Mammaprint 70-Gene Breast Cancer Recurrence Assay

Procedure addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
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<td>Mammaprint 70 Gene Signature</td>
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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. It is FDA cleared for use along with other standard prognostic methods, such as disease staging, grading and other tumor marker analyses.

- MammaPrint is intended to assist patients and providers considering treatment with adjuvant chemotherapy. Patients assigned a "low risk" may choose hormone therapy (tamoxifen) alone and forego chemotherapy. Patients assigned a "high risk" may benefit from more aggressive treatment and choose to do chemotherapy.
- MammaPrint is designed for women with breast cancer who have:
  - 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

- MammaPrint uses a microarray platform to analyze the expression level of 70 genes in the tumor. These 70 genes are thought to be critical in the cellular pathways to cancer metastasis.
- Based on the test results, patients are assigned either a low risk or a high risk for a distant recurrence. Low risk corresponds to a 10% risk of recurrence by 10 years
without any additional adjuvant treatment. In contrast, those in the high risk group have a 29% risk of recurrence by 10 years without any additional adjuvant treatment.\textsuperscript{1}

Guidelines and evidence

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) 2019 Clinical Practice Guidelines for Breast Cancer state that:\textsuperscript{3}

- MammaPrint is considered evidence and consensus category 1 for prognostic assessment in node-negative and 1-3 node positive breast cancer.
- Use of the test for predictive purposes has not been determined.

American Society of Clinical Oncology

Evidence-based clinical guidelines from the American Society of Clinical Oncology (ASCO, updated 2017) state the following:\textsuperscript{4}

- “If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).”
- “If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).”
- “If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate).”
- “If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the
clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)."

- “If a patient has HER2-positive breast cancer, the clinician should not use the 70-gene assay (MammaPrint) to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: low. Strength of recommendation: moderate)."

- “If a patient has TN breast cancer, the clinician should not use the 70-gene assay (MammaPrint) to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong).”

**St. Gallen International Expert Consensus**

St. Gallen International Expert Consensus (updated 2017):

- “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 scoreVR, the EpClin scoreVR, and the Breast Cancer Index VR. 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.”
European Society of Medical Oncology

European Society of Medical Oncology (ESMO) 2015:

- “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.”

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 concludes:

- “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.”
US Food and Drug Administration

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

Literature Review

While the clinical validity of the test has been established, data regarding the clinical utility of MammaPrint is still emerging.8-24

• The current evidence base, consisting of a single open-label RCT and a number of small, retrospective studies, is limited and of poor to moderate quality, to conclude that foregoing chemotherapy is a safe and will not lead to increased risk of recurrence and death. It remains unclear if decisions to forego adjuvant chemotherapy based on MammaPrint results lead to significantly improved patient health outcomes, including long-term overall survival, distant-free survival, and QOL.

• There is a lack of direct evidence regarding clinical utility. Future well-designed clinical studies with long-term follow-up data are necessary to capture late distant recurrence occurring beyond 5 years. Study designs should include comparisons of survival outcomes following treatment guided by MammaPrint and clinical assessment to adequately assess clinical utility including quality of life measures in well-designed clinical trials are also necessary to help understand the complete value of MammaPrint and to help weigh the benefits and harms of foregoing chemotherapy in clinical practice.

Criteria

• Previous Testing:
  o No repeat MammaPrint testing on the same tumor when a result was successfully obtained, and
  o No previous gene expression assay (e.g. Prosigna) performed on the same tumor when a result was successfully obtained, AND

• Testing Multiple Samples:
  o 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
  - Patient has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0mm), and
  - Chemotherapy is a treatment option for the patient; 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.

References

1. MammaPrint website. Available at: https://www.agendia.com/our-tests/mammaprint


25. Clinicaltrials.gov. MammaPrint, BluePrint, and Full-genome Data Linked with Clinical Data to Evaluate New Gene Expression Profiles. NCT03053193. Available at: https://ClinicalTrials.gov/show/NCT03053193

26. Clinicaltrials.gov. NBRST: Prospective Neo-adjuvant REGISTRY Trial. NCT01479101. Available at: https://ClinicalTrials.gov/show/NCT01479101


28. Clinicaltrials.gov. NEOADjuvant Aromatase Inhibitor and Pertuzumab/Trastuzumab for Women with Breast Cancer. NCT02689921. Available at: https://ClinicalTrials.gov/show/NCT02689921