Prosigna is an in vitro diagnostic assay that uses the gene expression profile of tumour cells found in breast tissue to assess a patient’s risk of distant recurrence. Unlike other breast cancer gene expression assays, Prosigna also provides information on the intrinsic subtype of the cancer, which may help in decision-making about systemic therapy.

Intrinsic subtypes of breast cancer

Breast cancers can be characterised by a multitude of clinical and pathological features. These may provide **prognostic** information (risk of recurrence) and **predictive** information (response to therapy), but the accuracy of this information is often limited.

A molecular classification of breast cancer, based on patterns of activity in 1,753 genes, was first proposed in 2000. This study described four distinct patterns of gene activity, or ‘intrinsic subtypes’, called Luminal A, Luminal B, HER2-enriched and Basal-like. This classification has been repeatedly demonstrated to provide prognostic and predictive information in breast cancer, with more than 2,500 PubMed citations, and more than 80 prospective clinical trials, as of December 2015.

Basis of the Prosigna test

The same four patterns of gene activity can be reliably identified with a subset of 50 genes (called ‘PAM50’), thereby simplifying the molecular analysis of breast cancer. Various methods and analyses of the PAM50 set of genes have been described.

Prosigna is a new assay that is based on PAM50 and, in contrast to earlier PCR-based assays, uses a digital count of molecules.

Information provided by Prosigna

**Intrinsic subtype**

Prosigna analyses the activity of 50 genes in the patient sample. On the basis of the pattern of gene activity, it assigns the patient’s cancer to the most likely intrinsic subtype. This assignment of the patient to a diagnostic group is the basis for providing prognostic and predictive information.

**Prosigna score**

**Risk of recurrence score.** Prosigna goes a step further and utilises the activity of the 50 genes, the number of involved nodes and tumour size, to determine a score and risk category for the individual patient. Rather than provide prognostic and predictive information on the basis of the patient being in a diagnostic category, the test is able to provide this information for the individual patient.

The distinction between group-based versus individualised information is important, as the evidence for the utility of Prosigna may be based on either cohort information (outcomes for a subtype group), or on individual information (prognosis indicated by the score) or both. The prognosis or prediction for an individual may also be more precise than the probability cited for the group.

### The accuracy of Prosigna

The following studies have documented the accuracy of PAM50 (black refs) and Prosigna (pink refs) in a variety of settings.

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>References for prognosis by</th>
<th>References for prediction by</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subtype</td>
<td>Score</td>
</tr>
<tr>
<td>Unselected cohorts (no systemic therapy)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Post-menopausal breast cancer</td>
<td>2, 4–6</td>
<td>2, 4–6</td>
</tr>
<tr>
<td>Pre-menopausal breast cancer</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Neo-adjuvant chemotherapy</td>
<td>10, 11</td>
<td>3, 12</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Post-relapse</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
Other tests for intrinsic subtype

A combination of immunohistochemical stains (ER, PR, HER2, and Ki67) has been proposed as an alternative means of defining intrinsic subtype\(^6\). This surrogate definition of subtypes had the advantage of being more available than molecular testing, but there is a lack of concordance between IHC and molecular methods of defining subtype\(^6\). IHC methods also show less within-lab consistency in subtyping\(^1\) than Prosigna, even when Prosigna is compared between labs\(^5\).

PAM50 and Prosigna have also been tested against immunohistochemical and clinical indicators for prognosis, and have demonstrated better accuracy in pre- and post-menopausal breast cancers\(^1,3,5,6\).

Other tests for recurrence scores

Two other gene expression assays for prognosis or prediction in breast cancer using FFPE samples are available in Australia. The following table summarises their performance relative to Prosigna.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Prosigna</th>
<th>Oncotype Dx</th>
<th>Endopredict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodology</td>
<td>NanoString (digital)</td>
<td>PCR (analog)</td>
<td>PCR (analog)</td>
</tr>
<tr>
<td>Intrinsic subtype</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prediction by subtype</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Precision of estimate at 10% risk(^*)</td>
<td>+/- 1.5% (node -)</td>
<td>+/- 2.5% (node -)</td>
<td>+/- 2.0% (node +/-)</td>
</tr>
<tr>
<td>Accuracy versus IHC/clinical scores</td>
<td>Better(^*)</td>
<td>Worse/same(^*)</td>
<td>Better(^*)</td>
</tr>
<tr>
<td>Accuracy of risk prediction vs Oncotype DX</td>
<td>Better(^*)</td>
<td>Reference</td>
<td>Unknown</td>
</tr>
<tr>
<td>% patients at intermediate risk (ATAC trial)(^*)</td>
<td>24%</td>
<td>33%</td>
<td>Not studied</td>
</tr>
<tr>
<td>Australian laboratory</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Regulatory approval in Australia</td>
<td>TGA/NATA</td>
<td>Not applicable</td>
<td>TGA</td>
</tr>
</tbody>
</table>

\(^*\)Information from companies’ literature

There are multiple studies documenting the performance of Prosigna in predicting response to therapy (see above). There is only one study demonstrating the predictive performance of Endopredict. Studies regarding the predictive performance of Oncotype DX are compromised by reliance on a study from the NSABP-20 trial which used the same data set both to develop and then validate the claims\(^1\), and by the variable inclusion of additional clinical features in the Oncotype DX score.

**Uses of Prosigna**

Prosigna has demonstrated utility in decision-making about neo-adjuvant chemotherapy, adjuvant chemotherapy, adjuvant hormone therapy and chemotherapy after relapse. Prosigna has been specifically accredited by the FDA for use in post-menopausal women with early-stage hormone-sensitive breast cancer.

The utility of Prosigna extends to women at apparently low risk of recurrence by clinical criteria. One third of post-menopausal women at low risk of recurrence on clinical criteria were at high risk based on the more accurate estimates provided by Prosigna\(^5\).

Prosigna should be ordered by the clinician responsible for decision-making regarding adjuvant therapy for a woman with breast cancer. The test costs $2,900\(^*\); there is no Medicare rebate and the test must be prepaid. Your local Sonic laboratory can provide details regarding ordering the test.

**References**


*Current at December 2015

For further information, please refer to our website, www.sonicgenetics.com.au/tests/prosigna or call us on 1800 010 447

14 Giffnock Avenue, Macquarie Park, NSW 2113, Australia
T: (02) 9855 5389  |  F: (02) 9855 5446  |  E: info@sonicgenetics.com.au
www.sonicgenetics.com.au

The published evidence that is the basis for this leaflet is detailed in other leaflets about Prosigna available on the Sonic Genetics website.

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