Prosigna Breast Cancer Prognostic Gene Signature Assay

Procedures 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.

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<th>Procedure addressed by this guideline</th>
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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 node positive (Stage II), early stage breast cancer.\(^1,2\)
- This assay is intended to assist patients and providers considering treatment with adjuvant chemotherapy.\(^1,2\)

Test information

- 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.\(^3\)
Guidelines and evidence

- The National Comprehensive Cancer Network (NCCN) 2018 Clinical Practice Guidelines for Breast Cancer consider the 50-gene PAM50 assay suitable for prognostic purposes (with evidence category 2A) as follows:\(^4\)
  - “For patients with T1 and T2 hormone receptor-positive, HER2-negative, lymph node-negative tumors, a risk of recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0.”
  - “In patients with hormone receptor-positive, HER2-negative, 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 12 and no distant recurrence was seen at 10 years in TransATAC study in a similar group.”
  - These guidelines consider the therapeutic predictive value of this assay to be “not determined”.

- The National Institute for Health and Care Excellence (NICE) 2018 stated the following:\(^5\)
  - “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”

- Evidence-based clinical guidelines from the American Society of Clinical Oncology (ASCO) 2016 state:\(^6\)
  - “If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 risk of recurrence (ROR) score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA), in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.”
  - “If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.”
o “If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.”

o “If a patient has TN breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.”

• The European Society of Medical Oncology (ESMO) 2015 published new clinical practice guidelines and stated the following: 7

o “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.”

o “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.”

o “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.”

• The St. Gallen International Expert Consensus (2015) stated the following: 8

o “The Panel considered the role of multiparameter molecular marker assays for prognosis separately in years 1-5 and beyond 5 years, and their value in selecting patients who require chemotherapy. Oncotype DX®, MammaPrint®, PAM-50 ROR® score, EndoPredict® and the Breast Cancer Index® were all considered usefully prognostic for years 1-5. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX (despite the available data from NSABP Trial B-14 [32]); EndoPredict® (despite the report of Dubsky et al. [36]); and Breast Cancer Index (despite the report of Zhang et al. [37]). (All these reports show the respective tests to be prognostic beyond 5 years.) PAM50 ROR® score was agreed to be clearly prognostic beyond 5 years, and a clear majority rejected the prognostic value of MammaPrint® in this time period.”

• 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: 9
“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.”

- The US Food and Drug Administration (FDA) cleared Prosigna for clinical use in 2013.\textsuperscript{10}

**Criteria**

- This test is considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

**References**

2. Prosigna website. Available at: \url{http://prosigna.com/}
3. Prosigna Packet Insert US. Available at: \url{http://prosigna.com/docs/Prosigna_Packet_Insert_US.pdf}

9. Chang M, Ismaila N, Kamel-Reid S, Rutherford M, Hart J, Bedard P, Trudeau M, Eisen A, Molecular Oncology Advisory Committee. Comparison of Oncotype DX with multi-gene profiling assays (e.g., MammaPrint, PAM50) and other tests (e.g., Adjuvant! Online, Ki-67 and IHC4) in early-stage breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2013 Nov 20. 39 p. Available at: https://www.guideline.gov/summaries/summary/47790