Test Specific Guidelines

MammaPrint 70-Gene Breast Cancer Recurrence Assay

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v1.0.2023

Introduction

MammaPrint® 70-gene breast cancer recurrence assay is addressed by this guideline.

Procedure 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
MammaPrint [Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis]	81521
MammaPrint [Oncology (breast), next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis]	81523

What Is MammaPrint?

Definition

MammaPrint® is a 70-gene expression test designed to predict the chance of later-in-life recurrence of breast cancer in women with newly diagnosed, early stage breast cancer.[1-12] It is FDA cleared for use along with other standard prognostic methods, such as disease staging, grading and other tumor marker analyses.[13]

MammaPrint is intended to assist individuals and providers considering treatment with adjuvant chemotherapy. Individuals assigned a “low risk” may choose hormone therapy (tamoxifen) alone and forego chemotherapy. Individuals assigned a "high

risk" may benefit from more aggressive treatment and choose to do chemotherapy.[1-12]

MammaPrint is designed for women with breast cancer who have:[1-12]

Stage I or II invasive carcinoma

Tumor size <5.0 cm

Node-negative (no metastasis to lymph nodes)

Estrogen receptor-positive (ER+) or -negative (ER-) disease

Test Information

Introduction

MammaPrint uses either a microarray or a NGS platform to analyze the expression level of 70 genes in the tumor.[1-12]

These 70 genes are thought to be critical in the cellular pathways to cancer metastasis.[1-12]

Based on the test results, the expression profile of the tumor sample is then placed in one of the following risk categories for recurrence of distant metastases within 5 years: Low Risk or High Risk. A Low Risk result indicates that an individual has 1.3% chance that the cancer will recur within 5 years. A High Risk result suggests that an individual has an 11.7% chance that their cancer will recur within 5 years.[1-4]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to MammaPrint testing.

American Society of Clinical Oncology

The most recent evidence-based guideline from the American Society of Clinical Oncology (ASCO, 2022) stated:[14]

"If a patient is older than 50 and has high clinical risk breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)"

"If a patient is 50 years of age or younger and has high clinical risk, node-negative or node-positive with 1-3 positive nodes breast cancer, the clinician

should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong)."

"If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)"

"If a patient has node-positive breast cancer with 4 or more positive nodes, the evidence on the clinical utility of routine MammaPrint 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). Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making."

"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:[15]

“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, ESMO 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."[16]

Evaluation of Genomic Applications in Practice and Prevention

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP, 2009) Working Group reviewed the evidence for MammaPrint and concluded:[17]

"It is unclear what population of patients would derive benefit from use of the test, and what the magnitude of that benefit would be. Prospective data from trials like MINDACT will be extremely valuable."

"Overall, published evidence supports MammaPrint as a better predictor of the risk of distant recurrence than traditionally used tumor characteristics or algorithms, but its performance in therapeutically homogeneous populations is not yet known with precision, and it is unclear for how many women the lowest predicted risks are low enough to forgo chemotherapy."

"No evidence is available to permit conclusions regarding the clinical utility of MammaPrint to select women who will benefit from chemotherapy."

"To conclude, the literature on the 70-gene signature includes numerous studies that focused more on its biological underpinning and less on the clinical implications of this gene expression profile, although it has now received FDA approval for clinical use."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) Clinical Practice Guidelines for Breast Cancer stated:[18]

In the current NCCN guidelines for breast cancer MammaPrint is listed as a prognostic gene expression assay for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy.

MammaPrint is considered evidence and consensus category 1 for prognostic assessment in node-negative and 1-3 node positive breast cancer.

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

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 MammaPrint:[19]

"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."

"In postmenopausal patients with ER-positive/HER2-negative tumours and one to three nodes involved (N1a disease), clinicians may withhold chemotherapy based on a low-risk Oncotype DX or MammaPrint score if the decision is supported by other clinical, pathological, or patient-related factors."

St. Gallen International Expert Consensus

The St. Gallen International Expert Consensus (2017) stated:[20]

"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 scoreV 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"[21]

US Food and Drug Administration

The US Food and Drug Administration (FDA) cleared Mammaprint for clinical use on fresh tissue samples in 2007.[9] The FDA cleared Mammaprint for clinical use on FFPE samples in 2015.[1]

Criteria

Introduction

Request for MammaPrint testing are reviewed using these criteria.

Previous Testing:

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

No previous gene expression assay (e.g. Prosigna) 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 MammaPrint 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.

Required Clinical Characteristics:

Invasive breast cancer meeting all of the following criteria:

Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3), and

Estrogen receptor positive (ER+), and

HER2 negative, and

Individual has involvement of 0-3 ipsilateral axillary lymph nodes, and

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

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

Billing and Reimbursement Considerations

81521 and 81523 may not be reimbursed for the same specimen.

For billing purposes, the use of 81521 and 81523 are not interchangeable; MammaPrint must be billed with the code that reflects the platform used (81521 for microarray or 81523 for NGS).

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