Early and locally advanced breast cancer: diagnosis and management

[C] Evidence reviews for adjuvant systemic therapy planning

NICE guideline NG101

Evidence reviews

July 2018

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists
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Adjuvant systemic therapy planning

This evidence report contains information on 2 reviews relating to adjuvant systemic therapy planning.

- Review question 3.1. Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?
- Review question 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?
Review question 3.1. Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

Introduction

Current UK recommendations in the previous guideline CG80 (NICE 2009), and from the Royal College of Pathologists (RCPath, 2016), state that oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) biomarkers should be assessed in all invasive breast cancers. This biomarker analysis can provide important prognostic and predictive information to help direct further adjuvant management breast cancer after surgery.

ER positivity in breast cancers can predict a potential response to endocrine-based treatments and these cancers are known to have an overall better prognosis than ER-negative cancers. Progesterone receptor (PR) is from the same family of molecules as ER, but CG80 recommended not to routinely test all breast cancers for PR as, at the time, there was no strong evidence to support PR being predictive of a response to endocrine therapy (despite being independently prognostic for relapse-free survival and overall survival).

The co-expression of ER and PR does vary between breast cancers. Whilst the majority of breast cancers which are ER positive are also PR positive, many are PR negative, and studies have now shown these to have a worse prognosis and to be less responsive to endocrine therapies. Some people have breast cancers that are negative for each of ER, PR and HER2. As none of the 3 biomarkers are expressed in these cancers, they are conventionally referred to as ‘triple negative’ and are associated with a poor prognosis without treatment, but the cancer may respond well to certain forms of chemotherapy.

The purpose of this review question is to determine if establishing PR status affects planning for adjuvant chemotherapy.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults (18 or over) with invasive breast cancer (M0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>• ER and HER2 plus PR test followed by chemotherapy as indicated based on test results</td>
</tr>
<tr>
<td>Comparison</td>
<td>• ER and HER2 test followed by chemotherapy as indicated based on test results</td>
</tr>
<tr>
<td>Outcome</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>• Disease-free survival</td>
</tr>
<tr>
<td></td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td>Important</td>
</tr>
<tr>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; M0, no distant metastases; PR, progesterone receptor

For full details see review protocol in appendix A.
Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE’s 2014 conflicts of interest policy.

Clinical evidence

Included studies

There were no test and treat randomised controlled trials (RCTs) identified by the literature search. In test and treat studies, only participants who get discrepant test results (for example, chemotherapy indicated versus chemotherapy not indicated) would receive different treatment and only a proportion of those may benefit from differences in treatment. Therefore, the committee deemed it inappropriate to drop down the evidence hierarchy to include non-randomised studies as it is likely that bias inherent in such studies would dominate any treatment effect.

The study selection flow chart is in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Quality assessment of clinical studies included in the evidence review

No studies were included in this review question.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Formal consensus

The committee decided that a modified form of the nominal group technique would be the most appropriate method for producing recommendations regarding the appropriateness of PR testing. The method used for the nominal group technique is described in full within the methods chapter.

Key issues related to progesterone receptor testing were identified from relevant papers identified by the current search results (Duffy 2005; Hammond 2010, Harris 2007; Henry 2016) the previous guideline CG80 (NICE 2009), key papers and guidelines identified by the guideline committee (Early Breast Cancer Trialists’ Collaborative Group [EBCTCG] 2011), and from protocol discussions with the committee. These were used to generate statements covering the following areas: prognosis based on progesterone receptor status, impact of progesterone receptor status on endocrine therapy and chemotherapy, and assessment of progesterone receptor status. These statements were placed into a questionnaire and distributed to the guideline committee to be rated.

The first round of rating was completed by 11 of 16 committee members. Percentage agreement values were calculated and comments collated for each statement; the rankings
and comments were then presented to the committee members to facilitate a structured discussion. Two statements were redrafted based on the comments from the committee members and re-distributed for rating as a second questionnaire; this round was completed by 10 of 16 committee members. A blank copy of the questionnaire (including re-rated statements) can be found in appendix M and consensus ratings can be found in appendix N.

A brief summary of level of consensus is depicted in Table 2 below.

**Table 2: Summary of nominal group technique process followed for the development of recommendations on progesterone receptor testing**

<table>
<thead>
<tr>
<th>Round 1</th>
<th>Round 2</th>
<th>Number of recommendations generated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consensus</td>
<td>Statements N (total = 16)</td>
<td>Level of consensus</td>
</tr>
<tr>
<td>High (≥80%)</td>
<td>4</td>
<td>High (≥80%)</td>
</tr>
<tr>
<td>Moderate (60-80%)</td>
<td>1</td>
<td>Moderate (60-80%)</td>
</tr>
<tr>
<td>Low (&lt;60%)</td>
<td>11</td>
<td>Low (&lt;60%)</td>
</tr>
</tbody>
</table>

**Evidence statements**

The committee agreed that:

- positive progesterone receptor status is associated with favourable prognosis and negative progesterone receptor status is associated with worse prognosis
- progesterone receptor status provides additional information to oestrogen receptor status that may be beneficial when considering the benefit of adjuvant hormone treatment
- negative progesterone receptor status is one factor that may increase benefit from chemotherapy, and likelihood that it is offered in borderline cases
- progesterone receptor status is relevant when making decisions regarding adjuvant therapy and should be assessed in all newly diagnosed invasive breast cancers.

**The committee’s discussion of the evidence**

**Interpreting the evidence**

**The outcomes that matter most**

The committee identified disease-free survival and overall survival as critical outcomes. Treatment-related morbidity was selected as an important outcome to examine the impact of any additional treatment required as a result of progesterone receptor testing. These outcomes are valued by service users as increased survival is prioritised; however, treatment-related morbidities can have a significant impact on health-related quality of life and adherence to treatment.

No test and treat studies were identified from the literature search, therefore there was no evidence for any of the outcomes reported in the PICO.

The impact of PR status on prognosis, benefit from endocrine therapy and benefit from chemotherapy were identified through discussions with the committee as key areas related to the need for PR testing. These areas were used as guides for generating statements to be ranked by the committee using a modified form of the nominal group technique.
The quality of the evidence

No published evidence was identified for this review. Although there were high levels of agreement in the nominal group technique for statements which informed and supported recommendations, this formal consensus method constitutes low quality evidence.

Benefits and harms

The addition of PR testing to ER testing will provide further information on which to base decisions regarding adjuvant hormone therapy and chemotherapy resulting in better tailored treatment. Specifically, tumours that are negative for PR have a worse prognosis and therefore may receive greater benefit from chemotherapy. Determining negative PR status may therefore increase the likelihood of chemotherapy being offered in borderline cases.

Assessing PR status upfront in all newly diagnosed invasive cancers reduces delays in decision making that may occur if determining progesterone receptor status is carried out at a later stage, and not at the same time as ER testing. This may allow earlier commencement of treatment. Earlier treatment may lead to a reduction in recurrence and mortality. The committee made an additional recommendation therefore that the 3 tests (ER, PR and HER2) should all be requested simultaneously at the time of initial histopathological diagnosis, to prevent delays in treatment.

No harms were identified by the committee as no additional procedures are required for progesterone receptor testing. Treatment-related morbidities were discussed, but the committee thought that there would not be significant increases in morbidities as currently the majority of patients do receive progesterone receptor testing and corresponding treatment when indicated, but the testing is not routinely done upfront.

The benefits identified combined with the lack of harms led the committee to make a strong recommendation in this area despite the low quality of the evidence.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

There is the potential for cost increases associated with testing PR status. However the committee did not think the increase would be large as some centres are already performing upfront PR testing and it would be more expensive if a second test was required to determine PR status.

There is also a potential cost increase associated with additional adjuvant endocrine therapy and chemotherapy that may be indicated as a result of the PR test. This is unlikely to be large as the recommendation will have a greater impact on the timing of PR testing rather than whether the test, and indicated treatment, occurs.

In contrast, performing the PR test upfront will produce cost savings as pathology results will not need to be discussed at multiple multidisciplinary team meetings, and fewer second appointments will be required for decision making and adjuvant treatment planning; currently, an additional multidisciplinary team meeting may be required to discuss the impact of PR status if this information is not available at the initial meeting. There is also a potential for cost savings if treatment improvements reduce recurrence and/or mortality as there will be a decreased need for future procedures, treatments and hospice care.
Other factors the committee took into account

**Ethical considerations**

There are elevated rates of triple-negative breast cancer among some ethnic groups, for example Afro-Caribbean people, and they are therefore more likely to be affected by delays to optimal treatment if progesterone receptor status is not known. The current recommendation will reduce this inequality as progesterone receptor testing will be performed upfront allowing for earlier determination of triple-negative status.

**Methods for assessing and reporting progesterone-receptor status**

The committee recommended that PR status be assessed using immunohistochemical techniques. This is standard clinical practice and all UK laboratories using hormone receptor assays are subject to national quality assurance. Furthermore, the committee recommended that results are reported quantitatively (as opposed to dichotomously) as the degree of positivity is directly correlated with a better prognosis.

**References**

**Duffy 2005**


**EBCTCG 2011**


**Hammond 2010**


**Harris 2007**


**Henry 2016**

**NICE 2009**


**RCPath 2016**

Review question 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

Introduction

Planning adjuvant treatment is complex and incorporates a variety of prognostic and predictive factors. In order to identify which people would benefit from adjuvant therapy, a number of prognostic tools have been developed. These take into account a number of factors such as age, comorbidities, tumour staging and biomarkers, and assess the risk of an individual person developing recurrent disease and/or dying within 10 years when receiving a specific treatment. These prognostic tools can be used jointly by the person and their doctor to determine the most appropriate adjuvant treatment (chemotherapy, endocrine therapy, or no therapy).

The aim of this review is to determine which of the currently available prognostic tools is most reliable at correctly predicting survival and the benefits of adjuvant treatment.

See Table 3 for a description of the prognostic tools included in this review.

<table>
<thead>
<tr>
<th>Prognostic tool</th>
<th>Description</th>
<th>Factors included in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant! Online</td>
<td>Adjuvant! is an online tool that aims to help healthcare professionals and people with early cancer discuss the benefits and risks of receiving additional adjuvant therapy after surgery. For further details please see <a href="https://www.adjuvantonline.com/">https://www.adjuvantonline.com/</a></td>
<td>Adjuvant therapy Age Comorbidity ER status Menopausal status Number of positive lymph nodes Tumour size</td>
</tr>
<tr>
<td>PREDICT</td>
<td>The PREDICT tool is a free online computer programme developed by the NHS and the University of Cambridge, and it aims to help patients and healthcare professionals decide on the ideal course of treatment following surgery for breast cancer. There are different versions of PREDICT (personal communication,): v1.0 (2011) v1.1 (also known as PREDICT Plus) – modified version of PREDICT v1.0 + HER2 v1.2 – modified version of PREDICT v1.1 + Ki67 v2.0 (2017) – updated version with substantial modifications to the underlying model For further details please see <a href="http://www.predict.nhs.uk/index.html">http://www.predict.nhs.uk/index.html</a></td>
<td>Age at diagnosis ER status Gen chemo regimen HER2 status Ki67 status Mode of detection Number of positive nodes Tumour grade Tumour size in mm</td>
</tr>
<tr>
<td>Nottingham Prognostic Index (NPI)</td>
<td>The Nottingham prognostic index (NPI) is a tool used to determine prognosis following breast cancer surgery. For further details please see <a href="http://www.pmidcalc.org/?sid=3689666&amp;newtest=Y">http://www.pmidcalc.org/?sid=3689666&amp;newtest=Y</a></td>
<td>Grade of the tumour Number of involved lymph nodes Size of the lesion</td>
</tr>
<tr>
<td>FinProg</td>
<td>FinProg is an online-based system for individualised survival estimation in breast cancer. For further details please see <a href="http://www.finprog.org/">http://www.finprog.org/</a></td>
<td>Adjuvant therapy Age ER</td>
</tr>
</tbody>
</table>
Prognostic tool | Description | Factors included in the model
---|---|---
CancerMath | Cancer-Math is an online tool aimed to provide healthcare professionals with web-based calculators for: 1) accurately predicting the clinical outcome for people with cancer (including breast cancer), and 2) accurately estimating the impact of various treatment choices on that outcome. For further details please see http://www.lifemath.net/cancer/?cancer | Age, Chemotherapy, ER status, Grade, HER2 status, Histological type, Hormonal therapy, Number of positive nodes, PR status, Tumour diameter in mm
Oxford Prognostic Index (OPI) | The Oxford Prognostic Index (OPI) is a tool aimed to predict the long-term risk of a recurrent event in women diagnosed with early breast cancer. | Age, ER status, Nodal status, Tumour grade, Tumour size

*ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; NPI: Nottingham Prognostic Index; OPI: Oxford Prognostic Index; PR: progesterone receptor*

**PICOTS table**

See Table 4 for a summary of the population, intervention (predictive prognostic tool), comparison, outcome, timing and setting (PICOTS) characteristics of this review.

**Table 4: Summary of the protocol (PICOTS table)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults (18 or over) with invasive breast cancer (M0) who have undergone surgery and who are candidates for adjuvant systemic therapy. Only studies conducted with UK population will be considered for inclusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention (Predictive prognostic tools)</td>
<td>Any appropriate predictive prognostic tools, for example, • Adjuvant! Online • PREDICT • Nottingham Prognostic Index (NPI) • FinProg • CancerMath • Only studies assessing validated tools will be considered for inclusion.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Critical • Calibration • Discrimination (AUROC) Important • Accuracy of prediction (sensitivity, specificity)</td>
</tr>
</tbody>
</table>
For full details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE’s 2014 conflicts of interest policy.

Clinical evidence

We included validation studies that reported sensitivity, specificity, calibration and discrimination of validated predictive prognostic tools.

It was agreed with the committee that sensitivity or specificity would be considered high when sensitivity or specificity was 90% or higher, and moderate when sensitivity or specificity was between 75% and 89%. However none of the studies reported these outcomes.

The mortality ratio is defined as the ratio of observed number of deaths in a study population and the expected number of deaths. In this review, a tool was judged to have good calibration if the ratio ranged from 0.8 to 1.2 (as suggested by Debray 2017).

Discrimination is a measure to assess how well a tool identifies people with worse survival, and it is often reported by the concordance c-statistic (also known as AUC). In this review a tool was judged to have good discrimination if c-statistic was above 0.75 (as suggested by Debray 2017).

Included studies

Seven studies (number of participants, N=27,287) were included in this review (Blamey 2007, Campbell 2009, Campbell 2010, Candido dos Reis 2017, Maishman 2015, Wishart 2010 and Wishart 2014).

One study looked at the Nottingham Prognostic Index (NPI) (Blamey 2007), 1 study looked at Adjuvant! Online (Campbell 2009), 1 study looked at the Oxford Prognostic Index (OPI) (Campbell 2010), and 4 studies looked at PREDICT (Candido dos Reis 2017, Maishman 2015, Wishart 2010 and Wishart 2014). Because a number of versions of PREDICT exist, the authors were contacted to seek clarification.

All studies were conducted with a UK population.

The clinical evidence from these studies is summarised in Table 5. Please note that GRADE profiles are not applicable to this review question. See also the study selection flow chart in appendix C, forest plots in appendix E, study evidence tables in appendix D and exclusion list in appendix K.

This review updates a question from the previous guideline CG80 (NICE 2009). However no studies were identified in the previous guideline.
Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 5: Summary of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Predictive prognostic tool</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Blamey 2007        | Women diagnosed with or treated for primary operable invasive breast cancer at Nottingham city hospital Dates:  
|                   |                                                                             | Nottingham Prognostic Index (NPI) | • Observed and predicted 10-year breast cancer survival                                                          |                                                                                             |
| Campbell 2009      | Data from 1,065 women with early breast cancer diagnosed at the Churchill hospital Oxford Dates: 1986 to 1996 UK population | Adjuvant! Online             | • Observed and predicted 10-year overall survival (%)  
|                   |                                                                             |                              | • Observed and predicted 10-year breast cancer specific survival (%)  
|                   |                                                                             |                              | • Observed and predicted 10-year event free survival (%)                                                      |                                                                                             |
| Campbell 2010      | N=1787 women with invasive ductal carcinoma, a sub-set obtained from the Adjuvant Breast Cancer trial from 70 UK centres Dates: 1992 to 2000 UK population | Oxford Prognostic Index (OPI) | • Observed and predicted 5-year recurrence free survival                                                           |                                                                                             |
| Candido dos Reis 2017 | Tool development Data from 5738 people from the ECRIC database Dates: 1999 to 2003 Validations study Data from the following databases:  
|                   |                                                                             | PREDICT v2.0*                | • Observed and predicted 10-year breast-cancer mortality  
|                   |                                                                             |                              | • Observed and predicted 10-year all-cause mortality  
<p>|                   |                                                                             |                              | • This validation study reports data for PREDICT v2.0 and v1. Data for v1 was not used in the analysis as for many of the cases in the validation data the authors did not have either HER2 status or KI67 status* |                                                                                             |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Predictive prognostic tool</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maishman 2015</td>
<td>Data from 3000 women aged ≤40 years at diagnosis (POSH cohort) UK population</td>
<td>PREDICT v1.2*</td>
<td>• Observed and predicted 5-year all-cause mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NTBCS: n=1726 (dates: 1989 to 1998)</td>
<td></td>
<td>• Observed and predicted 10-year all-cause mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>POSH: n=2609 (dates: 2000 to 2008)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wishart 2010</td>
<td>Data from 5468 people with breast cancer from the West Midlands Cancer Intelligence Unit (WMCIU) Dates: 1999 to 2003 UK population</td>
<td>PREDICT v1.1*</td>
<td>• Observed and predicted 5-year all-cause mortality</td>
<td>Validation study (data from the primary analysis has not been reported)</td>
</tr>
<tr>
<td>Wishart 2014</td>
<td>Data for 2232 cases of invasive breast cancer treated in Nottingham - 506 node-negative cases were excluded, so data from n=1726 people was included in the study Dates: 1989 to 1998 UK population</td>
<td>PREDICT v1.1* and v1.2*</td>
<td>• Observed and predicted 10-year all-breast cancer mortality</td>
<td></td>
</tr>
</tbody>
</table>

*This information was provided by PREDICT (info@predict.nhs.uk)

BCOS, Breast Cancer Outcomes Simulator; ECRIC, East Anglia cancer registration and information centre; NPI, Nottingham Prognostic Index; NTBC, Nottingham Tenovus Breast Cancer; OPI, Oxford Prognostic Index; POSH, Prospective study of Outcomes in Sporadic versus Hereditary breast cancer; UK, United Kingdom; WMCIU, West Midlands Cancer Intelligence Unit

See appendix D for full evidence tables.

**Quality assessment of clinical studies included in the evidence review**

The included studies were individually assessed using the Critical Appraisal Skills Programme (CASP) tool for clinical prediction rule. Studies were rated as of moderate or high quality. The reasons for rating down the quality of the studies were that the tool had not been validated in a different population, or that the tool did not include all the relevant prognostic factors.

The clinical evidence profiles for this review question (prognostic tools) are presented in Table 6 to Table 9.
### Predictive prognostic tool 1: Adjuvant! Online

**Table 6: Summary of included studies and results for Adjuvant! Online**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell (2009)</td>
<td>Validation study</td>
<td>Study period: 1986 to 1996</td>
<td>Data from 1,065 women with early breast cancer diagnosed at the Churchill hospital I Oxford</td>
<td>Prognostic accuracy (sensitivity, specificity) Not reported Tool calibration All population (N=1065): 10-year overall survival (OS)</td>
<td>High quality, as assessed by CASP Clinical Prediction Rule checklist.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- OS ratio O:E = 0.93&lt;br&gt;- Difference O-E = -5.54 (p&lt;0.01)&lt;br&gt;Subgroup: age&lt;br&gt;- 20 to 35 (n=34)&lt;br&gt;  o OS ratio O:E = 0.97&lt;br&gt;  o Difference O-E = -2.27% (ns)&lt;br&gt;- 36 to 50 (n=363)&lt;br&gt;  o OS ratio O:E = 0.95&lt;br&gt;  o Difference O-E = -4.33% (p&lt;0.05)&lt;br&gt;- 51 to 65 (n=458)&lt;br&gt;  o OS ratio O:E = 0.95&lt;br&gt;  o Difference O-E = -4.02% (p&lt;0.05)&lt;br&gt;- 66 to 75 (n=194)&lt;br&gt;  o OS ratio O:E = 0.82&lt;br&gt;  o Difference O-E = -12.17% (p&lt;0.01)&lt;br&gt;- ≥76 (n=16)&lt;br&gt;  o OS ratio O:E = 0.94&lt;br&gt;  o Difference O-E = -3.11% (ns)&lt;br&gt;Subgroup: grade:&lt;br&gt;  • Grade 1 (n=152)</td>
<td>- Unknown confounders&lt;br&gt;- OS ratio O:E was calculated by the NGA technical team based on available data on the paper&lt;br&gt;- Other factors included in the model: histology, local therapy, systemic therapy</td>
<td>• High quality, as assessed by CASP Clinical Prediction Rule checklist.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OS ratio O:E: 0.96</td>
<td>Difference O-E: - 3.65% (ns)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (n=421)</td>
<td></td>
<td>OS ratio O:E: 0.91</td>
<td>Difference O-E: -7.05% (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (n=248)</td>
<td></td>
<td>OS ratio O:E: 0.86</td>
<td>Difference O-E: -9.82% (p&lt;0.01)</td>
<td></td>
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<tr>
<td>Unknown grade (n=244)</td>
<td></td>
<td>OS ratio O:E: 1.00</td>
<td>Difference O-E: 0.26% (ns)</td>
<td></td>
</tr>
<tr>
<td>Subgroup: tumour size:</td>
<td></td>
<td>OS ratio O:E: 0.93</td>
<td>Difference O-E: -6.10% (ns)</td>
<td></td>
</tr>
<tr>
<td>0.1 to 1 cm (n=150)</td>
<td></td>
<td>OS ratio O:E: 0.92</td>
<td>Difference O-E: -6.57% (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>1.1 to 2 cm (n=471)</td>
<td></td>
<td>OS ratio O:E: 0.94</td>
<td>Difference O-E: -4.26% (ns)</td>
<td></td>
</tr>
<tr>
<td>Subgroup: nodal status</td>
<td></td>
<td>OS ratio O:E = 0.94</td>
<td>Difference O-E = -4.70% (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Negative (n=733)</td>
<td></td>
<td>OS ratio O:E = 0.89</td>
<td>Difference O-E = -7.38% (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Positive (n=332)</td>
<td></td>
<td>OS ratio O:E = 0.89</td>
<td>Difference O-E = -7.38% (p&lt;0.01)</td>
<td></td>
</tr>
</tbody>
</table>
### Study details

**Study**

**Population**

**Findings**

- **Subgroup: ER status**
  - Negative (n=261)
    - OS ratio O:E = 0.97
    - Difference O-E = -1.93% (ns)
  - Positive (n=495)
    - OS ratio O:E = 0.89
    - Difference O-E = -9.00% (p<0.01)
  - Unknown (n=309)
    - OS ratio O:E = 0.96
    - Difference O-E = -3.04% (ns)

- **Tool discrimination**
  - Not reported

### 10-year breast cancer specific survival (BCSS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Campbell       | Validation study                      | Data from 1,065 women with early breast cancer diagnosed at the Churchill hospital I Oxford | Prognostic accuracy (sensitivity, specificity) Not reported Tool calibration All population (N=1058):  
  - BCSS ratio O:E: 0.95  
  - Difference O-E: -4.53% (p<0.01)  
  **Subgroup: age**  
  - 20 to 35 (n=34)  
    - BCSS ratio O:E: 0.99  
    - Difference O-E: -0.67% (ns)  
  - 36 to 50 (n=361)  
    - BCSS ratio O:E: 0.94  
    - Difference O-E: -4.62% (p<0.05)  
  - 51 to 65 (n=454)  
    - BCSS ratio O:E: 0.96  
    - Difference O-E: -3.51% (ns) | Unknown confounders BCSS ratio O:E was calculated by the NGA technical team based on available data on the paper Other factors included in the model: histology, local therapy, systemic therapy | High quality, as assessed by CASP Clinical Prediction Rule checklist. |
<table>
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<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
</table>
|       |               | 66 to 75 (n=193) | • BCSS ratio O:E = 0.89  
○ Difference O-E = -9.28% (p<0.05)  
• ≥76 (n=16)  
○ BCSS ratio O:E = 1.08  
○ Difference O-E = 7.04% (ns)  
*Subgroup: grade:*  
• Grade 1 (n=152)  
○ BCSS ratio O:E: 0.99  
○ Difference O-E: -1.29% (ns)  
• Grade 2 (n=420)  
○ BCSS ratio O:E: 0.93  
○ Difference O-E: -5.89% (p<0.01)  
• Grade 3 (n=243)  
○ BCSS ratio O:E: 0.92  
○ Difference O-E: -6.10 (p<0.05)  
• Unknown grade (n=243)  
○ BCSS ratio O:E: 0.96  
○ Difference O-E: -2.78 (ns)  
*Subgroup: tumour size:*  
• 0.1 to 1 cm (n=148)  
○ BCSS ratio O:E: 0.92  
○ Difference O-E: -7.95% (p<0.01)  
• 1.1 to 2 cm (n=470)  
○ BCSS ratio O:E: 0.95  
○ Difference O-E: -4.54% (p<0.01)  
• 2.1 to 5 cm (n=440)  
○ BCSS ratio O:E: 0.95  
○ Difference O-E: -3.53% (ns) |
### Study details

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Wishart (2010)</td>
<td>Validation study</td>
<td>Data from 5468 people with breast cancer</td>
<td>Prognostic accuracy (sensitivity, specificity)</td>
<td>PREDICT v1.0</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**BCSS, breast cancer specific survival; CASP, Critical Appraisal Skills Programme; ER, oestrogen receptor; NGA, National Guideline Alliance; ns, not significant; O-E, observed minus expected; O:E, observed/expected; OS, overall survival; UK, United Kingdom**

### Predictive prognostic tool 2: PREDICT

**Table 7: Summary of included studies and results for PREDICT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year all-cause mortality [PREDICT v1.0]</td>
<td>Validation study</td>
<td>Data from 5468 people with breast cancer</td>
<td>Prognostic accuracy (sensitivity, specificity)</td>
<td>PREDICT v1.0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Study</td>
<td>Study details</td>
<td>Population</td>
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<td>from the West Midlands Cancer Intelligence Unit (WMCIU)</td>
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<td></td>
<td>Study period: 1999 to 2003</td>
<td></td>
<td>• Not reported</td>
<td>• Validation study (data from the primary analysis has not been reported)</td>
<td>CASP Clinical Prediction Rule checklist</td>
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<td></td>
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<td>• Tool calibration</td>
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<td>• Total cohort (N=5468)</td>
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<td>• Mortality ratio O:E = 0.91</td>
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<td>• Difference O-E = -1.61%</td>
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<td><strong>Subgroup: age</strong></td>
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<td>• &lt;35 (n=108)</td>
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<td>  o Mortality ratio O:E = 0.88</td>
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<td>  o Difference O-E = -2.78%</td>
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<td>• 35 to 49 (n=1195)</td>
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<td>  o Mortality ratio O:E = 0.83</td>
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<td>  o Difference O-E = -2.68%</td>
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<td>• 50 to 67 (n=2393)</td>
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<td>  o Mortality ratio O:E = 0.90</td>
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<td>  o Difference O-E = -1.34%</td>
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<td>• 65 to 74 (n=1101)</td>
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<td>  o Mortality ratio O:E = 0.98</td>
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<td>  o Difference O-E = -0.45%</td>
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<td>• 75+ (n=671)</td>
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<td>  o Mortality ratio O:E = 0.98</td>
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<td>  o Difference O-E = -0.75%</td>
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<td><strong>Subgroup: grade</strong></td>
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<td>• Grade 1 (n=1017)</td>
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<td>  o Mortality ratio O:E = 0.98</td>
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<td>  o Difference O-E = -0.1%</td>
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<td>• Grade 2 (n=2442)</td>
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<td>  o Mortality ratio O:E = 0.98</td>
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<td>  o Difference O-E = -0.16%</td>
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<td>• Grade 3 (n=2009)</td>
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<td>  o Mortality ratio O:E = 0.87</td>
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<td>  o Difference O-E = -3.58%</td>
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<td><strong>Subgroup: tumour size</strong></td>
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<tr>
<td>Study</td>
<td>Study details</td>
<td>Population</td>
<td>Findings</td>
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<td>• &lt;10 mm (n=485)</td>
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<td>o Mortality ratio O:E = 0.84</td>
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<td>o Difference O-E = -1.03%</td>
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<td>• 10 to 19 mm (n=2136)</td>
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<td>o Mortality ratio O:E = 0.88</td>
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<td>o Difference O-E = -2.01%</td>
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<td>• 20 to 29 mm (n=1566)</td>
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<td>o Mortality ratio O:E = 0.94</td>
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<td>o Difference O-E = -0.96%</td>
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<td>• 30 to 49 mm (n=923)</td>
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<td>o Mortality ratio O:E = 0.99</td>
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<td>o Difference O-E = -0.11%</td>
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<td>• 50+ mm (n=358)</td>
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<td>o Mortality ratio O:E = 0.91</td>
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<td>o Difference O-E = -3.91%</td>
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<td>• Subgroup: nodal status</td>
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<td>• Negative (n=3184)</td>
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<td>o Mortality ratio O:E = 0.80</td>
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<td>o Difference O-E = -2.14%</td>
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<td>• Positive (n=2284)</td>
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<td>o Mortality ratio O:E = 0.98</td>
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<td>o Difference O-E = -0.39%</td>
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<td>• Subgroup: ER status</td>
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<td>• Negative (n=1116)</td>
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<td>o Mortality ratio O:E = 0.87</td>
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<td>o Difference O-E = -4.21%</td>
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<td>• Positive (n=4352)</td>
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<td>o Mortality ratio O:E = 0.95</td>
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<td>o Difference O-E = -0.69%</td>
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<td>• Tool discrimination</td>
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<td>• ER+: AUC=0.81; SE=0.0111</td>
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<td>• ER-: AUC=0.75; SE=0.0169</td>
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<td>Study</td>
<td>Study details</td>
<td>Population</td>
<td>Findings</td>
<td>Comments</td>
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</table>
| Maishman (2015) | Validation study Study period: 2000 to 2008 | Data from 3000 women aged ≤40 years at diagnosis (POSH cohort) | • **Prognostic accuracy** *(sensitivity, specificity)*  
  • Not reported  
  • **Tool calibration**  
  • Total cohort (N=2827)  
  • Mortality ratio O:E = 1.33  
  • Difference O-E = 25% (n=152)  
  • **Subgroup: age at diagnosis**  
  • 18 to 25 (n=40)  
  o Mortality ratio O:E = 1.4  
  o Difference O-E = 28.6% (n=2)  
  • 26 to 30 (n=258)  
  o Mortality ratio O:E = 1.35  
  o Difference O-E = 25.8% (n=16)  
  • 31 to 35 (n=864)  
  o Mortality ratio O:E = 1.38  
  o Difference O-E = 27.6% (n=58)  
  • 36 to 40 (n=1665)  
  o Mortality ratio O:E = 1.30  
  o Difference O-E = 23.2% (n=76)  
  • **Subgroup: grade**  
  • Grade 1 (n=156)  
  o Mortality ratio O:E = 1.25  
  o Difference O-E = 20% (n=1)  
  • Grade 2 (n=929)  
  o Mortality ratio O:E = 2.40  
  o Difference O-E = 58.4% (n=94)  
  • Grade 3 (n=1676)  
  o Mortality ratio O:E = 1.13  
  o Difference O-E = 11.9% (n=51)  
  • Unknown (n=66) | • PREDICT v1.2  
  • Other factors in the tool: menopausal status, morphology, LV invasion, ER status, local treatment, systemic treatment, HER2 status, ethnicity  
  • Other outcomes reported: 8-year all-cause mortality | • High quality, as assessed by CASP Clinical Prediction Rule checklist |
<table>
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<tr>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
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<th>Quality</th>
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<tr>
<td></td>
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<td>o Mortality ratio O:E = 1.71</td>
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<td>o Difference O-E = 41.7% (n=5)</td>
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<td>Subgroup: tumour size</td>
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<td>0 to 10 mm (n=265)</td>
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<td>o Mortality ratio O:E = 2.1</td>
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<td>o Difference O-E = 52.4% (n=22)</td>
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<td>11 to 20 mm (n=930)</td>
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<td>o Mortality ratio O:E = 1.25</td>
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<td>o Difference O-E = 20% (n=25)</td>
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<td>21 to 50 mm (n=1229)</td>
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<td>o Mortality ratio O:E = 1.26</td>
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<td>o Difference O-E = 22.8% (n=69)</td>
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<td>&gt;50 mm (n=244)</td>
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<td>o Mortality ratio O:E = 1.16</td>
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<td>o Difference O-E = 14% (n=85)</td>
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<td>Unknown (n=159)</td>
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<td>o Mortality ratio O:E = 2.44</td>
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<td>Negative (n=1370)</td>
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<td>o Mortality ratio O:E = 1.26</td>
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<td>o Difference O-E = 20.5% (n=33)</td>
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<td>Positive (n=1431)</td>
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<td>o Mortality ratio O:E = 1.35</td>
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<td>o Difference O-E = 26.2% (n=115)</td>
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<td>o Mortality ratio O:E = 1.75</td>
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<td>o Difference O-E = 42.9% (n=3)</td>
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<td>Negative (n=965)</td>
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<td>o Mortality ratio O:E = 0.82</td>
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### Study Details and Findings

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<td>o Difference O-E = -21.2% (n=52)</td>
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<td>Mortality ratio O:E = 2.29</td>
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<td>o Difference O-E = 56.4% (n=204)</td>
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<td>• Positive (n=679)</td>
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<td>o Difference O-E = 13.1% (n=24)</td>
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<td>• Borderline (n=40)</td>
<td>Mortality ratio O:E = 1.67</td>
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<td>o Difference O-E = 40% (n=4)</td>
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<td>• Unknown (n=335)</td>
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<td>• Tool discrimination</td>
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<td>AUC ER- vs ER+ = 0.718 vs 0.730</td>
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### 8-year all-cause mortality [PREDICT 1.0] (proxy for long-term OS)

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<td>Wishart (2010)</td>
<td>Validation study</td>
<td>Data from 5468 people with breast cancer from the West Midlands Cancer Intelligence Unit (WMCIU)</td>
<td>Prognostic accuracy (sensitivity, specificity)</td>
<td>PREDICT v1.0</td>
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<td>Study period: 1999 to 2003</td>
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<td>• Not reported</td>
<td>Validation study (data from the primary analysis has not been reported)</td>
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<td></td>
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<td>• Tool calibration and discrimination</td>
<td>10-year all-cause mortality was not reported in the paper. 8-year all-cause mortality was taken as a proxy outcome instead</td>
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<td>Total cohort (N=5468):</td>
<td>Moderate quality, as assessed by CASP Clinical Prediction Rule checklist.</td>
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<td>Mortality ratio O:E = 0.95</td>
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<td>Difference O-E = -0.93%</td>
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<td>• Subgroup: age</td>
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### Study Details

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<td>&lt;35 (n=108)</td>
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<td>- Mortality ratio O:E = 1.08</td>
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<td>- Difference O-E = 1.85%</td>
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<td>35 to 49 (n=1195)</td>
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<td>- Mortality ratio O:E = 0.87</td>
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<td>50 to 67 (n=2393)</td>
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<td>- Mortality ratio O:E = 0.92</td>
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<td>- Difference O-E = -1%</td>
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<td>65 to 74 (n=1101)</td>
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<td>75+ (n=671)</td>
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<td>Grade 2 (n=2442)</td>
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<td>- Difference O-E = 0.61%</td>
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<td>- Difference O-E = -1.03%</td>
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<td>10 to 19 mm (n=2136)</td>
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<td>• 20 to 29 mm (n=1566)</td>
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<td>o Difference O-E = -0.57%</td>
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<td>• 30 to 49 mm (n=923)</td>
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<td>o Mortality ratio O:E = 0.98</td>
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<td>o Difference O-E = -0.25%</td>
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<td>• <strong>Tool discrimination (AUC)</strong></td>
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<td>• Total cohort (N=5468): AUC (SE)</td>
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<td>= 0.79 (0.008)</td>
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<td>• <strong>Subgroup: age</strong></td>
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<td>• &lt;35 (n=108); AUC (SE) = 0.70 (0.057)</td>
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<td>• 35 to 49 (n=1195); AUC (SE) = 0.79 (0.018)</td>
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<td>• 50 to 67 (n=2393); AUC (SE) = 0.80 (0.013)</td>
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### Study details

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<td>65 to 74 (n=1101); AUC (SE) =0.76 (0.018)</td>
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<td>75+ (n=671); AUC (SE) = 0.72 (0.021)</td>
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<td>Subgroup: grade</td>
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<td>Grade 1 (n=1017): AUC (SE) = 0.79 (0.029)</td>
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<td>Grade 2 (n=2442): AUC (SE) = 0.77 (0.013)</td>
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<td>Grade 3 (n=2009): AUC (SE) = 0.75 (0.012)</td>
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<td>Subgroup: tumour size</td>
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<td>&lt;10 mm (n=485): AUC (SE) = 0.82 (0.040)</td>
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<td>10 to 19 mm (n=2136): AUC (SE) = 0.76 (0.018)</td>
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<td>20 to 29 mm (n=1566): AUC (SE) = 0.71 (0.017)</td>
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<td>30 to 49 mm (n=923): AUC (SE) = 0.72 (0.018)</td>
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<td>50+ mm (n=358): AUC (SE) = 0.72 (0.027)</td>
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<td>Negative (n=3184): AUC (SE) = 0.74 (0.015)</td>
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<td>Positive (n=2284): AUC (SE) = 0.75 (0.011)</td>
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<td>Subgroup: ER status</td>
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<td>Negative (n=1116): AUC (SE) = 0.76 (0.016)</td>
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<td>Positive (n=4352): AUC (SE) = 0.78 (0.010)</td>
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10-year all-cause mortality [PREDICT v1.2]
### Study Details

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<td>Maishman (2015)</td>
<td>Validation study Study period: 2000 to 2008</td>
<td>Data from 3000 women aged ≤40 years at diagnosis (POSH cohort)</td>
<td>- <strong>Prognostic accuracy (sensitivity, specificity)</strong></td>
<td>- PREDICT v1.2</td>
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<td>- <strong>Tool calibration</strong></td>
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<td>- Total cohort (N=597)</td>
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<td>- Grade 3 (n=351)</td>
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<td>o Difference O-E = -25.5% (n=26)</td>
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**Tool calibration:** Total cohort (N=597)
- Mortality ratio O:E = 0.93
- Difference O-E = -7.9% (n=12)

**Subgroup: age at diagnosis**
- 18 to 25 (n=8)
  - Mortality ratio O:E = 1
  - Difference O-E = 0% (n=0)
- 26 to 30 (n=55)
  - Mortality ratio O:E = 0.94
  - Difference O-E = -6.7% (n=1)
- 31 to 35 (n=203)
  - Mortality ratio O:E = 1.05
  - Difference O-E = 5% (n=3)
- 36 to 40 (n=331)
  - Mortality ratio O:E = 0.84
  - Difference O-E = -18.4% (n=14)

**Subgroup: grade**
- Grade 1 (n=31)
  - Mortality ratio O:E = 1.5
  - Difference O-E = 33% (n=1)
- Grade 2 (n=200)
  - Mortality ratio O:E = 1.42
  - Difference O-E = 30% (n=13)
- Grade 3 (n=351)
  - Mortality ratio O:E = 0.80
  - Difference O-E = -25.5% (n=26)

**Comments:**
- PREDICT v1.2
- Other factors in the tool: menopausal status, morphology, LV invasion, local treatment, systemic treatment, ethnicity
- Tool discrimination: very limited data reported (based on ER status and HER2 status)

**Quality:**
- High quality, as assessed by CASP Clinical Prediction Rule checklist
### Study details

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<td>o Difference O-E = 8% (n=9)</td>
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## Study details

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|       |            | o Mortality ratio O:E = 0.68  
|       |            | o Difference O-E = -46.9% (n=30)  
|       |            | • Positive (n=366)  
|       |            | o Mortality ratio O:E = 1.26  
|       |            | o Difference O-E = 20.5% (n=18)  
|       |            | • Subgroup: HER2 status  
|       |            | • Negative (n=327)  
|       |            | o Mortality ratio O:E = 0.99  
|       |            | o Difference O-E = -1.2% (n=1)  
|       |            | • Positive (n=140)  
|       |            | o Mortality ratio O:E = 0.94  
|       |            | o Difference O-E = -6% (n=3)  
|       |            | • Borderline (n=14)  
|       |            | o Mortality ratio O:E = 1.25  
|       |            | o Difference O-E = 20% (n=1)  
|       |            | • Unknown (n=116)  
|       |            | o Mortality ratio O:E = 0.62  
|       |            | o Difference O-E = -60% (n=9)  
|       |            | • Tool discrimination  
|       |            | • AUC ER- vs ER+ = 0.694 vs  
|       |            | 0.724 (discrimination was better  
|       |            | for ER+ tumours, compared to  
|       |            | ER- tumours)  
|       |            | • AUC HER2- vs HER2+ =0.724 vs  
|       |            | 0.592 (discrimination was better  
|       |            | for HER2- tumours, compared to  
|       |            | HER2+ tumours)  

### 10-year breast cancer mortality [PREDICT v1.1]

| Study | Study period: 1989 to 1998 | Data for 2232 cases of invasive breast cancer treated in Nottingham - 506 node-negative cases were excluded, | Prognostic accuracy (sensitivity, specificity)  
|-------|--------------------------|-----------------------------------------------------------------|-----------------------------------------------|
| Wishart (2014) | Validation study | • Prognostic accuracy (sensitivity, specificity)  
|       | Study period: 1989 to  
|       | 1998 | • PREDICT v1.1  
|       | Data for 2232 cases of  
|       | invasive breast cancer  
|       | treated in Nottingham -  
|       | 506 node-negative  
|       | cases were excluded, | • Moderate quality, as assessed by CASP Clinical Prediction Rule checklist |
|       |            | • Prognostic accuracy  
|       |            | (sensitivity, specificity)  
|       |            | • Not reported  
<p>|       |            | • Tool calibration |</p>
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<td>so data from n=1726 people was included in the study</td>
<td>Total cohort (N=1726)</td>
<td>• BC mortality ratio O:E = 1.13</td>
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<td>&lt;40 (n=67)</td>
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<td>40 to 49 (n=274)</td>
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<td>50 to 59 (n=436)</td>
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<td>60+ (n=497)</td>
<td>• BC mortality ratio O:E = 1.06</td>
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<td>Subgroup: tumour size</td>
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<td>&lt;10 (n=144)</td>
<td>• BC mortality ratio O:E = 0.78</td>
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<td>10 to 19 (n=574)</td>
<td>• BC mortality ratio O:E = 1.09</td>
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<td>20 to 29 (n=404)</td>
<td>• BC mortality ratio O:E = 1.32</td>
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<td>30 to 49 (n=140)</td>
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<td>5 to 9+ (n=37)</td>
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| Wishart (2014) | Validation study Study period: 1989 to 1998 | Data for 2232 cases of invasive breast cancer treated in Nottingham - 506 node-negative cases were excluded, so data from n=1726 people was included in the study | o **BC mortality ratio O:E = 1.10**  
• 10+ (n=6)  
• Missing (n=97)  
• **Subgroup: grade**  
• Grade 1 (n=235)  
• Grade 2 (n=528)  
• Grade 3 (n=395)  
• Missing grade (n=116)  
• **Subgroup: HER2 status**  
• Negative (n=792)  
• Positive (n=77)  
• Missing (n=405)  
• **Tool discrimination**  
• AUC = 0.7611 (CI not reported) | o **Prognostic accuracy (sensitivity, specificity)**  
• Not reported  
• **Tool calibration**  
• Total cohort (N=1726)  
• BC mortality ratio O:E = 1.08  
• **Subgroup: age**  
• <40 (n=67) | **PREDICT v1.2**  
• High quality, as assessed by CASP Clinical Prediction Rule checklist |
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<td>40 to 49 (n=274)</td>
<td>BC mortality ratio O:E = 1.13</td>
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<td>50 to 59 (n=436)</td>
<td>BC mortality ratio O:E = 1.15</td>
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<td>BC mortality ratio O:E = 1.01</td>
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<td>10 to 19 (n=574)</td>
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<td>• BC mortality ratio O:E = 1.17</td>
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<td>• • Positive (n=77)</td>
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<td>• • Missing (n=405)</td>
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<td>• Tool discrimination</td>
<td>• AUC = 0.7676 (CI not reported)</td>
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<td>• Significant improvement</td>
<td>• compared to v1.1 (p-value = 0.0008) (see Wishart 2014, data for v1.1.)</td>
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10-year breast cancer mortality [PREDICT v2.0]

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<th>Study period:</th>
<th>Prognostic accuracy (sensitivity, specificity)</th>
<th>Tool calibration</th>
<th>Validation study (data from the primary analysis has not been reported)</th>
<th>High quality, as assessed by CASP Clinical Prediction Rule checklist</th>
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<td>Candido dos Reis (2017)</td>
<td>Validation study Validations study Study period:</td>
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<td>• Total cohort: not reported</td>
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<td>• NTBCS: 1989 to 1998</td>
<td>• Tool calibration</td>
<td>• POSH: 2000 to 2008</td>
<td>• Subgroup: age at diagnosis</td>
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<td>o difference O:E = -6% (p-value = 0.76)</td>
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<td>20 to 29 (n=140):</td>
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<td>o difference O:E = -11% (p-value = 0.16)</td>
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<td>50 to 59 (n=467):</td>
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<td>60 to 69 (n=517):</td>
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<td>70 to 79 (n=55):</td>
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<td>o BC mortality ratio = 0.38; o difference O:E = -26% (p-value = 0.54)</td>
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<td>Subgroup: tumour size</td>
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<td>0 to 9 mm (n=96):</td>
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<td>o BC mortality ratio = 0.90; o difference O:E = -10% (p-value = 0.73)</td>
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<td>10 to 19 mm (n=559):</td>
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<td>o BC mortality ratio = 0.92; o difference O:E = -8% (p-value = 0.41)</td>
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<td>20 to 29 mm (n=524):</td>
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<td>o BC mortality ratio = 0.97; o difference O:E = -3% (p-value = 0.72)</td>
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<td>30 to 49 mm (n=354):</td>
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<td>o BC mortality ratio = 0.99; o difference O:E = -1% (p-value = 0.91)</td>
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<td>50+ mm (n=121):</td>
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<td>o difference O:E = -33% (p-value = 0.04)</td>
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<td>0 to 9 mm (n=352):</td>
<td>BC mortality ratio = 1.54;</td>
<td>BC mortality ratio = 35% (p-value = 0.024)</td>
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<td>10 to 19 mm (n=1428):</td>
<td>BC mortality ratio = 1.06;</td>
<td>BC mortality ratio = 6% (p-value = 0.46)</td>
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<td>20 to 29 mm (n=1111):</td>
<td>BC mortality ratio = 0.98;</td>
<td>BC mortality ratio = -2% (p-value = 0.80)</td>
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<td>30 to 49 mm (n=695):</td>
<td>BC mortality ratio = 0.87;</td>
<td>BC mortality ratio = -15% (p-value = 0.07)</td>
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<td>50+ mm (n=289):</td>
<td>BC mortality ratio = 0.74;</td>
<td>BC mortality ratio = -35% (p-value = 0.00)</td>
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<td>Subgroup: tumour grade</td>
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<td>1 (n=44):</td>
<td>BC mortality ratio = 0.96;</td>
<td>BC mortality ratio = -4% (p-value = 0.91)</td>
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<td>2 (n=183):</td>
<td>BC mortality ratio = 0.86;</td>
<td>BC mortality ratio = -17% (p-value = 0.33)</td>
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<td>3 (n=1427):</td>
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Early and locally advanced breast cancer: diagnosis and management: evidence reviews for adjuvant systemic therapy planning July 2018
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<th>Comments</th>
<th>Quality</th>
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<td>o BC mortality ratio = 0.94;</td>
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<td>o difference O:E = -7% (p-value = 0.19)</td>
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<td>• ER+</td>
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<td>• 1 (n=658):</td>
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<td>o BC mortality ratio = 0.86;</td>
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<td>o difference O:E = -16% (p-value = 0.43)</td>
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<td>• 2 (n=1730):</td>
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<td>o BC mortality ratio = 0.95;</td>
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<td>o difference O:E = -5% (p-value = 0.44)</td>
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<td>• Subgroup: nodes positive</td>
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<td>• 0 (n=937):</td>
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<td>o difference O:E = 1% (p-value = 0.89)</td>
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<td>• 1 (n=232):</td>
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<td>o BC mortality ratio = 0.86;</td>
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<td></td>
<td>o difference O:E = -17% (p-value = 0.23)</td>
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<td>• 2 to 4 (n=300):</td>
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<td>o BC mortality ratio = 0.88;</td>
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<td>o difference O:E = -13% (p-value = 0.19)</td>
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<td>• 5 to 9 (n=101):</td>
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<td>o BC mortality ratio = 0.96;</td>
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<td>o difference O:E = -4% (p-value = 0.77)</td>
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## Study details

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<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
<td>10+ (n=84):</td>
<td>o BC mortality ratio = 0.85; o difference O:E = -17% (p-value = 0.28)</td>
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<td>ER+</td>
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<td>0 (n=2085):</td>
<td>o BC mortality ratio = 0.99; o difference O:E = -1% (p-value = 0.85)</td>
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<td>1 (n=675):</td>
<td>o BC mortality ratio = 0.92; o difference O:E = -9% (p-value = 0.39)</td>
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<td>2 to 4 (n=734):</td>
<td>o BC mortality ratio = 0.96; o difference O:E = -4% (p-value = 0.63)</td>
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<td>5 to 9 (n=245):</td>
<td>o BC mortality ratio = 0.86; o difference O:E = -17% (p-value = 0.14)</td>
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<td>10+ (n=136):</td>
<td>o BC mortality ratio = 0.87; o difference O:E = -15% (p-value = 0.25)</td>
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<td>Tool discrimination</td>
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<td>ER-: AUC = 0.696</td>
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<td>ER+: AUC = 0.760</td>
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<td>All population: AUC = 0.752</td>
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AUC, area under the curve; BC, breast cancer; BCOS, Breast Cancer Outcomes Simulator; BCS, breast cancer survival; CASP, Critical Appraisal Skills Programme; ER, oestrogen receptor; HER2, Human epidermal growth factor receptor 2; LV, lymphovascular; NGA, National Guideline Alliance; NTBC, Nottingham Tenovus Breast Cancer; O:E, observed/expected; POSH, Prospective study of Outcomes in Sporadic versus Hereditary breast cancer; SE, standard error; UK, United Kingdom; WMCIU, West Midlands Cancer Intelligence Unit
Predictive prognostic tool 3: Nottingham Prognostic Index (NPI)

Table 8: Summary of included studies and results for Nottingham Prognostic Index (NPI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blamey (2007)</td>
<td>Validation study</td>
<td>Women diagnosed with or treated for primary operable invasive breast cancer at Nottingham city hospital</td>
<td><strong>Prognostic accuracy (sensitivity, specificity)</strong>&lt;br&gt;Not reported&lt;br&gt;&lt;br&gt;<strong>Tool calibration</strong>&lt;br&gt;Results only available for the 2000 to 2009 cohort&lt;br&gt;Total cohort = not reported&lt;br&gt;EPG (n=320)&lt;br&gt;BCS ratio O:E = 0.98&lt;br&gt;GPG (n=475)&lt;br&gt;BCS ratio O:E = 0.99&lt;br&gt;MPG I (n=634)&lt;br&gt;BCS ratio O:E = 1.03&lt;br&gt;MPG II (n=489)&lt;br&gt;BCS ratio O:E = 1.00&lt;br&gt;PPG (n=233)&lt;br&gt;BCS ratio O:E = 1.02&lt;br&gt;VPG (n=86)&lt;br&gt;BCS ratio O:E = 0.89&lt;br&gt;&lt;br&gt;<strong>Tool discrimination</strong>&lt;br&gt;Not reported</td>
<td>• Observed survival was adjusted by subtracting expected number of deaths for all causes was subtracted. Data was obtained from the Office of National Statistics for England and Wales&lt;br&gt;• BCS ratio O:E was calculated by the NGA technical team based on available data on the paper</td>
<td>• High quality, as assessed by CASP Clinical Prediction Rule checklist.</td>
</tr>
</tbody>
</table>

BCS: breast cancer survival; CASP: Critical Appraisal Skills Programme; NGA: National Guideline Alliance; NPI: Nottingham Prognostic Index; O:E: observed: expected; UK: United Kingdom

Predictive prognostic tool 4: FinProg

No studies were identified for this prognostic tool.
Predictive prognostic tool 5: CancerMath

No studies were identified for this prognostic tool.

Predictive prognostic tool 6: Oxford Prognostic Index (OPI)

Table 9: Summary of included studies and results for Oxford Prognostic Index (OPI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell (2010)</td>
<td>Validation study Study period: 1992 to 2000</td>
<td>N=1787 women with invasive ductal carcinoma, a sub-set obtained from the Adjuvant Breast Cancer trial from 70 UK centres</td>
<td>Prognostic accuracy (sensitivity, specificity) Not reported Tool calibration Total cohort (N=1789) o RFS ratio O:E:1.01 o Difference O-E: 0.7% Subgroup: age • ≤50 years (n=1097) o RFS ratio O:E: 1.03 o Difference O-E: 1.92% • &gt; 50 years (n=690) o RFS ratio O:E: 1.00 o Difference O-E: -0.10% Subgroup: tumour grade • Grade 1 (n=196) o RFS ratio O:E: 1.06 o Difference O-E: 5.15% • Grade 2 (n=772) o RFS ratio O:E: 1.03 o Difference O-E: 2.44% • Grade 3 (n=819) o RFS ratio O:E: 0.98 o Difference O-E: -1.04% Subgroup: tumour size</td>
<td>• Study provided data as E:O. The NGA technical team has calculated the RFS ratio O:E and the difference O-E • No other factors were in the tool</td>
<td>Moderate quality, as assessed by CASP Clinical Prediction Rule checklist.</td>
</tr>
</tbody>
</table>
### Study details

<table>
<thead>
<tr>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
<th>Quality</th>
</tr>
</thead>
</table>
| ≤2 cm (n=954) | RFS ratio O:E: 1.06  
| Difference O-E: 4.6% | | |
| >2 cm to ≤5 cm (n=772) | RFS ratio O:E: 0.95  
| Difference O-E: -3.16% | | |
| >5 cm (n=61) | RFS ratio O:E: 1.04  
| Difference O-E: -2.47% | | |

**Subgroup: nodal status**

- Negative (n=674)  
  - RFS ratio O:E: 1.02  
  - Difference O-E: 1.82  

- Positive (n=1113)  
  - RFS ratio O:E: 1.01  
  - Difference O-E: 0.71%  

**Subgroup: ER status**

- Negative (n=1097)  
  - RFS ratio O:E: 1.03  
  - Difference O-E: 1.92%  

- Positive (n=690)  
  - RFS ratio O:E: 1.00  
  - Difference O-E: -0.10%  

**Tool discrimination**

- Overall C = 0.720 (95%CI 0.693 to 0.746)

---

**BCS**, breast cancer survival; **NGA**, National Guideline Alliance; **O:E**, observed/expected; **OPI**, Oxford Prognostic Index; **RFS**, recurrence free survival; **UK**, United Kingdom

Full GRADE tables are not available as GRADE is not appropriate to assess the quality of evidence for prediction model performance reviews.
Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Predictive prognostic tool 1: Adjuvant! Online

Critical outcomes

Tool calibration - 10-year breast cancer specific survival

There was good quality evidence from 1 validation study conducted in the UK with 1065 (data available for n=1058) women with early breast cancer that reported the following:

- For the whole cohort (N=1058), Adjuvant! Online showed good calibration (O:E = 0.95). The tool overestimated 10-year breast cancer specific survival by 4.53% (p-value <0.01).

The study also reported the calibration according to different factors:

Subgroup: age

- for women aged 20 to 35 (n=34), Adjuvant! Online showed good calibration (O:E = 0.99). This tool overestimated 10-year breast cancer specific survival by 0.67% (p-value: ns);
- for women aged 36 to 50 (n=361), Adjuvant! Online showed good calibration (O:E = 0.94). This tool overestimated 10-year breast cancer specific survival by 4.62% (p-value <0.05);
- for women aged 51 to 65 (n=454), Adjuvant! Online showed good calibration (O:E = 0.96). This tool overestimated 10-year breast cancer specific survival by 3.51% (p-value: ns);
- for women aged 66 to 75 (n=193), Adjuvant! Online showed good calibration (O:E = 0.89). This tool underestimated 10-year breast cancer specific survival by 7.04% (p-value <0.05);
- for women aged ≥76 (n=16), Adjuvant! Online showed good calibration (O:E = 0.94). This tool overestimated 10-year breast cancer specific survival by 3.11% (p-value: n.s).

Subgroup: tumour grade

- for women with grade 1 breast cancer (n=152), Adjuvant! Online showed good calibration (O:E = 0.99). This tool overestimated 10-year breast cancer specific survival by 1.29% (p-value: ns);
- for women with grade 2 breast cancer (n=420), Adjuvant! Online showed good calibration (O:E = 0.93). This tool overestimated 10-year breast cancer specific survival by 5.89% (p-value <0.01);
- for women with grade 3 breast cancer (n=243), Adjuvant! Online showed good calibration (O:E = 0.92). This tool overestimated 10-year breast cancer specific survival by 6.10% (p-value <0.05);
- for women with unknown grade (n=243), Adjuvant! Online showed good calibration (O:E = 0.96). This tool overestimated 10-year breast cancer specific survival by 2.78% (p-value: ns).

Subgroup: tumour size

- for women with tumour size 0.1 to 1 cm (n=148), Adjuvant! Online showed good calibration (O:E = 0.92). This tool overestimated 10-year breast cancer specific survival by 7.95% (p-value <0.01);
for women with tumour size 1.1 to 2 cm (n=470), Adjuvant! Online showed good calibration (O:E = 0.95). This tool overestimated 10-year breast cancer specific survival by 4.54% (p-value < 0.01);

for women with tumour size 2.1 to 5 cm (n=440), Adjuvant! Online showed good calibration (O:E = 0.95). This tool overestimated 10-year breast cancer specific survival by 3.53% (p-value: n.s).

Subgroup: nodal status

for women with negative nodal status (n=729), Adjuvant! Online showed good calibration (O:E = 0.96). This tool overestimated 10-year breast cancer specific survival by 3.53% (p-value < 0.01);

for women with positive nodal status (n=329), Adjuvant! Online showed good calibration (O:E = 0.91). This tool overestimated 10-year breast cancer specific survival by 6.73% (p-value < 0.01).

Subgroup: ER status

for women with negative ER status (n=259), Adjuvant! Online showed good calibration (O:E = 0.97). This tool overestimated 10-year breast cancer specific survival by 2.76% (p-value: n.s);

for women with positive ER status (n=491), Adjuvant! Online showed good calibration (O:E = 0.89). This tool overestimated 10-year breast cancer specific survival by 6.62% (p-value < 0.01);

for women with unknown ER status (n=308), Adjuvant! Online showed good calibration (O:E = 0.96). This tool overestimated 10-year breast cancer specific survival by 2.74% (p-value: n.s).

Tool calibration - 10-year overall survival

There was good quality evidence from 1 validation study conducted in the UK with 1065 women with early breast cancer that reported the following:

- For the whole cohort (N=1065), Adjuvant! Online showed good calibration (O:E = 0.93). The tool overestimated 10-year overall survival by 5.54% (p-value < 0.01).

The study also reported the tool calibration according to different factors:

Subgroup: age

- for women aged 20 to 35 (n=34), Adjuvant! Online showed good calibration (O:E = 0.97). This tool overestimated 10-year overall survival by 2.27% (p-value: n.s);

- for women aged 36 to 50 (n=363), Adjuvant! Online showed good calibration (O:E = 0.95). This tool overestimated 10-year overall survival by 4.33% (p-value < 0.05);

- for women aged 51 to 65 (n=458), Adjuvant! Online showed good calibration (O:E = 0.95). This tool overestimated 10-year overall survival by 4.02% (p-value < 0.05);

- for women aged 66 to 75 (n=194), Adjuvant! Online showed good calibration (O:E = 0.82). This tool overestimated 10-year overall survival by 11.17% (p-value < 0.01);

- for women aged ≥76 (n=16), Adjuvant! Online showed good calibration (O:E = 0.94). This tool underestimated 10-year overall survival by 3.11% (p-value: ns).

Subgroup: tumour grade

- for women with grade 1 breast cancer (n=152), Adjuvant! Online showed good calibration (O:E = 0.96). This tool overestimated 10-year overall survival by 3.6% (p-value: ns);

- for women with grade 2 breast cancer (n=421), Adjuvant! Online showed good calibration (O:E = 0.91). This tool overestimated 10-year overall survival by 7.0% (p-value < 0.01);

- for women with grade 3 breast cancer (n=248), Adjuvant! Online showed good calibration (O:E = 0.86). This tool overestimated 10-year overall survival by 9.8% (p-value < 0.01);
for women with unknown grade (n=244), Adjuvant! Online showed perfect calibration (O:E = 1.00). This tool overestimated 10-year overall survival by 0.2% (p-value: ns).

Subgroup: tumour size
- for women with tumour size 0.1 to 1 cm (n=150), Adjuvant! Online showed good calibration (O:E = 0.93). This tool overestimated 10-year overall survival by 6.10% (p-value: ns);
- for women with tumour size 1.1 to 2 cm (n=471), Adjuvant! Online showed good calibration (O:E = 0.92). This tool overestimated 10-year overall survival by 6.57% (p-value <0.01);
- for women with tumour size 2.1 to 5 cm (n=444), Adjuvant! Online showed good calibration (O:E = 0.94). This tool overestimated 10-year overall survival survival by 4.26% (p-value: ns).

Subgroup: nodal status
- for women with negative nodal status (n=733), Adjuvant! Online showed good calibration (O:E = 0.94). This tool overestimated 10-year overall survival by 4.70% (p-value <0.01);
- for women with positive nodal status (n=332), Adjuvant! Online showed good calibration (O:E = 0.89). This tool overestimated 10-year overall survival survival by 7.38% (p-value <0.01).

Subgroup: ER status
- for women with negative ER status (n=261), Adjuvant! Online showed good calibration (O:E = 0.97). This tool overestimated 10-year overall survival by 6.57% (p-value: ns);
- for women with positive ER status (n=495), Adjuvant! Online showed good calibration (O:E = 0.89). This tool overestimated 10-year overall survival survival by 4.26% (p-value <0.01);
- for women with unknown ER status (n=309), Adjuvant! Online showed good calibration (O:E = 0.96). This tool overestimated 10-year overall survival survival by 4.26% (p-value: ns).

Tool discrimination
- No evidence was found for this outcome.

Important outcomes

Prognostic accuracy (sensitivity, specificity)
- No evidence was found for this outcome.

Predictive prognostic tool 2: PREDICT

Critical outcomes

Tool calibration and discrimination - 5 year all-cause mortality [PREDICT v1.0]
There was moderate quality evidence from 1 validation study conducted in the UK with 5648 women diagnosed with invasive breast cancer that reported the following:
- for the whole cohort (N=5468), PREDICT v1.0 showed good calibration (O:E = 0.91). The tool overestimated the number of deaths at 5 years by 1.61%.

The study also reported the tool calibration and discrimination according to different factors:

Subgroup: age at diagnosis
- for the women aged <35 (n=108), PREDICT v1.0 showed good calibration (O:E = 0.88). The tool overestimated the number of deaths at 5 years by 2.78%;
- for the women aged 35 to 49 (n=1195), PREDICT v1.0 showed good calibration (O:E = 0.83). The tool overestimated the number of deaths at 5 years by 2.68%;
for the women aged 50 to 67 (n=2393), PREDICT v1.0 showed good calibration (O:E = 0.90). The tool overestimated the number of deaths at 5 years by 1.34%;

for the women aged 65 to 74 (n=1101), PREDICT v1.0 showed good calibration (O:E = 0.98). The tool overestimated the number of deaths at 5 years by 0.45%;

for the women aged 75+ (n=671), PREDICT v1.0 showed good calibration (O:E = 0.98). The tool overestimated the number of deaths at 5 years by 0.75%.

**Subgroup: tumour grade**

- for women with grade 1 tumour (n=1017), PREDICT v1.0 showed good calibration (O:E = 0.98). The tool overestimated the number of deaths at 5 years by 0.1%;
- for women with grade 2 tumour (n=2442), PREDICT v1.0 showed good calibration (O:E = 0.98). The tool overestimated the number of deaths at 5 years by 0.16%;
- for women with grade 3 tumour (n=2009), PREDICT v1.0 showed good calibration (O:E = 0.87). The tool overestimated the number of deaths at 5 years by 3.58%.

**Subgroup: tumour size**

- for women with tumours <10 mm. (n=485), PREDICT v1.0 showed good calibration (O:E = 0.84). The tool overestimated the number of deaths at 5 years by 1.03%;
- for women with tumours 11 to 19 mm. (n=2136), PREDICT v1.0 showed good calibration (O:E = 0.88). The tool overestimated the number of deaths at 5 years by 2.01%;
- for women with tumours 20 to 19 mm. (n=1566), PREDICT v1.0 showed good calibration (O:E = 0.94). The tool overestimated the number of deaths at 5 years by 0.96%;
- for women with tumours 30 to 49 mm. (n=923), PREDICT v1.0 showed good calibration (O:E = 0.99). The tool overestimated the number of deaths at 5 years by 0.11%;
- for women with tumours 50+ mm. (n=358), PREDICT v1.0 showed good calibration (O:E = 0.91). The tool overestimated the number of deaths at 5 years by 3.91%.

**Subgroup: nodal status**

- for women with negative nodal status (n=3184), PREDICT v1.0 showed good calibration (O:E = 0.80). The tool overestimated the number of deaths at 5 years by 2.14%;
- for women with positive nodal status (n=2284), PREDICT v1.0 showed good calibration (O:E = 0.98). The tool overestimated the number of deaths at 5 years by 0.39%.

**Subgroup: ER status**

- for women with negative ER status (n=1116), PREDICT v1.0 showed good calibration (O:E = 0.87). The tool overestimated the number of deaths at 5 years by 4.21%. The tool also showed good discrimination (AUC = 0.81);
- for women with positive ER status (n=4352), PREDICT v1.0 showed good calibration (O:E = 0.95). The tool overestimated the number of deaths at 5 years by 0.69%. The tool also showed good discrimination (AUC = 0.75).

**Tool calibration - 5 year all-cause mortality [PREDICT v1.2]**

There was good quality evidence from 1 validation study conducted in the UK with 3000 women aged ≤40 years at diagnosis that reported the following:

- for the whole cohort (N=2827), PREDICT v1.2 showed poor calibration (O:E = 1.33). The tool overestimated the number of deaths at 5 years by 25%. The tool also showed poor discrimination for both ER- (AUC=0.718) and ER+ and (AUC=0.730) groups.

The study also reported the calibration according to different factors:

**Subgroup: age at diagnosis**
for the women aged 18 to 25 (n=40), PREDICT v1.2 showed poor calibration (O:E = 1.4). The tool underestimated the number of deaths at 5 years by 28.6%;

for the women aged 26 to 30 (n=258), PREDICT v1.2 showed poor calibration (O:E = 1.35). The tool underestimated the number of deaths at 5 years by 25.8%;

for the women aged 31 to 35 (n=864), PREDICT v1.2 showed poor calibration (O:E = 1.38). The tool underestimated the number of deaths at 5 years by 27.6%;

for the women aged 36 to 40 (n=1665), PREDICT v1.2 showed poor calibration (O:E = 1.30). The tool underestimated the number of deaths at 5 years by 23.2%.

Subgroup: tumour grade

- for women with grade 1 tumour (n=156), PREDICT v1.2 showed poor calibration (O:E = 1.25). The tool underestimated the number of deaths at 5 years by 20%;
- for women with grade 2 tumour (n=929), PREDICT v1.2 showed poor calibration (O:E = 2.40). The tool underestimated the number of deaths at 5 years by 58.4%;
- for women with grade 3 tumour (n=1676), PREDICT v1.2 showed good calibration (O:E = 1.13). The tool underestimated the number of deaths at 5 years by 11.9%;
- for women with unknown grade tumour (n=66), PREDICT v1.2 showed poor calibration (O:E = 1.71). The tool underestimated the number of deaths at 5 years by 41.7%.

Subgroup: tumour size

- for women with tumours 0 to 10 mm. (n=265), PREDICT v1.2 showed poor calibration (O:E = 2.1). The tool underestimated the number of deaths at 5 years by 52.4%;
- for women with tumours 11 to 20 mm. (n=930), PREDICT v1.2 showed poor calibration (O:E = 1.25). The tool underestimated the number of deaths at 5 years by 20%;
- for women with tumours 21 to 50 mm. (n=1229), PREDICT v1.2 showed poor calibration (O:E = 1.26). The tool underestimated the number of deaths at 5 years by 22.8%;
- for women with tumours >50 mm. (n=244), PREDICT v1.2 showed good calibration (O:E = 1.16). The tool underestimated the number of deaths at 5 years by 14%.
- for women with unknown size tumours (n=159), PREDICT v1.2 showed poor calibration (O:E = 2.44). The tool underestimated the number of deaths at 5 years by 59%.

Subgroup: nodal status

- for women with negative nodal status (n=1370), PREDICT v1.2 showed poor calibration (O:E = 1.26). The tool underestimated the number of deaths at 5 years by 20.5%;
- for women with positive nodal status (n=1431), PREDICT v1.2 showed poor calibration (O:E = 1.35). The tool underestimated the number of deaths at 5 years by 26.2%;
- for women with unknown nodal status (n=26), PREDICT v1.2 showed poor calibration (O:E = 1.75). The tool underestimated the number of deaths at 5 years by 42.9%.

Subgroup: ER status

- for women with negative ER status (n=965), PREDICT v1.2 showed good calibration (O:E = 0.82). The tool overestimated the number of deaths at 5 years by 21.2%;
- for women with unknown ER status (n=1862), PREDICT v1.2 showed poor calibration (O:E = 2.29). The tool underestimated the number of deaths at 5 years by 56.4%.

Subgroup: HER2 status

- for women with negative HER2 status (n=1773), PREDICT v1.2 showed poor calibration (O:E = 1.50). The tool underestimated the number of deaths at 5 years by 33.4%;
- for women with positive HER2 status (n=679), PREDICT v1.2 showed good calibration (O:E = 1.15). The tool underestimated the number of deaths at 5 years by 13.1%;
• for women with borderline HER2 status (n=40), PREDICT v1.2 showed poor calibration (O:E = 1.67). The tool underestimated the number of deaths at 5 years by 40%.
• for women with unknown HER2 status (n=335), PREDICT v1.2 showed good calibration (O:E = 0.88). The tool overestimated the number of deaths at 5 years by 12.9%.

Tool calibration and discrimination - 8 year all-cause mortality [PREDICT v1.0] (proxy outcome for long term all-cause mortality)

There was good moderate evidence from 1 validation study conducted in the UK with 5648 women diagnosed with invasive breast cancer that reported the following:
• for the whole cohort (N=5468), PREDICT v1.0 showed good calibration (O:E = 0.95) and good discrimination (AUC = 0.79). The tool overestimated the number of deaths at 8 years by 0.93%.

The study also reported the tool calibration according to different factors:

Subgroup: age at diagnosis
• for the women aged <35 (n=108), PREDICT v1.0 showed good calibration (O:E = 1.08) but poor discrimination (AUC = 0.70). The tool underestimated the number of deaths at 8 years by 1.85%.
• for the women aged 35 to 49 (n=1195), PREDICT v1.0 showed good calibration (O:E = 0.87) and good discrimination (AUC = 0.79). The tool overestimated the number of deaths at 8 years by 2.18%.
• for the women aged 50 to 67 (n=2393), PREDICT v1.0 showed good calibration (O:E = 0.92) and good discrimination (AUC = 0.80). The tool overestimated the number of deaths at 8 years by 0.09%.
• for the women aged 65 to 74 (n=1101), PREDICT v1.0 showed good calibration (O:E ≈ 1.00) and good discrimination (AUC = 0.76). The tool underestimated the number of deaths at 8 years by 0.45%.
• for the women aged 75+ (n=671), PREDICT v1.0 showed good calibration (O:E = 0.98) but poor discrimination (AUC = 0.72). The tool overestimated the number of deaths at 8 years by 0.6%.

Subgroup: tumour grade
• for women with grade 1 tumour (n=1017), PREDICT v1.0 showed good calibration (O:E = 1.04) and good discrimination (AUC = 0.79). The tool underestimated the number of deaths at 8 years by 0.29%.
• for women with grade 2 tumour (n=2442), PREDICT v1.0 showed good calibration (O:E = 1.04) and good discrimination (AUC = 0.77). The tool underestimated the number of deaths at 8 years by 0.61%.
• for women with grade 3 tumour (n=2009), PREDICT v1.0 showed good calibration (O:E = 0.88) and good discrimination (AUC = 0.75). The tool overestimated the number of deaths at 8 years by 3.38%.

Subgroup: tumour size
• for women with tumours <10 mm. (n=485), PREDICT v1.0 showed good calibration (O:E = 0.85) and good discrimination (AUC = 0.82). The tool overestimated the number of deaths at 8 years by 1.03%.
• for women with tumours 11 to 19 mm. (n=2136), PREDICT v1.0 showed good calibration (O:E = 0.84) and good discrimination (AUC = 0.76). The tool overestimated the number of deaths at 8 years by 1.73%.
for women with tumours 20 to 19 mm. (n=1566), PREDICT v1.0 showed good calibration (O:E = 0.97) but poor discrimination (AUC = 0.71). The tool overestimated the number of deaths at 8 years by 0.57%;

for women with tumours 30 to 49 mm. (n=923), PREDICT v1.0 showed good calibration (O:E = 0.98) but poor discrimination (AUC = 0.72). The tool overestimated the number of deaths at 8 years by 0.43%;

for women with tumours 50+ mm. (n=358), PREDICT v1.0 showed poor calibration (O:E = 0.56) and poor discrimination (AUC = 0.72). The tool overestimated the number of deaths at 8 years by 3.35%.

Subgroup: nodal status

for women with negative nodal status (n=3184), PREDICT v1.0 showed good calibration (O:E = 0.84) but poor discrimination (AUC = 0.74). The tool overestimated the number of deaths at 8 years by 1.76%;

for women with positive nodal status (n=2284), PREDICT v1.0 showed good calibration (O:E = 1.01) and good discrimination (AUC = 0.75). The tool underestimated the number of deaths at 8 years by 0.26%.

Subgroup: ER status

for women with negative ER status (n=1116), PREDICT v1.0 showed good calibration (O:E = 0.90) and good discrimination (AUC = 0.76). The tool overestimated the number of deaths at 8 years by 3.49%;

for women with positive ER status (n=4352), PREDICT v1.0 showed good calibration (O:E = 0.98) and good discrimination (AUC = 0.78). The tool overestimated the number of deaths at 8 years by 0.25%.

Tool calibration and discrimination - 10 year all-cause mortality [PREDICT v1.2]

There was good quality evidence from 1 validation study conducted in the UK with 3000 women aged ≤40 years at diagnosis that reported the following:

for the whole cohort (N=597), PREDICT v1.2 showed good calibration (O:E = 0.93). The tool overestimated the number of deaths at 10 years by 7.9%.

The study also reported the tool calibration and discrimination according to different factors:

Subgroup: age at diagnosis

for the women aged 18 to 25 (n=8), PREDICT v1.2 showed perfect calibration (O:E = 1);

for the women aged 26 to 30 (n=55), PREDICT v1.2 showed good calibration (O:E = 0.94). The tool overestimated the number of deaths at 10 years by 6.7%;

for the women aged 31 to 35 (n=203), PREDICT v1.2 showed good calibration (O:E = 1.05). The tool underestimated the number of deaths at 10 years by 5%;

for the women aged 36 to 40 (n=331), PREDICT v1.2 showed good calibration (O:E = 0.84). The tool overestimated the number of deaths at 10 years by 18.4%.

Subgroup: tumour grade

for women with grade 1 tumour (n=31), PREDICT v1.2 showed poor calibration (O:E = 1.5). The tool underestimated the number of deaths at 10 years by 33%;

for women with grade 2 tumour (n=200), PREDICT v1.2 showed poor calibration (O:E = 1.42). The tool underestimated the number of deaths at 10 years by 30%;

for women with grade 3 tumour (n=351), PREDICT v1.2 showed good calibration (O:E = 0.80). The tool overestimated the number of deaths at 10 years by 25.5%;

for women with unknown grade tumour (n=15), PREDICT v1.2 showed perfect calibration (O:E = 1).
**Subgroup: tumour size**

- for women with tumours 0 to 10 mm. (n=48), PREDICT v1.2 showed poor calibration (O:E = 2). The tool underestimated the number of deaths at 10 years by 50%;
- for women with tumours 11 to 20 mm. (n=221), PREDICT v1.2 showed good calibration (O:E = 0.91). The tool overestimated the number of deaths at 10 years by 9.8%;
- for women with tumours 21 to 50 mm. (n=244), PREDICT v1.2 showed good calibration (O:E = 0.99). The tool overestimated the number of deaths at 10 years by 1.3%;
- for women with tumours >50 mm. (n=54), PREDICT v1.2 showed poor calibration (O:E = 0.46). The tool overestimated the number of deaths at 10 years by 115.4%;
- for women with unknown size tumours (n=30), PREDICT v1.2 showed good calibration (O:E = 1.2). The tool underestimated the number of deaths at 5 years by 16.7%.

**Subgroup: node status**

- for women with negative nodal status (n=266), PREDICT v1.2 showed good calibration (O:E = 0.93). The tool overestimated the number of deaths at 10 years by 7.7%;
- for women with positive nodal status (n=327), PREDICT v1.2 showed good calibration (O:E = 0.92). The tool overestimated the number of deaths at 10 years by 8%;
- for women with unknown nodal status (n=4), PREDICT v1.2 showed perfect calibration (O:E = 1).

**Subgroup: ER status**

- for women with negative ER status (n=231), PREDICT v1.2 showed poor calibration (O:E = 0.68). The tool overestimated the number of deaths at 10 years by 46.9%. The tool also showed poor discrimination (AUC=0.694);
- for women with unknown ER status (n=366), PREDICT v1.2 showed poor calibration (O:E = 1.26). The tool underestimated the number of deaths at 10 years by 20.5%. The tool also showed poor discrimination (AUC=0.694).

**Subgroup: HER2 status**

- for women with negative HER2 status (n=327), PREDICT v1.2 showed good calibration (O:E = 0.99). The tool overestimated the number of deaths at 10 years by 1.2%. However the tool showed poor discrimination (AUC=0.724);
- for women with positive HER2 status (n=140), PREDICT v1.2 showed good calibration (O:E = 0.94). The tool overestimated the number of deaths at 10 years by 6%. However the tool showed poor discrimination (AUC=0.592);
- for women with borderline HER2 status (n=14), PREDICT v1.2 showed poor calibration (O:E = 1.25). The tool underestimated the number of deaths at 10 years by 20%;
- for women with unknown HER2 status (n=116), PREDICT v1.2 showed poor calibration (O:E = 0.62). The tool overestimated the number of deaths at 10 years by 60%.

**Tool calibration and discrimination - 10 year breast cancer mortality [PREDICT v1.1 and v1.2]**

There was good quality evidence from 1 validation study conducted in the UK with 1726 cases of invasive breast cancer and ER+ that reported the following:

- for the whole cohort (N=1726), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.13 and 1.08 respectively). The tool also showed good discrimination [AUC = 0.7611 and 0.7676 respectively – (p-value = 0.0008)].

The study also reported the tool calibration according to different factors:

**Subgroup: age**
• for the women aged <40 (n=67), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.15 and 1.07 respectively);
• for the women aged 40 to 49 (n=274), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.18 and 1.13 respectively);
• for the women aged 50 to 59 (n=436), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.18 and 1.15 respectively);
• for the women aged 60+ (n=497), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.06 and 1.01 respectively).

Subgroup: tumour size
• for women with tumours <10 mm (n=144), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 0.78 and 0.78 respectively);
• for the women with tumours 10 to 19 mm (n=574), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.09 and 1.05 respectively);
• for the women with tumours 20 to 29 mm (n=404), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 1.32 and 1.26 respectively);
• for the women with tumours 30 to 49 mm (n=140), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 1.32 and 1.26 respectively);
• for the women with tumours 50+ mm (n=11), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 0.5 and 0.5 respectively).
• for the women with tumours of unknown size (n=1), both PREDICT v1.1 and PREDICT v1.2 showed perfect calibration (O:E = 1 and 1 respectively).

Subgroup: nodal status
• for women with negative nodal status (n=709), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.19 and 1.15 respectively);
• for the women with 1+ nodes (n=241), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 1.23 and 1.17 respectively);
• for the women with 2 to 4+ nodes (n=184), PREDICT v1.1 showed good calibration (O:E = 1.05) and PREDICT v1.2 showed perfect calibration (O:E = 1);
• for the women with 5 to 9+ nodes (n=37), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.10 and 1.05 respectively);
• for the women with 10+ nodes (n=6), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 0.8 and 0.8 respectively).
• for the women with unknown nodal status (n=97), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.07 and 1.07 respectively).

Subgroup: grade
• for women with grade 1 breast cancer (n=235), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 1.8 and 1.8 respectively);
• for the women with grade 2 breast cancer (n=528), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.16 and 1.14 respectively);
• for the women with grade 3 breast cancer (n=395), both PREDICT v1.1 and PREDICT v1.2 showed good calibration (O:E = 1.14 and 1.07 respectively);
• for the women with unknown graded (n=116), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 0.31 and 0.31 respectively).

Subgroup: HER2 status
• for women with negative HER2 status (n=792), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 1.35 and 1.29 respectively);
• for the women with positive HER2 status (n=77), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 1.35 and 1.24 respectively);
• for the women with unknown HER2 status (n=405), both PREDICT v1.1 and PREDICT v1.2 showed poor calibration (O:E = 0.44 and 0.44 respectively).

Tool discrimination and collaboration - 10-year breast cancer mortality [PREDICT 2.0]

There was good evidence from 1 validation study conducted with combined data sets (N=5316) that assessed the tool calibration and discrimination of a new version of PREDICT.

The tool calibration was reported according to different factors, and segregated by ER status (total cohort data was not reported).

Subgroup: age at diagnosis (segregated by ER- and ER+)

ER-
• for the women aged 20 to 29 and negative ER status (n=92), PREDICT v2.0 showed good calibration (O:E = 0.94). The tool overestimated breast cancer mortality by 6%;
• for the women aged 30 to 39 and negative ER status (n=855), PREDICT v2.0 showed good calibration (O:E = 0.92). The tool overestimated breast cancer mortality by 9%;
• for the women aged 40 to 49 and negative ER status (n=414), PREDICT v2.0 showed good calibration (O:E = 0.98). The tool overestimated breast cancer mortality by 2%;
• for the women aged 50 to 59 and negative ER status (n=165), PREDICT v2.0 showed good calibration (O:E = 0.97). The tool overestimated breast cancer mortality by 3%;
• for the women aged 60 to 69 and negative ER status (n=117), PREDICT v2.0 showed good calibration (O:E = 0.82). The tool overestimated breast cancer mortality by 21%;
• for the women aged 70 to 79 and negative ER status (n=11), PREDICT v2.0 showed poor calibration (O:E = 0.36). The tool overestimated breast cancer mortality by 180%.

ER+
• for the women aged 20 to 29 and positive ER status (n=140), PREDICT v2.0 showed poor calibration (O:E = 0.71). The tool overestimated breast cancer mortality by 40%;
• for the women aged 30 to 39 and positive ER status (n=1633), PREDICT v2.0 showed good calibration (O:E = 0.96). The tool overestimated breast cancer mortality by 4%;
• for the women aged 40 to 49 and positive ER status (n=1063), PREDICT v2.0 showed good calibration (O:E = 0.90). The tool overestimated breast cancer mortality by 11%;
• for the women aged 50 to 59 and positive ER status (n=467), PREDICT v2.0 showed good calibration (O:E = 0.96). The tool overestimated breast cancer mortality by 4%;
• for the women aged 60 to 69 and positive ER status (n=517), PREDICT v2.0 showed good calibration (O:E = 1.08). The tool underestimated breast cancer mortality by 7%;
• for the women aged 70 to 79 and positive ER status (n=55), PREDICT v2.0 showed poor calibration (O:E = 0.38). The tool overestimated breast cancer mortality by 26%.

Subgroup: tumour size (segregated by ER- and ER+)

ER-
• for women with tumours 0 to 9 mm and negative ER status (n=96), PREDICT v2.0 showed good calibration (O:E = 0.90). The tool overestimated breast cancer mortality by 10%;
• for women with tumours 10 to 19 mm and negative ER status (n=559), PREDICT v2.0 showed good calibration (O:E = 0.92). The tool overestimated breast cancer mortality by 8%;
for women with tumours 20 to 29 mm and negative ER status (n=524), PREDICT v2.0 showed good calibration (O:E = 0.97). The tool overestimated breast cancer mortality by 3%;

for women with tumours 30 to 49 mm and negative ER status (n=354), PREDICT v2.0 showed good calibration (O:E = 0.99). The tool overestimated breast cancer mortality by 1%;

for women with tumours 50+ mm and negative ER status (n=121), PREDICT v2.0 showed poor calibration (O:E = 0.75). The tool overestimated breast cancer mortality by 33%.

**ER+**

for women with tumours 0 to 9 mm and positive ER status (n=352), PREDICT v2.0 showed poor calibration (O:E = 1.54). The tool underestimated breast cancer mortality by 6%;

for women with tumours 10 to 19 mm and negative ER status (n=1428), PREDICT v2.0 showed good calibration (O:E = 1.06). The tool underestimated breast cancer mortality by 8%;

for women with tumours 20 to 29 mm and positive ER status (n=1111), PREDICT v2.0 showed good calibration (O:E = 0.98). The tool overestimated breast cancer mortality by 0.80%;

for women with tumours 30 to 49 mm and positive ER status (n=695), PREDICT v2.0 showed good calibration (O:E = 0.87). The tool overestimated breast cancer mortality by 15%;

for women with tumours 50+ mm and positive ER status (n=289), PREDICT v2.0 showed poor calibration (O:E = 0.74). The tool overestimated breast cancer mortality by 35%.

**Subgroup: number of positive nodes (segregated by ER- and ER+)**

**ER-**

for women with 0 positive nodes and negative ER status (n=937), PREDICT v2.0 showed good calibration (O:E = 1.01). The tool underestimated breast cancer mortality by 0.89%;

for women with 1 positive node and negative ER status (n=232), PREDICT v2.0 showed good calibration (O:E = 0.86). The tool overestimated breast cancer mortality by 17%;

for women with 2 to 4 positive nodes and negative ER status (n=300), PREDICT v2.0 showed good calibration (O:E = 0.88). The tool overestimated breast cancer mortality by 13%;

for women with 5 to 9 positive nodes and negative ER status (n=101), PREDICT v2.0 showed good calibration (O:E = 0.96). The tool overestimated breast cancer mortality by 4%;

for women with 10+ positive nodes and negative ER status (n=84), PREDICT v2.0 showed good calibration (O:E = 0.85). The tool overestimated breast cancer mortality by 17%.

**ER+**

for women with 0 positive nodes and positive ER status (n=2085), PREDICT v2.0 showed good calibration (O:E = 0.99). The tool overestimated breast cancer mortality by 1%;

for women with 1 positive node and positive ER status (n=675), PREDICT v2.0 showed good calibration (O:E = 0.92). The tool overestimated breast cancer mortality by 9%;

for women with 2 to 4 positive nodes and positive ER status (n=734), PREDICT v2.0 showed good calibration (O:E = 0.96). The tool overestimated breast cancer mortality by 4%;
• for women with 5 to 9 positive nodes and positive ER status (n=245), PREDICT v2.0 showed good calibration (O:E = 0.86). The tool overestimated breast cancer mortality by 17%;
• for women with 10+ positive nodes and positive ER status (n=136), PREDICT v2.0 showed good calibration (O:E = 0.87). The tool overestimated breast cancer mortality by 15%.

Subgroup: tumour grade (segregated by ER- and ER+)

ER-
• for women with grade 1 tumour and negative ER status (n=44), PREDICT v2.0 showed good calibration (O:E = 0.96). The tool overestimated breast cancer mortality by 4%;
• for women with grade 2 tumour and negative ER status (n=183), PREDICT v2.0 showed good calibration (O:E = 0.86). The tool overestimated breast cancer mortality by 17%;
• for women with grade 3 tumour and negative ER status (n=1427), PREDICT v2.0 showed good calibration (O:E = 0.94). The tool overestimated breast cancer mortality by 7%.

ER+
• for women with grade 1 tumour and positive ER status (n=658), PREDICT v2.0 showed good calibration (O:E = 0.96). The tool overestimated breast cancer mortality by 4%;
• for women with grade 2 tumour and positive ER status (n=1730), PREDICT v2.0 showed good calibration (O:E = 0.86). The tool overestimated breast cancer mortality by 17%;
• for women with grade 3 tumour and positive ER status (n=1487), PREDICT v2.0 showed good calibration (O:E = 0.94). The tool overestimated breast cancer mortality by 7%.

Tool discrimination was also reported by ER status:
• for women with negative ER status, the tool discrimination was poor (AUC=0.696);
• however for women with positive ER status, the tool discrimination was good (AUC=0.790).

Important outcomes

Prognostic accuracy (sensitivity, specificity)
• No evidence was found for this outcome.

Predictive prognostic tool 3: Nottingham Prognostic Index (NPI)

Critical outcomes

Tool calibration - 10-year breast cancer survival

There was good quality evidence from 1 validation study conducted in the UK with 2238 women diagnosed with or treated for primary operable invasive breast cancer that reported the following:
• for women in the excellent prognosis group according to their NPI score (n=320), the tool showed good calibration (O:E = 0.98);
• for women in the good prognosis group according to their NPI score (n=475), the tool showed good calibration (O:E = 0.99);
• for women in the moderate prognosis group I according to their NPI score (n=634), the tool showed good calibration (O:E = 1.03);
• for women in the moderate prognosis group II according to their NPI score (n=489), the tool showed perfect calibration (O:E = 1.00);
for women in the poor prognosis group according to their NPI score (n=233), the tool showed good calibration (O:E = 1.02);
for women in the very poor prognosis group according to their NPI score (n=86), the tool showed good calibration (O:E = 0.89).

**Tool discrimination**
- No evidence was found for this outcome.

**Important outcomes**

**Prognostic accuracy (sensitivity, specificity)**
- No evidence was found for this outcome.

**Predictive prognostic tool 4: FinProg**

**Critical outcomes**

**Tool calibration**
- No evidence was found for this outcome.

**Tool discrimination**
- No evidence was found for this outcome.

**Important outcomes**

**Prognostic accuracy (sensitivity, specificity)**
- No evidence was found for this outcome.

**Predictive prognostic tool 5: CancerMath**

**Critical outcomes**

**Tool calibration**
- No evidence was found for this outcome.

**Tool discrimination**
- No evidence was found for this outcome.

**Important outcomes**

**Prognostic accuracy (sensitivity, specificity)**
- No evidence was found for this outcome.

**Predictive prognostic tool 6: Oxford Prognostic Index (OPI)**

**Critical outcomes**

**Tool calibration and discrimination - 5-year recurrence-free survival**

There was moderate quality evidence from 1 validation study with 1787 women treated for invasive ductal carcinoma that reported the following:
for the whole cohort (N=1789), OPI showed good calibration (O:E = 1.01). The tool underestimated 5-year recurrence free survival by 0.7%. However the tool showed poor discrimination (overall C-statistic = 0.720).

The study also reported the calibration according to different factors (tool discrimination was not reported):

**Subgroup: age**
- for women ≤50 years (n=1097), OPI showed good calibration (O:E = 1.03). The tool underestimated 5-year recurrence free survival by 1.92%;
- for women >50 years (n=690), OPI showed perfect calibration (O:E ≈ 1.00). The tool overestimated 5-year recurrence free survival by 0.10%.

**Subgroup: tumour grade**
- for women with grade 1 tumour (n=196), OPI showed good calibration (O:E = 1.06). The tool underestimated 5-year recurrence free survival by 5.15%;
- for women with grade 2 tumour (n=772), OPI showed good calibration (O:E = 1.03). The tool underestimated 5-year recurrence free survival by 2.44%;
- for women with grade 3 tumour (n=819), OPI showed good calibration (O:E = 0.98). The tool overestimated 5-year recurrence free survival by 1.04%.

**Subgroup: tumour size**
- for women with tumours ≤2 cm (n=954), OPI showed good calibration (O:E = 1.06). The tool overestimated 5-year recurrence free survival by 0.89%;
- for women with tumours >2 cm to ≤5 cm(n=772), OPI showed good calibration (O:E = 0.95). The tool underestimated 5-year recurrence free survival by 2.7%;
- for women with tumours >5 cm (n=61), OPI showed good calibration (O:E = 1.04). The tool overestimated 5-year recurrence free survival by 3.71%.

**Subgroup: nodal status**
- for women with negative nodal status (n=674), OPI showed good calibration (O:E = 1.02). The tool overestimated 5-year recurrence free survival by 1.82%;
- for women with positive nodal status (n=1113), OPI showed good calibration (O:E = 1.01). The tool underestimated 5-year recurrence free survival by 0.71%.

**Subgroup: ER status**
- for women with negative ER status (n=1097), OPI showed good calibration (O:E = 1.03). The tool overestimated 5-year recurrence free survival by 1.92%;
- for women with positive ER status (n=690), OPI showed perfect calibration (O:E ≈ 1.00). The tool underestimated 5-year recurrence free survival by 0.10%.

**Important outcomes**

**Prognostic accuracy (sensitivity, specificity)**
- No evidence was found for this outcome.
The committee’s discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to determine which prognostic prediction tool is most helpful at predicting survival, and therefore identifying women who may benefit from adjuvant treatment.

The committee agreed that tool calibration and tool discrimination were the critical outcomes for decision making. This is because identifying people with a worse prognosis would guide decisions regarding the use of adjuvant treatment. In addition they also included sensitivity and specificity as important outcomes.

The quality of the evidence

This review included validation studies. The quality of the individual studies was assessed using the CASP tool for clinical prediction rule. The overall judgement of the quality was based on the consideration of the individual domains.

One study evaluated the Adjuvant! Online tool, and was assessed as high quality.

Four studies looked at PREDICT. Results were reported separately for each study, as they assessed different versions of PREDICT. Studies using older versions of the tool were rated down because they did not consider all relevant prognostic factors.

One study evaluated the NPI tool, and was assessed as high quality.

One study evaluated the OPI tool, and was rated as moderate quality. The main reason for rating down the quality of the study was because the tool is not available in clinical practice, and therefore is of limited use.

Benefits and drawbacks

The committee discussed the benefits and drawbacks of the various tools.

Four studies reported on the prognostic accuracy of PREDICT, although studies assessed different versions. The results of 1 study showed that the first version of PREDICT (v1.0) was well calibrated to estimate 5-year mortality in the whole cohort, and across different prognostic groups (including age at diagnosis, tumour grade, tumour size, nodal status and ER status). The tool also showed good discrimination for the ER positive and negative models. Likewise, the tool showed good calibration and good discrimination to estimate 8-year mortality in the whole cohort. The tool was well calibrated for all prognostic subgroups, except those with tumours over 50 mm, but it showed poor discrimination for young and old women (those <35 and 75+), those with negative nodal status, and in women with tumours over 20 mm.

Another study looked at versions v1.1 and v1.2 of PREDICT in women with invasive breast cancer and ER-positive. Results were quite similar for both versions, showing good calibration to estimate 10-year breast cancer mortality in the whole cohort and across most subgroups, the exceptions being those based on tumour size, HER2 status and grade 1 tumours. Discrimination was also good for both versions, but the authors of the study noted that discrimination significantly improved in v1.2.

Another study that looked at an updated version of PREDICT (v1.2) showed poor calibration and poor discrimination to predict all-cause mortality at 5 years in a cohort of women aged ≤40 years. The tool also showed poor calibration across most prognostic subgroups (including age at diagnosis, tumour grade, tumour size, nodal status, and negative HER2
status). The tool showed good calibration to predict all-cause mortality at 10 years in a cohort of women aged ≤40 years; however there was poor calibration for prognostic subgroups based on tumour grade, tumour size, nodal status and ER status.

A recent study evaluated the most updated model, PREDICT version 2.0 (version release in 2017). The new tool was shown to have good prognostic accuracy to estimate 10-year breast cancer mortality across most subgroups, including age, tumour size, tumour grade and number of positive nodes, independent of ER status. The committee noted the improved performance of this version of the tool among young women, however calibration was still poor in women aged 20 to 29 who were ER-positive. There was also poor calibration in women aged 70 to 79 and those with tumours greater than 50 mm, independent of ER status, and women with ER-positive tumours smaller than 10 mm.

The evidence suggested that Adjuvant! Online was a well calibrated tool to predict survival at 10 years. This was shown consistently for the total cohort of women on whom the tool was validated, and for the different subgroups (age, tumour grade, tumour size, nodal status and ER status). This supported the committee’s experience in clinical practice, as they agreed it is a very useful tool. Indeed this tool was extensively used in clinical practice, however they noted this tool is no longer available. Therefore they agreed this tool could not be recommended.

The evidence suggested that the NPI is also a well calibrated tool to predict 10-year cancer survival. However, the committee agreed it has now been superseded by other tools which take into account more factors such as ER and HER2 status.

The committee also discussed the results for the OPI. The evidence included in this review suggested that this is a well calibrated tool to predict recurrence-free survival at 5 years for the total cohort of women on whom the tool was validated, and for the different subgroups (age, tumour grade, tumour size, nodal status and ER status). However they noted they were not aware of this tool, as it is not actually available in practice. Based on this they agreed it could not be recommended.

No studies were found reporting on the prognostic accuracy of CancerMath and FinProg, and the committee agreed they could not make recommendations in favour or against their use.

The committee agreed that using accurate prognostic tools helps to have more informed decision making, but noted that over-reliance on the results of a prognostic tool could result in over- or under-treatment for some people, if individual characteristics are not taken into consideration (for example significant comorbidities or age group variations).

In addition they note that as there is limited evidence by population age it is not possible to confirm the accuracy of the tool for all groups. This is because although studies report results by age groups, the sample size for young women is too small to allow sufficient statistical power.

Overall, the committee agreed that a validated prognostic tool provides important guidance in treatment, but clinical judgement should also play an important role.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

It was thought that the economic impact of recommendations made in this area would be relatively small because there is little difference in resource use between the prognostic tools (they are freely available and the time taken to complete them is similar).

The committee have recommended the use of PREDICT which is a change from the previous guideline (CG80), in which Adjuvant! Online was recommended. It might therefore
be considered a change in practice. However, in reality most professionals are already using PREDICT because adjuvant! Online is no longer available.

It is possible that the use of a different tool may have implications for the numbers of patients receiving adjuvant treatment because of differences in prognostic accuracy. Therefore there could be a cost impact associated with changes in patient management. While it is difficult to speculate fully on the direction of this effect, it was considered likely that the scale of the effect would be relatively small and that in most cases the decision on whether to use adjuvant therapy or not would be similar with PREDICT or with Adjuvant! Online.

Other factors the committee took into account

The committee agreed that this recommendation would make the same prognostic tool available to all populations nationally, and this could potentially reduce inequalities. At the time of guideline publication, PREDICT v2.0 was the version available on the PREDICT homepage (http://predict.nhs.uk/), although version 1.2 can still be accessed on the website. Although the evidence had considered previous versions of PREDICT, the committee made their recommendations based on PREDICT v2.0. If future versions of PREDICT are released, the recommendations relating to groups in whom the tool is less accurate may no longer be applicable, and this information is provided in a footnote.

However the committee recognised that the validation of the model may under-represent some ethnic groups. Similarly, this tool has not been validated in men, therefore it is not possible to know if it is applicable to them. They also noted that the very young and older ages are under-represented.

The committee pointed out that the availability of the prognostic tools affected the recommendations, therefore the long-term adoption of prognostic tools is dependent on continued support and availability.

Finally the committee highlighted this review did not include gene profiling tools as these will be covered by NICE diagnostic guidance (Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammastrat; DG10 update), and a link was included to this guidance.

References

Blamey 2007

Campbell 2009

Campbell 2010

Candido Dos Reis 2017

Debray 2017

Maishman 2015

NICE 2009

Riley 2015

Wishart 2010

Wishart 2014
Appendices

Appendix A – Review protocols

Review protocol for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

<table>
<thead>
<tr>
<th>Field (based on PRISMA-P)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question</td>
<td>Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?</td>
</tr>
<tr>
<td>Type of review question</td>
<td>Intervention review</td>
</tr>
<tr>
<td>Objective of the review</td>
<td>The objective of this review is to establish the role and benefit of the pathological assessment of PR in breast cancers for planning adjuvant chemotherapy. Recommendations will cover whether PR testing should occur.</td>
</tr>
<tr>
<td>Eligibility criteria – population/disease/condition/issue/domain</td>
<td>Adults (18 or over) with invasive breast cancer (M0)</td>
</tr>
<tr>
<td>Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)</td>
<td>ER and HER2 plus PR test followed by chemotherapy as indicated based on test results</td>
</tr>
<tr>
<td>Eligibility criteria – comparator(s)/control or reference (gold) standard</td>
<td>ER and HER2 test followed by chemotherapy as indicated based on test results</td>
</tr>
<tr>
<td>Outcomes and prioritisation</td>
<td>Critical (up to 3 outcomes)</td>
</tr>
<tr>
<td></td>
<td>Disease-free survival (MID: any statistically significant difference)</td>
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<td></td>
<td>Overall survival (MID: any statistically significant difference)</td>
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<tr>
<td></td>
<td>Important but not critical</td>
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<tr>
<td></td>
<td>Treatment-related morbidity (MID: GRADE default values)</td>
</tr>
<tr>
<td></td>
<td>5 and 10 year follow-up periods will be prioritised if multiple time points are reported.</td>
</tr>
<tr>
<td>Eligibility criteria – study design</td>
<td>Systematic reviews/meta-analyses of ‘test and treat’ RCTs</td>
</tr>
<tr>
<td></td>
<td>‘Test and treat’ RCTs</td>
</tr>
<tr>
<td></td>
<td>Modified nominal group technique will be used to make recommendations regarding the appropriateness of PR testing if no published test and treat RCTs are identified</td>
</tr>
<tr>
<td>Other inclusion exclusion criteria</td>
<td>Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.</td>
</tr>
<tr>
<td>Field (based on PRISMA-P)</td>
<td>Content</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Proposed sensitivity/subgroup analysis, or meta-regression</td>
<td>N/A</td>
</tr>
<tr>
<td>Selection process – duplicate screening/selection/analysis</td>
<td>Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question.</td>
</tr>
<tr>
<td>Data management (software)</td>
<td>Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.</td>
</tr>
<tr>
<td>Information sources – databases and dates</td>
<td>The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline &amp; Medline in Process and Embase through OVID. Additionally we may search Web of Science and consideration will be given to subject-specific databases and used as appropriate. The search will be undertaken from 1984, when the first studies of immunohistochemical determination of progesterone receptor status were published, as opposed to updating the search from the previous guideline due to substantial change in the focus of the review question.</td>
</tr>
</tbody>
</table>
| Identify if an update                                                                  | Previous question: Does progesterone receptor status add further, useful information to that of oestrogen receptor status in patients with invasive breast cancer?  
Date of search: 27/02/2008  
Relevant recommendation(s) from previous guideline: 1) Do not routinely assess progesterone receptor status of tumours in patients with invasive breast cancer. |
| Author contacts                                                                        | Please see guideline in development page on the web site.                                                                                                                                              |
| Highlight if amendment to previous protocol                                           | For details please see Section 4.5 of Developing NICE guidelines: the manual                                                                                                                               |
| Search strategy – for one database                                                     | For details please see appendix B.                                                                                                                                                                    |
| Data collection process – forms/duplicate                                             | A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).                                                       |
| Data items – define all variables to be collected                                      | For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).                                                                               |
| Methods for assessing bias at outcome/study level                                       | Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual                                               |
The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/

Criteria for quantitative synthesis
For details please see Section 6.4 of Developing NICE guidelines: the manual

Methods for quantitative analysis – combining studies and exploring (in)consistency
For details please see the methods chapter.

Meta-bias assessment – publication bias, selective reporting bias
For details please see Section 6.2 of Developing NICE guidelines: the manual.

Confidence in cumulative evidence
For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual

Rationale/context – what is known
For details please see the introduction to the evidence review in the main file.

Describe contributions of authors and guarantor
A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods supplement.

Sources of funding/support
NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Name of sponsor
NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Roles of sponsor
NICE funds NGA to develop guidelines for the NHS in England.

PROSPERO registration number
N/A

GRADE, Grading of Recommendations Assessment, Development and Evaluation; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial
### Review protocol for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Field (based on PRISMA-P)</th>
<th>What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question</td>
<td>What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?</td>
</tr>
<tr>
<td>Type of review question</td>
<td>Prediction model performance</td>
</tr>
<tr>
<td>Objective of the review</td>
<td>The objective of this review is to determine the accuracy of prognostic tools for predicting survival and benefit of treatment. Recommendations will aim to cover which tools should be used to aid decision adjuvant treatment planning.</td>
</tr>
<tr>
<td>Eligibility criteria – population/disease/condition/issue/domain</td>
<td>Adults (18 or over) with invasive breast cancer (M0) who have undergone surgery and who are candidates for adjuvant systemic therapy</td>
</tr>
<tr>
<td>Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)</td>
<td>Any appropriate predictive prognostic tools, e.g., Adjuvant! Online PREDICT Nottingham Prognostic Index (NPI) FinProg CancerMath Other relevant validated tools will also be considered for inclusion</td>
</tr>
<tr>
<td>Eligibility criteria – comparator(s)/control or reference (gold) standard</td>
<td>N/A</td>
</tr>
<tr>
<td>Outcomes and prioritisation</td>
<td>Accuracy (sensitivity/specificity) (important outcome) Tool discrimination (AUC or C-statistic) (critical outcome) Tool calibration (mortality ratio or survival ratio) (critical outcome) For the following: Disease free survival Overall survival/ death At the following time points: Short-term: 5 years</td>
</tr>
</tbody>
</table>
### Field (based on PRISMA-P)

<table>
<thead>
<tr>
<th><strong>What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?</strong></th>
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</thead>
<tbody>
<tr>
<td>Long-term: 10 years</td>
</tr>
<tr>
<td>Note:</td>
</tr>
<tr>
<td>It was agreed with the committee that sensitivity or specificity would be considered high when sensitivity or specificity was 90% or higher, and moderate when sensitivity or specificity was between 75% and 89%.</td>
</tr>
<tr>
<td>The mortality ratio is defined as the ratio of observed number of deaths in a study population and the expected number of deaths. In this review, a tool will be considered to have good calibration if the ratio ranges from 0.8 to 1.2 (as suggested by Debray 2017).</td>
</tr>
<tr>
<td>Discrimination is a measure to assess how well a tool identifies people with worse survival, and it is often reported by the concordance c-statistic (also known as AUC). In this review a tool will be considered to have good discrimination if c-statistic is above 0.75 (as suggested by Debray 2017).</td>
</tr>
</tbody>
</table>

### Eligibility criteria – study design

- Systematic reviews/meta-analyses of prognostic studies
- Prospective cohort studies
- Retrospective cohort studies

### Other inclusion exclusion criteria

- Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.

### Proposed sensitivity/sub-group analysis, or meta-regression

- Factors/sub-groups to look at separately: age, tumour size, tumour grade, ER status, HER2 status and nodal involvement
- Accuracy of each tool will be presented separately.

### Selection process – duplicate screening/selection/analysis

- Sifting, data extraction, and appraisal of methodological quality will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer.
- Dual sifting will be performed on at least 10% of records and where possible all records as this is a prognostic review; 90% agreement is required and any discussions will be resolved through discussion and consultation with senior staff where necessary.

### Data management (software)

- Study sifting and data extraction will be undertaken in STAR.
- Meta-analysis will not be performed
- The CASP clinical prediction rule checklist will be used to assess the quality of included studies.
<table>
<thead>
<tr>
<th>Field (based on PRISMA-P)</th>
<th>What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information sources – databases and dates</td>
<td>The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline &amp; Medline in Process and Embase through OVID. Additionally we may search Web of Science and consideration will be given to subject-specific databases and used as appropriate. The search will be undertaken from 1982 when the Nottingham Prognostic Index (the oldest of the tools identified above) was first published. Date limit: 1982 (first publication - Nottingham Prognostic Index)</td>
</tr>
<tr>
<td>Identify if an update</td>
<td>N/A</td>
</tr>
<tr>
<td>Author contacts</td>
<td>Please see guideline in development page on the web site.</td>
</tr>
<tr>
<td>Highlight if amendment to previous protocol</td>
<td>For details please see Section 4.5 of Developing NICE guidelines: the manual</td>
</tr>
<tr>
<td>Search strategy</td>
<td>For details please see appendix B.</td>
</tr>
<tr>
<td>Data collection process – forms/duplicate</td>
<td>A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).</td>
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<td>Data items – define all variables to be collected</td>
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<td>Methods for assessing bias at outcome/study level</td>
<td>Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a></td>
</tr>
<tr>
<td>Criteria for quantitative synthesis</td>
<td>For details please see Section 6.4 of Developing NICE guidelines: the manual</td>
</tr>
<tr>
<td>Methods for quantitative analysis – combining studies and exploring (in)consistency</td>
<td>For details please see the methods chapter.</td>
</tr>
<tr>
<td>Meta-bias assessment – publication bias, selective reporting bias</td>
<td>For details please see Section 6.2 of Developing NICE guidelines: the manual.</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual</td>
</tr>
<tr>
<td>Rationale/context – what is known</td>
<td>For details please see the introduction to the evidence review.</td>
</tr>
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<td>Field (based on PRISMA-P)</td>
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</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Describe contributions of authors and guarantor</td>
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</tr>
<tr>
<td>Sources of funding/support</td>
<td>NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.</td>
</tr>
<tr>
<td>Name of sponsor</td>
<td>NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.</td>
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<tr>
<td>Roles of sponsor</td>
<td>NICE funds NGA to develop guidelines for the NHS in England.</td>
</tr>
<tr>
<td>PROSPERO registration number</td>
<td>N/A</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CASP, Critical Appraisal Skills Programme; ER, oestrogen receptor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HER2, Human epidermal growth factor receptor 2; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; NPI, Nottingham prognostic index; RCT, randomised controlled trial
Appendix B – Literature search strategies

Literature search strategies for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

Database: Medline & Embase (Multifile)

Last searched on Embase 1974 to 2017 March 03, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.

Date of last search: 6 March 2017.

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<tr>
<td>5</td>
<td>exp breast tumor/ use oemezd</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>exp &quot;Neoplasms, Ductal, Lobular, and Medullary&quot;/ use prmz</td>
</tr>
<tr>
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<td>Carcinoma, Intraductal, Noninfiltrating/ use prmz</td>
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<td>1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10</td>
</tr>
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<tr>
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<td>exp Breast/ use prmz</td>
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<tr>
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<tr>
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</tr>
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<td>16</td>
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</tr>
<tr>
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<td>(breast adj tender$).tw.</td>
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<td>18</td>
<td>16 or 17</td>
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<tr>
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<td>15 not 18</td>
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</tr>
<tr>
<td>25</td>
<td>(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd</td>
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<td>26</td>
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</table>
Early and locally advanced breast cancer: diagnosis and management: evidence reviews for adjuvant systemic therapy planning

### Database: Cochrane Library via Wiley Online

**Date of last search:** 6 March 2017.

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<tr>
<td>#3</td>
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<td>#7 or #8</td>
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</tr>
<tr>
<td>#11</td>
<td>(breast next tender*):ti,ab,kw (Word variations have been searched)</td>
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<tr>
<td>#12</td>
<td>#10 or #11</td>
</tr>
<tr>
<td>#13</td>
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<td>#13 and #14</td>
</tr>
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</table>
Adjuvant systemic therapy planning

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Literature search strategies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

Database: Medline & Embase (Multifile)

Last searched on Embase 1974 to 2017 September 20, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.

Date of last search: 22 September 2017

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Adjuvant therapy planning

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<td>11 or 31</td>
</tr>
<tr>
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<td>46</td>
<td>32 and 45</td>
</tr>
<tr>
<td>47</td>
<td>limit 46 to yr=&quot;1982 -Current&quot;</td>
</tr>
<tr>
<td>48</td>
<td>decision support system/ use oemezd</td>
</tr>
<tr>
<td>49</td>
<td>Decision Making, Computer-Assisted/ use prmz</td>
</tr>
<tr>
<td>50</td>
<td>computer/ use oemezd</td>
</tr>
<tr>
<td>51</td>
<td>Computers/ use prmz</td>
</tr>
</tbody>
</table>
Early and locally advanced breast cancer: diagnosis and management: evidence reviews for adjuvant systemic therapy planning

Database: Cochrane Library via Wiley Online

Date of last search: 22 September 2017.

<table>
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<tr>
<th>#</th>
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<tbody>
<tr>
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</tr>
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</tr>
<tr>
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<td>MeSH descriptor: [Carcinoma, Lobular] this term only</td>
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<td>5</td>
<td>MeSH descriptor: [Carcinoma, Medullary] this term only</td>
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<td>breast:ti,ab,kw (Word variations have been searched)</td>
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<td>#10 or #11</td>
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<td>#13</td>
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<td>MeSH descriptor: [Neoplasms] explode all trees</td>
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<td>#15</td>
<td>#13 and #14</td>
</tr>
<tr>
<td>#16</td>
<td>(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#17</td>
<td>(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)</td>
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<td>(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)</td>
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<td>#15 or #16 or #17 or #18 or #19</td>
</tr>
<tr>
<td>#21</td>
<td>#6 or #20</td>
</tr>
<tr>
<td>#22</td>
<td>(adjuvant* next (online or model* or program* or tool*)):ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#23</td>
<td>&quot;www.adjuvantonline.com&quot;:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#24</td>
<td>adjuvantonline*:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#25</td>
<td>(PREDICT near/2 (online or model* or program* or tool* or estimat*)):ti,ab,kw (Word variations have been searched)</td>
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<td>#26</td>
<td>&quot;www.predict.nhs.uk&quot;:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#27</td>
<td>(predict next plus):ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#28</td>
<td>(prognost* next index):ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#29</td>
<td>&quot;Nottingham Prognostic Index&quot;:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#30</td>
<td>NPI:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#31</td>
<td>FinProg*:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#32</td>
<td>CancerMath*:ti,ab,kw (Word variations have been searched)</td>
</tr>
<tr>
<td>#33</td>
<td>&quot;www.CancerMath.net&quot;:ti,ab,kw (Word variations have been searched)</td>
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<td>#35</td>
<td>#21 and #34 Publication Year from 1982 to 2017</td>
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<td>#37</td>
<td>MeSH descriptor: [Computers] explode all trees</td>
</tr>
<tr>
<td>#38</td>
<td>MeSH descriptor: [Decision Support Systems, Clinical] explode all trees</td>
</tr>
<tr>
<td>#39</td>
<td>MeSH descriptor: [Software] explode all trees</td>
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<td>#40</td>
<td>MeSH descriptor: [Decision Support Techniques] explode all trees</td>
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<tr>
<td>#41</td>
<td>MeSH descriptor: [Decision Making] explode all trees</td>
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<td>#42</td>
<td>#36 or #37 or #38 or #39 or #40 or #41</td>
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<td>#</td>
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</tr>
<tr>
<td>-----</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>#44</td>
<td>#21 and #42 and #43 Publication Year from 2007 to 2017</td>
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<td>#45</td>
<td>MeSH descriptor: [Survival Analysis] explode all trees</td>
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<td>MeSH descriptor: [Internet] explode all trees</td>
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<tr>
<td>#47</td>
<td>MeSH descriptor: [Databases, Factual] explode all trees</td>
</tr>
<tr>
<td>#48</td>
<td>MeSH descriptor: [Online Systems] explode all trees</td>
</tr>
<tr>
<td>#49</td>
<td>MeSH descriptor: [Web Browser] explode all trees</td>
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<tr>
<td>#50</td>
<td>MeSH descriptor: [User-Computer Interface] explode all trees</td>
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<td>#51</td>
<td>#46 or #47 or #48 or #49 or #50</td>
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<td>#52</td>
<td>#21 and #45 and #51 Publication Year from 1982 to 2017</td>
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<tr>
<td>#53</td>
<td>#35 or #44 or #52</td>
</tr>
</tbody>
</table>
Appendix C – Clinical evidence study selection

Clinical evidence study selection for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

Figure 1: Flow diagram of clinical article selection for progesterone receptor testing

- Titles and abstracts identified, N=2,827
- Excluded, N=2,816 (not relevant population, design, intervention, comparison, outcomes, unable to retrieve)
- Full copies retrieved and assessed for eligibility, N=11
- Publications included in review, N=0
- Publications excluded from review, N=11 (refer to excluded studies list)
Clinical evidence study selection for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

Figure 2: Flow diagram of clinical article selection for prognostic tools review
Appendix D – Clinical evidence tables

Clinical evidence tables for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

There are no clinical evidence tables for this evidence review as no studies met the inclusion criteria.
Clinical evidence tables for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

### Table 10: Clinical evidence tables for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study details</th>
<th>Number of participants and participants characteristics</th>
<th>Prognostic tool</th>
<th>Methods</th>
<th>Outcomes and results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full citation</td>
<td>Sample size</td>
<td>Prognostic tool</td>
<td>Details</td>
<td>Results</td>
<td>Limitations</td>
</tr>
<tr>
<td></td>
<td>1980–1986 cohort: N = 892</td>
<td>Nottingham Prognostic Index (NPI)</td>
<td>Nottingham Prognostic Index (NPI) Women were divided in six NPI groups: an Excellent Prognostic Group (EPG) with an observed NPI range of 2.08–2.4; Good Prognostic Group (GPG) 2.42 to 63.4; Moderate I Prognostic Group (MPG I) 3.42 to 64.4; Moderate II Prognostic Group (MPG II) 4.42 to 65.4; Poor Prognostic Group (PPG) 5.42 to 66.4; and Very Poor Prognostic Group (VPG) 6.5–6.8.</td>
<td>Prognostic accuracy (sensitivity, specificity)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>1990–1999 cohort: N = 2238</td>
<td>Excellent Prognostic Group (EPG)</td>
<td>Women were divided in six NPI groups:</td>
<td>Model calibration</td>
<td>Results only available for the 2000 to 2009 cohort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good Prognostic Group (GPG) 2.42 to 63.4; Moderate I Prognostic Group (MPG I) 3.42 to 64.4; Moderate II Prognostic Group (MPG II) 4.42 to 65.4;</td>
<td></td>
<td>10-year breast cancer survival</td>
<td>Total cohort = not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate II Prognostic Group (MPG II) 4.42 to 65.4; Poor Prognostic Group (PPG) 5.42 to 66.4; and Very Poor Prognostic Group (VPG) 6.5–6.8.</td>
<td></td>
<td>Excellent prognostic group (EPG) (n=320): Mortality ratio (%) O:E = 0.98</td>
<td>2 The population from which the rule was derived included an appropriate spectrum of patients? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample selection</td>
<td>Consecutive women diagnosed with and treated for primary operable invasive breast cancer at Nottingham City</td>
<td>Good prognostic group (GPG) (n=475): Mortality ratio (%) O:E = 0.99</td>
<td>3 Was the rule validated in a different group of patients? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate prognostic group 1 (MPG I) (n=634): Mortality ratio (%) O:E = 1.03</td>
<td>4 Were the predictor variables and the outcome evaluated in a blinded fashion? Not applicable (the outcome is mortality)</td>
</tr>
<tr>
<td>Study details</td>
<td>Number of participants and characteristics</td>
<td>Prognostic tool</td>
<td>Methods</td>
<td>Outcomes and results</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>To report the predicted and actual survival figures for each NPI group.</td>
<td>Poor Prognostic Group (PPG) 5.42 to 66.4; Very Poor Prognostic Group (VPG) 6.5–6.8.</td>
<td>Hospital between the years 1980–1986 inclusive (n = 892) and 1990–1999 inclusive (n = 2238)</td>
<td>Cases in the 1980–1986 set came under the care of a single surgeon (RWB), with pathology by a single pathologist (CWE)</td>
<td>Moderate prognostic group 2 (MPG II) (n=489): Mortality ratio (%) O:E = 1.00</td>
<td>5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes</td>
</tr>
<tr>
<td><strong>Study dates</strong></td>
<td></td>
<td></td>
<td>Cases in the 1990s set were under the care of the integrated Breast Team at Nottingham City Hospital. Cases referred after an initial operation for diagnosis or following treatment carried out elsewhere were excluded.</td>
<td>Poor prognostic group (PPG) (n=233): Mortality ratio (%) O:E = 1.02</td>
<td>6 Are the statistical methods used to construct and validate the rule clearly described? Yes</td>
</tr>
<tr>
<td>1980 to 1986 and 1990 to 1999</td>
<td></td>
<td></td>
<td>Note that authors excluded cases diagnosed in the years 1987–1989 because major changes in diagnosis and treatment were made in those years (for example the introduction of population screening, of expertise in radiology, case management by a</td>
<td>Very poor prognostic group (VPG) (n=86): Mortality ratio (%) O:E = 0.89</td>
<td></td>
</tr>
<tr>
<td><strong>Source of funding</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Tool discrimination</strong></td>
<td>B. What are the results?</td>
</tr>
<tr>
<td>Not reported.</td>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
<td>7 Can the performance of the rule be calculated? No (not enough data is available to calculate sensitivity, specificity, LR+, LR+, ROC curve. Mortality ratio can be calculated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 How precise was the estimate of the treatment effect? The model considers the most relevant variables</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C. Will the results help locally? Are the results</td>
</tr>
</tbody>
</table>

Early and locally advanced breast cancer: diagnosis and management: evidence reviews for adjuvant systemic therapy planning July 2018
### Study details

<table>
<thead>
<tr>
<th>Number of participants and participants characteristics</th>
<th>Prognostic tool</th>
<th>Methods</th>
<th>Outcomes and results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>team of breast specialists in all disciplines, strict criteria for selection for breast conserving therapy, the introduction of selective local, regional and systemic adjuvant therapies.</td>
<td></td>
<td></td>
<td></td>
<td>applicable to the scenario?</td>
</tr>
</tbody>
</table>

**Data collection**

Women were followed up regularly and indefinitely in the hospital Primary Breast Clinic (PBC) and data on survival and recurrence recorded.

At death the hospital notes are examined and deaths allocated to ‘With/from breast cancer’ or ‘Without known breast cancer’. Women with distant metastatic spread were allocated to the first group, even if the disease appeared to be in complete remission.

**Data analysis**

9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population)

10 Is the rule acceptable in your case? Yes

11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes

**Indirectness**

This study includes direct population (UK).

**Other information**
<table>
<thead>
<tr>
<th>Study details</th>
<th>Number of participants and participants characteristics</th>
<th>Prognostic tool</th>
<th>Methods</th>
<th>Outcomes and results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Life table survival curves for both breast cancer specific and all causes of death and for both time sets were done using SPSS version 13. Note that although in the early reports of the NPI, survival was from all causes of death, in this study the survival curves were constructed for death from breast cancer.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Full citation**

**Ref Id**
583803

**Sample size**
Tool development
N=1844 women with early invasive ductal carcinoma of the breast were used to develop the model (Churchill Hospital in London)

**Prognostic tool**
Oxford Prognostic Index (OPI)

**Details**

**Sample selection**
Tool development
Women were consecutively diagnosed. All of them underwent surgery at the Churchill Hospital, Oxford. They were followed-up was until

**Results**
Results reported for external validation of the tool only

**Prognostic accuracy (sensitivity, specificity)**
Not reported

**Tool calibration**
5-year recurrent free survival
Total cohort (n=1789)
- RFS ratio O:E: 1.01
- Difference O-E: 0.7%

**Limitations**
The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1. Is the CPR clearly defined? Yes
2. The population from which the rule was derived included an appropriate spectrum of patients? Yes
### Study details

<table>
<thead>
<tr>
<th>Number of participants and participants characteristics</th>
<th>Prognostic tool</th>
<th>Outcomes and results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country/ies where the study was carried out</td>
<td>N=1787 women with invasive ductal carcinoma</td>
<td>Sub-group: age</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>Characteristics</td>
<td>Tool validation</td>
<td>3 Was the rule validated in a different group of patients? Yes (the study shows results for both development and validation)</td>
</tr>
<tr>
<td>Aim of the study</td>
<td>Age:</td>
<td>The ABC subset</td>
<td>4 Were the predictor variables and the outcome evaluated in a blinded fashion? Not applicable (the outcome is mortality)</td>
</tr>
<tr>
<td>To develop and validate a new prognostic tool (Oxford Prognostic Index, OPI), for predicting recurrence in women with early breast cancer.</td>
<td>≤50 years (n=1097)</td>
<td>The ABC subset included 1789 patients from 70 hospitals from the UK. Dates 1992 to 2000.</td>
<td>5 Were the predictor variables and the outcome evaluates in the whole sample selected initially? Yes</td>
</tr>
<tr>
<td>Study dates</td>
<td>≤50 years</td>
<td>Sub-group: tumour grade</td>
<td>6 Are the statistical methods used to construct and validate the rule clearly described? Yes</td>
</tr>
<tr>
<td>1986 to 2001</td>
<td>≤50 years</td>
<td>• Grade 1 (n=196)</td>
<td>B. What are the results?</td>
</tr>
<tr>
<td>Source of funding</td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 1.03</td>
<td>7 Can the performance of the rule be calculated? No (not enough data is available to calculate sensitivity,</td>
</tr>
<tr>
<td>The Cancer Research UK and the Oxford NHS Comprehensive Biomedical Research Centre.</td>
<td>≤50 years</td>
<td>o Difference O:E: 1.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>• &gt; 50 years (n=690)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o Difference O:E: -0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>Sub-group: tumour grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>• Grade 2 (n=772)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 1.03</td>
<td></td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>o Difference O:E: 5.15%</td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>• Grade 3 (n=819)</td>
<td></td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 0.98</td>
<td></td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>o Difference O:E: -0.10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>Sub-group: tumour size</td>
<td></td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>• ≤2 cm (n=954)</td>
<td></td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 1.06</td>
<td></td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>o Difference O:E: 4.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>• &gt;2 cm to ≤5 cm (n=772)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 0.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o Difference O:E: -3.16%</td>
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</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>• &gt;5 cm (n=61)</td>
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<td>≤50 years</td>
<td>o RFS ratio O:E: 1.04</td>
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</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o Difference O:E: 2.47%</td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>Sub-group: nodal status</td>
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</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>• Negative (n=674)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>o RFS ratio O:E: 1.02</td>
<td></td>
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<td>≤50 years</td>
<td>o Difference O:E: 1.82%</td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>• Positive (n=1113)</td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>Sub-group: positve nodes:</td>
<td></td>
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<td></td>
<td>≤50 years</td>
<td>0: 1070 (60.45%)</td>
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<td></td>
<td>≤50 years</td>
<td>1: 258 (14.58%)</td>
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</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>2: 142 (8.02%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 years</td>
<td>Sub-group: age</td>
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<tr>
<td></td>
<td>≤50 years</td>
<td>≤50 years (n=1097)</td>
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<td>≤50 years</td>
<td>o RFS ratio O:E: 1.03</td>
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<td>≤50 years</td>
<td>o Difference O:E: 1.92</td>
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<td>≤50 years</td>
<td>• &gt; 50 years (n=690)</td>
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<td>≤50 years</td>
<td>o RFS ratio O:E: 1.00</td>
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<td>≤50 years</td>
<td>o Difference O:E: -0.10</td>
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<td>without any previous diagnosis of recurrence.</td>
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<td>3: 92 (5.20%)</td>
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<td>o RFS ratio O:E: 1.01 o Difference O:E: 0.71%</td>
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<td>4: 52 (2.94%)</td>
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<td>5: 33 (1.86%)</td>
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<td>6: 35 (1.98%)</td>
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<td>7: 21 (1.19%)</td>
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<td>8: 16 (0.90%)</td>
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<td>9: 10 (0.56%)</td>
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<td>10+: 41 (2.32%)</td>
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<tr>
<td>Unknown: 74 (0%)</td>
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<tr>
<td>Tumour size</td>
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<tr>
<td>&lt;1 cm: 204 (11.16%)</td>
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<tr>
<td>≥1 cm and &lt;2 cm: 644 (35.23%)</td>
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<td>≥2 cm and &lt;3 cm: 562 (30.74%)</td>
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<td>≥3 cm and &lt;4 cm: 238 (13.02%)</td>
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<td>≥4 cm and &lt;5 cm: 77 (4.21%)</td>
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<td>≥5 cm: 103 (5.63%)</td>
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<td>Unknown: 16 (0%)</td>
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<td>Tumour grade</td>
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<td></td>
<td>1: 329 (18.97%)</td>
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<td>2: 770 (44.41%)</td>
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<td>3: 635 (36.62%)</td>
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<td>Unknown: 110 (0%)</td>
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<td>ER status</td>
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<td>Negative: 477 (33.33%)</td>
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<td>Positive: 954 (66.67%)</td>
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<td>Unknown: 413 (0%)</td>
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<td>Tool validation</td>
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<td>Not reported</td>
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<td></td>
<td><strong>Inclusion criteria</strong></td>
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<td>Tool validation</td>
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<td></td>
<td>A sub-set of women from the UK obtained from the the Adjuvant</td>
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</tbody>
</table>

**Indirectness**

The study includes direct UK population.

**Other information**

Conflict of interest: not reported (however sources of funding have been reported).

Results for the external validation of the tool are reported here.

has never been made available in clinical practice)
### Study details

<table>
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<tr>
<th>Number of participants and participants characteristics</th>
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<tbody>
<tr>
<td>Breast Cancer (ABC) trial. All women had invasive ductal cancer.</td>
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<td><strong>Exclusion criteria</strong></td>
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<td>Not reported</td>
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**Full citation**


**Ref Id**

583804

**Country/ies where the study was carried out**

UK

**Aim of the study**

To evaluate the performance of the

**Sample size**

N=1065 women with early breast cancer

**Characteristics**

Not reported

**Inclusion criteria**

Up to 85 years

With complete data on nodal status, tumour size, and adjuvant systemic therapy

People who had undergone complete local therapy

Complete 10-year follow-up.

**Exclusion criteria**

Not reported

**Sample selection**

All people diagnosed with breast cancer patients consecutively between 1986 and 1996 at the Churchill Hospital in Oxford.

**Data collection**

Patients were followed up on an annual basis through the Cancer Intelligence Network and General Practitioners, who provided information on recurrence and survival status. Observed 10-year outcomes for each

**Results**

**Prognostic accuracy (sensitivity, specificity)**

Not reported

**Tool calibration**

10-year overall survival

All population (N=1065): Mortality ratio O:E = 0.93; Difference O-E = -5.54 (p<0.01)

**Sub-group: age**

20 to 35 (n=34): Mortality ratio O:E = 0.97; Difference O-E = -2.27% (n.s.)

36 to 50 (n=363): Mortality ratio O:E = 0.95; Difference O-E = -4.33% (p<0.05)

**Limitations**

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).

1. Are the results valid? Yes
2. The population from which the rule was derived included an appropriate spectrum of patients? Yes
3. Was the rule validated in a different group of patients? Yes
4. Were the predictor variables and the outcome evaluated in a blinded fashion? Not
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<tbody>
<tr>
<td>Adjuvant! Online programme by comparing its 10-year predictions with observed outcomes in people with early breast cancer.</td>
<td>Women with locally advanced disease (those with T3 (45 cm tumour) and T4 (tumour of any size growing into the skin or chest wall) tumours, and those with N2 (4–9 nodes involved) and N3 (10 or more lymph nodes involved) tumours)</td>
<td>woman were available from the Churchill Hospital data set. The programme was used to generate 10-year predictions of OS, BCSS, and EFS by entering information on each patient’s age, tumour size, number of positive nodes, grade, ER status, and adjuvant systemic therapies received (types of hormone and chemotherapies).</td>
<td>51 to 65 (n=458): Mortality ratio O:E = 0.95; Difference O-E = 4.02% (p&lt;0.05) 66 to 75 (n=194): Mortality ratio O:E = 0.82; Difference O-E = 12.17% (p&lt;0.01) ≥76 (n=16): Mortality ratio O:E = 0.94; Difference O-E = -3.11% (n.s.) <strong>Sub-group: grade:</strong> Grade 1 (n=152): Mortality ratio O:E: 0.96; Difference O-E: -3.65% (n.s.) Grade 2 (n=421): Mortality ratio O:E: 0.91; Difference O-E: -7.05% (p&lt;0.01) Grade 3 (n=248): Mortality ratio O:E: 0.86; Difference O-E: -9.82% (p&lt;0.01) Unknown grade (n=244): Mortality ratio O:E: 1.00; Difference O-E: 0.26% (n.s.) <strong>Sub-group: tumour size:</strong> 0.1 to 1 cm (n=150): Mortality ratio O:E: 0.93; Difference O-E: -6.10% (n.s.)</td>
<td>applicable (the outcome is mortality) 5 Were the predictor variables and the outcome evaluates in the whole sample selected initially? Yes 6 Are the statistical methods used to construct and validate the rule clearly described? Yes</td>
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<td><strong>Study dates</strong></td>
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<td>1986 to 1996</td>
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<td><strong>Source of funding</strong></td>
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<td>NIHR Biomedical Research Centre Programme, Oxford, and by Cancer Research UK</td>
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<td><strong>Data analysis</strong></td>
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<td>Comparisons between predicted and observed outcomes (OS, BCSS, and EFS) were conducted for the whole cohort, and for clinically important subgroups. For each of these separate analyses, Kaplan–Meier survival analysis provided observed 10-year percentages. Predicted 10-year percentages</td>
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<td><strong>5</strong> Were the predictor variables and the outcome evaluates in the whole sample selected initially? <strong>Yes</strong> 6 Are the statistical methods used to construct and validate the rule clearly described? <strong>Yes</strong> 7 Can the performance of the rule be calculated? <strong>No</strong> (not enough data is available to calculate sensitivity, specificity, LR+, LR+, ROC curve. Mortality ratio can be calculated) 8 How precise was the estimate of the treatment effect? <strong>Yes</strong> (the model considers the most relevant variables)</td>
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<td>1.1 to 2 cm (n=471):</td>
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<td>-6.57% (p&lt;0.01)</td>
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<td>Sub-group: nodal</td>
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<td>Mortality ratio O:E:</td>
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<td>0.94; Difference O-E:</td>
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<td>-4.70% (p&lt;0.01)</td>
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<td>Positive (n=332):</td>
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<td>Mortality ratio O:E:</td>
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<td>-7.38% (p&lt;0.01)</td>
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<td>Sub-group: ER status</td>
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<td>Negative (n=261):</td>
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<td>-1.93% (n.s.)</td>
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<td>Positive (n=495):</td>
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<td>Mortality ratio O:E:</td>
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<td>Unknown (n=309):</td>
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<td>Mortality ratio O:E:</td>
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<td>-3.04% (n.s.)</td>
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<td>C. Will the results help locally? Are the results applicable to the scenario?</td>
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<td>9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population)</td>
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<td>10 Is the rule acceptable in your case? No (this tool is not currently available)</td>
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<td>11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes (although as noted above this tool is no longer available)</td>
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<tr>
<td>Indirectness</td>
<td>This study includes direct population (UK based study).</td>
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<td>Study details</td>
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<td><strong>10-year breast cancer specific survival</strong></td>
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<td>All population (N=1058): Mortality ratio O:E: 0.95; Difference O-E: -4.53% (p&lt;0.01)</td>
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<td><strong>Sub-group: age</strong></td>
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<td>20 to 35 (n=34): Mortality ratio O:E = 0.99; Difference O-E = -0.67% (n.s.)</td>
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<td>36 to 50 (n=361): Mortality ratio O:E = 0.94; Difference O-E = -4.62% (p&lt;0.05)</td>
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<td>51 to 65 (n=454): Mortality ratio O:E = 0.96; Difference O-E = -3.51% (n.s.)</td>
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<td>66 to 75 (n=193): Mortality ratio O:E = 0.89; Difference O-E = -9.28% (p&lt;0.05)</td>
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<td>≥76 (n=16): Mortality ratio O:E = 1.08; Difference O-E = 7.04% (n.s.)</td>
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<td><strong>Sub-group - grade:</strong></td>
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<td>Grade 1 (n=152): Mortality ratio O:E: 0.99; Difference O-E: -1.29% (n.s.)</td>
<td>Conflict of interest: not explicitly reported</td>
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Conflict of interest: not explicitly reported
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<thead>
<tr>
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<td>Grade 2 (n=420): Mortality ratio O:E: 0.93; Difference O-E: -5.89% (p&lt;0.01)</td>
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<td>Grade 3 (n=243): Mortality ratio O:E: 0.92; Difference O-E: -6.10 (p&lt;0.05)</td>
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<td></td>
<td>Unknown grade (n=243): Mortality ratio O:E: 0.96; Difference O-E: -2.78 (n.s.)</td>
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<td><strong>Sub-group – tumour size:</strong></td>
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<td>0.1 to 1 cm (n=148): Mortality ratio O:E: 0.92; Difference O-E: -7.95% (p&lt;0.01)</td>
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<td>1.1 to 2 cm (n=470): Mortality ratio O:E: 0.95; Difference O-E: -4.54% (p&lt;0.01)</td>
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<td>2.1 to 5 cm (n=440): Mortality ratio O:E: 0.95; Difference O-E: -3.53% (n.s.)</td>
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<td><strong>Sub-group: nodal involvement</strong></td>
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<td>Negative (n=729): Mortality ratio O:E = 0.96; Difference O-E = -3.53% (p&lt;0.01)</td>
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<td>Positive (n=329): Mortality ratio O:E = 0.91; Difference O-E = -6.73% (p&lt;0.01)</td>
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<td>Study details</td>
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<td><strong>Sub-group: ER status</strong></td>
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<td>Negative (n=259): Mortality ratio O:E = 0.96; Difference O-E = -2.76% (n.s.)</td>
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<td>Positive (n=491): Mortality ratio O:E = 0.92; Difference O-E = -6.62% (p&lt;0.01)</td>
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<td>Unknown (n=308): Mortality ratio O:E = 0.96; Difference O-E = -2.74% (n.s.)</td>
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<td><strong>Tool discrimination</strong></td>
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<td>Not reported</td>
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<td></td>
<td>Note: mortality ratios were calculated by the NGA technical team with the data available in the study</td>
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</table>

Full citation

Sample size
N=3000 young women diagnosed with breast cancer

Characteristics

Prognostic tool
PREDICT version 1.2

Details
Sample selection
This study used data from the POSH multicentre prospective

Results
Prognostic accuracy (sensitivity, specificity)
Not reported

Limitations
The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Evaluation of the prognostic model PREDICT using the POSH cohort of women aged &lt;40 years at breast cancer diagnosis, British journal of cancer, 112, 983-991, 2015</td>
<td>Young women ≤40 diagnosed with breast cancer</td>
<td>Observational cohort study. This study included 3000 young women diagnosed with breast cancer between 2000 and 2008 in the UK.</td>
<td>Tool calibration</td>
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<tr>
<td>Ref Id</td>
<td>Inclusion criteria</td>
<td>Prognostic tool</td>
<td>Methods</td>
<td>Outcomes and results</td>
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<tr>
<td>584799</td>
<td>Women from the POSH multicentre prospective observational cohort study</td>
<td>5-year all-cause mortality</td>
<td>Total cohort (N=2827)</td>
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<tr>
<td>Country/ies where the study was carried out UK</td>
<td>Exclusion criteria</td>
<td>Mortality ratio O:E = 1.33; Difference O-E = 25% (n=152)</td>
<td>Sub-group: age at diagnosis</td>
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<tr>
<td>Aim of the study</td>
<td>Not reported.</td>
<td>18 to 25 (n=40): Mortality ratio O:E = 1.4; Difference O-E = 28.6% (n=2)</td>
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<tr>
<td>To assess how well PREDICT v1.2 performs in estimating survival in a cohort of young women.</td>
<td>26 to 30 (n=258): Mortality ratio O:E = 1.35; Difference O-E = 25.8% (n=16)</td>
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<tr>
<td>Study dates 2000 to 2008</td>
<td>31 to 35 (n=864): Mortality ratio O:E = 1.38; Difference O-E = 27.6% (n=58)</td>
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<tr>
<td>Source of funding Cancer Research UK provided funding for data collection and analysis for the POSH study. The study was sponsored by University Hospital</td>
<td>36 to 40 (n=1665): Mortality ratio O:E = 1.30; Difference O-E = 23.2% (n=76)</td>
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<td>Sub-group: grade</td>
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<td></td>
<td>Grade 1 (n=156): Mortality ratio O:E = 1.25; Difference O-E = 20% (n=1)</td>
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<td>A. Are the results valid?</td>
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<td>Grade 2 (n=929): Mortality ratio O:E = 2.40; Difference O-E = 58.4% (n=94)</td>
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<td>1 Is the CPR clearly defined? Yes</td>
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<td>2 The population from which the rule was derived included an appropriate spectrum of patients? Yes</td>
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<td>3 Was the rule validated in a different group of patients? Yes (this tool has been validated in a number of studies, this study aims to evaluate it in a cohort of young women)</td>
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<td>4 Were the predictor variables and the outcome evaluated in a blinded fashion? Not applicable (the outcome is mortality)</td>
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<td>5 Were the predictor variables and the outcome evaluates in the whole sample selected initially? Yes</td>
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| | | | | 6 Are the statistical methods used to
<table>
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<tr>
<td>Southampton NHS Foundation Trust.</td>
<td></td>
<td>breast cancer diagnosis to death from any cause; BCSS = time to death from breast cancer, with deaths from other causes censored at the time of last follow-up.</td>
<td></td>
<td>Grade 3 (n=1676): Mortality ratio O:E = 1.13; Difference O-E = 11.9% (n=51)</td>
<td>construct and validate the rule clearly described? Yes</td>
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<td>Unknown (n=66): Mortality ratio O:E = 1.71; Difference O-E = 41.7% (n=5)</td>
<td>B. What are the results?</td>
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<td>Sub-group: tumour size</td>
<td>7 Can the performance of the rule be calculated? No (not enough data is available to calculate sensitivity, specificity, LR+, LR-, ROC curve. Mortality ratio can be calculated)</td>
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<td>0 to 10 mm (n=265): Mortality ratio O:E = 2.1; Difference O-E = 52.4% (n=22)</td>
<td>8 How precise was the estimate of the treatment effect? The model considers the most relevant variables</td>
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<td>11 to 20 mm (n=930): Mortality ratio O:E = 1.25; Difference O-E = 20% (n=25)</td>
<td>C. Will the results help locally? Are the results applicable to the scenario?</td>
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<td>21 to 50 mm (n=1229): Mortality ratio O:E = 1.26; Difference O-E = 22.8% (n=69)</td>
<td>9 Would the prediction rule be reliable and and the results interpretable if used for your patient? Yes (UK population, but this study shows the tool</td>
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<td>&gt;50 mm (n=244): Mortality ratio O:E = 1.16; Difference O-E = 14% (n=85)</td>
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<td>Unknown (n=159): Mortality ratio O:E = 2.44; Difference O-E = 59% (n=23)</td>
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<td>Sub-group: node status</td>
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<td>Negative (n=1370): Mortality ratio O:E = 1.26; Difference O-E = 20.5% (n=33)</td>
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<td>Study details</td>
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<td><strong>Positive</strong> (n=1431): Mortality ratio O:E = 1.35; Difference O-E = 26.2% (n=115)</td>
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<td>is not accurate in young women)</td>
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<td><strong>Unknown</strong> (n=26): Mortality ratio O:E = 1.75; Difference O-E = 42.9% (n=3)</td>
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<td>10 Is the rule acceptable in your case? Yes (this tool cannot be used in young women)</td>
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<td><strong>ER status</strong></td>
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<td>11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes (this tool cannot be used in young women)</td>
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<td>Negative (n=965): Mortality ratio O:E = 0.82; Difference O-E = -21.2% (n=-52)</td>
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<td><strong>Indirectness</strong></td>
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<td><strong>Positive</strong> (n=1862): Mortality ratio O:E = 2.29; Difference O-E = 56.4% (n=204)</td>
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<td>This study includes direct population (UK based).</td>
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<td><strong>HER2 status</strong></td>
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<td><strong>Other information</strong></td>
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<td>Negative (n=1773): Mortality ratio O:E = 1.50; Difference O-E = 33.4% (n=128)</td>
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<td>Conflict of interest: EC received honoraria from Roche. All other authors declare no conflict of interest.</td>
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<td><strong>Positive</strong> (n=679): Mortality ratio O:E = 1.15; Difference O-E = 13.1% (n=24)</td>
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<td>PREDICT was contacted to determine which version of PREDICT was used in</td>
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<td><strong>Borderline</strong> (n=40): Mortality ratio O:E = 1.67; Difference O-E = 40% (n=4)</td>
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<td>10-year all-cause mortality</td>
<td>this study (<a href="mailto:info@predict.nhs.uk">info@predict.nhs.uk</a>)</td>
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<td>Total cohort (N=597): Mortality ratio O:E = 0.93; Difference O-E = -7.9% (n=-12)</td>
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<td>Sub-group: age at diagnosis</td>
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<td>18 to 25 (n=8): Mortality ratio O:E = 1 o Difference O-E = 0% (n=0)</td>
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<td>26 to 30 (n=55): Mortality ratio O:E = 0.94 o Difference O-E = -6.7% (n=-1)</td>
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<td>31 to 35 (n=203): Mortality ratio O:E = 1.05 o Difference O-E = 5% (n=3)</td>
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<td>36 to 40 (n=331): Mortality ratio O:E = 0.84 o Difference O-E = -18.4% (n=-14)</td>
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<td>Sub-group: grade</td>
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<td>Grade 1 (n=31): Mortality ratio O:E = 1.5 o Difference O-E = 33% (n=1)</td>
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<td>Grade 2 (n=200): Mortality ratio O:E = 1.42 o Difference O-E = 30% (n=13)</td>
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<td>Grade 3 (n=351): Mortality ratio O:E = 0.80; Difference O-E = -25.5% (n=-26)</td>
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<td>Unknown (n=15): Mortality ratio O:E = 1; Difference O-E = 0% (n=0)</td>
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<td>Sub-group: tumour size</td>
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<td>0 to 10 (n=48): Mortality ratio O:E = 2; Difference O-E = 50% (n=7)</td>
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<td>11 to 20 (n=221): Mortality ratio O:E = 0.91; Difference O-E = -9.8% (n=-4)</td>
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<td>21 to 50 (n=244): Mortality ratio O:E = 0.99; Difference O-E = -1.3% (n=-1)</td>
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<td>&gt;50 (n=54): Mortality ratio O:E = 0.46; Difference O-E = -115.4% (n=-15)</td>
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<td>Unknown (n=30): Mortality ratio O:E = 1.2; Difference O-E = 16.7% (n=1)</td>
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<td>Sub-group: node status</td>
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<td>Negative (n=266): Mortality ratio O:E = 0.93; Difference O-E = -7.7% (n=-3)</td>
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### Study details

<table>
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<tr>
<td>Positive (n=327): Mortality ratio O:E = 0.92; Difference O-E = 8% (n=9)</td>
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<td>Unknown (n=4): Mortality ratio O:E = 1; Difference O-E = 0% (n=0)</td>
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<tr>
<td>Sub-group: ER status</td>
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<tr>
<td>Negative (n=231): Mortality ratio O:E = 0.68; Difference O-E = -46.9% (n=-30)</td>
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<tr>
<td>Positive (n=366): Mortality ratio O:E = 1.26; Difference O-E = 20.5% (n=18)</td>
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<tr>
<td>Sub-group: HER2 status</td>
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<tr>
<td>Negative (n=327): Mortality ratio O:E = 0.99; Difference O-E = -1.2% (n=-1)</td>
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<tr>
<td>Positive (n=140): Mortality ratio O:E = 0.94; Difference O-E = -6% (n=3)</td>
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<tr>
<td>Borderline (n=14): Mortality ratio O:E = 1.25; Difference O-E = 20% (n=1)</td>
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<tr>
<td>Unknown (n=116): Mortality ratio O:E = 0.62; Difference O-E = -60% (n=9)</td>
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<tr>
<td>Study details</td>
<td>Number of participants and participants characteristics</td>
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<td>PREDICT v1.0</td>
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</tbody>
</table>

**Tool discrimination**

**5-year all-cause mortality**

AUC ER- vs ER+ = 0.718 vs 0.730 (discrimination was better for ER+ tumours, compared to ER- tumours)

**10-year all-cause mortality**

AUC ER- vs ER+ = 0.694 vs 0.724 (discrimination was better for ER+ tumours, compared to ER- tumours)

AUC HER2- vs HER2+ = 0.724 vs 0.592 (discrimination was better for HER2- tumours, compared to HER2+ tumours)

**Full citation**


**Sample size**

N=5468 patients from the West Midlands Cancer Intelligence Unit (WMCIU)

**Characteristics**

**Prognostic tool**

PREDICT v1.0

**Details**

Model discrimination was assessed using the area under the receiver-operator-characteristic (ROC) curve (AUC) calculated for the

**Results**

Prognostic accuracy (sensitivity, specificity)

Not reported

**Limitations**

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).

A. Are the results valid?
### Study details

<table>
<thead>
<tr>
<th>Number of participants and participants characteristics</th>
<th>Prognostic tool</th>
<th>Methods</th>
<th>Outcomes and results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (years): 4.85 (0.07 to 8.00)</td>
<td>overall deaths at 8 years after diagnosis.</td>
<td>Tool calibration and discrimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis: 58 (22 to 93)</td>
<td>Model calibration was calculated using a simplified goodness-of-fit method for the Cox proportional hazards mode, where observed and model-based predicted deaths at 5 and 8 years were compared. Observed and predicted deaths were compared using a standard Chi-squared test.</td>
<td>5-year all-cause mortality</td>
<td></td>
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<tr>
<td><strong>Age, years</strong></td>
<td>The analyses were conducted using STATA, version 9.2.</td>
<td>Total cohort (N=5468): Mortality ratio O:E = 0.91; Difference O-E = -1.61%</td>
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<tr>
<td>&lt;35: 2% (n=108)</td>
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<td>Sub-group: age</td>
<td></td>
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<tr>
<td>35 to 49: 22% (n=1,195)</td>
<td>&lt;35 (n=108); Mortality ratio O:E = 0.88; Difference O-E = -2.78%</td>
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<tr>
<td>50 to 64: 44% (n=2,393)</td>
<td>35 to 49 (n=1195); Mortality ratio O:E = 0.83; Difference O-E = -2.68%</td>
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<tr>
<td>65 to 74: 20% (n=1,101)</td>
<td>50 to 67 (n=2393); Mortality ratio O:E = 0.90; Difference O-E = -1.34%</td>
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<tr>
<td>75+: 12% (n=671)</td>
<td>65 to 74 (n=1101); Mortality ratio O:E = 0.98; Difference O-E = -0.45%</td>
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<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td>Sub-group: grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0: 58% (n=3,184)</td>
<td>75+ (n=671); Mortality ratio O:E = 0.98; Difference O-E = -0.75%</td>
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<tr>
<td>1: 14% (n=746)</td>
<td></td>
<td>Grade 1 (n=1017): Mortality ratio O:E = 0.98; Difference O-E = -0.1%</td>
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<td></td>
</tr>
<tr>
<td>2 to 4: 14% (n=792)</td>
<td></td>
<td>1 Is the CPR clearly defined? Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9: 8% (n=451)</td>
<td>2 The population from which the rule was derived included an appropriate spectrum of patients? Yes</td>
<td></td>
<td></td>
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<tr>
<td>10+: 5% (n=295)</td>
<td>3 Was the rule validated in a different group of patients? Yes (this study aims to develop and validate the tool. A different group of women was used to validate the tool)</td>
<td></td>
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</tr>
</tbody>
</table>

### Survival following surgery for invasive breast cancer

[Erratum appears in Breast Cancer Res. 2010;12(2):401], Breast Cancer Research, 12, R1, 2010

**Ref Id**: 585712

**Country/ies where the study was carried out**: UK

**Aim of the study**: To develop and validate a model to predict overall and breast cancer specific survival for women treated for early breast cancer.

**Study dates**: 1999 and 2003

**Source of funding**: Educational grant from Pfizer Limited. GCW & CC receive research funding from the Cambridge NIHR Biomedical Research Centre.

**Sample selection**: The primary analysis was based on data from patients with invasive breast cancer diagnosed in East Anglia, UK between 1999 and 2003 identified by the Eastern Cancer Registration and Information Centre. The validation study was conducted using STATA, version 9.2.

**Tool calibration and discrimination**: 5-year all-cause mortality

- Total cohort (N=5468): Mortality ratio O:E = 0.91; Difference O-E = -1.61%
- Sub-group: age
  - <35 (n=108); Mortality ratio O:E = 0.88; Difference O-E = -2.78%
  - 35 to 49 (n=1195); Mortality ratio O:E = 0.83; Difference O-E = -2.68%
  - 50 to 64 (n=2393); Mortality ratio O:E = 0.90; Difference O-E = -1.34%
  - 65 to 74 (n=1101); Mortality ratio O:E = 0.98; Difference O-E = -0.45%
  - 75+ (n=671); Mortality ratio O:E = 0.98; Difference O-E = -0.75%

**Sub-group: grade**

- Grade 1 (n=1017): Mortality ratio O:E = 0.98; Difference O-E = -0.1%

1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes (this study aims to develop and validate the tool. A different group of women was used to validate the tool)
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Not applicable (the outcome is mortality)
5 Were the predictor variables and the outcome evaluates in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate...
## Study details

### Number of participants and participants characteristics

<table>
<thead>
<tr>
<th>Number of participants and participants characteristics</th>
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</thead>
<tbody>
<tr>
<td>&lt;10: 9% (n=485)</td>
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<tr>
<td>10 to 19: 39% (n=2,136)</td>
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<tr>
<td>20 to 29: 29% (n=1,566)</td>
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<tr>
<td>30 to 49: 17% (n=923)</td>
<td></td>
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<tr>
<td>50+: 7% (n=358)</td>
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</tbody>
</table>

### Prognostic tool

Data from the West Midlands Cancer Intelligence Unit (WMCIU). This cohort included all women diagnosed with invasive breast cancer between 1999 and 2003.

### Methods

Data collection

The following information was obtained from WMCIU database: age at diagnosis, number of lymph nodes sampled and number of lymph nodes positive (categorised as 0, 1, 2 to 4, 5 to 9, and 10+ nodes positive), tumour size (categorised as <10 mm, 10 to 19 mm, 20 to 29 mm, 30 to 49 mm, 50+ mm), histological grade (I, II, III), oestrogen receptor (ER) status (positive or negative), mode of detection (screening vs. clinical), information on local therapy (wide local excision, mastectomy, radiotherapy), and type.

### Outcomes and results

#### Grade 2 (n=2442)

- Mortality ratio O:E = 0.98; Difference O-E = -0.16%

#### Grade 3 (n=2009)

- Mortality ratio O:E = 0.87; Difference O-E = -3.58%

#### Sub-group: tumour size

- **<10 mm (n=485)**: Mortality ratio O:E = 0.84; Difference O-E = -1.03%
- **10 to 19 mm (n=2136)**: Mortality ratio O:E = 0.88; Difference O-E = -2.01%
- **20 to 29 mm (n=1566)**: Mortality ratio O:E = 0.94; Difference O-E = -0.96%
- **30 to 49 mm (n=923)**: Mortality ratio O:E = 0.99; Difference O-E = -0.11%
- **50+ mm (n=358)**: Mortality ratio O:E = 0.91; Difference O-E = -3.91%

#### Sub-group: nodal status

- **Negative (n=3184)**: Mortality ratio O:E = 0.80; Difference O-E = -2.14%

### Comments

- Can the performance of the rule be calculated? No (not enough data is available to calculate sensitivity, specificity, LR+, LR+, ROC curve. Mortality ratio can be calculated)
- How precise was the estimate of the treatment effect? The model considers many relevant variables, but updates of this version include additional factors
- Would the prediction rule be reliable and and the results interpretable

---

**Inclusion criteria**

West Midlands Cancer Intelligence Unit (WMCIU) registry data. No details reported.

**Exclusion criteria**

Not reported.
<table>
<thead>
<tr>
<th>Study details</th>
<th>Number of participants and participants characteristics</th>
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<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td>of adjuvant systemic therapy (chemotherapy, endocrine therapy, both).</td>
<td></td>
<td>Data analysis</td>
<td>Positiv e(n=2284): Mortality ratio O:E = 0.98; Difference O-E = -0.39%</td>
<td>if used for your patient? Yes (UK population)</td>
</tr>
<tr>
<td></td>
<td>Sub-group: ER status</td>
<td>Negative (n=1116):</td>
<td></td>
<td>Mortality ratio O:E = 0.87; Difference O-E = -4.21%</td>
<td>10 Is the rule acceptable in your case? Yes</td>
</tr>
<tr>
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<td></td>
<td>AUC 0.81 (SE 0.0111)</td>
<td>11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Positive (n=4352): Mortality ratio O:E = 0.95; Difference O-E = -0.69%</td>
<td>Indirectness</td>
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<td>AUC 0.75 (SE 0.0169)</td>
<td>This study includes direct population (UK based).</td>
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<tr>
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<td>8-year all-cause mortality (proxy for long-term)</td>
<td>Other information</td>
</tr>
<tr>
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<td>Total cohort (N=5468): Mortality ratio O:E = 0.95; Difference O-E = -0.93%</td>
<td>Conflict of interest: none</td>
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<tr>
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<td>Sub-group: age</td>
<td>For the purpose of this review, we have only considered the validation data (WMCIU cohort).</td>
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<td>&lt;35 (n=108): Mortality ratio O:E = 1.08; Difference O-E = 1.85%</td>
<td>Breast cancer specific deaths were not reported in detail in the published study.</td>
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<td>35 to 49 (n=1195): Mortality ratio O:E = 0.87; Difference O-E = -2.18%</td>
<td>PREDICT was contacted to determine</td>
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Early and locally advanced breast cancer: diagnosis and management: evidence reviews for adjuvant systemic therapy planning July 2018
<table>
<thead>
<tr>
<th>Study details</th>
<th>Number of participants and participants characteristics</th>
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<tbody>
<tr>
<td></td>
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<td>which version of PREDICT was used in this study (<a href="mailto:info@predict.nhs.uk">info@predict.nhs.uk</a>)</td>
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<td></td>
<td>50 to 67 (n=2393); Mortality ratio O:E = 0.92; Difference O-E = -1%</td>
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<td>65 to 74 (n=1101); Mortality ratio O:E = 1.00; Difference O-E = -0.09%</td>
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<td>75+ (n=671); Mortality ratio O:E = 0.98; Difference O-E = -0.6%</td>
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<td>Sub-group: grade</td>
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<td>Grade 1 (n=1017): Mortality ratio O:E = 1.04; Difference O-E = 0.29%</td>
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<td>Grade 2 (n=2442): Mortality ratio O:E = 1.04; Difference O-E = 0.61%</td>
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<td>Grade 3 (n=2009): Mortality ratio O:E = 0.88; Difference O-E = -3.38%</td>
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<td>Sub-group: tumour size</td>
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<td>&lt;10 mm (n=485): Mortality ratio O:E = 0.85; Difference O-E = -1.03%</td>
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<td>10 to 19 mm (n=2136): Mortality ratio O:E = 0.84; Difference O-E = -1.73%</td>
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<tr>
<td>Study details</td>
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<td>20 to 29 mm (n=1566): Mortality ratio O:E = 0.97; Difference O-E = -0.57%</td>
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<td>30 to 49 mm (n=923): Mortality ratio O:E = 0.98; Difference O-E = -0.43%</td>
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<td>50+ mm (n=358): Mortality ratio O:E = 0.56; Difference O-E = -3.35%</td>
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<td><strong>Sub-group: nodal status</strong></td>
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<tr>
<td>Negative (n=3184): Mortality ratio O:E = 0.84; Difference O-E = -1.76%</td>
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<tr>
<td>Positive (n=2284): Mortality ratio O:E = 1.01; Difference O-E = 0.26%</td>
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<td><strong>Sub-group: ER status</strong></td>
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<tr>
<td>Negative (n=1116): Mortality ratio O:E = 0.90; Difference O-E = -3.49%</td>
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<td>Positive (n=4352): Mortality ratio O:E = 0.98; Difference O-E = -0.25%</td>
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*8-year all-cause mortality (proxy for long-term)*
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<tr>
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</table>

**Total cohort (N=5468):** AUC (SE) = 0.79 (0.008)

**Sub-group: age**

- <35 (n=108); AUC (SE) = 0.70 (0.057)
- 35 to 49 (n=1195); AUC (SE) = 0.79 (0.018)
- 50 to 67 (n=2393); AUC (SE) = 0.80 (0.013)
- 65 to 74 (n=1101); AUC (SE) = 0.76 (0.018)
- 75+ (n=671); AUC (SE) = 0.72 (0.021)

**Sub-group: grade**

- Grade 1 (n=1017); AUC (SE) = 0.79 (0.029)
- Grade 2 (n=2442); AUC (SE) = 0.77 (0.013)
- Grade 3 (n=2009); AUC (SE) = 0.75 (0.012)

**Sub-group: tumour size**

- <10 mm (n=485); AUC (SE) = 0.82 (0.040)
<table>
<thead>
<tr>
<th>Study details</th>
<th>Number of participants and participants characteristics</th>
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<tr>
<td></td>
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<td>PREDICT v1.1 and v1.2</td>
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</table>

**Full citation**
Wishart, G. C., Rakha, E., Green, A., Ellis, I., Ali, H. R., Provenzano, E., Blows, F. M., Caldas, C.

**Sample size**
Data for 2232 cases of invasive breast cancer treated in Nottingham - 506 node-negative

**Prognostic tool**
PREDICT v1.1 and v1.2

**Details**
Sample selection, Data collection

**Results**
Results for PREDICT v1.1
Prognostic accuracy (sensitivity, specificity)

**Limitations**
The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
<table>
<thead>
<tr>
<th>Study details</th>
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<tbody>
<tr>
<td>Pharoah, P. D., Inclusion of KI67 significantly improves performance of the PREDICT prognostication and prediction model for early breast cancer, BMC cancer, 14, 908, 2014</td>
<td>cases were excluded, so data from n=1726 people was included in the study</td>
<td>The data was obtained from the Nottingham dataset. This included: age at diagnosis, histological grade, tumour size, number of positive lymph nodes, ER status, HER2 status, KI67 and type of adjuvant systemic therapy (none, chemotherapy, endocrine therapy, both). The missing data was replaced with the mean for that variable.</td>
<td>Not reported</td>
<td>Tool calibration</td>
<td></td>
</tr>
<tr>
<td><strong>10-year breast cancer mortality</strong></td>
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<td></td>
<td><strong>Sub-group: age</strong></td>
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<td>40 to 49 (n=274): BC mortality ratio O:E = 1.18</td>
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<td>50 to 59 (n=436): BC mortality ratio O:E = 1.18</td>
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<td>60+ (n=497): BC mortality ratio O:E = 1.06</td>
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<td><strong>Sub-group: tumour size</strong></td>
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<td>&lt;10 (n=144): BC mortality ratio O:E = 0.78</td>
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<td>10 to 19 (n=574): BC mortality ratio O:E = 1.09</td>
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<td>20 to 29 (n=404): BC mortality ratio O:E = 1.32</td>
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<tr>
<td><strong>A. Are the results valid?</strong></td>
<td>Yes</td>
<td>1 Is the CPR clearly defined? Yes</td>
<td>2 The population from which the rule was derived included an appropriate spectrum of patients? Yes</td>
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<tr>
<td></td>
<td>Yes (this study aims to validate a new version of the tool)</td>
<td>3 Was the rule validated in a different group of patients? Yes</td>
<td>4 Were the predictor variables and the outcome evaluated in a blinded fashion? Not applicable (the outcome is mortality)</td>
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<tr>
<td></td>
<td>Not applicable (the outcome is mortality)</td>
<td>5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes</td>
<td>6 Are the statistical methods used to construct and validate the rule clearly described? Yes</td>
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### Study details

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>the area under the receiver-operator-characteristic curve (AUC), for 10-year mortality.</td>
<td>30 to 49 (n=140): BC mortality ratio O:E = 0.95</td>
<td>B. What are the results?</td>
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<td>50+ (n=11): BC mortality ratio O:E = 0.5</td>
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<td>Missing (n=1): BC mortality ratio O:E = 1</td>
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<td>Sub-group: node status</td>
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<td>Negative (n=709): BC mortality ratio O:E = 1.19</td>
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<td>1+ (n=241): BC mortality ratio O:E = 1.23</td>
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<td>2 to 4+ (n=184): BC mortality ratio O:E = 1.05</td>
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<td>5 to 9+ (n=37): BC mortality ratio O:E = 1.10</td>
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<td>10+ (n=6): BC mortality ratio O:E = 0.8</td>
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<td>Missing (n=97): BC mortality ratio O:E = 1.07</td>
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<td>Sub-group: grade</td>
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<td>Grade 1 (n=235): BC mortality ratio O:E = 1.8</td>
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<td>Grade 2 (n=528): BC mortality ratio O:E = 1.16</td>
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<td>50+ (n=11): BC mortality ratio O:E = 0.5</td>
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<td>Missing (n=1): BC mortality ratio O:E = 1</td>
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<td>Grade 2 (n=528): BC mortality ratio O:E = 1.16</td>
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</tbody>
</table>

7 Can the performance of the rule be calculated? No (not enough data is available to calculate sensitivity, specificity, LR+, LR+, ROC curve. Mortality ratio can be calculated)

8 How precise was the estimate of the treatment effect? The updated model considers additional factors

9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population)

10 Is the rule acceptable in your case? Yes
### Study details

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<thead>
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<tr>
<td>Grade 3 (n=395): BC mortality ratio O:E = 1.14</td>
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<tr>
<td>Missing grade (n=116): BC mortality ratio O:E = 0.31</td>
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<tr>
<td>Sub-group: HER2 status</td>
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<tr>
<td>Negative (n=792): BC mortality ratio O:E = 1.35</td>
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<tr>
<td>Positive (n=77): BC mortality ratio O:E = 1.35</td>
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<tr>
<td>Missing (n=405): BC mortality ratio O:E = 0.44</td>
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<tr>
<td>Tool discrimination</td>
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<tr>
<td>AUC = 0.7611 (CI not reported)</td>
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<tr>
<td>Results for PREDICT v1.2</td>
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<tr>
<td>Prognostic accuracy (sensitivity, specificity)</td>
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<tr>
<td>Not reported</td>
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<tr>
<td>Tool calibration</td>
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<tr>
<td>10-year breast cancer mortality</td>
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</table>

11. Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes

**Indirectness**

This study includes direct population (UK based).

**Other information**

Conflict of interest: none

PREDICT was contacted to determine which versions of PREDICT were used in this study (info@predict.nhs.uk)
### Study details

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<tr>
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<td>Total cohort (N=1726): BC mortality ratio O:E = 1.08</td>
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<td>Sub-group: age</td>
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<td>&lt;40 (n=67): BC mortality ratio O:E = 1.07</td>
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<td>40 to 49 (n=274): BC mortality ratio O:E = 1.13</td>
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<td>50 to 59 (n=436): BC mortality ratio O:E = 1.15</td>
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<td>60+ (n=497): BC mortality ratio O:E = 1.01</td>
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<td>Sub-group: tumour size</td>
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<td>30 to 49 (n=140): BC mortality ratio O:E = 0.91</td>
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<td>50+ (n=11): BC mortality ratio O:E = 0.5</td>
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<td>Missing (n=1): BC mortality ratio O:E = 1</td>
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<td>Sub-group: node status</td>
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<td>Negative (n=709): BC mortality ratio O:E = 1.15</td>
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<td>1+ (n=241): BC mortality ratio O:E = 1.17</td>
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<td>2 to 4+ (n=184): BC mortality ratio O:E = 1</td>
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<td>10+ (n=6): BC mortality ratio O:E = 0.8</td>
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<td>Missing (n=97): BC mortality ratio O:E = 1.07</td>
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<td>Sub-group: grade</td>
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<td>Grade 1 (n=235): BC mortality ratio O:E = 1.8</td>
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<td>Grade 2 (n=528): BC mortality ratio O:E = 1.14</td>
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<tr>
<td>Negative (n=792): BC mortality ratio O:E = 1.29</td>
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<td>Positive (n=77): BC mortality ratio O:E = 1.24</td>
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<tbody>
<tr>
<td>Sample size</td>
<td>N tool development = 5738 (ECRIC database)</td>
<td>PREDICT v2.0</td>
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<td></td>
<td>N validations study</td>
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<td>BCOS: n=981</td>
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<td>NTBCS: n=1726</td>
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<td>POSH: n=2609</td>
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<tr>
<td>Characteristics</td>
<td>Not reported.</td>
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### Prognostic tool

- **Sample selection**
  - For the tool development, data was obtained from the ECRIC database (n=5738), which includes patients with invasive breast cancer diagnosed in East Anglia, UK, between 1999 and 2003.
  - For the validation study, data consisted in

- **Sample size**
  - N tool development = 5738 (ECRIC database)
  - N validations study
    - BCOS: n=981
    - NTBCS: n=1726
    - POSH: n=2609

- **Prognostic tool**
  - PREDICT v2.0
  - Note: This validation study reports data for PREDICT v2.0 and v1. Data for v1 was not used in the analysis as for many of the cases in the validation data the authors did not have either HER2 status or Ki67 status

- **Results**
  - Prognostic accuracy (sensitivity, specificity)
    - Not reported
  - **Tool calibration**
    - 10-year breast cancer specific mortality
      - Total cohort (n=11272):
        - BC mortality ratio = 0.95; difference O:E = -5% (p-value = 0.027)
      - **Sub-group: age at diagnosis**

### Limitations

- The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
  - A. Are the results valid?
    - 1 Is the CPR clearly defined? Yes
    - 2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
  - 3 Was the rule validated in a different group of patients? Yes (this study
<table>
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<tr>
<td><strong>Ref Id</strong></td>
<td><strong>657670</strong></td>
<td><strong>Inclusion criteria</strong></td>
<td>Not reported.</td>
<td><strong>ER-</strong></td>
</tr>
<tr>
<td>Country/ies where the study was carried out</td>
<td>UK</td>
<td><strong>Exclusion criteria</strong></td>
<td>Not reported.</td>
<td>20 to 29 (n=92): BC mortality ratio = 0.94; difference O:E = -6% (p-value = 0.76)</td>
</tr>
<tr>
<td><strong>Aim of the study</strong></td>
<td>To develop and validate a new version of PREDICT (v2.0)</td>
<td><strong>Methods</strong></td>
<td>combined data sets from the :</td>
<td><strong>5</strong> Were the predictor variables and the outcome evaluates in the whole sample selected initially? Yes</td>
</tr>
<tr>
<td><strong>Study dates</strong></td>
<td>Tool development: single dataset: East Anglia Cancer Registration and Information Centre (ECRIC), between 1999 to 2003</td>
<td>1) the NTBCS study (n=1726); included patients treated in Nottingham from 1989 to 1998. 506 node-negative cases were initially excluded because of inadequate axillary node staging (initial N=2232, but 506 node negative cases were excluded because of inadequate node staging) (ER-negative, n = 452; ER-positive, n = 1274)</td>
<td><strong>ER-</strong></td>
<td>6 Are the statistical methods used to construct and validate the rule clearly described? Yes</td>
</tr>
<tr>
<td>Validation study: combined datasets: 1) the Nottingham/ Tenovus Breast Cancer Study (NTBCS) between 1989 and 1998; 2) the Breast Cancer Outcome Study of Mutation Carriers (BCOS) between 1990 and 2000; and 3) the Prospective study of Outcomes in Sporadic and Hereditary</td>
<td></td>
<td>2) the BCOS study (n=981) used data from a cohort of consecutive females diagnosed at &lt;50 years of age with invasive breast cancer between 1990 and 2000, identified through medical registries of participating hospitals or the Netherlands Cancer Registry</td>
<td>30 to 39 (n=855): BC mortality ratio = 0.92; difference O:E = -9% (p-value = 0.18)</td>
<td>B. What are the results?</td>
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<tr>
<td></td>
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<td>3) the POSH study (n=2609) included young women</td>
<td>40 to 49 (n=414): BC mortality ratio = 0.98; difference O:E = -2% (p-value = 0.83)</td>
<td>7 Can the performance of the rule be calculated? No (not enough data is available to calculate sensitivity, specificity, LR+, LR+, ROC curve. Mortality ratio can be calculated)</td>
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<td>50 to 59 (n=165): BC mortality ratio = 0.97; difference O:E = -3% (p-value = 0.85)</td>
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<td>60 to 69 (n=117): BC mortality ratio = 0.82; difference O:E = -21% (p-value = 0.32)</td>
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<td>70 to 79 (n=11): BC mortality ratio = 0.36; difference O:E = -180% (p-value = 0.28)</td>
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<td><strong>ER+</strong></td>
<td>20 to 29 (n=140): BC mortality ratio = 0.71; difference O:E = -40% (p-value = 0.047)</td>
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<td>30 to 39 (n=1633): BC mortality ratio = 0.96; difference O:E = -4% (p-value = 0.48)</td>
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<td>Study details</td>
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<tr>
<td><strong>Source of funding</strong></td>
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<td><strong>Data collection</strong></td>
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<tr>
<td>The BCOS study was funded by the Netherlands Cancer Institute (NKI2007-3839).</td>
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<td>The primary analysis was conducted using data from the ECRIC database. This included: age at diagnosis, number of lymph nodes sampled and number of lymph nodes positive, tumour size, histological grade, ER status, mode of detection (screening vs. clinical), information on local therapy (wide local excision, mastectomy, radiotherapy), and type of adjuvant systemic therapy (chemotherapy, endocrine therapy, both). n=1977 (34%) had less than 10 years of potential follow-up.</td>
<td></td>
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<tr>
<td>The POSH study was funded by Cancer Research UK (C1275/A9896, C1275/A11699, and C1275/A15956) and Breast Cancer Now (2005Nov63).</td>
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<td>PDPP was funded by the National Institute for Health Research Biomedical Research Centre at the University of Cambridge.</td>
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<td><strong>Source of funding</strong></td>
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<td><strong>Outcomes and results</strong></td>
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<td>40 to 49 (n=1063): BC mortality ratio = 0.90; difference O:E = -11% (p-value = 0.16)</td>
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<td>50 to 59 (n=467): BC mortality ratio = 0.96; difference O:E = -4% (p-value = 0.77)</td>
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<td>60 to 69 (n=517): BC mortality ratio = 1.08; difference O:E = 7% (p-value = 0.53)</td>
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<td>70 to 79 (n=55): BC mortality ratio = 0.38; difference O:E = -26% (p-value = 0.54)</td>
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<td><strong>Sub-group: tumour size</strong></td>
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<td>0 to 9 mm (n=96): BC mortality ratio = 0.90; difference O:E = -10% (p-value = 0.73)</td>
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<td>10 to 19 mm (n=559): BC mortality ratio = 0.92; difference O:E = -8% (p-value = 0.41)</td>
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<td>20 to 29 mm (n=524): BC mortality ratio = 0.97; difference O:E = -3% (p-value = 0.72)</td>
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<tr>
<td><strong>Indirectness</strong></td>
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<td>This study includes a mixed population (38%)</td>
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<td>C. Will the results help locally? Are the results applicable to the scenario?</td>
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<td>9 Would the prediction rule be reliable and and the results interpretable if used for your patient? Yes (UK population)</td>
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<td>10 Is the rule acceptable in your case? Yes</td>
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<td>11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes</td>
<td></td>
</tr>
<tr>
<td>Study details</td>
<td>Number of participants and participants characteristics</td>
<td>Prognostic tool</td>
<td>Methods</td>
<td>Outcomes and results</td>
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<td>30 to 49 mm (n=354): BC mortality ratio = 0.99; difference O:E = -1% (p-value = 0.91)</td>
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<td>50+ mm (n=121): BC mortality ratio = 0.75; difference O:E = -33% (p-value = 0.04)</td>
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<td>ER+</td>
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<td>0 to 9 mm (n=352): BC mortality ratio = 1.54; difference O:E = 35% (p-value = 0.024)</td>
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<td>10 to 19 mm (n=1428): BC mortality ratio = 1.06; difference O:E = 6% (p-value = 0.46)</td>
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<td>20 to 29 mm (n=1111): BC mortality ratio = 0.98; difference O:E = -2% (p-value = 0.80)</td>
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<td></td>
<td>30 to 49 mm (n=695): BC mortality ratio = 0.87; difference O:E = -15% (p-value = 0.07)</td>
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<tr>
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<td></td>
<td>50+ mm (n=289): BC mortality ratio = 0.74; difference O:E = -35% (p-value = 0.00)</td>
</tr>
</tbody>
</table>

**Sub-group: nodes positive**

**ER-**

The Netherlands, 62% UK.

**Other information**

Conflict of interest: none

PREDICT was contacted to determine which versions of PREDICT were used in this study (info@predict.nhs.uk)
<table>
<thead>
<tr>
<th>Study details</th>
<th>Number of participants and participants characteristics</th>
<th>Prognostic tool</th>
<th>Methods</th>
<th>Outcomes and results</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and adjuvant hormone therapy.</td>
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<td>4) data from the ECRIC database (primary analysis)</td>
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<td><strong>Data analysis</strong></td>
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<td>Model calibration. was calculated for 10-year predicted breast cancer specific mortality and other mortality using the current online version of PREDICT (v1.3). It was obtained by comparing the predicted mortality estimates from each model with the observed mortality. This was done for the complete data set, and within strata of other prognostic variables.</td>
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<td>Model discrimination was calculated using the AUC calculated for 10-year mortality. The comparison between version 2.0 and version 1 was made using the method of DeLong.</td>
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</tbody>
</table>

**ER+**

|               |                                                          |                |         | 0 (n=937): BC mortality ratio = 1.01; difference O:E = 1% (p-value = 0.89) |          |
|               |                                                          |                |         | 1 (n=232): BC mortality ratio = 0.86; difference O:E = -17% (p-value = 0.23) |          |
|               |                                                          |                |         | 2 to 4 (n=300): BC mortality ratio = 0.88; difference O:E = -13% (p-value = 0.19) |          |
|               |                                                          |                |         | 5 to 9 (n=101): BC mortality ratio = 0.96; difference O:E = -4% (p-value = 0.77) |          |
|               |                                                          |                |         | 10+ (n=84): BC mortality ratio = 0.85; difference O:E = -17% (p-value = 0.28) |          |

<p>|               |                                                          |                |         | 0 (n=2085): BC mortality ratio = 0.99; difference O:E = -1% (p-value = 0.85) |          |
|               |                                                          |                |         | 1 (n=675): BC mortality ratio = 0.92; difference O:E = -9% (p-value = 0.39) |          |
|               |                                                          |                |         | 2 to 4 (n=734): BC mortality ratio = 0.96; difference O:E = -4% (p-value = 0.63) |          |</p>
<table>
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<th>Comments</th>
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<tbody>
<tr>
<td></td>
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<td>All analyses were carried out using Stata version 14 software (StataCorp, College Station, TX, USA).</td>
<td>5 to 9 (n=245): BC mortality ratio = 0.86; difference O:E = -17% (p-value = 0.14)</td>
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<td>10+ (n=136): BC mortality ratio = 0.87; difference O:E = -15% (p-value = 0.25)</td>
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<td><strong>Sub-group: tumour grade</strong></td>
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<td><strong>ER-</strong></td>
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<td>1 (n=44): BC mortality ratio = 0.96; difference O:E = -4% (p-value = 0.91)</td>
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<td>2 (n=183): BC mortality ratio = 0.86; difference O:E = -17% (p-value = 0.33)</td>
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<td>3 (n=1427): BC mortality ratio = 0.94; difference O:E = -7% (p-value = 0.19)</td>
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<td><strong>ER+</strong></td>
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<td>1 (n=658): BC mortality ratio = 0.86; difference O:E = -16% (p-value = 0.43)</td>
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<td>2 (n=1730): BC mortality ratio = 0.95; difference O:E = -5% (p-value = 0.44)</td>
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<td>Study details</td>
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<td>3 (n=1487): BC mortality ratio = 0.93; difference O:E = -7% (p-value = 0.17)</td>
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<td>10-year all-cause mortality</td>
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<td>Total cohort (n=11272): Mortality ratio = 0.99; difference O:E = -4% (p-value = 0.023)</td>
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<td>Tool discrimination</td>
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<td>Combined dataset: ER-: AUC = 0.696 ER+: AUC = 0.760 All population: AUC = 0.752</td>
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<td>ECRIC dataset: ER-: AUC = 0.726 ER+: AUC = 0.796 All population: AUC = 0.805</td>
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<td>NTBCS dataset:</td>
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<td>Study details</td>
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<td>ER-: AUC = 0.680</td>
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<td>ER+: AUC = 0.790</td>
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<td>All population: AUC = 0.772</td>
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<td>POSH dataset:</td>
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<td>ER-: AUC = 0.696</td>
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<td>ER+: AUC = 0.760</td>
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<td></td>
<td>All population: AUC = 0.752</td>
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</tbody>
</table>

ABC, adjuvant breast cancer; AUC, area under the curve; BC, breast cancer; BCOS, Breast Cancer Outcomes Simulator; BCSS, breast cancer specific survival; CASP, Critical Appraisal Skills Programme; CPR, clinical prediction rule; ECRIC, East Anglia cancer registration and information centre; EFS, event free survival; ER, oestrogen receptor; HER2, Human epidermal growth factor receptor 2; NIHR, National Institute for Health Research; NPI, Nottingham Prognostic Index; NTBC, Nottingham Tenovus Breast Cancer; OPI, Oxford Prognostic Index; OS, overall survival; POSH, Prospective study of Outcomes in Sporadic versus Hereditary breast cancer; PR, progesterone receptor; SE, standard error; UK, United Kingdom; WMCIU, West Midlands Cancer Intelligence Unit
Appendix E – Forest plots

Forest plots for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

There are no forest plots for this evidence review as no studies met the inclusion criteria.

Forest plots for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

Forest plots are not applicable to this review as no meta-analysis was undertaken.
Adjuvant systemic therapy planning

Appendix F – GRADE tables

GRADE tables for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

There are no GRADE tables for this evidence review as no studies met the inclusion criteria.

GRADE tables for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

There are no GRADE tables for this evidence review as GRADE is not appropriate to assess the quality of evidence for prediction model performance reviews.
Appendix G – Economic evidence study selection

Economic evidence study selection for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

See Supplement 1: Health economics literature review for details of economic study selection.
Appendix H – Economic evidence tables

Economic evidence tables for 3.1. Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

No economic evidence was identified for this review question.

Economic evidence tables for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

No economic evidence was identified for this review question.
Appendix I – Health economic evidence profiles

Health economic evidence profiles for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

No economic evidence was identified for this review question.

Health economic evidence profiles for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

No economic evidence was identified for this review question.
Appendix J – Health economic analysis

Health economic analysis for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

No health economic analysis was carried out for this review question.

Health economic analysis for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

No health economic analysis was carried out for this review question.
# Appendix K – Excluded studies

## Excluded studies for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

### Clinical studies

<table>
<thead>
<tr>
<th>Excluded studies - RQ3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer, K., Parise, C., Caggiano, V., Use of ER/PR/HER2 subtypes in conjunction with the 2007 St Gallen Consensus Statement for early breast cancer, BMC Cancer, 10 (no pagination), 2010</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Clark, Gm, McGuire, Wl, Hubay, Ca, Pearson, Oh, Marshall, Js, Progesterone receptors as a prognostic factor in Stage II breast cancer, The New England journal of medicine, 309, 1343-7, 1983</td>
<td>Not 'test and treat' design</td>
</tr>
<tr>
<td>Collett, K., Skjaerven, R., Maehle, B. O., The prognostic contribution of estrogen and progesterone receptor status to a modified version of the Nottingham Prognostic Index, Breast cancer research and treatment, 48, 1-9, 1998</td>
<td>Non-RCT</td>
</tr>
</tbody>
</table>
Excluded studies - RQ3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams, C., Brunskill, S., Altman, D., Briggs, A., Campbell, H., Clarke, M., Glanville, J., Gray, A., Harris, A., Johnston, K., Lodge, M., Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy, Health Technology Assessment, 10, 1-153, 2006</td>
<td>Does not include any 'test and treat' studies</td>
</tr>
</tbody>
</table>

RCT, randomised controlled trial

Economic studies for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

See Supplement 1: Health economics literature review for list of excluded economic studies.
### Excluded studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

#### Clinical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaltomaa, S., Lipponen, P., Prognostic factors in breast-cancer (review), International Journal of Oncology, 1, 153-9, 1992</td>
<td>Aim not relevant (prediction of lymph node involvement).</td>
</tr>
<tr>
<td>Anwar, K., Edmiston, K., Khan, A., Walsh, W., To compare the results of Adjuvant Online and Oncotype DX in estimating risk for relapse in hormone receptor positive stage I breast cancer patients, Journal of clinical oncology, 26, 22069, 2008</td>
<td>No relevant outcomes reported.</td>
</tr>
<tr>
<td>Balslev, I., Axelsson, C. K., Zedeler, K., Rasmussen, B. B., Carstensen, B., Mouridsen, H. T., The Nottingham Prognostic Index applied to 9,149 patients from the studies of the Danish Breast Cancer Cooperative Group (DBCG), Breast cancer research and treatment, 32, 281-290, 1994</td>
<td>Not relevant population (Denmark).</td>
</tr>
</tbody>
</table>
### Excluded studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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</table>
### Excluded studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kraft Rovere, R., Dos Santos Borges, G., Staak Jr, M. C., Colchon, P. H., Rebello, J. R., Adjuvant! Online: Mind the gap!, Klinicka Onkologie, 26, 110-113, 2013</td>
<td>Not relevant population (Brazil).</td>
</tr>
<tr>
<td>Lundin, J., The Nottingham Prognostic Index - from relative to absolute risk prediction, European journal of cancer, 43, 1498-1500, 2007</td>
<td>Editorial comment</td>
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</tbody>
</table>
### Excluded studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
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<tr>
<td>Okugawa, H., Yamamoto, D., Uemura, Y., Sakaida, N., Yamada, M., Tanaka, K., Kamiyama, Y., Prognostic factors in breast cancer: The value of the Nottingham Prognostic Index for patients treated in a single institution [Erratum: Surgery Today 2009; 39(8): 738], Surgery Today, 35, 907-911, 2005</td>
<td>Not relevant population (Japan), and no relevant outcomes reported. Note that this paper has been retracted, as Substantial portions of this article were found to have been published previously by Dâ€™Eredità G. et al.</td>
</tr>
</tbody>
</table>
Excluded studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintyne, K. I., Woulfe, B., Coffey, J. C., Gupta, R. K., Correlation between Nottingham Prognostic Index and Adjuvant! Online Prognostic tools in patients with early-stage breast cancer in Mid-Western Ireland, Clinical breast cancer, 13, 233-238, 2013</td>
<td>No relevant outcomes reported.</td>
</tr>
<tr>
<td>Sauerbrei, W., Hubner, K., Schmoor, C., Schumacher, M., Validation of existing and development of new prognostic classification schemes in node negative breast cancer, Breast cancer research and treatment, 42, 149-163, 1997</td>
<td>No relevant outcomes reported.</td>
</tr>
<tr>
<td>Suen, D., Chow, L. W. C., Prognostic contribution of the HER-2 oncogene overexpression to the Nottingham Prognostic Index in breast cancer, Biomedicine and Pharmacotherapy, 60, 293-297, 2006</td>
<td>No relevant outcomes reported.</td>
</tr>
</tbody>
</table>
### Excluded studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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</thead>
</table>

*HTA, Health Technology Assessment; IBCSG, International Breast Cancer Study Group*

### Economic studies for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

See Supplement 1: Health economics literature review for list of excluded economic studies.
Appendix L – Research recommendations

Research recommendations for 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

No research recommendations were made for this review question.

Research recommendations for 3.2 What predictive prognostic tools, excluding gene profiling tests, should be used for determining adjuvant systemic therapy?

No research recommendations were made for this review question.
Appendix M – 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

Nominal group technique questionnaire for progesterone receptor testing

<table>
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<tr>
<th>Name:</th>
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<tbody>
<tr>
<td><strong>Prognosis</strong></td>
<td><strong>Strongly disagree</strong></td>
</tr>
<tr>
<td>Positive progesterone receptor status is associated with favourable prognosis</td>
<td>1</td>
</tr>
<tr>
<td>Comments:</td>
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<tr>
<td>Tumours that are negative for progesterone receptors have a worse prognosis</td>
<td>1</td>
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<td>Comments:</td>
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Endocrine therapy
Positive progesterone receptor status predicts response to endocrine therapy in people with oestrogen receptor negative breast cancer

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<tr>
<th>Strongly disagree</th>
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<th></th>
<th>Insufficient knowledge</th>
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Comments:

Endocrine therapy should be offered to individuals whose tumour is oestrogen receptor negative, but progesterone receptor positive

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<th>Strongly disagree</th>
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<th></th>
<th>Insufficient knowledge</th>
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</tbody>
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Comments:

Positive progesterone receptor status is indicative of benefit from endocrine therapy

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<tr>
<th>Strongly disagree</th>
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<th></th>
<th>Insufficient knowledge</th>
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Comments:

Tumours that are negative for progesterone receptors are less responsive to endocrine therapy

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Comments:

Combined measurement of oestrogen receptor status and progesterone receptor status more accurately predicts benefit from adjuvant hormone treatment for invasive breast cancer than oestrogen receptor status alone

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Comments:
### Adjuvant systemic therapy planning

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### Chemotherapy

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<table>
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<th>Progesterone receptor negative tumours should be considered high risk and, therefore, candidates for chemotherapy</th>
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### Assessment of PR status

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Early and locally advanced breast cancer: diagnosis and management: evidence reviews for adjuvant systemic therapy planning July 2018

139
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<td>Progesterone receptor status does not provide useful information in oestrogen receptor positive breast cancer</td>
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<tr>
<td>Progesterone receptor status is relevant when making decisions regarding adjuvant therapy</td>
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<tr>
<td>Progesterone receptor status should be assessed in all newly diagnosed invasive breast cancers</td>
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<td>Progesterone receptor status of tumours in patients with invasive breast cancer should not be routinely assessed</td>
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### Re-rated statements (Round 2)

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<th>Progesterone receptor status provides additional information to oestrogen receptor status that may be beneficial when considering the likely benefit of adjuvant hormone treatment for invasive breast cancer</th>
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<td>Insufficient Knowledge</td>
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Comments:

Negative progesterone receptor status is one factor that may increase the benefit from chemotherapy and may increase the likelihood chemotherapy is offered in borderline cases

<table>
<thead>
<tr>
<th>Negative progesterone receptor status is one factor that may increase the benefit from chemotherapy and may increase the likelihood chemotherapy is offered in borderline cases</th>
<th>1</th>
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Comments:
### Appendix N - 3.1 Is there a benefit of progesterone receptor (PR) testing for adjuvant chemotherapy planning?

#### Nominal group technique results

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<th>Area</th>
<th>Statement</th>
<th>Agreement (%)</th>
<th>Action</th>
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<td><strong>Prognosis</strong></td>
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<tr>
<td>1</td>
<td>Positive progesterone receptor status is associated with favourable prognosis</td>
<td>80</td>
<td>Used to inform recommendation</td>
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<td>2</td>
<td>Tumours that are negative for progesterone receptors have a worse prognosis</td>
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<td><strong>Endocrine therapy</strong></td>
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<td>3</td>
<td>Positive progesterone receptor status predicts response to endocrine therapy in people with oestrogen receptor negative breast cancer</td>
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<td>Discarded as less than 60% agreement</td>
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<td>Endocrine therapy should be offered to individuals whose tumour is oestrogen receptor negative, but progesterone receptor positive</td>
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<td>5</td>
<td>Positive progesterone receptor status is indicative of benefit from endocrine therapy</td>
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<td>Discarded as less than 60% agreement</td>
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<td>Tumours that are negative for progesterone receptors are less responsive to endocrine therapy</td>
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<td>Combined measurement of oestrogen receptor status and progesterone receptor status more accurately predicts benefit from adjuvant hormone treatment for invasive breast cancer than oestrogen receptor status alone</td>
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<td>Re-drafted and re-rated.</td>
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<td>Discarded as less than 60% agreement</td>
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<td>9</td>
<td>For breast cancer where the benefit of chemotherapy is borderline, it should be offered if individuals have progesterone receptor negative breast cancer</td>
<td>40</td>
<td>Re-drafted and re-rated despite low agreement (&lt;60%) due</td>
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<td>Area</td>
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<td>Progesterone receptor negative tumours should be considered high risk and, therefore, candidates for chemotherapy</td>
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<td>Assessment of PR status</td>
<td>11</td>
<td>Progesterone receptor status does not provide useful information in oestrogen receptor positive breast cancer</td>
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<td>Progesterone receptor status is relevant when making decisions regarding adjuvant therapy</td>
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<td>Progesterone receptor status should be assessed in all newly diagnosed invasive breast cancers</td>
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<td>Progesterone receptor status provides additional information to oestrogen receptor status that may be beneficial when considering the likely benefit of adjuvant hormone treatment for invasive breast cancer</td>
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<td>Negative progesterone receptor status is one factor that may increase the benefit from chemotherapy and may increase the likelihood chemotherapy is offered in borderline cases</td>
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