National Horizon Scanning Centre

Oncotype DX prognostic and predictive test for early breast cancer

April 2008

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Oncotype DX prognostic and predictive test for early breast cancer

Target group
- Breast cancer: early (stage I or II), oestrogen receptor positive (ER+) and axillary lymph node negative (N0).

Technology description
Oncotype DX is an in vitro multi-gene breast cancer assay to be used in conjunction with traditional histopathology for assessing the risk of disease recurrence in the target patient group. Using routine formalin-fixed paraffin-embedded tumour tissue blocks, it measures the expression of 21 cancer-related and reference genes by reverse transcriptase polymerase chain reaction (RT-PCR) and predicts the risk of disease recurrence at 10 years in terms of a recurrence score (RS) between zero and 100. The RS may be used to predict the likely magnitude of chemotherapy benefit. Samples are processed at the Genomic Health reference laboratory in the USA, with results available within 13-17 days after dispatch from the UK.

Innovation and/or advantages
Oncotype DX is intended to provide more accurate prognostic and predictive information to improve the targeting of cytotoxic adjuvant chemotherapy to those patients who are most likely to benefit, and to spare those who are unlikely to do so.

Developer
Genomic Health Inc; UK distributor: Medical Solutions plc.

Availability, launch or marketing dates, and licensing plans:
Oncotype DX is commercially available in the UK and currently in use in the private sector. FDA marketing approval is not required for Oncotype DX, as it is marketed as a laboratory service (all samples being analysed at one CLIA certified, CAP approved laboratorya). The company state that Oncotype DX is widely used in the USA (>46,000 tests provided since 2004), and that all of the major US health insurance plans reimburse for Oncotype testing (including Medicare).

NHS or Government priority area:
This topic is relevant to the NHS Cancer Plan (2000).

Relevant guidance
- HTA. Hormonal therapies for early breast cancer: systematic review and economic evaluation. 20074.

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1 CLIA: Clinical Laboratory Improvement Amendments; CAP: College of American Pathologists.
HTA. Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy. 2006\(^5\).

SIGN. Management of breast cancer in women. 2005 (review expected December 2008)\(^6\).

NHS Cancer Screening Programme/Royal College of Pathologists. Pathology reporting of breast disease. 2005\(^7\).

BlueCross BlueShield Association. Gene expression profiling of breast cancer to select women for adjuvant chemotherapy. 2007\(^8\).

American Society of Clinical Oncology (ASCO). Update of recommendations for the use of tumor markers in breast cancer. 2007\(^9\).

Institute for Prospective Technologi cal Studies. Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU. 2006\(^10\).

Clinical need and burden of disease
Breast cancer is the commonest malignancy affecting women in the UK.\(^11\) It accounted for 10,969 deaths registered in 2005 in England and Wales, and 39,301 new cases diagnosed in 2004\(^11\). An estimated 50% of newly diagnosed breast cancers are both hormone-receptor positive and lymph node negative\(^12\), equating to approximately 19,700 women in England and Wales in 2004. Expert opinion is that currently around 21,000-23,000 new cases per year are both N0 and ER+. Of the total incident breast cancer population, one expert estimates that between 5% and 10% may be considered for adjuvant chemotherapy (approximately 2,000–4,000 patients in England and Wales per year).

Existing comparators and treatments
Hormonal therapy using tamoxifen and/or aromatase inhibitors is the standard adjuvant treatment for women with ER+ early breast cancer. In addition, some N0 patients may also be considered for adjuvant chemotherapy (e.g. with AC: doxorubicin and cyclophosphamide x 4 cycles, or FEC: fluorouracil, epirubicin & cyclophosphamide x 6 cycles) prior to receiving hormonal therapy.

The benefit to be derived from chemotherapy depends on the patient’s baseline risk of disease recurrence. Conventional risk classifiers include the Nottingham Prognostic Index (NPI), St Gallen consensus recommendations, and ‘Adjuvant’ (www.adjuvantonline.com), and (less so in the UK) National Comprehensive Cancer Network (NCCN) guidelines. These are based on a range of clinical and pathological criteria such as patient age, tumour size, type, grade, histological characteristics, hormone receptor status, and lymph node status. There is currently no generally accepted gold standard for risk assessment in this patient group.

Two multi-gene expression profiling assays for risk assessment are commercially available, in addition to Oncotype DX:

- Breast Cancer Gene Expression Ratio Test (also known as H/I, 2-gene ratio or HOXB13/IL-17BR ratio test, developed by AvariaDx Inc; licensed to Quest Diagnostics).

The Rotterdam Signature 76-gene panel (Veridex LLC) is in still development and not yet commercially available.
Efficacy and safety

A 2008 review of the evidence\textsuperscript{13} for gene expression profiling assays in early breast cancer concluded that Oncotype DX offers clinically relevant, improved risk stratification over standard predictors\textsuperscript{14,15} and, compared to MammaPrint and H/I, is supported by the strongest evidence base. Oncotype DX is also said to be the only gene expression test with evidence to suggest that in addition to providing information on disease prognosis, it can predict the clinical benefit of chemotherapy (i.e. that is has clinical utility)\textsuperscript{16}.

<table>
<thead>
<tr>
<th>Trial code and name</th>
<th>National Surgical Adjuvant breast and Bowel Project (NSABP) B14 trial.</th>
<th>National Surgical Adjuvant breast and Bowel Project (NSABP) B20 trial.</th>
<th>Kaiser Permanente Study; clinical validation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>National Cancer Institute, NSABP, Genomic Health Inc.</td>
<td>National Institutes of Health, NSABP, Genomic Health Inc.</td>
<td>Genomic Health Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Published\textsuperscript{17}.</td>
<td>Published\textsuperscript{16}. Original trial published\textsuperscript{18}.</td>
<td>Published\textsuperscript{19}.</td>
</tr>
<tr>
<td>Location</td>
<td>USA</td>
<td>USA</td>
<td>USA</td>
</tr>
<tr>
<td>Design</td>
<td>Retrospective validation study of distant recurrence; prospectively-defined endpoints; tissue samples and data from the NSABP B14 trial.</td>
<td>Retrospective analysis to evaluate chemotherapy benefit; prospectively-defined endpoints; tissue samples and data from the NSABP B20 trial.</td>
<td>Nested case-control study to evaluate breast cancer mortality.</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>Original trial N0 ER+ primary invasive breast cancer. N=2,892 randomised to placebo or tamoxifen (TAM) and n=1,235 treated with TAM only. Retrospective study n=668; archived tumour blocks from TAM-treated patients from B14 trial.</td>
<td>Original trial n=2,363 N0 ER+ primary invasive breast cancer. Randomised to TAM vs TAM + chemotherapy (either CMF or MF). Retrospective study n=651; B20 trial patients randomised to: TAM (n=227) or TAM + chemo-therapy (n=424). RS measured retrospectively from archived tumour blocks.</td>
<td>n=790; N0 invasive breast cancer diagnosed 1985-1994, not treated with adjuvant chemotherapy Cases (n=220) first event was death from breast cancer. Controls (n=570) matched by age, race, diagnosis year, medical facility, follow-up time, and treated or not-treated with TAM (TAM+ or -).</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Median 14.1 years.</td>
<td>Median 11.0 years.</td>
<td>Until death, bilateral breast cancer, or the end of 2002. Median follow-up 4.9 for cases and 12.9 years for controls.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>RS prediction of distant recurrence.</td>
<td>Distant recurrence.</td>
<td>RS prediction of breast cancer mortality for ER+ N0 TAM+.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Relapse-free interval; overall survival.</td>
<td>Relapse-free interval; overall survival.</td>
<td>As above for TAM-.</td>
</tr>
<tr>
<td>Key results</td>
<td>Distant recurrence at 10 years: low-risk (RS&lt;18, 51%) 6.8% (95% CI 4.0-9.6); intermediate-risk (RS 18-30, 22%) 14.3% (95% CI 8.3-20.6); high-risk (RS≥31): Relative risk of distant recurrence 0.26 (95% CI 0.13-0.53); decrease in absolute risk 27.6%. Low-risk (RS&lt;18): RR 1.31;</td>
<td>RS associated with risk of breast cancer mortality in ER+ TAM+ (p=0.003) and ER+ TAM- (p=0.03). Absolute risks of breast cancer death at 10 years for</td>
<td></td>
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</table>
Recurrence in low-risk was significantly lower than high-risk (p<0.001). RS also predictive of relapse-free interval and overall survival (p<0.001).

<table>
<thead>
<tr>
<th>Trial code and name</th>
<th>TAILORx NCT00310180(^{20,21}); phase III; clinical utility.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>US National Cancer Institute; coordinated by ECOG(^{b}).</td>
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<tr>
<td>Status</td>
<td>Recruiting (started May 2006).</td>
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<tr>
<td>Location</td>
<td>USA and Canada</td>
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<td>Design</td>
<td>Prospective, controlled partially-randomised</td>
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<td>Participants in trial</td>
<td>n=10,046; N0 and/or ER+ early-stage breast cancer. Midrange RS 11-25: randomised to hormonal therapy + chemotherapy or hormonal therapy alone. High RS &gt;25: hormonal therapy + chemotherapy. Low RS &lt;11: hormonal therapy alone.</td>
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<tr>
<td>Follow-up</td>
<td>20 years.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>RS 11-25: disease-free survival, distant recurrence-free interval, recurrence-free interval, overall survival.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>As above for RS &lt;11.</td>
</tr>
<tr>
<td>Key results</td>
<td>Expected by 2016.</td>
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</table>

**Estimated cost and cost impact**

The estimated cost of Oncotype DX is £1,850 (US$3,650) per test (inclusive of transportation to the USA for analysis). A US study of the potential economic impact of using Oncotype DX both as a prognostic and predictive test has been published\(^{22}\).

**Potential or intended impact - speculative**

**Patients**
- ☑ Reduced morbidity
- ☑ Reduced mortality or increased survival
- ☑ Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ None identified

**Services**
- ☐ Increased use
- ☐ Service reorganisation required
- ☑ Staff or training required
- ☐ Decreased use
- ☐ Other:
- ☐ None identified

**Costs**
- ☑ Increased unit cost compared to alternative
- ☑ Increased costs: more patients coming for treatment
- ☑ Increased costs: capital investment needed
- ☐ New costs:
- ☑ Savings: reduced use of chemotherapy
- ☐ Other:

\(^{b}\) The Eastern Cooperative Oncology Group.
References

10. Institute for Prospective Technological Studies (IPTS). Pharmacogenetics and pharmacogenomics