



EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Directorate F - Health, Consumers & Reference Materials (Ispra)
Health in Society

European Commission Initiative on Breast Cancer (ECIBC):

European guidelines on breast cancer screening and diagnosis

Evidence profile

Healthcare question	Should 70 gene signature test vs. no testing be used for patients who have hormone receptor positive, HER-2 negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer to guide the use of chemotherapy (<u>subgroup: high clinical risk</u>)?
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Abbreviations	CI: Confidence interval HR: Hazard ratio

TABLE 1/2: Knauer 2010 – high clinical risk; low and high genomic risk

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy plus chemotherapy	Endocrine therapy	Relative (95% CI)	Absolute (95% CI)		
Distant free survival - low genomic risk group												
1 ¹	observational studies ^a	serious _{b,c,d}	not serious	serious ^e	serious ^f	none	1/78 (1.3%)	12/174 (6.9%)	HR 0.26 (0.03 to 2.02)	51 fewer per 1,000 (from 67 fewer to 65 more)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy plus chemotherapy	Endocrine therapy	Relative (95% CI)	Absolute (95% CI)		
Distant free survival - high genomic risk group												
1 ¹	observational studies ^a	serious ^{b,c,d}	not serious	serious ^e	not serious ^f	none	18/148 (12.2%)	34/141 (24.1%)	HR 0.35 (0.17 to 0.71)	149 fewer per 1,000 (from 195 fewer to 63 fewer)	⊕○○○ VERY LOW	CRITICAL
Breast cancer specific survival - low genomic risk group ^b												
1 ¹	observational studies ^a	serious ^{b,c,d}	not serious	not serious ^e	serious ^f	none	1/78 (1.3%)	5/174 (2.9%)	HR 0.58 (0.07 to 4.98)	12 fewer per 1,000 (from 27 fewer to 106 more)	⊕○○○ VERY LOW	CRITICAL
Breast cancer specific survival - high genomic risk group												
1 ¹	observational studies ^a	serious ^{b,c,d}	not serious	serious ^e	not serious ^f	none	9/148 (6.1%)	27/141 (19.1%)	HR 0.21 (0.07 to 0.59)	148 fewer per 1,000 (from 177 fewer to 74 fewer)	⊕○○○ VERY LOW	CRITICAL

Explanations

- Individual patient-pooled analysis from previously reported studies.
- Follow-up was censored at 5 years. The follow-up time might be short to assess of the outcomes of interest, other studies have shown a high risk of disease recurrence after the 5 years of treatment.
- Data included in the patient data pooled analysis were previously used in validation studies. The test was trained to identify the prognosis of these patients, which might lead to overfitting in the subsequent analysis.
- Results were not provided by strata of negative and positive lymph nodes (up to 3), instead as adjusted estimations. Adjustment might be inappropriate if there is interaction between outcome and number of lymph node positive, which were not assessed in the analysis.
- The study enrolled patients that were treated more than ten years ago, the chemotherapy regime is very different now which preclude the applicability of the results. The study design used did not provide the relevant clinical information of interest (i.e. number of chemotherapies avoided, direct comparison between use or not of the test) thus extrapolation of those events from the study's results is required.
- There were a low number of events in each genomic risk group. The effect size estimates were imprecise which also led to a low power to test interaction.

References

1. Knauer M, Mook S, Rutgers EJ, Bender RA, Hauptmann M, van de Vijver MJ, Koornstra RH, Bueno-de-Mesquita JM, Linn SC, van 't Veer LJ. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. *Breast Cancer Res Treat*; 2010.

TABLE 2/2: Cardoso 2016 – high clinical risk; low genomic risk

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy plus chemotherapy	Endocrine therapy	Relative (95% CI)	Absolute (95% CI)		
Survival without distant metastasis												
1 ^{1,a}	randomised trials ^b	serious _{c,d,e}	not serious	not serious ^f	serious ^g	none	22/592 (3.7%)	37/636 (5.8%)	HR 0.65 (0.38 to 1.10)	20 fewer per 1,000 (from 36 fewer to 6 more)	⊕⊕○○ LOW	CRITICAL
Disease-free survival												
1 ^{1,a}	randomised trials ^b	serious _{c,d,e}	not serious	not serious ^f	serious ^g	none	39/592 (6.6%)	66/636 (10.4%)	HR 0.64 (0.43 to 0.95)	36 fewer per 1,000 (from 58 fewer to 5 fewer)	⊕⊕○○ LOW	CRITICAL
Overall survival												
1 ^{1,a}	randomised trials ^b	serious _{c,d,e}	not serious	not serious ^f	serious ^g	none	10/592 (1.7%)	18/636 (2.8%)	HR 0.63 (0.29 to 1.37)	10 fewer per 1,000 (from 20 fewer to 10 more)	⊕⊕○○ LOW	CRITICAL

Explanations

- The trial aims to assess non-inferiority results for the test. We report here the per-protocol analysis, which is a more conservative approach in this context.
- The population was defined as High clinical Risk by the Adjuvant Online!: -Lymph node negative: 52%; HR positive: 98%; HER2 negative: 92%; Size >2cm: 58%

- c. Results were reported at 5 years. This follow-up time might be insufficient for the measured outcomes. This treatment effect may become more pronounced over the next five years because more events will occur (i.e. In ER-positive/HER2-negative (luminal-type) breast cancer, evidence shows that recurrences occur after five years in approximately one half of all distant recurrence cases -Sparano JA, Breast Cancer. J Clin Oncol. 2015;33(21):2353-60).
- d. There was imbalance between groups in the proportions of violations to the protocol. Additionally, a group of patients were incorrectly classified by test, and the sample had to be increased to handle the small number of patients recruited.
- e. The MINDACT trial does not have a formal non-inferiority design (would need to have a very large sample size or present a very long follow-up). Instead, propose does that if fewer patients are treated with chemotherapy while not adversely affecting survival without distant metastasis, it can be taken to be equivalent.
- f. The study design used did not provide the relevant clinical information of interest (i.e. number of chemotherapies avoided, direct comparison between use or not use of the test across genomic risk groups) thus extrapolation of those events from the study 's results is required.
- g. There were a low number of events in each genomic risk group. The effect size estimates were imprecise.

References

1. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. 2016.

DEFINITIONS OF OUTCOMES (ACCORDING TO THE STUDIES)		
Knauer 2010	Distant disease-free survival	Time from surgery to any distant metastasis
	Breast cancer specific survival	Time from surgery to breast cancer-related death and distant disease-free survival
Cardoso 2016	Free distant metastases survival (survival without distant metastases)	Time until the first distant metastatic recurrence or death from any cause.
	Distant-free survival	Time until first disease progression (locoregional, distant relapse, ipsilateral or contralateral invasive breast cancer, ductal carcinoma in situ, or an invasive second primary cancer) or death from any cause
	Overall survival	Time until death from any cause