To Optimize Treatment for your Breast Cancer Patients

EndoPredict®

One Test – Three Clinical Answers

myriad®

WHEN DECISIONS MATTER

Personalized medicine helps guide ER+, HER2-, N0 and N+, pre- or postmenopausal breast cancer treatment decisions

EndoPredict®
One Test – Three Clinical Answers

The ONLY test that answers the following three important clinical questions...

- **Can chemotherapy be avoided?** (Risk up to 15 years[1,3])
- **What is the absolute benefit from chemotherapy?** (Chemotherapy benefit[2])
- **Can endocrine therapy be stopped after 5 years?** (Risk between 5 and 15 years[3])

... to optimize treatment for your breast cancer patients

EndoPredict is designed for women with ER+, HER2- primary breast cancer (node-negative or node positive [micrometastases, 1-3 nodes], pre- or postmenopausal)

One Test – Three Clinical Answers

EndoPredict is a gene expression assay for patients with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) early-stage breast cancer who are lymph node negative or positive (N0, N+). This second generation test combines a molecular score with tumor size and nodal status to provide more prognostic power than first generation tests.

EndoPredict®

TARGET GROUP

- Invasive primary breast cancer
- ER-positive
- HER2-negative
- 0-3 positive lymph nodes
- G1-3
- Size: pT1-3

EndoPredict inclusion criteria

In the result report the individual risk, either low or high, is clearly indicated for each patient. In addition the risk of early and late distant recurrence with 5 years of adjuvant endocrine therapy alone and the estimated absolute benefit of chemotherapy are determined.

EndoPredict provides highly important and clear information for different stages of treatment planning.

Initial treatment planning:
10-year risk of recurrence for patients with node negative or node positive disease[1] and estimated absolute chemotherapy benefit at 10 years based on current treatment regimens.[2]

Long-term treatment planning:
Breast cancer recurrence risk out to 15 years.[3]

Patients at low risk of distant recurrence are usually treated initially without chemotherapy. Under endocrine therapy alone, more than 95% of EndoPredict low risk patients do not experience a distant recurrence in 10 years.[1]

Compared to risk stratification using clinical parameters or other gene expression tests, EndoPredict identifies the largest group of women with breast cancer at low risk (<10% risk of distant recurrence in 10 years) who might safely avoid chemotherapy.[4,5,6]

For even more treatment confidence, EndoPredict predicts the individual absolute chemotherapy benefit based on current treatment regimens.[2]

In addition, EndoPredict can support long-term treatment planning. Some patients can benefit from prolonged endocrine therapy up to ten years, but other patients can avoid this additional treatment and be safely treated with only 5 years of endocrine therapy.

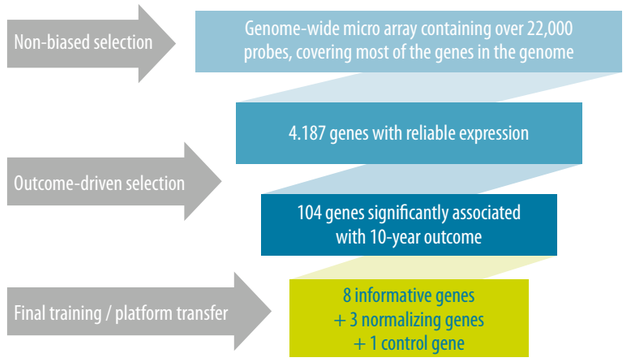
EndoPredict is the only test that provides your patients individual risk of breast cancer late distant recurrence within years 5-15[3] to help in deciding whether your patient can avoid extended endocrine therapy.

EndoPredict is the only prognostic test that can help in deciding whether your patient can safely avoid chemotherapy, how beneficial chemotherapy would be, and whether your patient can stop endocrine therapy after 5 years.

Measures 8 Genes Related to Early and Late Recurrence

EndoPredict was developed using consistent criteria for patients during training and independent validation studies on up to 15 years outcome data. ER+/HER2- breast cancer, both N0 and N+.

The **EndoPredict** algorithm was generated in a large training set of 964 ER+/HER2- breast cancer samples.[1]



Gene selection process for 12-Gene Molecular Score

Consistent study cohorts for training and validation

	Gene	Assigned biological processes
Proliferation associated Genes	UBE2C	Protein degradation, cell division
	BIRC5	Anti-apoptosis, cell division, cytokinesis, chromosome localization
	DHCR7	Cholesterol biosynthesis
Hormone Receptor associated Genes	STC2	Cell-to-cell communication
	AZGP1	Cell adhesion
	IL6ST	Various signal transduction pathways, cell proliferation, T cell proliferation
	RBBP8	DNA repair
	MGP	Transcriptional regulation

Genes and assigned biological processes

Variable	0-5 years HR (95% CI)	P-value	>5 years HR (95% CI)	P-value
PROLIFERATION	1.60 (1.33-1.92)	<0.001	1.19 (0.85-1.67)	0.298
ER SIGNALING	0.89 (0.75-1.06)	0.204	0.61 (0.46-0.81)	<0.001

A multivariate analysis of the contribution of variables to predict early and late distant recurrence showed proliferation genes provide important additional prognostic information within the first five years, while ER-associated genes are critical to predict late recurrences.[7]

Genes for early and late recurrence[7]

Proliferation and hormone receptor related genes for early and late recurrence

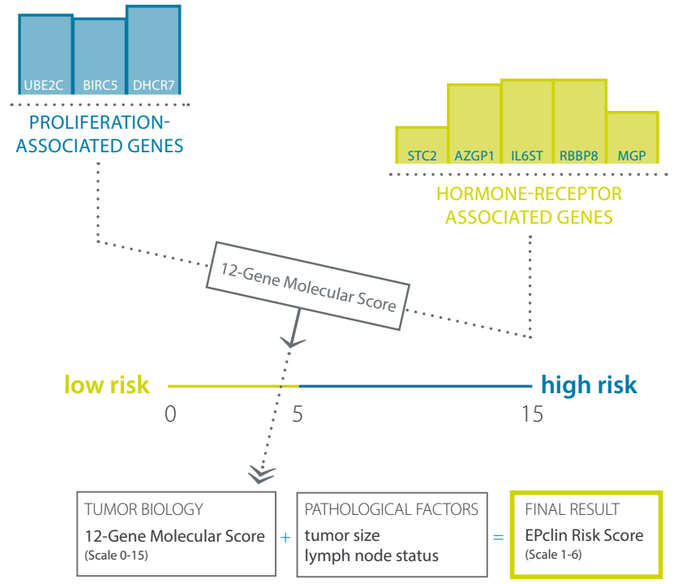
EndoPredict measures the activity of eight genes relevant to the course of disease (BIRC5, UBE2C, DHCR7, RBBP8, IL6ST, AZGP1, MGP, STC2). Inclusion of proliferation- and hormone receptor-related genes contributes to accurate assessment of early and late recurrence risk.[1, 7]

These eight genes are compared against three normalization genes (OAZ1, CALM2, RPL37A) and one control gene (HBB). Based on the activity of the genes, the **12-Gene Molecular Score** is calculated using a mathematical algorithm and reported on a scale of 0 to 15.

Combines Gene Expression and Clinical-Pathological Factors

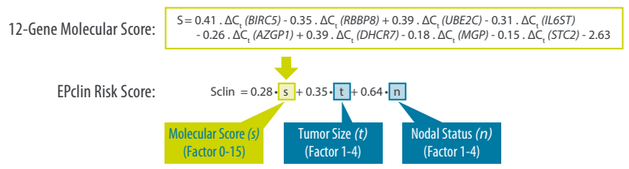
The final EndoPredict result, the **EPclin Risk Score**, is calculated combining the 12-Gene Molecular Score with clinical pathological prognostic factors (tumor size and lymph node status) as assessed by the pathologist. This makes EndoPredict a second generation gene expression test and a more powerful predictor of prognosis.

The EPclin Risk Score is reported on a scale of 1 to 6. The value of 3.32867 is associated with 10% risk of breast cancer recurrence within 10 years. Values below 3.32867 are associated with low risk and values above or equal to 3.32867 with high risk.

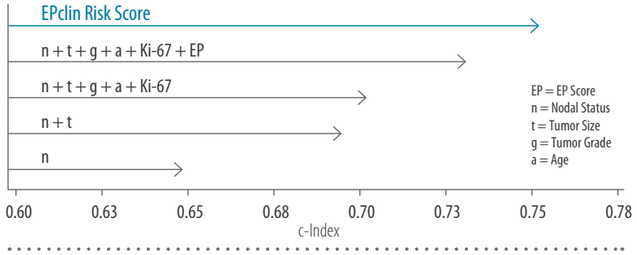


12-Gene Molecular Score and EPclin Risk Score

EndoPredict provides a clear classification into high risk and a low risk



Calculation of the EPclin Risk Score

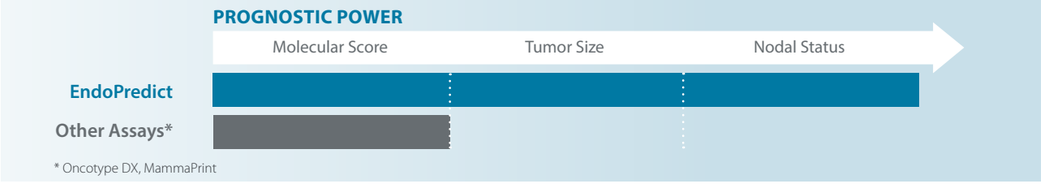


Prognostic power according to the c-index in comparison to prognostic factors

The EPclin Risk Score alone is a more powerful predictor of the prognosis than combinations of all classical prognostic factors.[1]

As a second generation gene expression test, EndoPredict is a more powerful predictor of prognosis than first generation assays. Prognostic power providing results you can trust.[6]

Second generation gene expression test for more prognostic power



Prognostic power of gene expression assays

Clearly Structured Result Report

EndoPredict result report front page (low risk)

An overview of the three individual clinical answers given by EndoPredict is organized by treatment planning stage.

Initial treatment planning

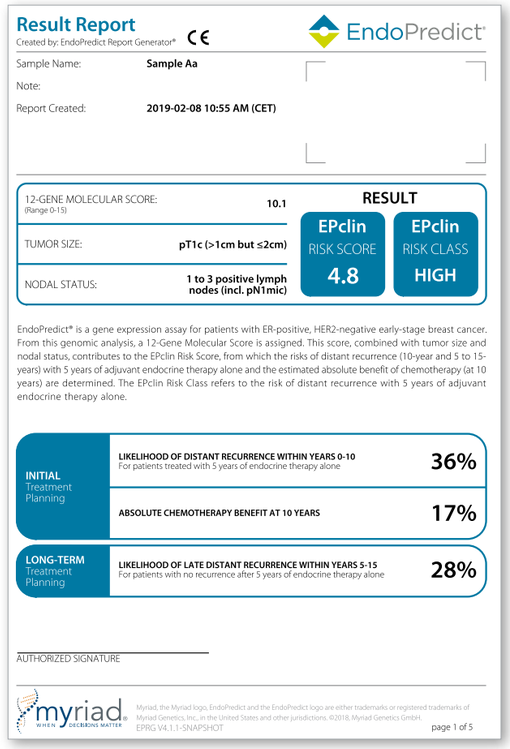
1. Risk at 10 years - Can chemotherapy be avoided?
2. Chemotherapy benefit - What is the absolute benefit from chemotherapy?

Long-term treatment planning

3. Risk between 5 and 15 years - Can the extension of endocrine therapy be avoided?

The EndoPredict Result Report documents the molecular data and the established prognostic factors of tumor size and lymph node status.

Using a mathematical algorithm, the 12-gene molecular score is combined with the clinical data. This results in the patient's individual **EPclin Risk Score** and subsequent classification as "**low risk**" or "**high risk**".



EndoPredict result report front page (high risk)

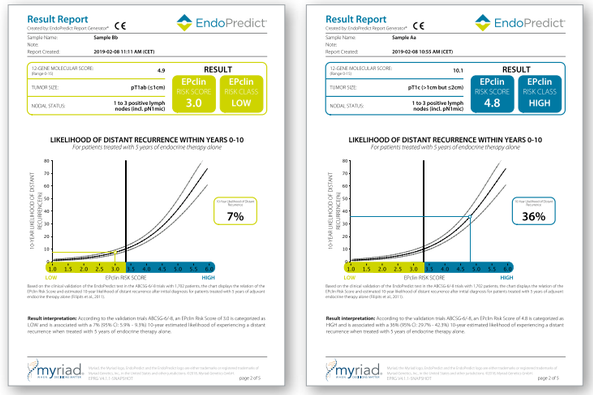
Information is summarized by treatment planning stage

Individual Information on Three Clinical Questions

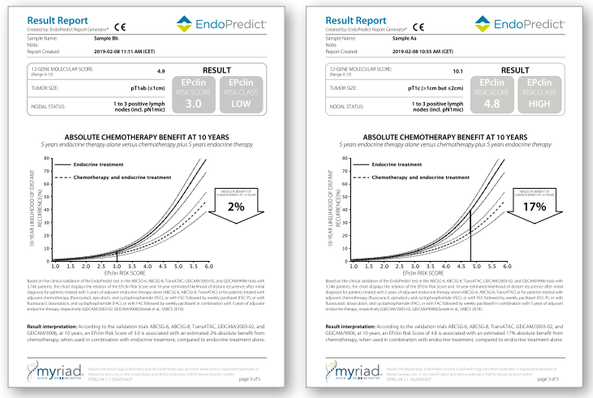
Can chemotherapy be avoided?

Each patient's report will show a graphic curve illustrating her individual risk of recurrence within years 0-10 after diagnosis.

This information helps you to identify your patients with a low risk of recurrence who might safely avoid chemotherapy.



EndoPredict result report second page (low and high risk)



EndoPredict result report third page (low and high risk)

What is the benefit from chemotherapy?

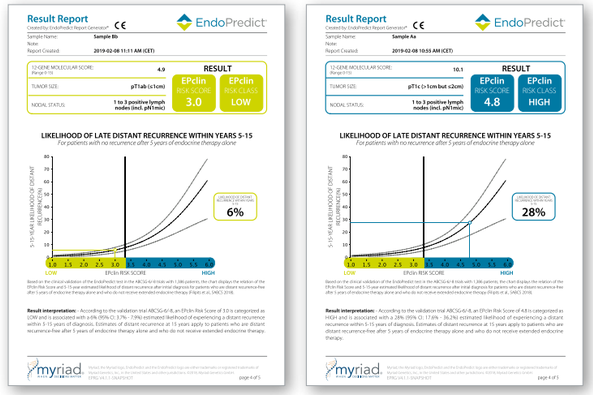
The second graph in the report illustrates the individual absolute chemotherapy benefit based on whether the patient receives endocrine therapy alone or endocrine plus chemotherapy.

This helps to make a confident chemo-therapy treatment decision.

Can the extension of endocrine therapy be avoided?

The third graph on the report illustrates your patient's individual risk of recurrence within years 5-15 after diagnosis.*

This information guides treatment decisions regarding endocrine therapy beyond 5 years.



EndoPredict result report fourth page (low and high risk)

** 5-15 year risk is based on treatment with 5 years of ET only – no chemo. The result assumes the patient has not recurred by 5 years.*

Independently Validated for Robust Prognostic Results

	Trial	# of patients	Breast cancer sub-type	Nodal Status	Treatment	10-year distant metastasis rate in low risk group
Training	Multicenter[1]	964	ER+/HER2-	N0, N+	E	7%
Validation I	ABCSG-6[1]	378	ER+/HER2-	N0, N+	E	4%
Validation II	ABCSG-8[1]	1,324	ER+/HER2-	N0, N+	E	4%
Validation III	GEICAM/9906[8]	555	ER+/HER2-	N+	E + CT	0%
Validation IV	TransATAC[5]	928	ER+/HER2-	N0, N+	E	5.8%

EndoPredict training and validation studies

Patients in training and validation studies

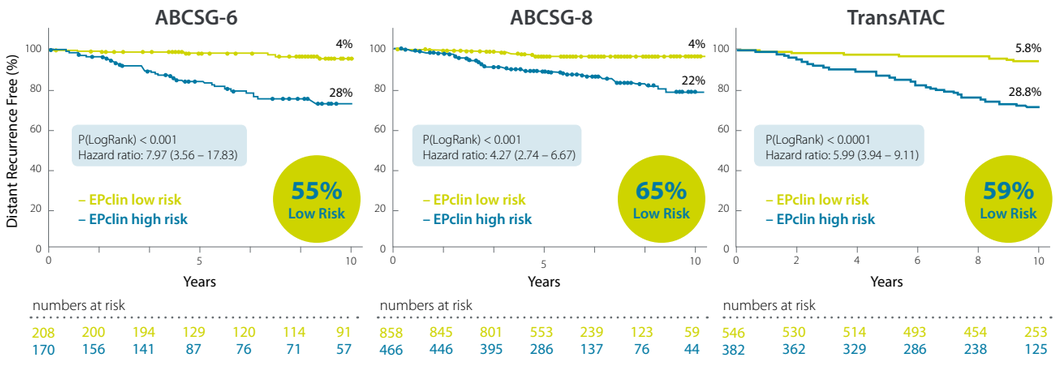
- Breast cancer subtype ER+, HER2-
- Nodal status N0 or N+
- Adjuvant treatment 5 years of endocrine therapy (not extended)

EndoPredict was developed using consistent criteria for patients during training and independent validation studies: ER+, HER2- patients, both node-negative (N0) and node-positive (N+). These "clean" (meaning solely ER+ HER2-) cohorts are one reason for the test's stronger performance compared to tests that included HER2+ patients in their training cohorts. The score and the cutoff value is consistent in all studies and has never changed.

The patients in the ABCSG6, ABCSG8 and TransATAC studies were treated with endocrine therapy alone. The prognostic value of EndoPredict under chemotherapy was demonstrated by the GEICAM/9906 study. All patients received only 5 years of hormone therapy.

Validated in four prospective-retrospective studies [1, 2, 3, 4, 5, 8] providing level 1 evidence

Consistently identifies a large low risk group with a recurrence risk of less than 10%



Analysis of ER+, HER2–, N+ and N0 patients from ABCSG-6, ABCSG-8 and TransATAC [1,5]

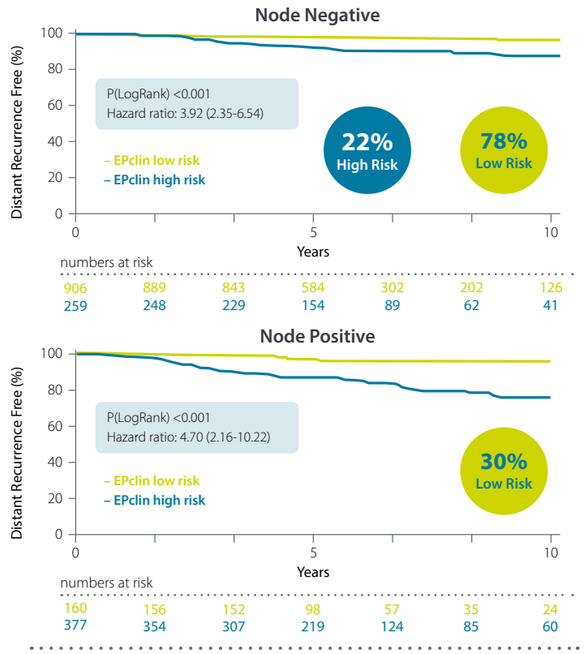
Identifies Clear Risk Groups in Different Subgroups

EndoPredict supplies additional prognostic information to supplement common prognostic factors such as nodal status, tumor grade or Ki67. This has been demonstrated in four validation studies.

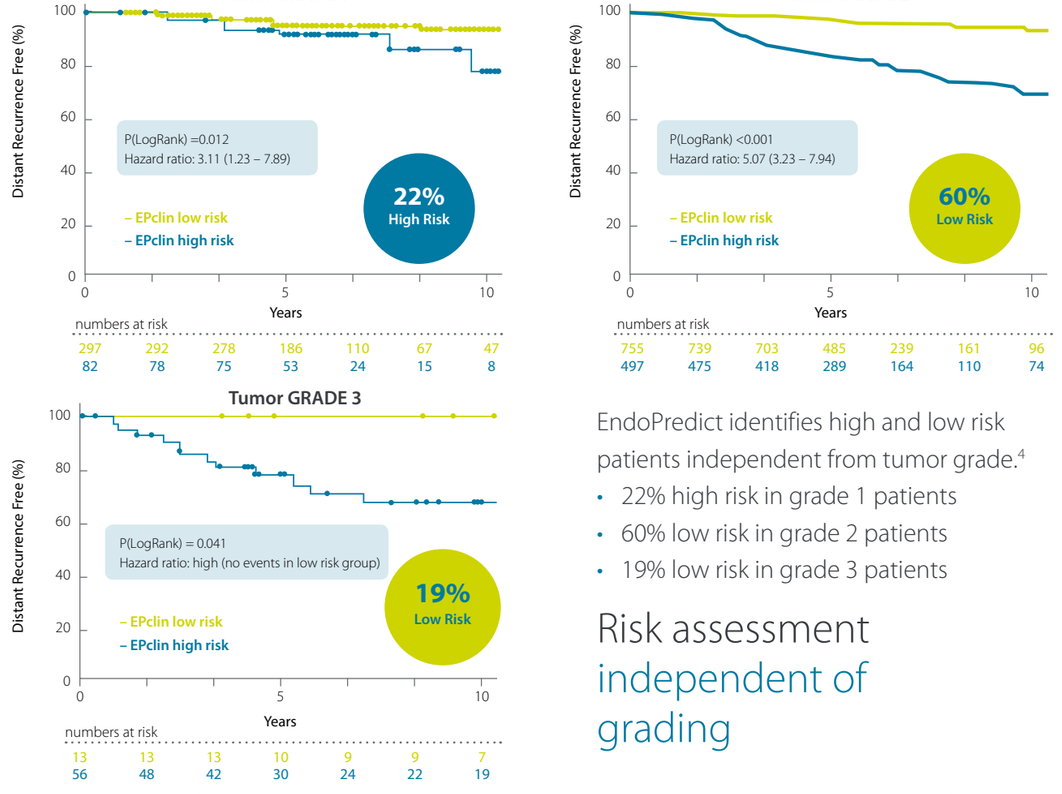
EndoPredict identifies a large percentage of low risk patients (4% to 5.8% recurrence) [1, 3, 5, 6]

- More than 70% of N0 patients
- Up to 30% of N+ patients

Risk assessment independent of nodal status



Analysis of ER+, HER2– patients from both ABCSG-6 and ABCSG-8 [7]



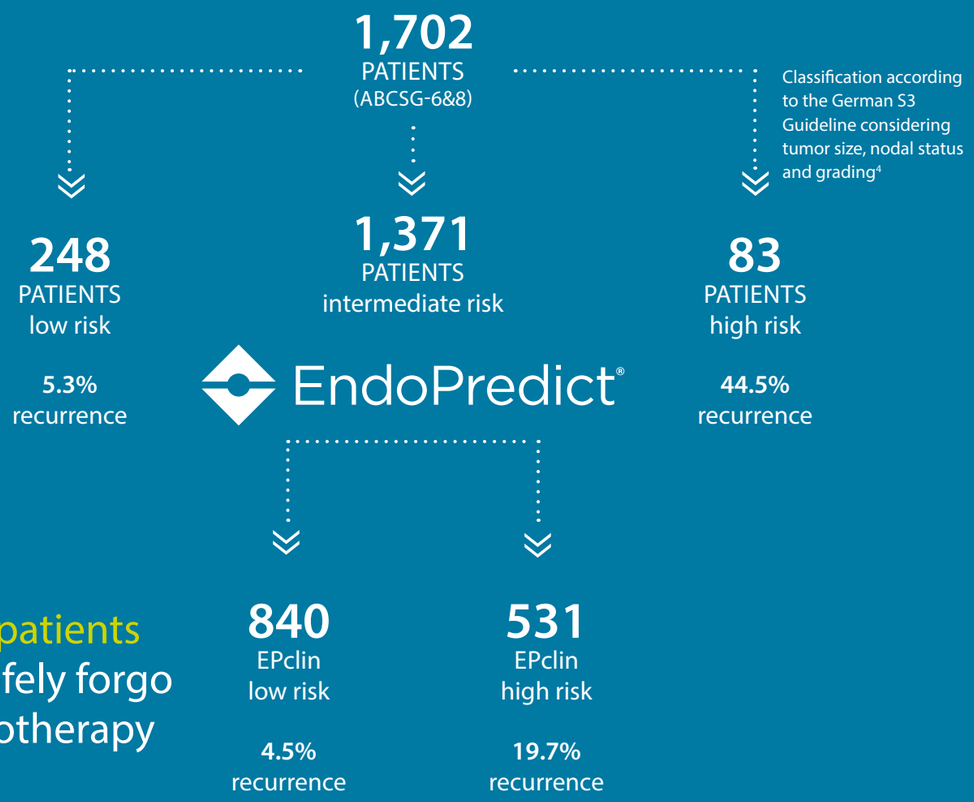
Analysis of ER+, HER2– patients from both ABCSG-6 and ABCSG-8 [4]

EndoPredict identifies high and low risk patients independent from tumor grade.[4]

- 22% high risk in grade 1 patients
- 60% low risk in grade 2 patients
- 19% low risk in grade 3 patients

Risk assessment independent of grading

Divides Uncertain Clinically Intermediate Risk Patients in Low and High Risk



More patients can safely forgo chemotherapy

A patient categorized as intermediate risk from the guidelines has an unclear treatment pathway. With EndoPredict, this intermediate risk group can be divided into a low risk and a high risk group.

The much larger EndoPredict low risk group shows a comparable risk of distant metastasis to the low risk group defined by clinical parameters only. [4]

The clear risk assessment for a period of more than ten years provides greater long-term therapeutic confidence for patients and physicians.

Current guidelines therefore recommend using gene expression analyses in intermediate risk cases (NCCN, ASCO, AGO, ESMO, St. Gallen, EGTM and AJCC).

Proven in Practice

Decision impact studies conducted at different centers documented how EndoPredict results affect the treatment decision in clinical practice.[9, 10, 11, 12, 13]

The treatment plan of each participating patient was discussed before and after release of the EndoPredict result. In the three studies performed in Germany and France in 25.4%, 28.4% and 38% of cases, the treatment decision in favor of chemotherapy was reversed, and the patient was advised to receive endocrine therapy alone. In 12.3%, 7.5% and 5% of cases, chemotherapy was recommended to avoid undertreatment.[9, 10, 11]

Leads to substantial change in chemotherapy decision

Country	Germany	France	Germany	UK	Mexico
Institution	Charité Berlin	Centre Jean Perrin Clermont-Ferrand	Technical University Munich	University of Sussex Brighton	National Institute of Cancerology Monterrey
Publication/ Conference	PlosOne 2013	SABCS 2016	PlosOne 2017	Psycho Oncology 2018	SABCS 2018
Reference	Mueller et al.[9]	Penault-Llorca et al.[10]	Ettl et al.[11]	Fallowfield et al.[12]	Villarreal-Garza al.[13]
# patients	167	201	395	149	91
EPclin low risk	46%	67%	63%	50%	46%
EPclin high risk	54%	33%	37%	50%	54%
N0	62%	91%	77%	67%	72%
N+	38%	9%*	23%	33%	28%
Change of therapy recommendation	**37.7%**	**35.8%**	**43.0%**	**36.9%**	**17.0%**
Net change CT	**-13.1%**	**-20.9%**	**-33.0%**	**+0.7%**	**-10.53%**

Decision Impact Studies with EndoPredict

** N+ patients in the French study were N1mic*

Predicts Absolute and Relative Benefit of Chemotherapy

EndoPredict predicts chemotherapy benefit in women with ER-positive, HER2-negative disease. Chemotherapy benefit was validated in a large study with over 3,700 patients with ER+, HER2- breast cancer.[2] 2,630 patients were treated with 5 years of endocrine therapy alone and 1,116 patients were treated with endocrine plus chemotherapy with current (taxane and/or anthracycline-containing) treatment regimens.

EPclin Risk Score		1	2	3	3.3	4	5	6
10-year risk of distant recurrence	ET alone	1.0% (0.6-1.4)	2.8% (2.1-3.5)	7.6% (6.4-8.8)	10.2% (8.8-11.6)	19.8% (17.6-22.0)	46.1% (40.2-51.4)	82.2% (72.1-88.6)
	ET + C	1.1% (0.5-1.7)	2.5% (1.5-3.5)	5.7% (4.1-7.2)	7.2% (5.4-8.9)	12.4% (10.1-14.6)	25.8% (22.0-29.5)	49.2% (40.5-56.7)
Absolute benefit		-0.1%	0.3%	1.9%	3.0%	7.4%	20.3%	33.0%
Relative benefit		-0.1	0.11	0.25	0.29	0.37	0.44	0.40

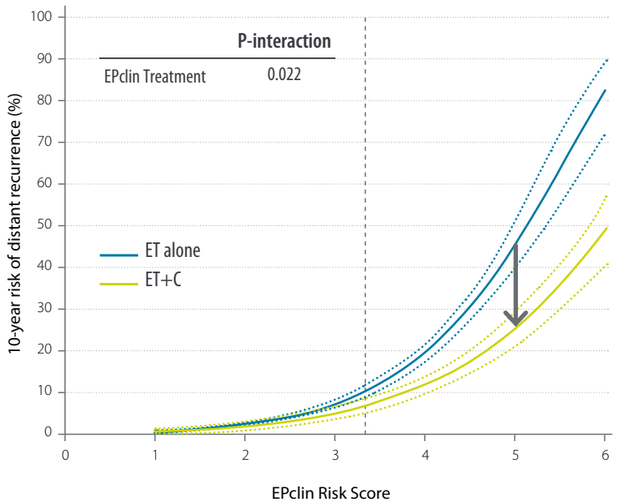
Prediction of absolute and relative chemotherapy benefit

In patients with low EPclin Risk Scores, no differences in 10 year risks was observed between endocrine treatment alone and endocrine treatment plus chemotherapy.

Patients with a low risk EndoPredict result did not benefit from the addition of chemotherapy.

Patients with a high risk EndoPredict result had a stronger benefit from chemotherapy. This benefit was more than proportional.

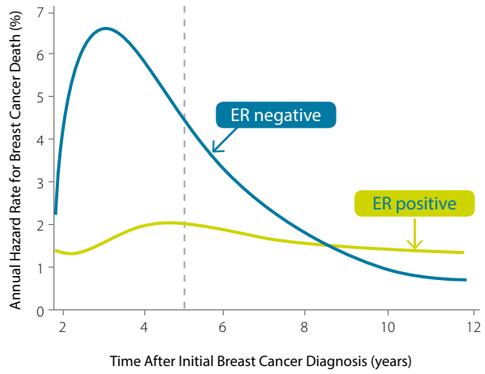
Personalized absolute chemotherapy benefit for confident treatment decisions



10-year risks by EPclin Risk Score for endocrine treatment (ET) vs. endocrine treatment plus chemotherapy (ET+C)[2]

For an EPclin score of 5.0, women receiving ET alone had a 10-year DRFI risk of 46.1% compared to 25.8% for women who received ET+C.

Provides Recurrence Risk up to 15 years



Risk of breast cancer death after initial diagnosis[14]

After 5 years of endocrine therapy, breast cancer recurrences in ER+ tumors continue to occur steadily even after 20 years after diagnosis. Of those patients with ER+ breast cancer who experience recurrent disease, more than 50% occur after 5 years.[14, 15]

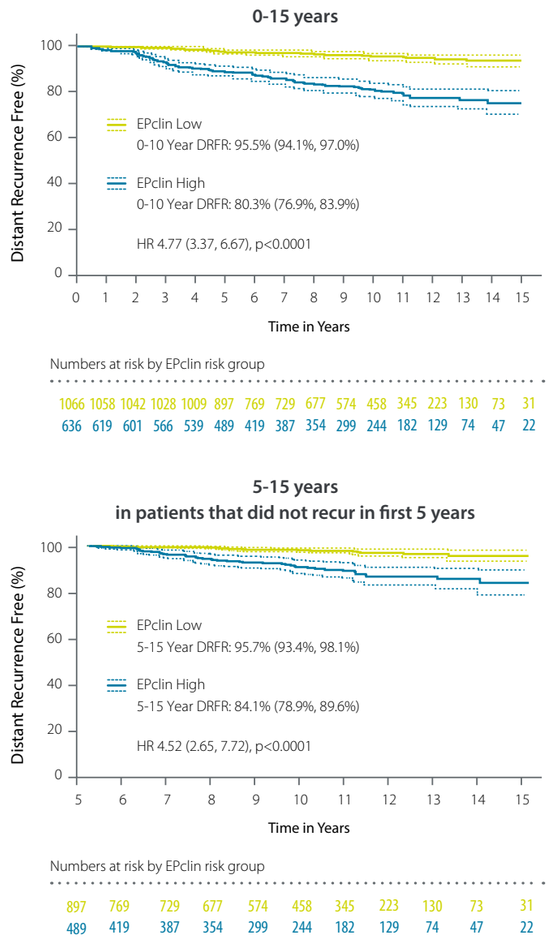
Therefore assessment of risk beyond five years is important to identify the subgroup of patients who may benefit from extended endocrine therapy beyond 5 years.

EndoPredict is the only prognostic test that successfully predicts risk of early (0-10 years) and late (5-15 years) recurrence for patients with node-negative and node-positive disease.[3]

Prediction of recurrence risk (up to 15 years) was validated in 1,702 ER+, HER2- patients. Analyses were performed for the overall cohort, by nodal status, and for 1,386 patients who were distant recurrence-free at year 5 (late recurrence).

EndoPredict low risk patients had a consistent low risk of recurrence in years 0-10 and 5-15. The results for the late distant recurrence period (5-15 years) indicate that EPclin Risk Score is informative for selecting patients who may safely forgo extended endocrine therapy.

Guides treatment decisions regarding extended endocrine therapy



Kaplan-Meier curves of estimated DRFR[3]

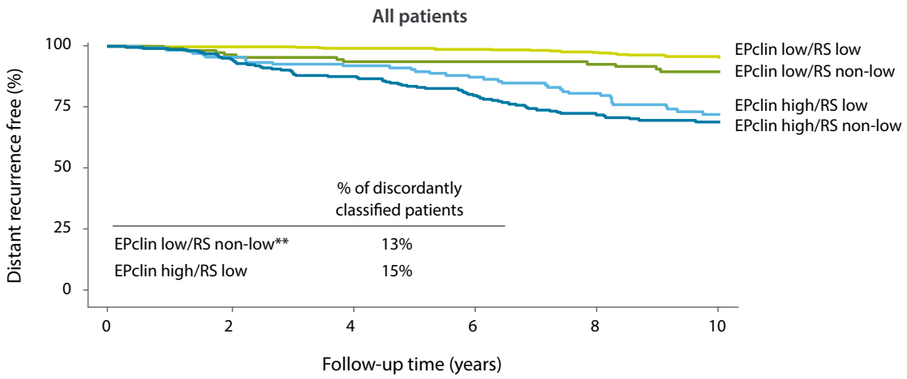
Low Risk Results you can Trust

Decisions on the use of adjuvant chemotherapy in ER+, HER2- primary breast cancer are guided by the risk of distant recurrence.

EndoPredict and Oncotype DX® are prognostic gene expression tests used for estimating distant recurrence risk. EndoPredict provides prognostic information from a molecular signature combined with tumor size and nodal status (EPclin Risk Score). Oncotype DX provides prognostic information from a molecular signature only (Recurrence Score RS).

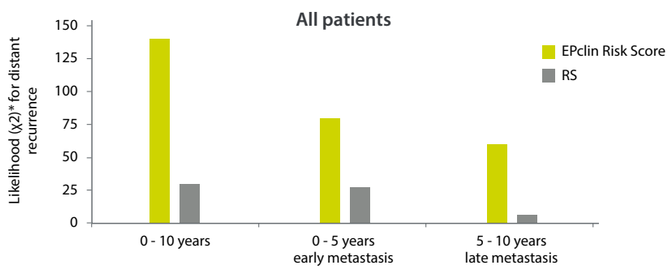
In the TransATAC study the prognostic abilities of EPclin Risk Score and RS were compared directly. A total of 928 patients treated with 5 years endocrine therapy only were included. The primary endpoint was 10 year distant recurrence free survival. [5]

The classification by EndoPredict aligns more closely with the patient outcomes



Distant recurrence free survival of ER+, HER2– patients within different risk groups from TransATAC

EndoPredict demonstrates superior prognostic performance independent from cutoff values



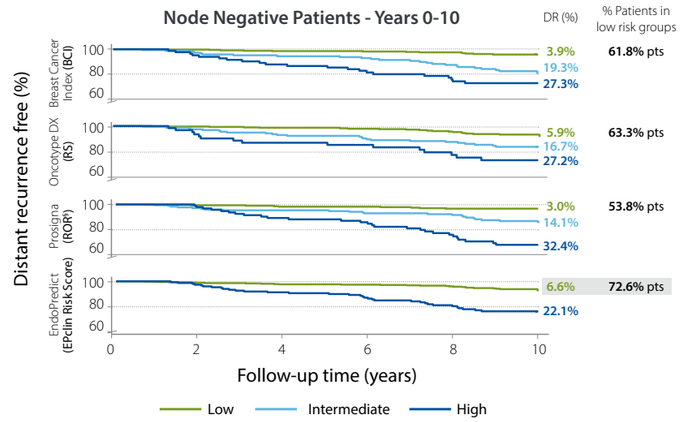
EPclin Risk Score and RS Prognostic Ability

*The χ2-value is a standard statistic for prognostic power that is used to compare prognostic accuracy of different tests. The greater the χ2-value, the better is the prognostic power of a test. The χ2-value reflects the prognostic power of the continuous score independent from cutoff values.

** RS non low = RS intermediate plus RS high.

Outperforms other Signatures

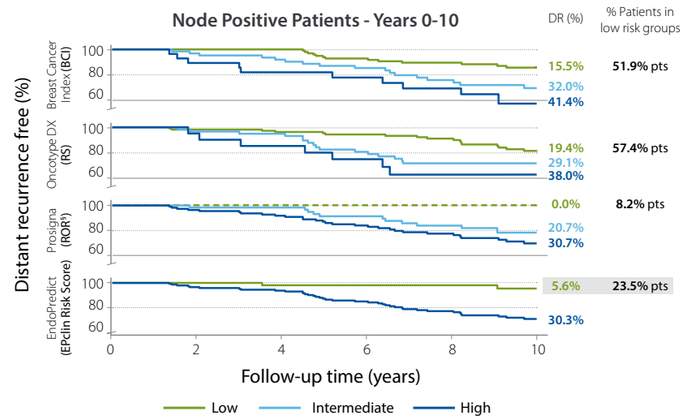
The TransATAC study also compared the performance of four commercially available prognostic signatures for breast cancer distant recurrence (DR) in years 0-10 and in years 5-10. A total of 774 patients treated with 5 years endocrine therapy only were included. [6]



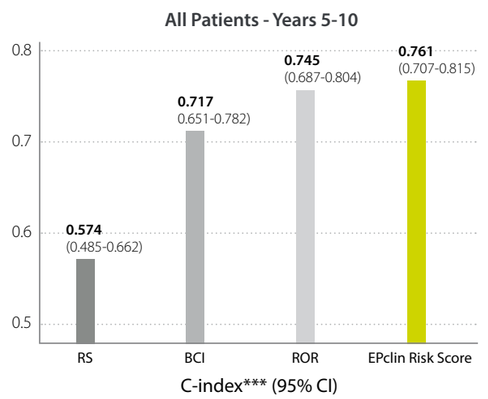
EndoPredict identified most node negative patients as low risk

Accuracy to Identify node negative low risk patients in years 0-10

EndoPredict identified most node positive patients with "true" low risk****



Accuracy to Identify node positive low risk patients in years 0-10



EndoPredict (EPclin Risk Score), Prosigna (ROR), Breast Cancer Index (BCI), Oncotype DX (RS)

EndoPredict was the most prognostic signature in years 0-10 and 5-10 independent from cutoff values

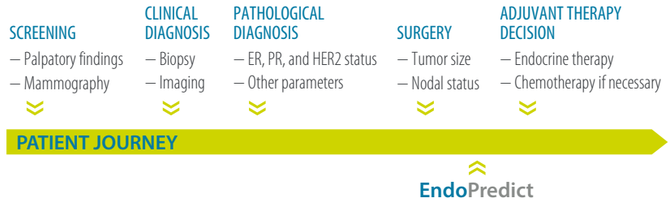
*** *The C-index is a standard statistic for prognostic power that is used to compare prognostic accuracy of different tests. The greater the C-Index, the better is the prognostic power of a test. The C-Index reflects the prognostic power of the continuous score independent from cutoff values.*

**** *Patients with less than 10% risk of recurrence within 10 years.*

Fast and Reliable

EndoPredict is performed on FFPE tumor tissue from biopsy[16] or surgical specimens[17] from patients who have not received systemic endocrine therapy and/or chemotherapy.

Once the sample has been sent to the laboratory, results are usually available within 1 week.



When performed on a surgical sample, the 12-gene molecular score and the **EPclin Risk Score** are provided in the test report.
If **EndoPredict** is performed on a biopsy specimen, information on surgical tumor size and nodal status can be added after surgery to calculate **EPclin Risk Score**, if the patient was not treated with systemic therapy before the surgery.

Use of EndoPredict during clinical course

Results within 1 week for fast therapy decisions

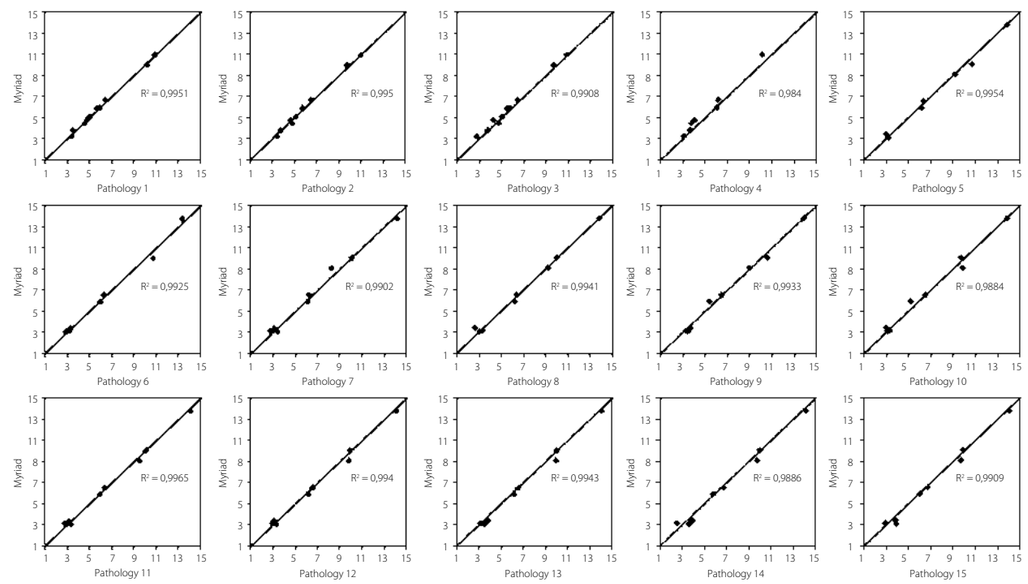
An EndoPredict assay takes less than 8 hours in the normal operation of a molecular pathology laboratory. Only a small section of the tumor block (10 μm) is required. The tumor content of the tissue sample must be at least 30%. The subsequent RNA extraction is followed by reverse transcription (transcription of RNA into the corresponding cDNA sequence) and quantitative PCR. The gene expression values of all the relevant genes are determined, and the 12-Gene Molecular Score is calculated.

Analysis and quality assurance remain in the hands of the local pathologists.

EndoPredict consistently delivers the same quality of results, regardless of the pathological institute conducting the assay, as has been demonstrated in round-robin testing.[17, 18, 19]

Implementing this procedure at a new site requires 2 days of installation and qualification.

This process guarantees the consistent reliability of the EndoPredict result, regardless of the laboratory conducting the assay.



Consistent results and correlations achieved in 15 sites with local implementation

Prospective Data

EndoPredict predicts response to neoadjuvant therapy

The decision regarding neoadjuvant chemotherapy is complex. Data from the prospectively defined ABCSG-34 study, presented at the San Antonio Breast Cancer Symposium,[20] indicate the 12-Gene Molecular Score may support neoadjuvant therapy choices.

The score predicted therapy response to neoadjuvant chemotherapy and neoendocrine therapy. The primary endpoint of the study was residual tumor burden at surgery.

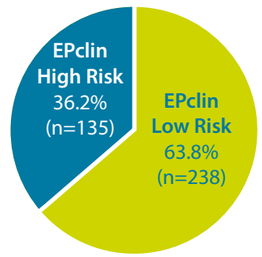
	Low 12-Gene Molecular Score n=9	High 12-Gene Molecular Score n=125	p value
Response to neoadjuvant chemotherapy n=134	0.0%	26.4%	0.0001
	Low 12-Gene Molecular Score n=44	**High 12-Gene Molecular Score n=39**	**p value**
Response to neoendocrine therapy n=83	27.3%	7.7%	0.015

Prediction of neoadjuvant therapy response as defined as RCB0/1

First prospective data on EndoPredict

A prospective evaluation of outcome data for patients whose adjuvant systemic therapy recommendation was based on the EndoPredict test result was recently presented.[21]

373 women with ER+, HER2-, N0-3 breast cancer were enrolled. Patients were evaluated for treatment compliance, local recurrence, distant metastases and survival. Median follow-up was 41.6 months.



Risk Classification by EPclin Risk Score

Patients with EPclin High Risk were at significant higher risk of experiencing distant metastases than patients with EPclin Low Risk. EPclin high risk patients receiving standard adjuvant chemotherapy experienced a 68% reduction in relapse compared to those patients who decided not to undergo the recommended chemotherapy.

Tumor Board recommended 128 patients for adjuvant chemotherapy (CTx). 92 (72%) were compliant and received chemotherapy.

3-year DMFS:		3-year DFS:
EPclin Low 99.6% **EPclin High 97.6%**	HR 5.18, p=0.0443	**EPclin High with CTx 96.3%** **EPclin High no CTx 91.5%**

Prospective data confirmed the data received in prospective-retrospective studies

Two ongoing prospective trials for EndoPredict

	UNIRAD (France, UK, Belgium)	RESCUE (Germany, Switzerland)
Title	Randomized, double-blind, multicenter phase III trial evaluating the safety and benefit of adding everolimus to adjuvant hormone therapy in women with high risk of relapse, ER+ and HER2- primary breast cancer who remain free of disease.	Prospective assessment of the clinical outcome of patients with primary breast cancer who have been tested with the EndoPredict gene expression test – a prospective care research study (RESCUE, Reaching for Evidence-baSed Chemotherapy Use in Endocrine Sensitive Breast Cancer).
Design	Prospective randomized	Prospective, care research study
Rationale	EPclin part: Using EndoPredict to identify high risk patients with 1-3 positive lymph nodes to be included in the trial; evaluation of outcome of EPclin low risk patients.	Systematic assessment of survival data of patients who have been tested with EndoPredict; prospective proof, that patients with low risk classification by EndoPredict (EPclin) can safely forgo chemotherapy.

Ongoing prospective trials for EndoPredict

CE Marked as *in vitro* Diagnostic

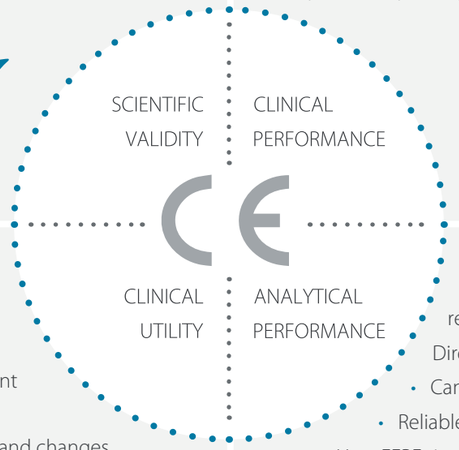
EndoPredict meets the European regulatory requirements for safety, scientific validity, and clinical benefit. It can be used to improve the quality and safety of treatment of breast cancer patients in different disease stages.

- Validated in four clinical studies, including endocrine only and current chemotherapy treatment
- Prospective-retrospective approach
- Level of evidence 1

References:
1, 5, 6, 8

- Identifies a large low risk group with “true” low risk (<10%)
- Is a more powerful predictor than combinations of all classical prognostic factors
- Provides substantially more prognostic information than other gene expression tests
- Predicts early (0-10 years) and late recurrences (5-15 years)
- Predicts chemotherapy benefit
- Prognostic in node positive and negative, pre- and postmenopausal patients

References:
1, 2, 3, 4, 5, 6, 7, 8, 22



- Answers three important clinical questions
- Results available within one week for fast treatment decisions
- Guides clinical treatment and changes therapy decision in 20-40% of patients
- Increases the size of the low risk group with very good prognosis
- Reduces chemotherapy associated costs with improvement of QALYs
- Recommended by international guidelines

References:
1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 13, 23, 24, 25, 26, 27, 28, 29, 30, 31

- Meets the essential requirements of European Directive 98/79/EC (IVDD)
- Can be performed locally
- Reliable decentralized procedure
- Uses FFPE tissue (punch biopsy or surgical specimen)

References:
16, 17, 18, 32, 33, 34

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EndoPredict®

One Test – Three Clinical Answers

Superior Prognostic Performance
Individual Results you can Trust

- Only prognostic test that can answer
  - whether your patient can safely avoid chemotherapy
  - how beneficial chemotherapy would be
  - whether your patient can stop endocrine therapy after 5 years
- Largest "true" low risk group for safe reduction of chemotherapy
  - more than 70% of N0 patients
  - up to 30% of N+ patients
- Second generation gene expression test for superior prognostic power
- Unique gene selection for accurate early and late risk assessment
- Consistent study cohorts and constant cutoff
- Clear result report (high or low risk)
- Fast individual result within 2 days by local testing

NICE recommends EndoPredict

Assessment finds EndoPredict clinically effective and cost-effective

INCLUDED
in international guidelines (ASCO, ESMO, St. Gallen, EGMT, AJCC, AGO, NCCN)

VALIDATED
in four large clinical studies with more than **3,200** patients

USED
to guide treatment selection in more than **30,000** patients worldwide

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