Assessment and Reimbursement of Gene Expression Tests in Breast Cancer in Europe: A Comparative Policy Analysis

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Background and Objectives

BACKGROUND

• Adjuvant chemoendocrine therapy is used to reduce the risk of recurrence in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) early breast cancer.

• Patients with early breast cancer do not benefit equally from chemotherapy and its use is associated with the risk of short- and long-term adverse events.

• Gene expression tests provide prognostic value by estimating patient outcomes. The Oncotype DX Breast Recurrence Score® test also predicts the likelihood of chemotherapy benefit, information that can guide treatment decisions. Some patients can be treated effectively with endocrine therapy alone.

• Despite efforts of a pan-European health technology assessment (HTA) process to evaluate the evidence level of gene expression tests, countries in Europe still perform individual national assessments and reimbursement procedures.

OBJECTIVE

To perform a comparative analysis of the benefit assessment and reimbursement procedures across Europe for 4 gene expression tests used in breast cancer.
Methods

• A literature search was done for assessments of gene expression tests and their reimbursement statuses.

• Websites for the European Network for HTA (EUnetHTA) and national HTA bodies were searched on 20 September 2020.

• Research focused on the EndoPredict, MammaPrint, Oncotype DX and Prosigna tests.

• The following countries were included: Austria, Belgium, France, Germany, the Netherlands, Switzerland, Scotland and the United Kingdom.

The national agencies

- **Belgium**: Belgian Healthcare Knowledge Center
  https://kce.fgov.be/
- **France**: Haute Autorité de Santé
  https://www.has-sante.fr/
- **Germany**: Der Gemeinsame Bundesausschuss (G-BA)
  https://www.g-ba.de/
  Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)
  https://www.iqwig.de/index.html
- **Netherlands**: Zorginstituut Nederland
  https://www.zorginstituutnederland.nl/
- **Switzerland**: Bundesamt für Gesundheit
  https://www.bag.admin.ch/bag/de/home.html
- **United Kingdom**: National Institute for Health Care and Excellence
  https://www.nice.org.uk/
- **Scotland**: NHS Scotland Molecular Pathology Evaluation Panel
  https://www.nss.nhs.scot/browse/specialist-healthcare
- **Austria**: Hauptverband der österreichischen Sozialversicherungsträger
  http://www.hauptverband.at/
  Ludwig Boltzmann Institut für HTA
  https://hta.lbg.ac.at/page/homepage/de
Methods: European Countries Included for Analysis

1. Which gene expression tests are assessed (report title)?
2. Which studies are assessed/considered?
3. What are the main outcomes regarding clinical evidence?
4. Which products are reimbursed (based on #3)?
5. What are the similarities/differences between the European countries?
## Results: Reimbursement of Gene Expression Tests

### United Kingdom – Germany

<table>
<thead>
<tr>
<th>Country</th>
<th>Sources</th>
<th>Test Assessed and Respective Clinical Studies</th>
<th>Clinical Evidence</th>
<th>Reimbursement of Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>United Kingdom</strong></td>
<td>• NICE DG 34 (2018): “Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer”</td>
<td>Oncotype DX® TAILORx (9 years)</td>
<td>☑</td>
<td>✓ €</td>
</tr>
<tr>
<td></td>
<td>• MPEP/MPC (2019): “Advice note: Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer.”</td>
<td>MammaPrint® MINDACT (5 years)</td>
<td>☑</td>
<td>✗</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prosigna® ---</td>
<td>☑</td>
<td>✓ €</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EndoPredict® ---</td>
<td>☑</td>
<td>✓ €</td>
</tr>
</tbody>
</table>

| **Germany** | • IQWiG-Report D14-01 (2016): “Biomarker-based tests for the decision for or against adjuvant systemic chemotherapy for primary breast cancer” | Oncotype DX® TAILORx (9 years) | ☑ | ✓ |
|             | • Addendum D18-01 to IQWiG report D14-01 G-BA decision: Reimbursement of Oncotype DX (2019) | MammaPrint® MINDACT (5 years) | ☑ | 🕒 |
|             | • Update: IQWiG-Report D19-01 (2020): benefit of Oncotype DX not transferable to other tests | Prosigna® --- | ☑ | 🕒 |
|             |                                                                         | EndoPredict® --- | ☑ | 🕒 |

Assessment ongoing; Temporary funding, selective/special agreements; Clinical evidence (none or insufficient/sufficient); Discounts granted by industry; Reimbursement status (not reimbursed/reimbursed); Data collection due to insufficient evidence.
## Results: Reimbursement of Gene Expression Tests
### Belgium – France - Switzerland

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</thead>
</table>
| **Belgium**   | • KCE Report 237 (2015): “Gene expression profiling and immunohistochemistry tests for personalized management of adjuvant chemotherapy decisions in early breast cancer (a rapid assessment)”
  • KCE Report 298 (2018): “MammaPrint® test for personalized management of adjuvant chemotherapy decisions in early breast cancer” |
|               | Oncotype DX®                                                            | ---                                           | ● ● ● €           |                       |
|               | MammaPrint®                                                             | MINDACT                                       | ● ● ● €           |                       |
|               | Prosigna®                                                               | ---                                           | ● ● ● ◻           |                       |
|               | EndoPredict®                                                            | ---                                           | ● ● ● ◻           |                       |
| **France**    | • HAS Report (2019): “Clinical utility of genomic signatures in early-stage breast cancer” |
|               | Oncotype DX®                                                            | TAILORx, Plan B, Optima (prelim)              | ● ● ◻             |                       |
|               | MammaPrint®                                                             | MINDACT, Optima (prelim)                      | ● ● ◻             |                       |
|               | Prosigna®                                                               | Optima (prelim)                               | ● ● ◻             |                       |
|               | EndoPredict®                                                            | ---                                           | ● ● ◻             |                       |
| **Switzerland**| • Ordinance of the Home Secretary (EDI) on benefits in compulsory health insurance (“Krankenpflege-Leistungsverordnung, KLV”) (2020) |
|               | Oncotype DX®                                                            | n/a                                           | ◻ ◻               |                       |
|               | MammaPrint®                                                             | n/a                                           | ◻ ◻               |                       |
|               | Prosigna®                                                               | n/a                                           | ◻ ◻               |                       |
|               | EndoPredict®                                                            | n/a                                           | ◻ ◻               |                       |
# Results: No Reimbursement in Austria and the Netherlands

<table>
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<tr>
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</table>
| Austria    | • Report from the Hauptverband der österreichischen Sozialversicherungsträger (2014): “Oncotype DX® for breast cancer”  
• The Austrian Institute for Health Technology Assessment GmbH refers to the German IQWiG reports 2016, 2018, and 2020 and the positive reimbursement decision on the Oncotype DX test | Oncotype DX®                                   | ✗                 | ✗                      |
| Netherlands| • Assessment for Oncotype DX® test ongoing  
• First assessment by CVZ 2010 concludes that based on the results of the literature search on the clinical effectiveness, the MammaPrint® medical test does not meet the criterion for state of science and practice  
• Reassessment Report from ZIN (2018): “MammaPrint® in women with early stage breast cancer” conclusion: the omission of chemotherapy based on MammaPrint® may lead to an increase in metastases and thus mortality. As a result, this test is not eligible for reimbursement from the basic package.  
• Assessment in the Netherlands is linked to EUnetHTA (Final Assessment Report, 2018): MammaPrint® Project ID: OTCA04 | Oncotype DX®                                   | ✗                 | ✗                      |
# Results: EUnetHTA Assessment and Future Projects for Gene Expression Tests on the Prioritization List

<table>
<thead>
<tr>
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<th>Clinical Evidence</th>
<th>Reimbursement of Test</th>
</tr>
</thead>
</table>
| EUnetHTA | EUnetHTA (Final Assessment Report, 2018): MammaPrint® Project ID: OTCA04  
- Author: Zorginstituut Nederland  
- Co-author: Belgian Health Care Knowledge Centre  
- Dedicated Reviewers: Ludwig Boltzmann Institute for HTA and Haute Autorité de Santé  
- EUnetHTA prioritization list: “Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer” | MammaPrint®  
MINDACT study (5 years) | n/a (EUnetHTA does not decide on reimbursement in European countries – this is exclusively decided on a national level) |                |
Conclusions

• HTA assessments were published between 2014 - 2020. The Oncotype DX test was assessed in 5 countries, MammaPrint in 6 countries, and EndoPredict and Prosigna each in 4 countries. Whereas France (2019), Belgium (2015), UK (2018), Scotland (2019), and Germany (2020) assessed all tests at the same time; the Netherlands and EUnetHTA (2018) assessed only the MammaPrint test. Austria (2014) assessed only the Oncotype DX test.

• HTA assessments varied in the tests chosen for assessment and the date of the assessment.

• Thus, the Assessments led to different results and reimbursement statuses of gene expression tests across Europe.

• Three different reimbursement approaches can be differentiated:
  • Different Tests reimbursed GER and UK
  • Innovation Funding with data collection
  • Explicit reimbursement rejection for the MammaPrint test in the Netherlands

Outlook

• We expect that national HTA bodies will update their assessments with new evidence coming (ie, new MINDACT, OPTIMA and RxPONDER results). In this regard, a EUnetHTA assessment of all gene expression tests as proposed in the prioritization list could be relevant.

• To date, the Oncotype DX test is the only one with long-term prospective randomized controlled trial data (TAILORx, 9 years) confirming CT benefit prediction for a defined patient population. To date these results have not yet led to harmonization of HTA assessment conclusions in Europe for Oncotype DX test.
References


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THANK YOU!