



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 70 gene signature test 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: low clinical risk)?	
POPULATION:	Patients with hormone receptor positive, HER2 negative, node negative or up to 3 nodes positive invasive breast cancer at low clinical risk breast cancer as defined in Cardoso 2016
INTERVENTION:	70 gene signature test
COMPARISON:	no testing
MAIN OUTCOMES:	Survival without distant metastases; Disease free survival; Overall survival
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 negative lymph nodes (2).</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 (6)(7). 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. (8) 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-PCR, microarray, etc), they have in common, that they mainly focus on genes involved in cell proliferation.</p>

	<p>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 (9)(10). Over time, interest has also grown to identify those patients who gain little or none from chemotherapy and who may safely avoid toxicities (11)(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>
<b>CONFLICT OF INTEREST:</b>	<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"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>70 gene signature</p> <ul style="list-style-type: none"> <li>• CE marked microarray</li> <li>• Designed to assess the risk of distant recurrence within 5 years and whether a woman would benefit from chemotherapy. Intended for use in pre- and postmenopausal women with stage I or stage II breast cancer with tumour size <math>\leq 5</math> cm and 0-3 positive LNs</li> <li>• Measures the expression of 70 genes involved in different parts of the metastatic pathway, including growth and proliferation, angiogenesis, local invasion etc.</li> <li>• Requires RNA extracted from formalin-fixed, paraffin-embedded tumour tissue (FFPE)</li> <li>• Test can be performed locally and off-site in a central lab of the Company in the -Netherlands.</li> <li>• Uses microarray technology</li> <li>• Results: Discriminates in low and high risk using a predefined cut-off corresponding to a 10% risk of developing distant metastases over the next 10 years without any adjuvant hormone or chemotherapy.</li> </ul> <p>References: (2)</p>	<p>The GDG prioritised this question for the ECIBC.</p>

### Desirable Effects

How substantial are the desirable anticipated effects?

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<ul style="list-style-type: none"><li>● Trivial</li><li>○ Small</li><li>○ Moderate</li><li>○ Large</li><li>○ Varies</li><li>○ Don't know</li></ul>	<p>We found evidence from two types of studies, a retrospective subgroup analysis (interaction) from several validation and observational studies (12), and from an RCT comparing clinical outcomes in patients with discordant clinical and genomic risk assessment (2); the results are presented in three separate summaries of findings.</p> <p><b>Knauer 2010</b></p> <table><tr><th rowspan="2">Outcomes</th><th rowspan="2">No 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 rowspan="2">Distant free survival - low genomic risk group</td><td rowspan="2">252 (1 observational study)<sup>1,a</sup></td><td rowspan="2"> VERY LOW<sup>b,c,d,e,f</sup></td><td rowspan="2">HR 0.26 (0.03 to 2.02)</td><td>Study population</td><td></td></tr><tr><td>69 per 1,000</td><td>51 fewer per 1,000 (67 fewer to 65 more)</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	Distant free survival - low genomic risk group	252 (1 observational study) <sup>1,a</sup>	 VERY LOW <sup>b,c,d,e,f</sup>	HR 0.26 (0.03 to 2.02)	Study population		69 per 1,000	51 fewer per 1,000 (67 fewer to 65 more)	<p>For this low clinical risk group, the GDG agreed the desirable effects were trivial.</p> <p>According to the results of the MINDACT trial (Cardoso et al. 2016), women in low clinical risk would have a very small or no benefit from chemotherapy whatever would be their genomic risk. Therefore the GDG assumed no change of chemotherapy in these women according to test result and no clinical utility of the test in this group.</p> <p><b>*Definitions of used to classify patients as having low clinical risk (of recurrence or mortality) according to the modified version of Adjuvant! Online tool (see table below).</b></p> <p>Among the patients classified at low clinical risk &amp; high genomic risk: 90% were hormone receptor-positive, 88% were HER2-negative and 98% had negative lymph nodes.</p> <table><tr><th>ER status</th><th>HER2 status</th><th>Grade</th><th>Nodal status</th><th>Tumour size</th></tr><tr><td rowspan="2">HR positive</td><td rowspan="2">HER2 negative</td><td rowspan="2">Well differentiated</td><td>Negative</td><td>≤3 cm</td></tr><tr><td>1-3 positive</td><td>≤2 cm</td></tr></table>	ER status	HER2 status	Grade	Nodal status	Tumour size	HR positive	HER2 negative	Well differentiated	Negative	≤3 cm	1-3 positive	≤2 cm
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Breast cancer specific survival - low genomic risk group <sup>d</sup>	252 (1 observational study) <sup>1,a</sup>	⊕○○○ VERY LOW <sup>b,c,d,e,f</sup>	HR 0.58 (0.07 to 4.98)	Study population	
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- a. Individual patient-pooled analysis from previously reported studies.
- b. 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.
- c. 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.
- d. 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.
- e. 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.
- f. Results were not provided by strata of negative and positive lymph nodes (up to 3), but 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.

#### Cardoso 2016: low clinical risk & high genomic risk

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
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HR negative		Well differentiated	Negative	≤2 cm
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Survival without distant metastasis	478 (1 RCT) <sup>1,a,b</sup>	 LOW <sup>c,d,e,f,g</sup>	<b>HR 0.90</b> (0.40 to 2.01)	Study population	
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Disease free survival	478 (1 RCT) <sup>1,a,b</sup>	 LOW <sup>c,d,e,f,g</sup>	<b>HR 0.74</b> (0.40 to 1.39)	Study population	
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Overall survival	478 (1 RCT) <sup>1,a,b</sup>	 LOW <sup>c,d,e,f,g</sup>	<b>HR 0.72</b> (0.23 to 2.24)	Study population	
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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.
- a. The population was defined as Low Clinical Risk by the Adjuvant Online!: Lymph node negative: 98%, HR(+): 90%, HER2(-): 88%, Size >2cm: 2%.
- b. 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.
- c. 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.
- d. There were a low number of events in each genomic risk group. The effect size estimates were imprecise.
- e. 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)
- f. 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.
- g. 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 (as primary outcome), it can be taken to be equivalent.

## Undesirable Effects

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- 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.

- The population was defined as Low Clinical Risk by the Adjuvant Online!: Lymph node negative: 98%,



	<p>HR(+): 90%, HER2(-): 88%, Size &gt;2cm: 2%.</p> <p>b. 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.</p> <p>c. 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.</p> <p>d. There were a low number of events in each genomic risk group. The effect size estimates were imprecise.</p> <p>e. 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)</p> <p>f. 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.</p> <p>g. 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 (as primary outcome), it can be taken to be equivalent.</p>	
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## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		The GDG agreed by consensus that the certainty of the evidence was low, due to issues around imprecision, and risk of bias (some patients were reclassified according to genomic risk in a post-hoc fashion).

## 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"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>● Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>		The GDG agreed by consensus that there is probably no important uncertainty or variability.

## 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"> <li>● Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		The GDG agreed by consensus that for the low clinical risk group the balance of effects favours the comparison.

## Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																										
<ul style="list-style-type: none"><li>● Large costs</li><li>○ Moderate costs</li><li>○ Negligible costs and savings</li><li>○ Moderate savings</li><li>○ Large savings</li><li>○ Varies</li><li>○ Don't know</li></ul>	<p>The cost of the assay is around EUR <b>3 153 per patient</b> (HR positive, HER2 negative, lymph node negative) in the included studies (13)(14).</p> <table><tr><th>Study ID</th><th>Country</th><th>Year value</th><th>Cost</th><th>Currency</th><th>US PPP</th></tr><tr><td colspan="6">Lymph-node negative</td></tr><tr><td>1</td><td>Ward</td><td>UK</td><td>2012</td><td>2675</td><td>British Pounds</td><td>3811</td></tr><tr><td>2</td><td>Kondo</td><td>Japan</td><td>2009</td><td>4222</td><td>US Dollar</td><td>4222</td></tr></table>	Study ID	Country	Year value	Cost	Currency	US PPP	Lymph-node negative						1	Ward	UK	2012	2675	British Pounds	3811	2	Kondo	Japan	2009	4222	US Dollar	4222	<p>For the low clinical risk group the GDG agreed it was a large cost for no potential benefit.</p> <p>Cost of testing is large = for 1 000 women about EUR 3 million. As reported by the back of the envelope calculation, these tests would avoid approximately zero chemotherapies in the low clinical risk group. Therefore, there is no potential savings due to avoidance of chemotherapy.</p>
Study ID	Country	Year value	Cost	Currency	US PPP																							
Lymph-node negative																												
1	Ward	UK	2012	2675	British Pounds	3811																						
2	Kondo	Japan	2009	4222	US Dollar	4222																						

<b>Certainty of evidence of required resources</b> What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	High certainty of the evidence of 70 gene signature cost. Very low certainty for harms. The studies consistently reported a similar cost of the 70 gene signature. Also, there are no concerns regarding the indirectness nor imprecision of the published costs. Very low certainty regarding the savings due to chemotherapy avoided calculated above.	The GDG agreed by consensus that the certainty of the evidence of required resources was very low.
<b>Cost effectiveness</b> Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	The cost-effectiveness evaluations available from the literature (15)(16) used models that do not fulfil the assumptions that were used in the 'back of the envelope' model developed ad-hoc for this PICO.	The GDG, therefore, did not include any studies.
<b>Equity</b> What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No systematic review was carried out.	The GDG agreed by consensus that equity would probably be reduced.

## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><li>● No</li><li>○ Probably no</li><li>○ Probably yes</li><li>○ Yes</li><li>○ Varies</li><li>○ Don't know</li></ul>	No systematic review was carried out.	The intervention would not be acceptable for low risk group as it has no benefit.

## Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><li>○ No</li><li>○ Probably no</li><li>○ Probably yes</li><li>○ Yes</li><li>● Varies</li><li>○ Don't know</li></ul>	No systematic review was carried out.	The GDG agreed by consensus that feasibility would vary depending on the availability of resources.

## 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 or up to 3 lymph nodes positive invasive breast cancer at low clinical risk\*, the ECIBC's Guidelines Development Group (GDG) recommends not using the 70 gene signature test to guide the use of chemotherapy (strong recommendation, low certainty of the evidence).

\*This recommendation applies to patients with HR-positive, HER2-Negative invasive breast cancer which are: G1 and node negative and  $\leq 3$ cm or G1 and 1-3 positive nodes and  $\leq 2$ cm or G2 and node negative and  $\leq 2$ cm or G3 and node negative and  $\leq 1$ cm.

### Justification

In the low clinical risk group the recommendation is strong against using the 70 gene signature test to guide the use of chemotherapy as there were no benefits to using the test and a very large cost.

### Subgroup considerations

The proportion of women with 2 or 3 node positive breast cancer were small, so the results may be less clear in this subgroup.

### Implementation considerations

Decreasing cost for the test would support widespread use - price negotiations may be appropriate.

### Monitoring and evaluation

None were considered. by the GDG.

### Research priorities

Longer follow up studies would be needed, as currently there is only a follow-up of five years.

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