Breast Cancer Recurrence Signature
ER/PR/HER2 Expression Assay
Molecular Subtyping Signature
Therapy Gene Assay
Argentina, Chile & Uruguay

SYMPHONY
Personalized Breast Cancer Genomic Profile

MammaPrint®
Breast Cancer Recurrence Signature

blueprint®
Molecular Subtyping Signature

targetprint®
ER/PR/HER2 Expression Assay

theraPrint®
Therapy Gene Assay

One Light Solution
Argentina, Chile & Uruguay

decoding cancer.
The SYMPHONY™ signature development process began by identifying two groups of women: those who had recurrence within five years following surgery and those who were cancer free at five years. The entire human genome of 25,000 genes was analyzed for both groups and the resulting differences in gene expression were captured. What’s more significant, is that none of the women in either group were treated with either chemo or hormonal therapy. This control process allowed the pure biology of the tumors to be followed for more than 20 years — ultimately ensuring a definitive, actionable result for each of your patients.

Achieving definitive results by analyzing the entire human genome.

Analyzing genome in all
1. Growth and proliferation
IGFBP5, TGFB3, FGF18, ESM1, RARRES3, PITRM1, EXT1, EXT3, SCUBE2, EIF4, CDA1, CDA7, CDA7L, GMPS, MELK, RFC4, WISP1, HRASL5, BCL3, DTL, FRKX3, ERN1, GNA2, MTDH, FLT1, ECT2, DAPIH2, NUSAP1, AAP2, NDC80, PRC1, ORC8L1, CENPA, DCK, CCNB2, MCM6, GSK2, STK32B

2. Angiogenesis
COL4A2, FLT1, FGF18, MMP9

3. Local invasion
FLT1, TGFB3, IGFBP5, FGF18, RARRES3, CDA7L, WISP1, DIAPH1, AKAP2, CDA42BPA, PALM2, DAPIH2, NUSAP1, NMUR1, NMUR2

5. Survival in circulation
COL4A2, FLT1, MMP9, MMRP, TGFB3, CDA7L, WISP1, DIAPH1, AKAP2, CDA42BPA, PALM2, DAPIH2, NUSAP1, NMUR1, NMUR2

6. Extravasation
COL4A2, FLT1, MMP9, TGFB3, MMRP, TM6H, DIAPH1, PALM2, DAPIH2, NUSAP1, NMUR1, NMUR2

7. Adaptation to microenvironment at secondary site
MMP9, COL4A2

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The benefit – 100% definitive results.
SYMPHONY results are valid at the time of diagnosis. Agendia’s signatures were developed independent of drug therapy. Thus, the actual test result will indicate the prognosis for your patient if no therapy is provided. You do not have to assume that your patient will remain on a course of therapy to validate the test results. Which makes the SYMPHONY suite of genomic assays the perfect accompaniment to your current protocols.

Can chemotherapy be withheld safely from patients identified as “Low Risk”?

What therapy is most appropriate for the patient’s molecular subtype?

Is the patient a candidate for targeted therapy?

What potential therapy options are available if the patient’s cancer recurs?

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Analyzing the entire human genome ensures gene coverage in all 7 Metastatic Pathway steps.

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Can chemotherapy be withheld safely from patients identified as “Low Risk”?

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SYMPhony™ MammaPrint®
A powerful, prognostic and predictive biomarker that helps you determine if you can safely withhold CT from “Low Risk” patients.

5 Year Prospective Evidence >97% DRFI
RASTER (MicroarRay PrognoSTics in Breast CancER)
Linn, et al – 427 patients with 5 years follow-up (EBCC, 2012)

Results
- Low Risk – 5yr DRFI = 97% (85% no chemotherapy)
  - Low Risk – 5yr DRFI = 97% (no chemotherapy)
- High Risk – 5yr DRFI = 91.7% (81% chemotherapy)
- MammaPrint helps to identify the right patients for the right therapy

MammaPrint identified 29% more Low Risk patients than traditional clinical parameters with 98.4% DRFI.

Distance Recurrence Free Interval

MammaPrint Low Risk (n=219)
MammaPrint High Risk (n=208)

P = 0.03
5 Year Retrospective Evidence >95% DMFS

Christofanilli, et al – 208 patients with 11.3 years follow-up (ASCO, 2012)

**Results**
- Low Risk – 5yr DMFS = 98% (36% chemo)
- Low Risk – 5yr DMFS (no chemo) = 100%
- High Risk – 5yr DMFS = 92%
  73% treated with adj CT

5 Year Neo-Adjuvant Evidence >94% DDFS


**Results**
- Low Risk – 5yr DDFS = 94%
- Low Risk – 3% pCR yet 94% DDFS

Independent FDA clearance validation

Buyse – 307 patients with 13.6 years follow-up (Journal National Cancer Institute, 2006)

**Results**
- Low Risk – 5yr DMFS = 95% DMFS
  (No Adjuvant therapy)
- High Risk – 5yr DMFS = 78% DMFS
  (No Adjuvant therapy)
- Independent FDA clearance validation
MammaPrint provides additional biological information on indeterminate cases.

Not all HER2+ and lymph node positive cases are High Risk and not all Node negative, small tumors are Low Risk. MammaPrint will stratify these cases into Low and High Risk. This information may be helpful for your treatment decisions with patients who have significant co-morbidities.

MammaPrint provides additional biological information even with traditional clinically determinate cases.

Pooled analysis included 1630 patients, 764 (47%) were classified as Low Risk and 866 (53%) were classified as High Risk by MammaPrint. Histological grading was centrally reviewed for all patients.

The MammaPrint gene signature has been extensively validated.

<table>
<thead>
<tr>
<th>Publications</th>
<th>Country</th>
<th>Reference</th>
<th>Patients</th>
</tr>
</thead>
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<tr>
<td>MammaPrint Discovery</td>
<td></td>
<td>van ’t Veer, et al. Nature</td>
<td>78</td>
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<tr>
<td>Primary Validation Study</td>
<td>USA</td>
<td>van de Vijver, et al. NEJM</td>
<td>295</td>
</tr>
<tr>
<td>Independent European Study</td>
<td>Europe</td>
<td>Buyse, et al. JNCI</td>
<td>302</td>
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<tr>
<td>Prospective Impact Study</td>
<td></td>
<td>de Mesquita, et al. Lancet Oncology</td>
<td>427</td>
</tr>
<tr>
<td>Core Needle Biopsies</td>
<td>Europe</td>
<td>Mayordomo, et al. ESMO Meeting</td>
<td>35</td>
</tr>
<tr>
<td>Validation in Older US Patients</td>
<td>USA</td>
<td>Wittner, et al. Clin Cancer Res</td>
<td>100</td>
</tr>
<tr>
<td>Validation in 1–3 LN+ Patients</td>
<td>Europe</td>
<td>Mook, et al. Br Cancer Res Tr</td>
<td>241</td>
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<tr>
<td>Patients Treated with Tamoxifen</td>
<td>Europe</td>
<td>Kok, et al. Eur J Can</td>
<td>192</td>
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<tr>
<td>Japanese Patient Cohort</td>
<td>Japan</td>
<td>Ishitobi, et al. JJCO</td>
<td>118</td>
</tr>
<tr>
<td>Validation in 4–9 LN+ Patients</td>
<td>Europe</td>
<td>Saghaestchian, et al. St. Gallen Conf</td>
<td>167</td>
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<tr>
<td>Predictiveness (Meta-Analysis) Study</td>
<td>Europe</td>
<td>Knauer, et al. Br Cancer Res Tr</td>
<td>1,696*</td>
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<tr>
<td>Comparison to German Guidelines</td>
<td>Germany</td>
<td>Gebensleben, et al. Int J Mol Med</td>
<td>140</td>
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<tr>
<td>Validation in T1 Tumors</td>
<td>Europe</td>
<td>Mook, et al. Ann Surg Oncol</td>
<td>964*</td>
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<tr>
<td>Prospective Validation MINDACT</td>
<td></td>
<td>Rutgers, et al. Eur J Can</td>
<td>6,600</td>
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<tr>
<td>Validation in US Patient Cohort</td>
<td>USA</td>
<td>Yao, et al. ASCO</td>
<td>208</td>
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<tr>
<td>5 Year Prospective Validation</td>
<td>USA</td>
<td>Linn, et al. EBCC</td>
<td>427</td>
</tr>
<tr>
<td>Predicting Local Recurrence</td>
<td>USA</td>
<td>Beitch, ASBS</td>
<td>594*</td>
</tr>
<tr>
<td>Neoadjuvant Prediction</td>
<td>USA</td>
<td>Glück, et al. ASCO</td>
<td>421*</td>
</tr>
</tbody>
</table>

* Pooled analysis
SYMPHONY™ BluePrint®.
Identifies molecular subtypes to help you select the right therapies for each patient.

In *Nature* 2000, Sorlie and Perou identified tumor subtypes that may respond differently to adjuvant therapy. Agendia has developed a multi-gene profile for the classification of breast cancer into Basal-type, Luminal-type and ERBB2-type (HER2) molecular subtypes. The BluePrint molecular subtyping signature provides a greater level of clinical information to assist in therapeutic decision-making.

BluePrint measures gene function – not just the presence of the protein receptor.

While the two common ways (IHC/FISH) to measure ER/PR/HER2 will determine if the receptor is present, they do not determine their functional activity. BluePrint gene signature was designed to measure actual gene function, alerting you to the potential effect of adjuvant therapy.
**SYMPHONY™ BluePrint®.**

MINDACT – Clinical data from the first 600 patients supports the clinical utility of BluePrint molecular subtyping.

**HER2+ and ER+ are often BluePrint Luminal.**
- There is a large group of clinical HER2+ cases that are BluePrint Luminal type (46%)
- In this group the tumor’s expression of the Luminal profile is dominant over the expression of the HER2+ profile
- These patients may have a lower response to Trastuzumab (von Minckwitz, et al, 2012)
- Patients with co-morbidities, where there is a concern about aggressive therapy, may fall within a recently identified subset

**Even the best Ki–67 assessment shows 30% discordance with MammaPrint.**
- Ki–67 is assumed to be a fairly reliable measure of proliferation. Ki–67 is utilized as a biomarker for chemotherapy
- The concordance between MammaPrint and centrally assessed Ki–67 in Luminal-type patients is 71%, with a k score of 0.35 (95% CI 0.26–0.45)
- The relatively high discordance with MammaPrint indicates that Ki–67 and MammaPrint cannot reliably substitute for each other

![BluePrint Molecular Subtyping](image)

<table>
<thead>
<tr>
<th>IHC/FISH</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2</th>
<th>Basal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+ and/or PR+/HER2-, Ki–67 low</td>
<td>263</td>
<td>19</td>
<td>4</td>
<td>1</td>
<td>287</td>
</tr>
<tr>
<td>ER+ and/or PR+/HER2-, Ki–67 high</td>
<td>111</td>
<td>70</td>
<td>4</td>
<td>11</td>
<td>196</td>
</tr>
<tr>
<td>ER+ and/or PR+/HER2+</td>
<td>25</td>
<td>3</td>
<td>31</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>ER–/PR–/HER2+</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>ER–/PR–/HER2–</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>81</td>
<td>62</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>400</td>
<td>92</td>
<td>53</td>
<td>76</td>
<td>621</td>
</tr>
</tbody>
</table>

*1. Viale, et al. (ISCO 2012)*

**20% of BluePrint Basals were IHC ER+.**
- These patients might not benefit from Endocrine therapy
- Of the BluePrint Basal cases, 20% are not pathological Basal (16% ER+, 4% HER2+)
- Of the 16% ER+ cases, the majority (80%) are IHC ER/PR borderline (≥1% and <10%)
The predictive advantage of adding BluePrint to MammaPrint.

The BluePrint gene signature, when combined with MammaPrint risk recurrence, provides additional information to therapy response.

Basal and HER2-type show significantly higher pCR rates when treated with standard neo-adjuvant chemotherapy.

Therapy response varies by molecular subtype.

<table>
<thead>
<tr>
<th>SYMPHONY Result</th>
<th>Prognosis</th>
<th>Chemosensitivity</th>
<th>Survival with recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk Luminal</td>
<td>Good baseline prognosis</td>
<td>Low pCR, no expected benefit from chemotherapy</td>
<td>Excellent</td>
</tr>
<tr>
<td>High Risk Luminal</td>
<td>Poor baseline prognosis</td>
<td>Relatively low pCR, some benefit from chemotherapy</td>
<td>Good</td>
</tr>
<tr>
<td>High Risk ERBB2</td>
<td>Poor baseline prognosis</td>
<td>High pCR, especially with targeted therapy</td>
<td>Increased with therapy</td>
</tr>
<tr>
<td>High Risk Basal</td>
<td>Poor baseline prognosis</td>
<td>High pCR, high benefit from chemotherapy</td>
<td>Increased with therapy</td>
</tr>
</tbody>
</table>

Glück, et al. (ASCO, 2012)
SYMPHONY™ TargetPrint.

Objectively measures mRNA to accurately quantify your patients’ ER/PR/HER2 levels.

In 2010, ASCO and CAP found in a review of the literature published since 1990, that up to 20% of current IHC determinations of ER/PR may be inaccurate due to pre-analytic variables, with thresholds for positivity and interpretation criteria being the major causes.

- Subsequently, Viale, et al reported false negative rates for ER/PR ranges from 20%-30% and up to 60%-70%.
- Perez, et al also reported that the false positive rates for HER2 ranged from 20%-30% for IHC and 10%-15% for FISH.
- Ma, et al found that “As part of our study, we demonstrated that determining hormonal receptor status by mRNA expression from FFPE tissues provided excellent concordance with IHC, as reported by others — and mRNA-derived receptor status is more strongly associated with clinical outcome”.

High concordance of protein (by centralized IHC using FDA-cleared kits), gene (by FISH; HER2 only) and microarray readout (by TargetPrint) of ER/PR/HER2: results from the MINDACT trial.

<table>
<thead>
<tr>
<th>TargetPrint</th>
<th>Concordance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>98% (96–99%)</td>
</tr>
<tr>
<td>PR</td>
<td>85% (82–88%)</td>
</tr>
<tr>
<td>HER2</td>
<td>96% (94–97%)</td>
</tr>
</tbody>
</table>


The microarray-based assessment of ER, PR and HER2 gives results comparable to IHC and FISH and provides an objective and quantitative assessment of tumor receptor status. TargetPrint is part of a multi-profile platform for breast cancer treatment management.

Working in concert with you for better patient care.

SYMPHONY is the most comprehensive decision support profile available for physicians treating breast cancer. By providing a complete profile of genomic assays, SYMPHONY gives you the tools needed to address complete decisions for any type and stage of breast cancer.

**Physician Summary Report**

A powerful prognostic and predictive biomarker that helps you determine if you can safely withhold chemotherapy.

Identifies targets for therapy.

Identifies molecular subtypes to help you select the right therapies for each patient.

Potential alternate therapy when there was no response to standard therapies.

**Mammprint**

- Breast Cancer Recurrence Assay
- Prognostic and predictive

**Theraprint**

- Therapy Gene Assay
- 56-gene measurement
- Gene expression analysis for alternative therapy

**Targetprint**

- ER/PR, HER2 expression
- Identifies molecular subtypes

**Bluelight**

- Molecular Subtyping Assay
- ER-positive, HER2-negative
- Luminal-type, HER2 subtypes

**General Summary**

- Low Risk: 10 year Disease-Free Survival (DFS) prior to treatment
- High Risk: 10 year DFS prior to treatment

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