## Supplemental Table 2. Characteristics of included systematic reviews

|--------------------------|----------------------------------------|-------------|------------|------------|----------------|--------------|
|                          |                                        | 2007 to September 2009  
- EMBASE  
- MEDLINE  
- The Cochrane Library  
- CINAHL  
  The searchers were limited to English (EMBASE, MEDLINE, and CINAHL). Non-human studies were excluded from EMBASE and MEDLINE searches. | 14 | 15 | 16 | 17 | 18 |
|                          |                                        | 1 January 2006 to 19 March 2010  
- OVID MEDLINE  
- MEDLINE In-process  
- EMBASE  
- CINAHL  
- INAHTA | January 2009 to May 2011  
- MEDLINE: 1950 to May 2011  
- MEDLINE In-process: 1950 to May 2011  
- EMBASE: 1980 to May 2011  
- Cochrane Central Register of Controlled Trials (CENTRAL): Issue 3, 2011  
- Cochrane Database of Systematic Reviews – Issue 8, 2011  
- BIOSIS previews: 1926 to May 2011  
- Web of Knowledge: 1899 to May 2011 | 2000 to 2011  
- PubMed  
- CINAHL  
- Cochrane Database of Systematic Reviews  
  Searches were supplemented by using Web of Science to identify additional studies, and searching publications from the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium, and the European Society of Medical Oncology. | 1 January 2002 to 7 January 2012  
- PubMed  
- Cochrane Library  
  HTA websites of the UK, Canada, Australia, and USA were searched  
  Conference proceedings were search from 2009 to 2012:  
- San Antonio Breast Cancer Symposium  
- American Society of Clinical Oncology  
- European Breast Cancer Conference  
- St. Gallen Oncology Conference  
- European Society of Medical Oncology  
- European Cancer Organization  
- International Society for Pharmacoeconomics and Outcomes Research |
| Population | Women with early-stage breast cancer | Women with early stage (I-IIa) invasive breast cancer that is:  
- Estrogen receptor (ER) positive and/or progesterone receptor (PR) positive  
- Lymph node (LN) negative  
- Human epidermal growth factor receptor 2 (HER2) negative | Women with early-stage invasive breast cancer (stage I, II, or III)  
- Lymph node (LN) negative or positive (up to 3)  
- Estrogen receptor (ER) positive or negative  
- HER2 positive or negative | Women with early-stage breast cancer |

**GEP test(s)**

| Women with early stage (I-IIa) invasive breast cancer that is:  
- Estrogen receptor (ER) positive and/or progesterone receptor (PR) positive  
- Lymph node (LN) negative  
- Human epidermal growth factor receptor 2 (HER2) negative | Women with early-stage invasive breast cancer (stage I, II, or III)  
- Lymph node (LN) negative or positive (up to 3)  
- Estrogen receptor (ER) positive or negative  
- HER2 positive or negative | Women with early-stage breast cancer |

| Oncotype DX | Oncotype DX | Randox Breast Cancer Array  
MammaPrint  
BluePrint  
PAM50  
Oncotype DX  
Breast Cancer Index | Mammastrat  
MammaPrint  
Oncotype DX  
Molecular Grade Index  
BreastOncPx | Commercially available multi-gene assasys (MGAs): OncotypeDx  
MammaPrint  
BluePrint  
PAM50  
Breast Cancer Index  
Mammostrat NPI+ |

**Aims and objectives/K key Questions focused on clinical utility**

| To assess the evidence of GEP tests for improving prognostic accuracy, treatment choice, and health outcomes.  
- What is the predictive value of Oncotype-DX?  
- How does Oncotype-DX impact patient quality of life and clinical/patient decision-making? | “The overall aim of the assessment is to assess the clinical effectiveness, effect on patient outcomes, and cost-effectiveness of the new GEP and expanded IHC tests”. | “The primary aim of our study was to systematically grade the Level-of-Evidence (LOE) instudies that assessed the clinical validity/utility of risk stratifiers for ESBC. A secondary aim was to document studies that provided evidence on changes in practice patterns and health economic implications of the stratifiers”. |

“early-stage, nonmetastatic breast cancer patients who underwent curative-intent surgery”
<table>
<thead>
<tr>
<th>Inclusion/exclusion criteria</th>
<th>Articles were considered to be ineligible if the study:</th>
<th>Inclusion Criteria</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
</table>
|                             | • only applied to breast cancer biology (ie were not clinical studies) | • Any observational trial, controlled clinical trial, randomized controlled trial (RCT), meta-analysis or systematic review that reported on the laboratory performance, prognostic value and/or predictive value of Oncotype-DX testing, or other outcome relevant to the Key Questions, specific to the target population was included. | • Animal models  
• Preclinical and biological studies  
• Editorials and opinion pieces  
• Non-English publications  
• Conference abstracts  
• Studies related to breast cancer biology  
• Studies conducted in the neo-adjuvant treatment setting  
“...studies will be excluded if they...appear to be methodologically unsound, or do not report methods and/or results in the necessary detail.” |
|                             | • did not involve OncotypeDX™ or MammaPrint® or H/I gene expression profiling tests | Exclusion Criteria | Inclusion criteria: |
|                             | • did not involve original data or original data analysis | • Studies that did not report original data or original data analysis, | • Original data on an assay’s ability to predict risk of progression or response to chemotherapy  
• Studies reporting assay’s impact on clinical decisions, practice patterns, or economics |
|                             | • did not involve breast cancer patients | • Studies published in a language other than English, | Exclusion criteria: |
|                             | • was not reported in English | • Studies reported only in abstract or as poster presentations (such publications were not sought nor included in this review since the Medical Advisory Secretariat (MAS) does not generally consider evidence that is not subject to peer review nor does the MAS consider evidence that lacks detailed description of methodology).” | • Studies reporting individual components of the assay  
• Pathophysiological or in vitro studies  
• No original data  
• Non early-stage breast cancer  
• Non-English language publication  
• Did not report on the clinical validity, clinical decisions, or economics |
<p>|                             | • did not apply to any of the key questions of the review | • other (give reason) eligibility was unclear. “ | Inclusion criteria: |
|                             | • other (give reason) | | “publications assessing the cost-effectiveness or budget impact of prognostic MGAs” |
|                             | • letters, editorial, comments and news articles were excluded | | |
|                             | conference abstracts were included if they presented relevant data | | |</p>
<table>
<thead>
<tr>
<th>Included studies addressing key questions related to clinical utility</th>
<th>Oncotype Dx:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• KQ 1: 3 studies (Akashi-Tanaka 2009 (^{20}); Kok 2009 (^{21}); Li 2009 (^{22}))</td>
<td>• KQ 1: 2 studies(Paik 2006 (^{23}); Albain 2010 (^{24}))</td>
</tr>
<tr>
<td>• KQ 2: 3 studies (Asad 2008 (^{27}); Henry 2009 (^{29}); Rayhanabad 2008 (^{28}))</td>
<td>• KQ 2: 4 studies (Ademuyiwa 2011 (^{32}); Geffen 2009 (^{30}); Lo 2010 (^{31}))</td>
</tr>
</tbody>
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<tr>
<th>MammaPrint:</th>
<th>Oncotype Dx:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• KQ 2: 1 study (Bueno-de-Mesquita 2007 (^{39}))</td>
<td>• KQ 1: 3 studies (Albain 2010 (^{24}); Tang 2011 (^{25}); Albain 2010 (^{24}))</td>
</tr>
<tr>
<td></td>
<td>• KQ 2: 1 study (Geffensleben 2010 (^{40}))</td>
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<tr>
<td>Quality of individual studies was assessed using a 44-item checklist based on REMARK criteria, and STARD criteria were used to compare quality between studies.</td>
<td>• KQ 1: 3 studies (Akashi-Tanaka 2009 (^{20}); Kok 2009 (^{21}); Li 2009 (^{22}))</td>
</tr>
<tr>
<td>The quality of the body of evidence was assessed according to the GRADE criteria for: 1) quality; 2) consistency; and 3) directness.</td>
<td>• KQ 1: 3 studies (Albain 2010 (^{24}); Tang 2011 (^{25}); Albain 2010 (^{24}))</td>
</tr>
<tr>
<td>Quality of individual studies was assessed according to the level of evidence outlined by Simon 2009 (^{19}).</td>
<td>• KQ 2: 10 studies (Ademuyiwa 2011 (^{32}); Asad 2008 (^{27}); Henry 2009 (^{29}); Hornberger 2011 (^{36}); Joh 2011 (^{37}); Klang 2010 (^{35}); Lo 2010 (^{31}); Oratz 2007 (^{34}); Partin 2011 (^{38}); Rayhanabad 2008 (^{28}))</td>
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<tr>
<td>Rated included studies according to the level of evidence outlined by Simon 2009 (^{19}).</td>
<td>• KQ 2: 1 study (Geffensleben 2010 (^{40}))</td>
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<tr>
<td>“The Quality Health Economic Studies (QHES) instrument was used to evaluate the quality of economic evaluations”</td>
<td>• KQ 3: 3 included studies were not considered in this overview as their methodological quality was not evaluated.</td>
</tr>
</tbody>
</table>

OncotypeDX: | • KQ 3: 3 studies (Paik 2006 \(^{23}\); Albain 2010 \(^{24}\); Tang 2011 \(^{25}\); Albain 2010 \(^{24}\)) |

MammaPrint: | • KQ 3: 5 studies (Oestreich 2005 \(^{64}\); Zarca 2009 \(^{65}\); Chen 2010 \(^{63}\); Retel 2010 \(^{61}\); Kondo 2012 \(^{62}\)) |

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