EXACT SCIENCES

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

Marie-Geneviève Plaud,[1] Elena Helk,[1] Thomas Ecker,[1] Kirsten H. Herrmann.[2]
[1]Ecker + Ecker GmbH, Hamburg, Germany; [2]Exact Sciences Deutschland GmbH, Cologne, Germany.

BBS, EFSPI,

„Precision & Innovative Medicine and Health Technology Assessment“

Kirsten H. Herrmann, PhD

June 28th, 2021

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

1. Burstein HJ, et al. *Ann Oncol*. 2019;30:1541-57. 2. Paik S, et al. *J Clin Oncol*. 2006;24:3726-34. 3. Sparano JA, et al. *N Engl J Med*. 2015;373:2005-14. 4. Sparano JA, et al. *N Engl J Med*. 2018;379:111-21.

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

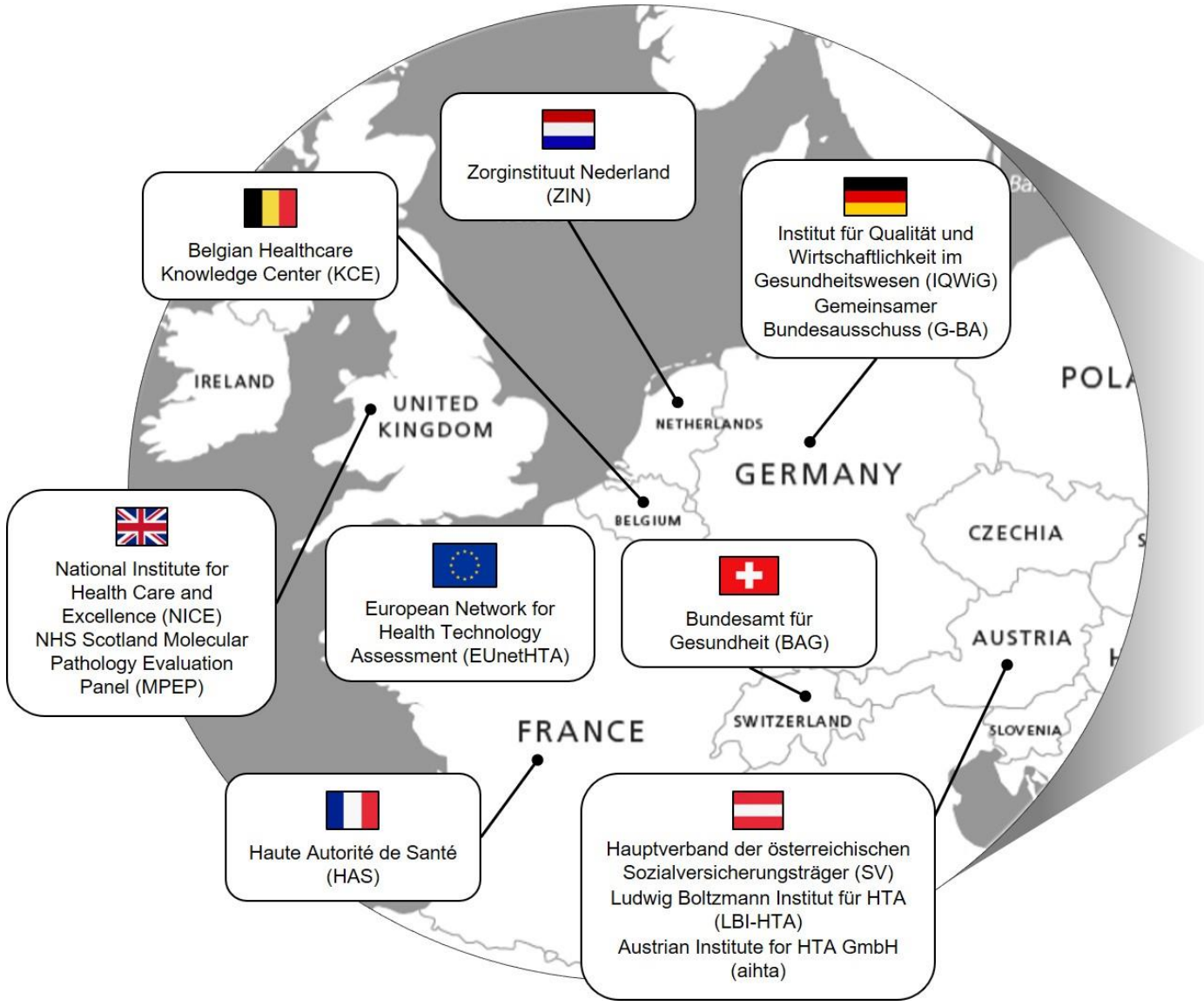
United Kingdom: National Institute for Health Care and Excellence
https://www.nice.org.uk/

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

Country	Sources	Test Assessed and Respective Clinical Studies		Clinical Evidence	Reimbursement of Test
United Kingdom	• **NICE DG 34 (2018):** "Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer" • **MPEP/MPC (2019):** "Advice note: Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer."	Oncotype DX®	TAILORx (9 years)		👍 €
		MammaPrint®	MINDACT (5 years)		👎
		Prosigna®	---		👍 €
		EndoPredict®	---		👍 €
Germany	• **IQWiG-Report D14-01 (2016):** "Biomarker-based tests for the decision for or against adjuvant systemic chemotherapy for primary breast cancer" • **Addendum D18-01 to IQWiG report D14-01 G-BA decision:** Reimbursement of Oncotype DX (2019) • **Update: IQWiG-Report D19-01 (2020):** benefit of Oncotype DX not transferable to other tests	Oncotype DX®	TAILORx (9 years)		👍
		MammaPrint®	MINDACT (5 years)		🕐
		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

G-BA: Gemeinsamer Bundesausschuss; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; MPEP: Molecular Pathology Evaluation Panel; MPC: Molecular Pathology Consortium; NICE: The National Institute for Health and Care Excellence.

Results: Reimbursement of Gene Expression Tests Belgium – France - Switzerland

Country	Sources	Test Assessed and Respective Clinical Studies		Clinical Evidence	Reimbursement of Test
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		

EDI: Eidgenössisches Departement des Innern; HAS: Haute Autorité de Santé; KCE: Kenniscentrum – Centre d'Expertise.

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: No Reimbursement in Austria and the Netherlands

Country	Sources	Test Assessed and Respective Clinical Studies		Clinical Evidence	Reimbursement of Test
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®	n/a		
		MammaPrint®	MINDACT		

CVZ: College voor Zorgverzekeringen; EUnetHTA: European Network for Health Technology Assessment; KCE: Kenniscentrum – Centre d'Expertise; ZIN: Zorginstituut Nederland.

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: EUnetHTA Assessment and Future Projects for Gene Expression Tests on the Prioritization List

Country	Sources	Test Assessed and Respective Clinical Studies		Clinical Evidence	Reimbursement of Test
EUnetHTA	• **EUnetHTA (Final Assessment Report, 2018):** MammaPrint® Project ID: OTCA04 • The clinical utility of the MammaPrint® is not proven. This conclusion is based on the absence of evidence on added value in terms QoL and on the fact that non-inferiority in terms of OS (surrogates 5-year DMFS, 5-year DFS and 5-year OS) is not shown. – **Author:** Zorginstituut Nederland – **Co-author:** Belgian Health Care Knowledge Centre – **Dedicated Reviewers:** Ludwig Boltzmann Institute for HTA and Haute Autorité de Santé	MammaPrint®	MINDACT study (5 years)		n/a *(EUnetHTA does not decide on reimbursement in European countries – this is exclusively decided on a national level)*
	• **EUnetHTA prioritization list:** "Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer"	Oncotype DX® MammaPrint® EndoPredict® Prosigna® IHC4 or IHC4+C	Unclear whether project to be started or not		

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

1. Burstein HJ, et al. *Ann Oncol*. 2019;30:1541-57. **2.** Paik S, et al. *J Clin Oncol*. 2006;24:3726-34. **3.** Sparano JA, et al. *N Engl J Med*. 2015;373:2005-14. **4.** Sparano JA, et al. *N Engl J Med*. 2018;379:111-21. \ **5.** NICE 2018. DG-34. https://www.nice.org.uk/guidance/dg34. **6.** MPEP Advice Note 2019. https://www.sglc.scot.nhs.uk/wp-content/uploads/2019/08/MPC-Advice-NICE-Guidance-DG34-v1.0.pdf. **7.** IQWiG Report D14-01 2016. https://www.iqwig.de/en/projects/d14-01.html. **8.** IQWiG Report D18-01 2018. https://www.iqwig.de/en/projects/d18-01.html. **9.** IQWiG.Report D19-01 2020. https://www.iqwig.de/projekte/d19-01.html. **10.** HAS Report 2019. https://www.has-sante.fr/jcms/c_2748998/en/clinical-utility-of-genomic-signatures-in-early-stage-breast-cancer-inahta-brief. **11.** EDI Ordinance 2020. https://fedlex.data.admin.ch/filestore/fedlex.data.admin.ch/eli/cc/1995/4964_4964_4964/20200430/de/pdf-a/fedlex-data-admin-ch-eli-cc-1995-4964_4964_4964-20200430-de-pdf-a.pdf. **12.** KCE Report 237 2015. https://kce.fgov.be/sites/default/files/atoms/files/KCE_237_Gene%20expression%20profiling_Report.pdf. **13.** KCE Report 298 2018. https://kce.fgov.be/sites/default/files/atoms/files/KCE_298_Mammaprint_tests_Report__0.pdf. **14.** ZIN Report 2018. https://www.zorginstituutnederland.nl/publicaties/standpunten/2018/09/27/standpunt-mammaprint-bij-vrouwen-met-vroeg-stadium-borstkanker-herbeoordeling. **15.** ZIN Report 2020. https://www.zorginstituutnederland.nl/werkagenda/kanker/standpunt-oncotype-dx. **16.** EUnetHTA Project OTCA04 2018. https://eunethta.eu/final-assessment-report-on-mammaprint-added-value-of-using-the-gene-expression-signature-test-mammaprint-for-adjuvant-chemotherapy-decision-making-in-early-breast-cancer/. **17.** SV Report 2014. https://www.sozialversicherung.at/cdscontent/load?contentid=10008.714932&version=1415777157. **18.** HTA Austria Report 2020. https://aihta.at/page/brustkrebs-biomarker-tests-zur-entscheidung-ueber-chemotherapie/de. **19.** Cardoso F, et al. *N Engl J Med*. 2016;375:717-29. **20.** Nitz U, et al. *Breast Cancer Res Treat*. 2017;165:573-83. **21.** Hall PS, et al. *Value Health*. 2017;20:1311-18

Disclosures: MGP, EH, and TE have nothing to declare. KHH is an employee of Exact Sciences GmbH.

EXACT SCIENCES

THANK YOU!