INTRODUCTION

The role of molecular information to guide treatment decisions has become increasingly important for patients with breast cancer. Molecular assays that enable clinicians to quantify patients’ risk of disease recurrence have been commercially available for over a decade, and some have received long-standing recommendations in clinical guidelines.\(^1,2\) These assays are used to identify patients who may or may not benefit from adjuvant chemotherapy in addition to endocrine therapy, and are utilized routinely in clinical practice.

THE ENDOPREDICT TEST

EndoPredict (EPclin), a breast cancer prognostic test, analyzes RNA expression of 8 target genes, 3 normalization genes, and 1 control gene, creating a 12-gene molecular score, which is then combined with clinical features of the tumor (tumor size and nodal status) to predict the 10-year distant recurrence (DR) rate. This information may be used by treating physicians to guide therapy decisions by identifying which patients have sufficiently low risk of DR and may safely forgo chemotherapy, and which patients are at high risk for DR and may need adjuvant chemotherapy in addition to endocrine therapy.\(^1,3-7,11\) EndoPredict improves upon earlier assays by incorporating clinical prognostic factors and providing substantially more accurate prognostic information that aligns more closely with patient outcomes.\(^3\) Moreover, EndoPredict provides patients and their health care providers with clearer information about their risk of breast cancer recurrence through a binary test result (low/high risk) that avoids the potential confusion with assays that distribute patients into an intermediate risk category.

The ability of EndoPredict to predict DR has been validated in prospective-retrospective studies in three different cohorts from phase III trials involving more than 2,600 patients.\(^3,7\) EndoPredict was incorporated into the most recent American Society of Clinical Oncology (ASCO) practice guidelines, as well as the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, and based on a review of published evidence, EndoPredict is recommended for use to guide decisions on adjuvant systemic chemotherapy by both organizations.\(^1,2\)

INTENDED USE POPULATION

EndoPredict is intended for use in patients with estrogen receptor-positive (ER+), human epidermal growth factor 2-negative (HER2-), early-stage breast cancer, node-negative or node-positive (1-3 positive nodes).

ANALYTICAL VALIDITY (AV)

Kronenwett et al. published an analytical validation study in 2012 assessing performance of the EndoPredict assay in a design consistent with Clinical Laboratory Standards Institute (CLSI) Guidelines.\(^8\) The authors concluded that EndoPredict showed reproducible performance characteristics with good precision. An additional analytical validation study published by Warf et al. in 2017 demonstrated similar findings. The assay was reported to be highly accurate, with highly correlated molecular and clinical scores relative to a previously validated reference laboratory.\(^8,9\) The EndoPredict assay was shown to have a broad linear range for input DNA, similar amplicon efficiencies for all genes, and good inter- and intrabatch precision with reproducible performance characteristics.
The EndoPredict 12-gene molecular score was developed with a training cohort of 964 ER+, HER2- breast cancer tumor samples from patients treated with tamoxifen only. EndoPredict scores were subsequently validated in three cohorts distinct from the training cohort and representative of the intended use population. These validation studies were conducted in a prospective-retrospective design utilizing samples from participants randomized to receive endocrine-only therapy in phase III prospective trials and produced similar results. Thus, EndoPredict is considered to satisfy the level of evidence of 1B according to the framework for assessment of prognostic biomarkers proposed by Simon, et al. and applied by ASCO in their evidence-based review and 2016 practice guideline.

Three key publications present validation studies and analyses performed utilizing clinical data and EndoPredict scores derived from 1702 samples from ABCSG-6 and ABCSG-8 trial participants who received endocrine therapy. These studies collectively demonstrate the ability of EndoPredict to predict distant metastases in both early and late time periods, to accurately classify patients into a low or high risk group, and to identify a large low risk group with excellent outcome after 10 years with 5 years of endocrine therapy only.

A published validation study by Buus et al. compared the performance of EndoPredict and Oncotype DX® Recurrence Score® (RS). This study reviewed the comparative effectiveness of biomarkers within the population of the Phase III Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. This study included 928 females from the ATAC trial who had ER+, HER2- breast cancer that was chemotherapy-naïve and was treated with endocrine therapy. The authors reported the following key findings about EPclin:

- Demonstrated good **prognostic strength** with a 10 year DR rate of 5.8% in the low risk group (compared to 10.1% for the RS low risk group) and 28.8% in the high risk group,
- Established **strong prognostic ability** for node-negative disease (5.9% DR for EPclin low vs. 20.0% DR for EPclin high) and even **stronger** prognostic **ability** for node-positive disease (5.0% DR for EPclin low vs. 36.9% DR for EPclin high),
  - Node-positive patients identified as low risk by Oncotype DX RS had an observed DR rate of 25%
- Provided **substantially more accurate prognostic** information and was found to have a better ability to predict metastasis compared to RS (Figure 1),
- In cases where EPclin and RS disagreed in risk categorization, classification by EPclin aligned more closely with the observed risks:
  - Of the 13% of patients who were classified as low risk by EPclin and non-low risk (intermediate or high risk) by RS, the observed rate of DR was 10.2%, i.e. more closely aligned with low risk, and
  - Of the 16% of patients who were classified as high risk by EPclin and low risk by RS, the observed rate of DR was 26.9%, i.e. **EPclin correctly identified these patients as high risk**.

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**FIGURE 1**

*Data from Buus et al. utilized X² likelihood ratio (standard for assessing prognostic power of biomarkers)*

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**CLINICAL VALIDITY (CV)**

EndoPredict Outperforms Oncotype DX

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<th>EPclin</th>
<th>RS</th>
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<tr>
<td>0-10 years</td>
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<td>90</td>
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<td>0-5 years</td>
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Amount of prognostic information captured by the two assays*
A comparative analysis of four breast prognostic tests, EndoPredict, Oncotype DX, Prosigna® and Breast Cancer IndexSM, and two prognostic algorithms, Clinical Treatment Score (CTS) and IHC4, was published in *JAMA Oncology*. The authors initiated a direct and comprehensive comparison of the added prognostic value of multigene expression tests in combination with CTS in predicting DR in years 0-10, and years 5-10, following diagnosis of breast cancer, using tumor blocks from the translational substudy of the ATAC randomized clinical trial. Key findings from the study include:

- **EndoPredict** was the best overall test in predicting DR in years 0-10 in both node-negative and node-positive patients (C-index 0.753; LR$_2^2$=69.3)
- EndoPredict identified the largest group of low-risk patients with 10 years DR below 10 percent in both node-negative and node-positive disease
- EndoPredict was a better predictor for overall DR and for late-DR than Oncotype DX Recurrence Score

**CLINICAL UTILITY AND IMPACT ON PATIENT CARE**

The clinical utility of breast prognostic assays is well-established after many years of clinical use. The clinical utility of EndoPredict as described in a peer-reviewed publication shows equivalence to current, available products, demonstrating the ability of EndoPredict to guide appropriate treatment decisions for ER+, HER2- early stage breast cancer patients. Müller et al. published a retrospective analysis of the performance and treatment impact of EndoPredict in a clinical setting. In this study, the impact of EndoPredict on therapeutic decisions was evaluated for 130 women with primary invasive ER+, HER2- breast cancer. EndoPredict was shown to impact treatment recommendations and reduce the use of unnecessary and costly chemotherapy in this population.

- A change in pre-test versus post-test therapy for 37.7% of patients with most of the changes due to reduction from combination therapy (chemotherapy plus endocrine) to endocrine therapy alone.
- 25.4% of patients moved from combination therapy to endocrine therapy alone, and 12.3% moved from endocrine therapy alone to combination therapy.
- Changes in therapy were directionally aligned with the EndoPredict result as low or high risk. (Figure 2)

**FIGURE 2**

*Change of Therapy and EPclin Score*
Adapted from Müller et al. *PLoS One*. June 2013
SUMMARY

The peer-reviewed, published data demonstrate that EndoPredict is well-validated for use in women with ER+, HER2- early stage breast cancer, as demonstrated by consistent results across studies performed with samples from three validation cohorts (level 1B evidence) reflective of the intended use population. EndoPredict has been proven to accurately predict both early and late DR, and identify a large low risk group with excellent outcome after 10 years with 5 years of endocrine therapy only. EndoPredict incorporates clinical information into the score (tumor size and nodal status) and classifies all patients as low or high risk, eliminating the challenging intermediate group identified by other assays. These features make the EPclin a driver of clinical utility through demonstrated impact of the result on critical treatment decisions. EndoPredict is one of the few breast cancer gene expression assays that meet the evidence bar for use per the current ASCO guideline, the National Comprehensive Cancer Network (NCCN) recommends EndoPredict for both node-negative and node-positive patients, and appropriate Medicare patients gained coverage for EndoPredict through a favorable local coverage determination (LCD). Also, a large head-to-head study and a comparative analysis of available breast prognostic tests demonstrate that EndoPredict is a superior predictor of a meaningful clinical endpoint for women with early stage breast cancer. EndoPredict provides many patients and their healthcare providers with the information needed to avoid the side effects and substantial cost associated with unnecessary chemotherapy treatment.

REFERENCES