndoPredict, and the Breast Cancer Index) to help guide the use of systemic therapy."

"In patients with early-stage node-negative ER-positive/HER2-negative disease, clinicians may use a low-risk result from Oncotype DX, MammaPrint, Prosigna, EndoPredict/EPclin, or Breast Cancer Index assays to support a decision not to use adjuvant chemotherapy."

St. Gallen International Expert Consensus

The St. Gallen International Expert Consensus (2017) stated:[12]

"The panel agreed that there was no role in clinical low risk cases [such as pT1a/b, grade 1 (G1), ER high, N0] and similar settings where chemotherapy would not be indicated under any circumstances."

"The Panel agreed that a number of gene expression signatures served as prognostic markers in the setting of adjuvant endocrine therapy in node-negative breast cancers, including the 21 gene recurrence score, the 70 gene signature, the PAM50 ROR scoreV R, the EpClin score V R, and the Breast Cancer Index V R. The Panel endorsed all of these assays for guiding the decision on adjuvant chemotherapy in node-negative tumors as they all identify node-negative cases at low risk, with an excellent prognosis that would not warrant chemotherapy."

"The Panel agreed that gene expression signatures offered information that can refine the prognosis for node-positive breast cancers. However, the Panel did not uniformly endorse the use of gene expression signatures for making treatment decisions regarding adjuvant chemotherapy in node positive cases."

"The Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting."

"In patients who are not candidates for adjuvant chemotherapy owing to comorbid health conditions or tumor stage/risk, or in patients who 'obviously' need adjuvant chemotherapy, typically including stage III breast cancer, there is no routine need for genomic tests."

"In general, the zone 'in between' is where genomic assays may be most valuable. These would often be patients with tumors between 1 and 3 cm, with zero to two or three positive lymph nodes, and intermediate proliferative fraction. Multigene assay should not be the only factor considered in making a decision to proceed or to avoid chemotherapy."

In 2019, the panel stated they "believed strongly that genomic assays are valuable for determining whether or not to recommend adjuvant chemotherapy in

T1/T2 N0 ER-positive breast cancers, and recognized the value of such tests in patients with ER-positive tumors and limited nodal involvement".[13]

Selected Relevant Publications

There is insufficient evidence in the peer-reviewed literature regarding the use of Prosigna/PAM50 ROR in women with early stage (ER+/HER2-), node-positive, breast cancer who are considering adjuvant chemotherapy.[14-30]

Limited evidence from a prospective-retrospective clinical validity study suggests that the low risk Prosigna/PAM50 ROR Score is associated with a relatively low 10-year distance recurrence rates in women with node-positive invasive breast cancer; however, a relatively wide confidence interval suggests imprecise an estimate of distant recurrence at 10 years.[15]

Of the recent studies, the best quality study was a prospective-retrospective study evaluating Prosigna to identify tumor dimensions in node-positive patients in the GEICAM/9906 clinical trial.[20] Results of a multivariable model found that PC1 tumor dimensions and nodal status were significantly associated with disease-free survival (DFS). As a proof-of-concept study, the findings were only preliminary and suggested that subtypes of node positive tumors may undergo differential treatment effects.

Prosigna has been evaluated in a few studies as a risk assessment method to assist in decisions to extend hormonal therapy beyond 5 years in recurrence-free individuals. The results were conflicting or inconclusive since the total number of recurrence events was very low.[14,16-19]

A retrospective cohort study assessed the real-world impact of Prosigna testing on adjuvant chemotherapy use in individuals with intermediate-risk early breast cancer.[30] Multiple study limitations were identified including: missing data on administered chemotherapy, lack of adherence to the indication for chemotherapy, low sample-size of node-positive individuals, and a lack of follow-up to determine if adherence to adjuvant chemotherapy indications improved outcomes.

The overall evidence base is low quality and does not adequately address the question regarding whether Prosigna used for risk assessment is sufficiently prognostic or predictive in individuals with node positive breast cancer who are considering adjuvant therapy or extended endocrine therapy after surgery. Well-designed studies with large enough study populations to capture higher rates of node positive cases are needed to ascertain if low risk Prosigna/PAM50 ROR scores are significantly associated with the low risk of distant recurrence at 10 years (with narrow precision estimates).

Future results from the ongoing OPTIMA trial may provide more evidence to definitively establish the clinical validity and clinical utility of Prosigna.[26-28]

Criteria

Introduction

Requests for Prosigna testing are reviewed using these criteria.

Previous Testing:

No repeat Prosigna testing on the same tumor when a result was successfully obtained, and

No previous gene expression assay (e.g. OncotypeDx Breast) performed on the same tumor when a result was successfully obtained, AND

Testing Multiple Samples:

When more than one breast cancer primary is diagnosed:

There should be reasonable evidence that the tumors are distinct (e.g., bilateral, different quadrants, different histopathologic features, etc.), and

There should be no evidence from either tumor that chemotherapy is indicated (e.g., histopathologic features or previous Gene Expression Assay result of one tumor suggest chemotherapy is indicated), and

If both tumors are to be tested, both tumors must independently meet the required clinical characteristics outlined below, AND

Required Clinical Characteristics:

Invasive breast cancer meeting all of the following criteria:

Tumor size ≥0.4cm (4mm) in greatest dimension (T1b-T3), and

Hormone receptor positive (ER+/PR+), and

HER2 negative, and

Individual has no regional lymph node metastasis, and

Chemotherapy is a treatment option for the individual; results from this Prosigna test will be used in making chemotherapy treatment decisions, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Introduction

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