



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

QUESTION	
Should 21 gene recurrence score vs. no testing be used for patients who have hormone receptor positive, HER2-negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer to guide the use of chemotherapy (subgroup: lymph node negative)?	
POPULATION:	patients who have hormone receptor positive, HER-2 negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer.
INTERVENTION:	21 gene recurrence score
COMPARISON:	no testing
MAIN OUTCOMES:	Freedom from distant recurrence - low genomic risk; Freedom from distant recurrence - intermediate genomic risk; Freedom from distant recurrence - high genomic risk ;
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	<p>Hormone receptor positive, HER2- negative invasive breast cancer represents about 70% of breast cancer diagnosed in western countries (3). About 60% of these have not spread in lymph nodes at time of diagnosis (3).</p> <p>Approximately 15% of these women diagnosed with a hormone receptor positive, HER2-negative, lymph node negative invasive breast cancer will develop recurrence within 10 years with adjuvant endocrine therapy alone. The risk of recurrence could be reduced by the addition of chemotherapy in 30% of these patients, which translates into an absolute benefit in the rate of freedom from recurrence of up to 5 percentage points (4)(5).</p> <p>Therefore, most of the women would be overtreated if all would receive chemotherapy. It is assumed that this is also true for patients with hormone receptor positive, HER2-negative invasive breast cancer with 1-3 positive lymph nodes (6).</p> <p>Prognostic factors that have been used to predict the risk recurrence in these women include clinicopathologic features such as age, tumour size, grade, percentage of ER and PR positive cells as well as Ki67 index (7)(8). Although these factors have been shown to discriminate different prognostic groups, they are limited in their ability to predict who might benefit from chemotherapy and who will not. The meta-analysis of Peto et al.(9) suggested, that the relative benefit of chemotherapy is only minimally affected by these conventional clinicopathological parameters. In consequence, adjuvant polychemotherapy was recommended to many patients with ER-/PR-positive, HER2-negative early breast cancer in the past.</p> <p>In the last 15 years different multigene tests have been developed to stratify patients with early breast cancer in different risk groups by analysing the activity of various genes. Although these tests analyse different genes and use various techniques (RT-</p>

	<p>PCR, microarray, etc), they have in common, that they mainly focus on genes involved in cell proliferation. The tests provide an individual risk profile of a breast cancer patient, whereby some of them combine the molecular result with clinicopathological features like tumour size and nodal status to improve the prediction of recurrence risk.</p> <p>The goal to use these tests has changed over time. Initially, studies aimed to identify patients with “favourable” clinical-pathological characteristics who might benefit from the addition of chemotherapy (10)(11). Over time, interest has also grown to identify those patients who gain little or none from chemotherapy and who may safely avoid toxicities (6)(1, 2), not least because the introduction of mammography screening has increased the proportion of prognostically favourable breast carcinomas in many countries.</p> <p>However, the tests vary not only in the used techniques, the analysed genes, and the number of risk groups (low/high vs. low/intermediate/high), they also differ in the type and scope of the studies analysing their impact. Only two tests have been analysed in prospective trials so far.</p> <p>The interpretation of the published study results and assessment of the clinical utility of these tests is internationally inconsistent, leading to differences in guideline recommendations and refundability.</p> <p>Originally, we aimed to assess the benefit of 4 standardised multigene tests available in Europe (12-gene molecular test, 70 gene signature, 21-gene recurrence score and PAM50 risk of recurrence score) to support the decision for or against adjuvant chemotherapy compared to endocrine therapy alone based on a multigene test decision strategy in patients who have hormone receptor positive, HER2-negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer. However, as priority was given to prospective data or randomised controlled trials, only two tests were analysed (21 gene recurrence score, and 70 gene signature).</p>
CONFLICT OF INTEREST:	<p><u>Management of Conflicts of Interest (Col):</u> Cols for all Guidelines Development Group (GDG) members were assessed and managed by the European Commission Joint Research Centre (JRC) following an established procedure in line with the institutional rules. GDG member participation in the development of the recommendations was restricted, according to Col disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Edoardo Colzani, Susan Knox, Elsa Pérez. Miranda Langendam, as external expert, was also not allowed to vote, according to the ECIBC rules of procedure.</p>

ASSESSMENT

Problem

Is the problem a priority?




JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>21 gene Recurrence Score</p> <ul style="list-style-type: none"> ○ Designed to quantify the 10-year risk of distant recurrence and predict the likelihood of chemotherapy benefit in pre- and postmenopausal women with ER-positive, HER2-negative stage I and II breast cancer with 0-3 positive LNs. It also reports the ER, PR and HER2 status. ○ Measures the expression of 21 genes: 16 cancer related genes correlated with distant recurrence-free survival, 5 reference genes (normalisation) ○ Requires RNA extracted from formalin-fixed, paraffin-embedded tumor tissue (FFPE) ○ Samples are processed centrally at one accredited lab of the company in the US. ○ Uses reverse transcription-quantitative polymerase chain reaction (RT-qPCR) ○ Results are given as a recurrence score of between 0 and 100, used to quantify the 10 year risk of distant recurrence, assuming 5 years of endocrine treatment. Low risk: score below 18; intermediate risk: score between 18 and 30; high risk: score of 31 or more. The score is also assumed to predict the benefit of chemotherapy: Score<18: little or no benefit; Score 18 – 30: no substantial benefit; Score >=31: large benefit <p>References: (12)(1, 2)</p>	<p>The GDG prioritised this question for the ECIBC.</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																
<div><div>○ Trivial</div><div>○ Small</div><div>○ Moderate</div><div>● Large</div><div>○ Varies</div><div>○ Don't know</div></div>	<div>Paik (lymph node negative)</div> <table><tr><th rowspan="3">Outcomes</th><th rowspan="3">№ of participants (studies) Follow up</th><th rowspan="3">Certainty of the evidence (GRADE)</th><th rowspan="3">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th>Risk with endocrine therapy</th><th>Risk difference with endocrine therapy plus chemotherapy</th></tr><tr><td colspan="2">Study population</td></tr><tr><td>Freedom from distant recurrence - low genomic risk^a</td><td>488 (1 RCT)¹</td><td>⊕○○○ VERY LOW^{b,c,d,e}</td><td>HR 1.31 (0.46 to 3.78)</td><td>31 per 1,000</td><td>9 more per 1,000</td></tr></table>	Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Risk with endocrine therapy	Risk difference with endocrine therapy plus chemotherapy	Study population		Freedom from distant recurrence - low genomic risk ^a	488 (1 RCT) ¹	⊕○○○ VERY LOW ^{b,c,d,e}	HR 1.31 (0.46 to 3.78)	31 per 1,000	9 more per 1,000	<div>Sparano 2018 (TAILORx)</div> <div>*Women with an intermediate recurrence score of 11 to 25 (ER+, HER2-, node negative).</div> <div>* 6711 women were randomised to endocrine or chemoendocrine therapy.</div> <div>*endocrine therapy was non inferior to chemoendocrine therapy in the analysis of invasive disease– free survival, HR 1.08;</div> <div>95% CI, 0.94 to 1.24.</div> <div>*There were no significant interactions between</div>
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					(17 fewer to 82 more)	chemotherapy treatment and recurrence score category (either 11 to 15 vs. 16 to 20 vs. 21 to 25, or 11 to 17 vs. 18 to 25). The panel decided to not include patients with 1 to 3 lymph nodes positive in the recommendation because the only identified study that provided results for this type of patients had critical issues such as: analysis were not specific for the subgroup of 1 to 3 lymph nodes (instead it was adjusted by any number lymph node positive), 12% of patients were HER2-positive, and the design was a post-hoc interaction analysis which did not provide direct clinically relevant comparisons ((10)). As agreement was not reached, voting was conducted among the 19 GDG members without conflict of interest: 4 voted for "moderate" desirable effects, 14 voted for "large" desirable effects and 1 member abstained.													
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<div><div><div>1. Paik, . Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor-Positive Breast Cancer. J Clin Oncol; 2006.</div><div><div>a. Contralateral disease, other second primary cancers, and deaths before distant recurrence were considered censoring events.</div><div>b. The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes 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.</div><div>c. There were a low number of events in each genomic risk group. The effect size estimates were imprecise which led to a low power to test interaction.</div><div>d. The original trial (B-20) did not provide information about the HER-2 status among the included patients. Given that the positivity of HER-2 is a strong predictive marker and is included in the 21-gene recurrence test, it can bias the results</div><div>e. Part of the sample was previously used to validate (although a previous version) the gene markers test which might lead to over fitting in subsequent analysis.</div></div><div>Albain (1 to 3 lymph node positive)</div><table><tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th>Risk with endocrine therapy</th><th>Risk difference with endocrine therapy plus chemotherapy</th></tr><tr><td>Disease free survival - stratified</td><td>0 (1 RCT)¹</td><td>⊕○○○</td><td>-</td><td colspan="2">The trend of recurrence over time as reported graphically showed a difference by the genomic</td></tr></table></div></div>						Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Risk with endocrine therapy	Risk difference with endocrine therapy plus chemotherapy	Disease free survival - stratified	0 (1 RCT) ¹	⊕○○○	-	The trend of recurrence over time as reported graphically showed a difference by the genomic	
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by genomic risk groups ^a		VERY LOW ^{b,c,d,e}		risk groups although there was overlapping in the confidence intervals of the trend lines. ^f	
Overall survival - low genomic risk group	146 (1 RCT) ¹	 VERY LOW ^{b,c,d,e,g}	HR 1.18 (0.55 to 2.54)	Low	
				240 per 1,000	37 more per 1,000 (100 fewer to 262 more)
Overall survival - intermediate genomic risk group	103 (1 RCT) ¹	 VERY LOW ^{b,c,d,e,g}	HR 0.84 (0.40 to 1.78)	Moderate	
				350 per 1,000	46 fewer per 1,000 (192 fewer to 185 more)
Overall survival - high genomic risk group	118 (1 RCT) ¹	 VERY LOW ^{b,c,d,e,g}	HR 0.56 (0.31 to 1.02)	High	
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<div>1. Albain KS, Barlow WE,Shak S,Hortobagyi GN,Livingston RB,Yeh IT,Ravdin P,Bugarini R,Baehner FL,Davidson NE,Sledge GW,Winer EP,Hudis C,Ingle JN,Perez EA,Pritchard KI,Shepherd L,Gralow JR,Yoshizawa C,Allred DC,Osborne CK,Hayes DF, America., Breast,Cancer,Intergroup,of,North. Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in a Randomized Trial of Chemotherapy for Postmenopausal, Node-Positive, Estrogen Receptor-Positive Breast Cancer. Lancet Oncol; 2010.</div> <div>a. Time elapsed from the enrolment to the first breast cancer relapse (local or distant), new primary breast cancer, or death due to any cause.</div> <div>b. The post-hoc analysis compared the sequential use of chemotherapy (CAF-T) versus tamoxifen; the arm of concomitant chemotherapy plus tamoxifen was not included in this sub-study due to less effectiveness in the parent trial.</div> <div>c. A 12% of the included subjects in the analysis were HER2-positive based on the 21-gene assay.</div> <div>d. The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes 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.</div> <div>e. There were a low number of events in each genomic risk group. The effect size estimates were imprecise.</div> <div>f. Interaction of test of linear RS, adjusting for number of positive nodes . Over the entire time period, the significance of the RS-treatment interaction is p=0.053 for DFS. However, the effect of the RS on treatment is not constant over time.</div>					

- g. Results were not provided by strata of the number of positive lymph nodes (ie.1 to 3 vs 4 or more), instead as adjusted estimations by number of nodes. Adjustment might be inappropriate if there is interaction between the outcome and the number positive lymph node, which were not assessed in the analysis.

Sparano (lymph node negative –intermediate risk only)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with endocrine therapy plus chemotherapy	Risk difference with endocrine therapy
Invasive disease-free survival	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 1.14 (0.99 to 1.31)	Study population	
				153 per 1,000	19 more per 1,000 (1 fewer to 43 more)
Freedom from recurrence at a distant site	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 1.03 (0.80 to 1.33)	Study population	
				71 per 1,000	2 more per 1,000 (14 fewer to 22 more)
Freedom from recurrence at a distant or local-regional site	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 1.12 (0.91 to 1.38)	Study population	
				50 per 1,000	6 more per 1,000 (4 fewer to 18 more)
Overall survival	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 0.97 (0.78 to 1.21)	Study population	
				62 per 1,000	2 fewer per 1,000 (13 fewer to 12 more)

	<ol style="list-style-type: none"> 1. Sparano JA, Gray RJ Makower DF Pritchard KI Albain KS Hayes DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer.. N Engl J Med.; 2018. a. A different threshold was used for interpreting the test`s results. Thus, the intermediate range was defined as those with a score from 11 to 25, which is not consistent with previous studies assessing the same test.. b. Clinical risk was defined as in the MINDACT trial (i.e., with low risk defined as low histologic grade and tumour size ≤ 3 cm, intermediate histologic grade and tumour size ≤ 2 cm, or high histologic grade and tumour size ≤ 1 cm; and with high risk defined as all other cases with known values for grade and tumour size). Among the randomised patients, 75% were of low clinical risk, and 25% were of high clinical risk. c. The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes 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 use the test across genomic risk groups) thus extrapolation of those events from the study`s results is required. d. The confidence interval of the effect sizes wereas wide, indicating a potential harmful effect for endocrine therapy alone for the upper limit. However, in absolute terms the difference was less evident. e. There was an important imbalance in the proportions of patients that broke the protocol (not received the intended intervention), which was larger in the chemotherapy plus endocrine therapy group f. The study did not use an appropriate non-inferiority design. Instead they tested difference between arms based in a 32% increase or risk. Additionally, the high rate of non-adherence lead to an increase of the sample size non-initially planned. <p>The PRU members developed a "back of the envelope" model to estimate the downstream consequences of testing patients with the 21-gene recurrence score versus using clinical risk scores (treating only those at high risk). Four different scenarios were hypothesised.</p> <p>The general model assumptions were:</p> <ol style="list-style-type: none"> 1) Results are based on a fixed observation time of 10 years. 2) Distribution according to multigene test is low 14%; intermediate 68%; high 18%, as reported by the authors of the TAILORx trial at recruitment in 2008 before the protocol was modified in order to increase the intermediate risk group recruitment. 3) The observed rate of events at 5 years in the MINDACT trial (Cardoso 2016) will remain constant at 10 years. 4) Rates of events observed in the RCTs were applied to the simulated clinical score arms. It was assumed that basal risk of events for clinical score groups was homogenous between the low and the high clinical risk groups within a given genomic risk group. <p>An approximately 40% reduction in the women receiving chemotherapy was considered as a desirable effect.</p>	
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Scenario 1:

In this scenario, the GDG made the extreme assumption that almost all women would be treated with chemotherapy if the multigene test would not be used (only 18,4% proportion of women would not be treated, i.e. the proportion of non-treated women among those assigned to the treatment arm in the Sparano trial).

	Chemotherapy for all	Multigene risk strategy	difference
Number of women	1000	1000	
Chemotherapies	816,0	180,0	-636,0
Invasive disease recurrence	77,6	79,7	2,0
Distant metastasis recurrence	25,8	27,2	1,4
Local or distant disease recurrence	38,3	39,0	0,7
Deaths	23,1	23,8	0,7

Scenario 2

In this scenario, the GDG made the assumption that, without multigene testing, women would be treated only if the clinical risk is high. The model also assumes that women with low clinical and high genomic risk have no advantage from chemotherapy.

Distribution of the clinical risk within the multigene risk strata are those reported by Sparano et al 2018.

	Chemotherapy only for high clinical risk	Multigene risk strategy	difference
Number of women	1000	1000	
Chemotherapies	313,6	180,0	-133,6
Invasive disease recurrence	79,1	79,7	0,5
Distant metastasis recurrence	26,8	27,2	0,4
Local or distant disease recurrence	38,8	39,0	0,2
Deaths	23,6	23,8	0,2

Scenario 3

In this scenario, the same as in scenario 2, the GDG made the assumption that, without multigene testing, women would be treated only if the clinical risk is high. The model assumes that women with low clinical and high genomic risk have the same advantage from receiving chemotherapy as that observed in the MINDACT trial (Cardoso et al 2016) at five years and that the difference is maintained at 10 years.

	Chemotherapy only for high clinical risk	Multigene risk strategy	difference
Number of women	1000	1000	
Chemotherapies	313,6	180,0	-133,6
Invasive disease recurrence	76,9	74,5	-2,4
Distant metastasis recurrence	26,1	24,8	-1,3
Local or distant disease recurrence	not estimated	not estimated	
Deaths	22,7	22,1	-0,7

Scenario 4

In this scenario, similarly to scenario 2 and 3, the GDG made the assumption that, without multigene testing, women would be treated only if the clinical risk is high. The model assumes that women with high genomic risk have all the advantages from chemotherapy, as observed in Paik 2006, independently from their clinical risk.

		Chemotherapy for all	Multigene risk strategy	difference
Number of women		1000	1000	
Chemotherapies		313,6	180,0	-133,6
Invasive disease recurrence		not estimated	not estimated	
Distant metastasis recurrence		57,5	36,2	-21,3
Local or distant disease recurrence		not estimated	not estimated	
Deaths		not estimated	not estimated	

Scenario 5

In this scenario, the GDG assumed that only women with high clinical risk would be tested with a multigene test. Women with low clinical risk would not receive chemotherapy in any case (thus there is no difference in outcomes in this subgroup between the two strategies). Women at high clinical risk, in the multigene risk strategy would receive chemotherapy only if they have high genomic risk, while in the clinical risk strategy all women with high clinical risk will receive chemotherapy.

		Only women with high clinical risk candidate for chemotherapy	
	Chemotherapy for all high clinical risk	Multigene risk strategy	difference
Number of women	314	314	
Chemotherapies	314,0	103,0	-211,0
Invasive disease recurrence	79,1	79,7	0,5
Distant metastasis recurrence	26,8	27,2	0,4
Local or distant disease recurrence	38,8	39,0	0,2
Deaths	23,6	23,8	0,2

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																										
<div><div>○ Large</div><div>○ Moderate</div><div>○ Small</div><div>● Trivial</div><div>○ Varies</div><div>○ Don't know</div></div>	<div>Paik (lymph node negative)</div> <table><tr><th>Outcomes</th><th>Nº of participants (studies) Follow up</th><th>Certainty of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th></th><th></th><th></th><th></th><th>Risk with endocrine therapy</th><th>Risk difference with endocrine therapy plus chemotherapy</th></tr><tr><td>Freedom from distant recurrence - low genomic risk^a</td><td>488 (1 RCT)¹</td><td>⊕○○○ VERY LOW^{b,c,d,e}</td><td>HR 1.31 (0.46 to 3.78)</td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>31 per 1,000</td><td>9 more per 1,000 (17 fewer to 82 more)</td></tr><tr><td>Freedom from distant recurrence - intermediate genomic risk^a</td><td>179 (1 RCT)¹</td><td>⊕○○○ VERY LOW^{b,c,d,e}</td><td>HR 0.61 (0.24 to 1.59)</td><td colspan="2">Study population</td></tr><tr><td></td><td></td><td></td><td></td><td>90 per 1,000</td><td>34 fewer per 1,000 (67 fewer to 49 more)</td></tr><tr><td>Freedom from distant</td><td>211</td><td>⊕⊕○○</td><td>HR 0.26</td><td colspan="2">Study population</td></tr></table>	Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)						Risk with endocrine therapy	Risk difference with endocrine therapy plus chemotherapy	Freedom from distant recurrence - low genomic risk ^a	488 (1 RCT) ¹	⊕○○○ VERY LOW ^{b,c,d,e}	HR 1.31 (0.46 to 3.78)	Study population						31 per 1,000	9 more per 1,000 (17 fewer to 82 more)	Freedom from distant recurrence - intermediate genomic risk ^a	179 (1 RCT) ¹	⊕○○○ VERY LOW ^{b,c,d,e}	HR 0.61 (0.24 to 1.59)	Study population						90 per 1,000	34 fewer per 1,000 (67 fewer to 49 more)	Freedom from distant	211	⊕⊕○○	HR 0.26	Study population		<div>As agreement was not reached, voting was conducted among the 19 GDG members without conflict of interest:</div> <div>6 voted for "small" undesirable effects, 12 voted for "trivial" undesirable effects and 1 member abstained</div>
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- c. There were a low number of events in each genomic risk group. The effect size estimates were imprecise which led to a low power to test interaction.
- d. The original trial (B-20) did not provide information about the HER-2 status among the included patients. Given that the positivity of HER-2 is a strong predictive marker and is included in the 21-gene recurrence test, it can bias the results
- e. Part of the sample was previously used to validate (although a previous version) the gene markers test which might lead to over fitting in subsequent analysis.

Albain (1 to 3 lymph node positive)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with endocrine therapy	Risk difference with endocrine therapy plus chemotherapy
Disease free survival - stratified by genomic risk groups ^a	0 (1 RCT) ¹	⊕○○○ VERY LOW ^{b,c,d,e}	-	The trend of recurrence over time as reported graphically showed a difference by the genomic risk groups although there was overlapping in the confidence intervals of the trend lines. ^f	
Overall survival - low genomic risk group	146 (1 RCT) ¹	⊕○○○ VERY LOW ^{b,c,d,e,g}	HR 1.18 (0.55 to 2.54)	Low	
				240 per 1,000	37 more per 1,000 (100 fewer to 262 more)
Overall survival -	103	⊕○○○	HR 0.84	Moderate	

intermediate genomic risk group	(1 RCT) ¹	VERY LOW ^{b,c,d,e,g}	(0.40 to 1.78)	350 per 1,000	46 fewer per 1,000 (192 fewer to 185 more)
Overall survival - high genomic risk group	118 (1 RCT) ¹	⊕○○○ VERY LOW ^{b,c,d,e,g}	HR 0.56 (0.31 to 1.02)	High	
				490 per 1,000	176 fewer per 1,000 (302 fewer to 7 more)

1. Albain KS, Barlow WE,Shak S,Hortobagyi GN,Livingston RB,Yeh IT,Ravdin P,Bugarini R,Baehner FL,Davidson NE,Sledge GW,Winer EP,Hudis C,Ingle JN,Perez EA,Pritchard KI,Shepherd L,Gralow JR,Yoshizawa C,Allred DC,Osborne CK,Hayes DF, America., Breast,Cancer,Intergroup,of,North. Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in a Randomized Trial of Chemotherapy for Postmenopausal, Node-Positive, Estrogen Receptor-Positive Breast Cancer. Lancet Oncol; 2010.

a. Time elapsed from the enrolment to the first breast cancer relapse (local or distant), new primary breast cancer, or death due to any cause.

b. The post-hoc analysis compared the sequential use of chemotherapy (CAF-T) versus tamoxifen; the arm of concomitant chemotherapy plus tamoxifen was not included in this sub-study due to less effectiveness in the parent trial.

c. A 12% of the included subjects in the analysis were HER2-positive based on the 21-gene assay.

d. The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes 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.

e. There were a low number of events in each genomic risk group. The effect size estimates were imprecise.

f. Interaction of test of linear RS, adjusting for number of positive nodes . Over the entire time period, the significance of the RS-treatment interaction is p=0.053 for DFS. However, the effect of the RS on treatment is not constant over time.

g. Results were not provided by strata of the number of positive lymph nodes (ie.1 to 3 vs 4 or more), instead as adjusted estimations by number of nodes. Adjustment might be inappropriate if there is interaction between the outcome and the number positive lymph node, which were not assessed in the analysis.

Sparano (lymph node negative –intermediate risk only)

Outcomes	No of	Certainty of	Relative	Anticipated absolute effects* (95% CI)
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	participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with endocrine therapy plus chemotherapy	Risk difference with endocrine therapy
Invasive disease-free survival	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 1.14 (0.99 to 1.31)	Study population 153 per 1,000	 19 more per 1,000 (1 fewer to 43 more)
Freedom from recurrence at a distant site	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 1.03 (0.80 to 1.33)	Study population 71 per 1,000	 2 more per 1,000 (14 fewer to 22 more)
Freedom from recurrence at a distant or local- regional site	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 1.12 (0.91 to 1.38)	Study population 50 per 1,000	 6 more per 1,000 (4 fewer to 18 more)
Overall survival	6712 (1 RCT) ^{1,a,b}	⊕⊕○○ LOW ^{c,d,e,f}	HR 0.97 (0.78 to 1.21)	Study population 62 per 1,000	 2 fewer per 1,000 (13 fewer to 12 more)

1. Sparano JA, Gray RJ Makower DF Pritchard KI Albain KS Hayes DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer.. N Engl J Med.; 2018.
- a. A different threshold was used for interpreting the test`s results. Thus, the intermediate range was defined as those with a score from 11 to 25, which is not consistent with previous studies assessing the same test..
- b. Clinical risk was defined as in the MINDACT trial (i.e., with low risk defined as low histologic grade and tumour size ≤3 cm, intermediate histologic grade and tumour size ≤2 cm, or high histologic grade and tumour size ≤1 cm; and with high risk

	<p>defined as all other cases with known values for grade and tumour size). Among the randomised patients, 75% were of low clinical risk, and 25% were of high clinical risk.</p> <ul style="list-style-type: none"> c. The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes 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 use the test across genomic risk groups) thus extrapolation of those events from the study's results is required. d. The confidence interval of the effect sizes wereas wide, indicating a potential harmful effect for endocrine therapy alone for the upper limit. However, in absolute terms the difference was less evident. e. There was an important imbalance in the proportions of patients that broke the protocol (not received the intended intervention), which was larger in the chemotherapy plus endocrine therapy group f. The study did not use an appropriate non-inferiority design. Instead they tested difference between arms based in a 32% increase or risk. Additionally, the high rate of non-adherence lead to an increase of the sample size non-initially planned. <p>The PRU members developed a "back of the envelope" model to estimate the downstream consequences of testing patients with the 21-gene recurrence score versus using clinical risk scores (treating only those at high risk). Four different scenarios were hypothesised.</p> <p>The general model assumptions were:</p> <ul style="list-style-type: none"> 1) Results are based on a fixed observation time of 10 years. 2) Distribution according to multigene test is low 14%; intermediate 68%; high 18%, as reported by the authors of the TAILORx trial at recruitment in 2008 before the protocol was modified in order to increase the intermediate risk group recruitment. 3) The observed rate of events at 5 years in the MINDACT trial (Cardoso 2016) will remain constant at 10 years. 4) Rates of events observed in the RCTs were applied to the simulated clinical score arms. It was assumed that basal risk of events for clinical score groups was homogenous between the low and the high clinical risk groups within a given genomic risk group. <p>An approximately 40% reduction in the women receiving chemotherapy was considered as a desirable effect.</p> <p>Scenario 1:</p> <p>In this scenario, the GDG made the extreme assumption that almost all women would be treated with chemotherapy if the multigene test would not be used (only 18,4% proportion of women would not be treated, i.e. the proportion of non-treated women among those assigned to the treatment arm in the Sparano trial).</p>	
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	Chemotherapy for all	Multigene risk strategy	difference
Number of women	1000	1000	
Chemotherapies	816,0	180,0	-636,0
Invasive disease recurrence	77,6	79,7	2,0
Distant metastasis recurrence	25,8	27,2	1,4
Local or distant disease recurrence	38,3	39,0	0,7
Deaths	23,1	23,8	0,7

Scenario 2

In this scenario, the GDG made the assumption that, without multigene testing, women would be treated only if the clinical risk is high. The model also assumes that women with low clinical and high genomic risk have no advantage from chemotherapy.

Distribution of the clinical risk within the multigene risk strata are those reported by Sparano et al 2018.

	Chemotherapy only for high clinical risk	Multigene risk strategy	difference
Number of women	1000	1000	
Chemotherapies	313,6	180,0	-133,6
Invasive disease recurrence	79,1	79,7	0,5
Distant metastasis recurrence	26,8	27,2	0,4
Local or distant disease recurrence	38,8	39,0	0,2
Deaths	23,6	23,8	0,2

Scenario 3

In this scenario, the same as in scenario 2, the GDG made the assumption that, without multigene testing, women would be treated only if the clinical risk is high. The model assumes that women with low clinical and high genomic risk have the same advantage from receiving chemotherapy as that observed in the MINDACT trial (Cardoso et al 2016) at five years and that the difference is maintained at 10 years.

	Chemotherapy only for high clinical risk	Multigene risk strategy	difference
Number of women	1000	1000	
Chemotherapies	313,6	180,0	-133,6
Invasive disease recurrence	76,9	74,5	-2,4
Distant metastasis recurrence	26,1	24,8	-1,3
Local or distant disease recurrence	not estimated	not estimated	
Deaths	22,7	22,1	-0,7

Scenario 4

In this scenario, similarly to scenario 2 and 3, the GDG made the assumption that, without multigene testing, women would be treated only if the clinical risk is high. The model assumes that women with high genomic risk have all the advantages from chemotherapy, as observed in Paik 2006, independently from their clinical risk.

		Chemotherapy for all	Multigene risk strategy	difference
Number of women		1000	1000	
Chemotherapies		313,6	180,0	-133,6
Invasive disease recurrence		not estimated	not estimated	
Distant metastasis recurrence		57,5	36,2	-21,3
Local or distant disease recurrence		not estimated	not estimated	
Deaths		not estimated	not estimated	

Scenario 5

In this scenario, the GDG assumed that only women with high clinical risk would be tested with a multigene test. Women with low clinical risk would not receive chemotherapy in any case (thus there is no difference in outcomes in this subgroup between the two strategies). Women at high clinical risk, in the multigene risk strategy would receive chemotherapy only if they have high genomic risk, while in the clinical risk strategy all women with high clinical risk will receive chemotherapy.

		Only women with high clinical risk candidate for chemotherapy		
		Chemotherapy for all high clinical risk	Multigene risk strategy	difference
Number of women		314	314	
Chemotherapies		314,0	103,0	-211,0
Invasive disease recurrence		79,1	79,7	0,5
Distant metastasis recurrence		26,8	27,2	0,4
Local or distant disease recurrence		38,8	39,0	0,2
Deaths		23,6	23,8	0,2

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 		<p>The GDG's primary concern was about very serious indirectness (the chemotherapy regime is very different now, so the GDG was concerned about the applicability of the results) and the minor concerns about risk of bias and imprecision (does not have an effect on decision-making) make this a very low rating.</p>

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 		<p>The GDG agreed by consensus that there is probably no important uncertainty or variability.</p>

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 		The GDG agreed by consensus that the balance probably favours the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																																																																																		
<ul style="list-style-type: none">● Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know	<p>The commercial cost of the assay was EUR 3 180 per patient (HR positive, HER2-negative, lymph node negative or up to 3 lymph node positives) in five out of the 11 included studies. This cost did not show significant differences among countries nor in time.</p>	<p>Cost of testing is large = for 1000 women about EUR 3 million for tests;</p>																																																																																																		
	<table><tr><th>Study ID</th><th>Country</th><th>Year</th><th>value</th><th>Cost</th><th>Currency</th><th>US PPP</th></tr><tr><td colspan="7">Lymph-node negative</td></tr><tr><td>1</td><td>Katz</td><td>France</td><td>2013</td><td>3180</td><td>Euro</td><td>3916</td></tr><tr><td>2</td><td>Ward</td><td>UK</td><td>2012</td><td>2580</td><td>British Pound</td><td>3675</td></tr><tr><td>3</td><td>Paulden</td><td>Canada</td><td>2012</td><td>4175</td><td>US Dollar</td><td>4175</td></tr><tr><td>4</td><td>Vataire</td><td>France</td><td>2011</td><td>3180</td><td>Euro</td><td>3781</td></tr><tr><td>5</td><td>Jahn</td><td>Austria</td><td>2011</td><td>3180</td><td>Euro</td><td>3827</td></tr><tr><td>6</td><td>OHTA</td><td>Ontario</td><td>2010</td><td>4075</td><td>US Dollar</td><td>4075</td></tr><tr><td>7</td><td>Davidson</td><td>Canada</td><td>2010</td><td>4450</td><td>Can Dollar</td><td>3645</td></tr><tr><td>8</td><td>Lyman</td><td>US</td><td>2006</td><td>3460</td><td>US Dollar</td><td>3460</td></tr><tr><td colspan="7">Lymph-node positive up to 3 lymph node positives</td></tr><tr><td>1</td><td>Nerich</td><td>France</td><td>2013</td><td>3180</td><td>Euro</td><td>3916</td></tr><tr><td>2</td><td>Blohmer</td><td>Germany</td><td>2011</td><td>3180</td><td>Euro</td><td>4030</td></tr><tr><td>3</td><td>Vanderlaan</td><td>US</td><td>2009</td><td>3975</td><td>US Dollar</td><td>3975</td></tr></table>	Study ID	Country	Year	value	Cost	Currency	US PPP	Lymph-node negative							1	Katz	France	2013	3180	Euro	3916	2	Ward	UK	2012	2580	British Pound	3675	3	Paulden	Canada	2012	4175	US Dollar	4175	4	Vataire	France	2011	3180	Euro	3781	5	Jahn	Austria	2011	3180	Euro	3827	6	OHTA	Ontario	2010	4075	US Dollar	4075	7	Davidson	Canada	2010	4450	Can Dollar	3645	8	Lyman	US	2006	3460	US Dollar	3460	Lymph-node positive up to 3 lymph node positives							1	Nerich	France	2013	3180	Euro	3916	2	Blohmer	Germany	2011	3180	Euro	4030	3	Vanderlaan	US	2009	3975	US Dollar	3975	<p>Potential savings with 21 gene recurrence score are associated with the reduction in the number of women who receive chemotherapy, which is 134/1000 patients according to the 'back of the envelope' model:</p> <p>1. Doxorubicin/cyclophosphamide x4 cycles</p> <p>2. Docetaxel/cyclophosphamide x4cycles</p> <p>3.Cyclophosphamide/methotrexate/5-flourouracil x6 cycles</p> <p>4. Doxorubicin/cyclophosphamide x4 cycles followed by Docetaxel x 4 cycles</p> <p>5. Dose dense doxorubicin /cyclophosphamide x4 cycles followed by dose dense docetaxel x 4 cycles</p> <p>6. Dose dense doxorubicin /cyclophosphamide x4 cycles followed by dose dense paclitaxel x 4 cycles</p> <p>Savings would occur due to avoidance of chemotherapy: approximately 130 chemotherapies avoided (EUR 10 000 per chemotherapy in Germany, data provided by a GDG member) = EUR 1.3 million saved in chemo according to the 'back of the envelope' model.</p>
	Study ID	Country	Year	value	Cost	Currency	US PPP																																																																																													
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	<p>US PPP rate: Purchasing power parities are the rates of currency conversion that equalise the purchasing power of different currencies by eliminating the differences in price levels between countries and are reported in USD.</p> <p>References:</p> <p>(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(13)</p>	<p>As agreement was not reached, voting was conducted among the 19 GDG members without conflict of interest:</p> <p>11 voted for "large" costs, 6 voted for "moderate", 1 voted for "large savings", 1 voted for "varies".</p>
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Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>High certainty of the evidence of test costs for the 21-gene recurrence score. The studies consistently reported similar test costs for the 21-gene recurrence score. Also, there are no concerns regarding the indirectness nor imprecision of the published costs of the test. Very low certainty regarding the savings due to chemotherapy avoided calculated above.</p>	<p>The GDG agreed by consensus that the certainty of the evidence of required resources was very low.</p>

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	<p>The cost-effectiveness evaluations available from the literature (24) (25) used models that do not fulfil the assumptions that are used in the 'back of the envelope' model developed ad-hoc for this PICO.</p>	<p>No cost-effectiveness studies were included.</p>

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	<p>No systematic review was carried out.</p>	<p>The GDG agreed by consensus that the impact on health equity would probably be reduced. The GDG agreed that it will depend on access to the test and whether the test is reimbursed or if patients have to pay out of pocket for it.</p>

Acceptability		
Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No systematic review was carried out.	<p>For patients, the GDG thought it would be acceptable.</p> <p>For healthcare providers, the GDG thought it would vary (due to costs, mainly due to having to send tissue specimens to a central company owned lab in the US).</p> <p>For policy makers, they did not know as it would need further discussion when there is evidence on cost-effectiveness.</p>
Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No systematic review was carried out.	<p>The GDG agreed by consensus that feasibility would vary depending on the availability of resources.</p> <p>The GDG did not see any feasibility issues around sample collection and sending them to the lab in the US, apart from possible compliance with General Data Protection Regulation.</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

For women with hormone receptor positive, HER2- negative, lymph node negative invasive breast cancer, the ECIBC's Guidelines Development Group suggests using the 21 gene recurrence score to guide the use of chemotherapy (conditional recommendation, very low certainty of the evidence).

Justification

The recommendation is conditional because there was uncertainty about the evidence and the corresponding exact effects, thus making the balance of benefits and harms not completely clear, together with large costs.

Please also see the subgroup considerations that provide additional information and rationale.

Subgroup considerations

The GDG did not consider women with node positive invasive breast cancer to be included in this recommendation.

Women with high clinical risk* and low genomic risk (larger tumour diameter and higher grade) may experience larger net desirable consequences and provide a better cost-benefit profile.

Women with low clinical risk* and high genomic risk may experience smaller or no net desirable consequences. Indirect evidence from other gene based testing (e.g. 70 gene signature) supports that former conclusion.

*Defined accordingly to the modified version of Adjuvant! Online (version 8.0 with HER2 Status) described in detail in the MINDACT trial (Cardoso 2016).

Implementation considerations

Decreasing cost for the test would support widespread use - price negotiations may be appropriate. Data protection issues may be of relevance because the samples are sent out (currently conducted only in the US) - providers should be aware.

Monitoring and evaluation

None were considered by the GDG.

Research priorities

Exploration of subgroups with anticipated larger benefits (risk stratification) or those that will not benefit from using the test for stratification to guide chemotherapy use e.g. women under 50.

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