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Budget impact analysis of gene expression tests to aid therapy decisions for breast cancer patients in Germany

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ABSTRACT

Objectives: Many women with early-stage, hormone receptor-positive breast cancer may not benefit from adjuvant chemotherapy. Gene expression tests can reduce chemotherapy over- and undertreatment by providing prognostic information on the likelihood of recurrence and, with Oncotype DX, predictive information on chemotherapy benefit. These tests are currently not reimbursed by German healthcare payers. An analysis was conducted to evaluate the budget impact of gene expression tests in Germany.
Materials and methods: Costs of gene expression tests and medical and non-medical costs associated with treatment were assessed from healthcare payer and societal perspectives. Costs were estimated from data collected at a university hospital and were combined with decision impact data for Oncotype DX, MammaPrint, Prosigna and EndoPredict (EPclin). Changes in chemotherapy use and budget impact were evaluated over 1 year for 20,000 women.
Results: Chemotherapy was associated with substantial annual costs of EUR 19,003 and EUR 84,412 per therapy from the healthcare payer and societal perspective, respectively. Compared with standard care, only Oncotype DX was associated with cost savings to healthcare payers and society (EUR 5.9 million and EUR 253 million, respectively). Scenario analysis showed that both women at high clinical but low genomic risk and low clinical but high genomic risk were important contributors to costs.
Conclusions: Oncotype DX was the only gene expression test that was estimated to reduce costs versus standard care in Germany. The reimbursement of Oncotype DX testing in standard clinical practice in Germany should be considered.

1. Introduction

Breast cancer is the most common malignant neoplasm in Germany but its age standardized mortality rate has decreased over the past decade [1,2]. Lower mortality is partly due to high-quality care, which places a substantial and continuously increasing economic burden on the German healthcare system [3–5]. Adjuvant chemotherapy in particular represents a considerable expenditure because of its high costs and widespread, guideline-recommended use [6–9]. The high costs and toxicity of chemotherapy imply that the healthcare system and patients would benefit from using chemotherapy as sparingly as clinically reasonable [5,10]. Many women with breast cancer are unlikely to benefit from adjuvant chemotherapy, so its frequent use reflects overtreatment at high economic and humanistic costs [8,11,12]. Consequently, the decision for or against adjuvant chemotherapy is complex and should be shared by patients and physicians, accounting for patients' professional and social situation and their expectations and preferences [13,14].

Gene expression tests aid decision-making by providing prognostic information about the likelihood of cancer recurrence [15–17]. The Oncotype DX® Breast Cancer Assay also provides predictive information about the benefit of chemotherapy [18,19]. Decision impact studies of gene expression tests have

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demonstrated that the using tests is associated with changes in treatment recommendations [20–24].

In Germany, guidelines recommend gene expression tests in selected patient groups if a treatment decision cannot be reached otherwise [6,7,25]. The *Leitlinienprogramm Onkologie*, in its 2012 guideline, does not recommend their routine use although this recommendation is anticipated to change in the upcoming version of the guideline [6]. The German Institute for Quality and Efficiency in Healthcare concluded that there was insufficient evidence on long-term outcomes to support the use of biomarker-based tests although this conclusion was based on only two studies [26]. However, it was suggested that Onco*type* DX might be used to identify women unlikely to benefit from chemotherapy if 5-year results from TAILORx are confirmed by long-term results [19,26]. Tests are not generally reimbursed by German healthcare payers.

Given the potential of gene expression testing to reduce the burden of breast cancer treatment, a short-term budget impact analysis was developed for the use of gene expression tests in the German setting, to provide additional evidence on their benefits to patients and the healthcare system.

2. Material and methods

2.1. Patient population

Women with early-stage, estrogen receptor-positive, HER2-negative, 0–3 positive lymph node-positive breast cancer formed the target population of the analysis. These women are eligible for adjuvant chemotherapy and their treatment decisions would be informed by gene expression tests, particularly in patients with luminal B breast cancer with higher tumor grades or Ki67 positivity.

2.2. Interventions

Four tests were included in the evaluation (Table 1). Onco*type* DX is a 21-gene gene expression assay that provides a Recurrence Score (RS) of the 10-year risk of distant recurrence [19,27,28]. Based on RS, women are classified to have low (RS $<$ 18), intermediate (18 $\leq$ RS $\leq$ 30) or high (RS $\geq$ 31) risk of distant recurrence. The prognostic ability of RS has been demonstrated in clinical studies, with Onco*type* DX classifying more patients at low risk of distant recurrence than other tests [18,19,29–31]. Uniquely, Onco*type* DX also provides predictive information about the benefit of chemotherapy. Women classified as low risk are unlikely to benefit from chemotherapy as are women classified at intermediate risk although research is ongoing for this category [19,30,32]. In contrast, chemotherapy is likely beneficial for women classified as high risk [30].

MammaPrint® is a 70-gene expression assay classifying patients as low or high risk of distant recurrence [17,33,34]. The assay was validated in a heterogeneous population, including node-positive, node-negative, ER-positive and ER-negative breast cancer patients treated with a variety of therapies [35]. The prognostic ability of MammaPrint has been demonstrated in clinical studies but its ability to predict chemotherapy benefit is poorly validated [17,33,36]. The MINDACT trial suggested that MammaPrint might be associated with an overall chemotherapy-sparing effect of 14.3% [17]. Whilst the high failure rate of the MammaPrint assay and substantial protocol revisions in the MINDACT trial are of concern, the findings may be of interest if they can be confirmed in decision-impact studies in clinical practice [17,37].

Prosigna® is an assay based on PAM50 [20,38]. Prosigna was validated in postmenopausal women and provides a classification of intrinsic breast cancer subtypes and a Risk of Recurrence (ROR) score, which classifies women as low, intermediate or high risk of recurrence [20,39]. The prognostic ability of ROR has been demonstrated in several studies but Prosigna cannot not predict chemotherapy benefit [20,40,41].

EndoPredict® (EP) is based on the expression of 12 genes, which yields the molecular EP score that, combined with clinical factors, gives the EPclin score [21,42]. EndoPredict was validated in postmenopausal women at low risk of distant recurrence [43]. Both EP and EPclin scores provide prognostic information on recurrence in postmenopausal women but neither score is validated to predict chemotherapy benefit [43–45].

These tests were chosen as they are the most widely used.

Table 1
Decision impact studies used in the budget impact evaluation.

Study	Population	Comparator	Net change in CT decision with gene expression test
EndoPredict (12-gene assay [42]; tissue: FFPE; technique: RT-qPCR; central laboratory: no; predictive of chemotherapy benefit: no)			
Bloomfield et al., 2017 [23] UK	• N = 149 • Mean age: not reported • Women with ER-positive, HER2-negative early-stage breast cancer	Chemotherapy recommendation made by oncologists/clinical teams	Increase of 0.7%
MammaPrint (70-gene assay [34]; tissue: fresh frozen or FFPE; technique: mini- and whole-genome arrays; central laboratory: yes; predictive of chemotherapy benefit: poorly validated)			
Wuerstlein et al., 2017 [24] Germany	• N = 430 • Median age: 58 years • Women with ≤1 lymph node-positive early stage breast cancer • German, Austrian, Swiss oncology centers	Chemotherapy recommendation made by oncologists based on clinicopathological factors and/or local IHC	Increase of 1.9%
Oncotype DX (21-gene assay [18]; tissue: FFPE; technique: RT-qPCR; central laboratory: yes; predictive of chemotherapy benefit: yes)			
Blohmer et al., 2013 [23] Germany	• N = 366 • Mean age: 56 years • Women with ER-positive, HER2-negative, 0–3 node-positive early-stage breast cancer	Chemotherapy recommendation by multidisciplinary tumor boards	Decrease of 18.9%
Prosigna (50-gene assay [38]; tissue: FFPE; technique: direct hybridization; central laboratory: no; predictive of chemotherapy benefit: no)			
Wuerstlein et al., 2016 [20] Germany	• N = 198 • Median age: 64 years • Women with ER-positive, HER2-negative, node-negative early-stage breast cancer	Chemotherapy recommendation by physicians based on standard clinical and pathological parameters	Increase of 8.6%

AO, Adjuvant! Online; CBO, Dutch Institute for Healthcare Improvement; CT, chemotherapy; FFPE, formalin-fixed paraffin-embedded; NPI, Nottingham Prognostic Index; RT-qPCR, reverse transcription-quantitative real-time polymerase chain reaction; UK, United Kingdom.