IMPACT OF REIMBURSEMENT ON THE UTILIZATION OF GENE EXPRESSION PROFILES AND CHEMOTHERAPY DECISION-MAKING IN DUTCH BREAST CANCER PATIENTS

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Abstract

Introduction

Gene expression profiles (GEPs) have emerged as supportive tests in refining breast cancer treatment decisions regarding chemotherapy. This study investigated the reimbursement of MammaPrint and Oncotype DX, the impact on usage and chemotherapy decisions, and the factors influencing the odds of undergoing a GEP test.

Methods

Invasive non-metastatic breast cancer patients aged ≥18 years and treated surgically between 2011 and 2023 were selected from the Netherlands Cancer Registry. GEP test utilization among different patient groups, whether eligible for reimbursement or guidelines, was presented in a flowchart, categorizing patients by MammaPrint, Oncotype DX, or no test and further dividing them based on chemotherapy received. Further analyses were conducted exclusively on patients eligible for reimbursement. For the descriptive analyses, percentages were presented separately regarding GEP test usage in associations with chemotherapy, trends from 2011 to 2023, and the utilization across different regions. The GEP test utilization trends and regional transitions were assessed. The Chi-squared test was applied to compare test types and reimbursement periods across regions (p <0.05). Additionally, logistic regression analyses were conducted to show which factors influence GEP test use. First, the univariable analysis was conducted (p <0.1), followed by the multivariable analysis (p <0.05), which included the significant variables from the univariable analysis.

Results

Of all patients included (n=173,022), 8% received a GEP test, with 36% of them undergoing chemotherapy and 64% not. In the no GEP test group, 38% received chemotherapy, while 62% did not. Among the patients eligible for reimbursement (n=17,836), 17% received a GEP test. Those who received a GEP test tended to get more adjuvant chemotherapy (32%) and less neoadjuvant chemotherapy (3%) compared to those without a GEP test (23% and 9%, respectively).
When Oncotype DX was reimbursed in 2021, a significant shift was observed between 2021 and 2022 from using MammaPrint to Oncotype DX across all regions. Oncotype DX was increasingly used from 2022 onward, while the use of MammaPrint declined. The Chi-squared test results showed significant associations (p <0.05) in each region between the type of test and the reimbursement periods from 2011 to 2023. Additionally, there was a significant relationship between the utilization of GEP tests and the reimbursement of these tests. The reimbursement periods had higher odds of receiving a GEP test. The odds of undergoing a GEP test in relation to the reimbursement periods were corrected by factors such as age at diagnosis, tumor size, lymph node involvement, geographic region, and tumor grade. When both MammaPrint and Oncotype DX were reimbursed, the odds of receiving a GEP was highest (odds ratio: 5.59, 95% CI 3.7 to 8.5).

Conclusion

In the Netherlands, next to patient and tumor characteristics, reimbursement periods significantly influenced the use of a GEP test. The reimbursement of Oncotype DX led to a shift from MammaPrint to Oncotype DX across several regions in the Netherlands between 2021 and 2022. Inconsistent policies about reimbursement had led to potential inequities, emphasizing the need for standardized, clear reimbursement policies to ensure fair access to GEP testing.

Introduction

Breast cancer is a commonly occurring type of cancer worldwide and particularly affects women in western nations such as the Netherlands. Representing 31% of all cancer diagnoses, breast cancer stands as the most prevalent cancer type among Dutch women, especially those aged 50 and older(1). Statistics reveal that roughly 1 in every 7 women will confront breast cancer during their lifetime, with 1 in every 27 women succumbing to the disease(2).

Especially in the early stages, breast cancer prognosis sees marked enhancements owing to timely diagnoses (e.g. supported by the national screening program) and improved treatments(3). The focus now extends to managing quality of life during and after treatment. Expensive treatments that have partly improved the prognosis still cause side effects, even in the long term. This should be prevented by making treatments more personalized, thereby avoiding side effects, and reducing costs(4, 5). Notably, there is a noticeable trend towards treatment de-escalation, reflected in the declining rates of chemotherapy administration(6, 7). This shift is crucial, given the significant impact chemotherapy side effects can have on patients' wellbeing, overall quality of life during treatment and also after treatment, often persisting during lifetime(8, 9).

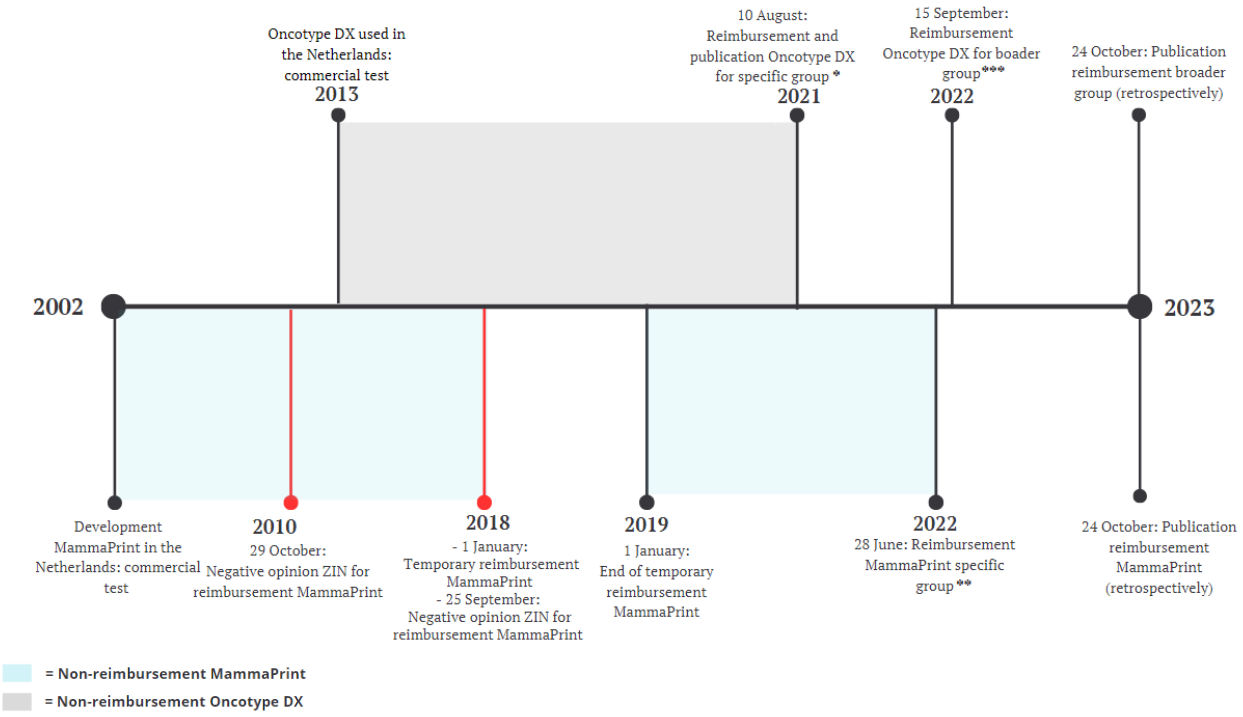
To prevent unnecessary treatment such as chemotherapy, two genetic tests named MammaPrint and Oncotype DX have been developed for breast cancer management. These tests serve to augment standard risk assessments by gauging the risk of breast cancer metastasis. After a biopsy before surgery or tumor removal at surgery, the risk determination can be conducted with the objective of ascertaining whether chemotherapy can be omitted. Notably, if the results indicate a low risk of acquiring metastases, patients may safely forego additional chemotherapy(10).

One of these tests, the MammaPrint, was developed in Europe by the Antoni van Leeuwenhoek-Netherlands Cancer Institute(11, 12). The MammaPrint examines the activity levels of 70 different genes in breast cancer tissue to help predict the likelihood of cancer recurrence or metastasis. It is used for individuals with early-stage invasive breast cancer, tumors less than 5 cm in size, and a maximum of 3 lymph nodes affected. If the test indicates a low risk of cancer recurrence or spread, chemotherapy may be avoided(13).

Oncotype DX is another genetic test developed in the United States(14). This test analyzes the behavior of 21 specific genes within the tumor. The Oncotype DX test is for women diagnosed with early stage breast cancer, tumors less than 5 cm in size, and a maximum spread of 3 lymph nodes(15). The Oncotype DX provides results indicating low, intermediate, or high risk levels. In cases where the result indicates an intermediate risk level, the necessity of chemotherapy can be deliberated based on individual clinical circumstances. Furthermore, the test can assess the potential benefits of chemotherapy(16), aiding in the decision-making process regarding the necessity of chemotherapy for a patient(17).

These two gene expression profile (GEP) tests incur considerable expenses. The Dutch National Health Care Institute (ZIN) assesses the reimbursement of these tests based on factors such as health benefits versus costs(18). The ZIN questioned the reimbursement for the MammaPrint, despite its development in 2002. The MammaPrint already had two negative reviews from the ZIN. On October 24, 2023, it was disclosed that retrospective reimbursement for the MammaPrint, dating back to June 28, 2022, had been approved. The MammaPrint did receive temporary reimbursement for a while, but given that it subsequently received a negative decision in 2018, this was reversed. The reimbursement since 2022 is specific eligibility for women over 50 with specific criteria (Figure 1)(10).
The Oncotype DX became eligible for reimbursement starting on August 10, 2021, and applies to a specific group of patients (Figure 1). On October 24, 2023, it was revealed that retroactive reimbursement had been approved for the expanded group of Oncotype DX, effective September 15, 2022 (10). For both tests, before reimbursement, a hospital had to make a financial construction so that they could still offer the test to patients or it was reimbursed through supplementary insurance(19).

It is unknown whether the reimbursement for these tests may have influenced their application and subsequent chemotherapy decisions. And thereby, what factors, like tumor and patient characteristics, have influenced getting a GEP test. Therefore, this study aims to investigate the utilization of GEP tests, specifically MammaPrint and Oncotype DX, in relation to reimbursement and their impact on chemotherapy decision making among breast cancer patients in the Netherlands from 2011 to 2023, taking into account other influencing factors for receiving a GEP test.



*= : Besides using the standard risk assessment, is it eligible for women older than 50 years, HR+(ER + and/or PR+)/HER2-/N0, with a grade 1 tumor size between 3.1 and 5 cm, a grade 2 tumor size between 2.1 and 5 cm, or a grade 3 tumor size between 1.1 and 2 cm.

**= Besides using the standard risk assessment, is it eligible for women older than 50 years with HR+(ER + and/or PR+)/HER2-/N0 status and a grade 1 tumor between 3.1 and 5 cm, a grade 2 between 2.1 and 5 cm, or a grade 3 between 1.1 and 2 cm. And for women over 50 years old with HR+(ER + and/or PR+)/HER2-/N1 status and 1-3 axillary lymph node metastases, a grade 1 tumor between 2.0 and 5 cm or a grade 2 tumor between 0 and 5 cm.

***= This group was expanded to include women older than 50 years, N1 (1-3 axillary lymph node metastases), with a grade 1 tumor size between 2.0 and 5 cm, or a grade 2 tumor size between 0 and 5 cm.

Figure 1. Time path reimbursement MammaPrint and Oncotype DX according the Dutch National Health Care Institute (8) (10) (11) (20) (21) (22).

Methods

Patients and data collection

All women ≥18 years diagnosed with primary invasive non-metastatic breast cancer in the period 2011-2023 and treated with local surgery in the Netherlands were included in this retrospective population-based study. Data were selected from the Netherlands Cancer Registry (NCR), which registers all newly diagnosed malignancies based on notification by the Nationwide Pathology Databank (PALGA) since 1989 and is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL)(23). Since 2011, data regarding the test results using GEP has been available.
For patients included in this study, the following data were selected: patient characteristics (eg, age at diagnosis and incidence year), tumor characteristics (eg, stadium and size), the use and results of genetic tests (eg, MammaPrint and Oncotype DX), type of treatments (eg, chemotherapy and radiotherapy), and the region where patients underwent the main treatment.

Seven patients who received MammaPrint and Oncotype DX were excluded from the research. Even as there were 4,368 patients who had a missing test result and five patients who were reported to have had surgery, but underwent only minor surgery. Additionally, the last two patients that were excluded from the research did not have a known PN and CN status.

Definitions

For all patients, age at diagnosis was grouped into ages <40, 40-49, 50-59, 60-69, and ≥ 70. The TNM classification (8th edition) was used for staging the tumor(24), if the PN status was missing, the CN status was utilized instead. The differentiation grade was classified as grade 1, 2, or 3(25).
The tumor size classification aligned with the reimbursement criteria for both GEP tests: <1.1 cm, 1.1-2.0 cm, 2.1-3.0 cm, 3.1-5.0 cm, and >5.0 cm. The status of estrogen, progesterone, and Her2Neu receptors was classified as positive or negative. For reimbursement, the hormone receptor (HR) was classified as positive if the progesterone receptor (PR) was positive and/or the estrogen receptor (ER) was positive. MammaPrint results were classified as "high risk" or "low risk", while Oncotype DX provided a numerical "Recurrence Score" that was expressed from 0 to 100. In this study, Oncotype DX results were delineated as follows: a “low” Recurrence Score (<18), an “intermediate” Recurrence Score (18-30), and a “high” Recurrence Score (>30)(26, 27).
The incidence date was used if the test result date was not documented. Dates were presented in month and year format. The patients’ eligibility for reimbursement of MammaPrint or Oncotype DX was determined based on the criteria outlined in Figure 1.
The Dutch guideline stated that patients aged 30-49 were also eligible for GEP tests(28), but not for reimbursement regulations. Other patients who did not meet these criteria were classified as ineligible conform to the guidelines and reimbursement of GEP tests.

The selected period was divided into five periods based on whether reimbursement was available or publicized, delineated in month and year format: before GEP reimbursement (January 2011-December 2017), only MammaPrint reimbursed (January 2018-December 2018), no GEP reimbursed (January 2019-July 2021), only Oncotype DX reimbursed (August 2021-October 2023), and reimbursement MammaPrint and broader group Oncotype DX (November 2023-December 2023(15, 29).

Statement of Ethics

Approval for this study was granted by the Privacy Review Board of the Netherlands Cancer Registry and by the scientific committee of the National Breast Cancer Consultation Netherlands (NABON-BOOG). In these committees, it was decided to limit the incidence dates to the month and year rather than specifying the exact date in order to comply with patient privacy regulations.

Statistical analysis

To assess whether GEP testing was also employed outside the designated indication area or reimbursement criteria, a flowchart was constructed to illustrate the utilization of GEP tests for patients who were eligible for reimbursement(10, 17), those who were guideline-eligible, but ineligible for reimbursement (10, 28), and those who were ineligible according to both the guidelines and reimbursement criteria. Next, they were subsequently grouped according to the test they had undergone and whether they had received chemotherapy. Further analyses in this study were conducted exclusively on patients eligible for reimbursement to assess whether there has been a shift in test utilization over time. The percentages of patient characteristics eligible for reimbursement and those who received either MammaPrint or Oncotype DX were outlined and compared to the no-test group using the Chi-squared test.

The administration of chemotherapy was charted to determine when and if patients received chemotherapy, guided by GEP test or not. To delineate trends in the usage of MammaPrint and Oncotype DX from 2011 to 2023, the annual percentages of MammaPrint, Oncotype DX, and no test usage were calculated. To assess whether hospitals in different regions switched from MammaPrint to Oncotype DX, the annual percentages of MammaPrint, Oncotype DX and no test usage were charted per region. A Chi-squared analysis was conducted to examine whether a significant difference existed between the type of test and the reimbursement periods within different regions.
Additionally, logistic regression analyses were conducted to determine if the reimbursement periods influenced the use of a GEP test, with separate analyses for MammaPrint and Oncotype DX. The regressions were adjusted for the following possible confounders: age, tumor size, lymph node involvement, region, and tumor grade. First, a univariable analysis was conducted ($p < 0.1$), followed by a multivariable analysis, with the significance level set at < 0.05. The factors that were significant in the univariable analysis were taken into account in the multivariable analysis.

StataSE version 17.0 software was used to analyze the data. The Chi-squared was performed with a significance level set at a 2-sided *p*-value of <0.05.

Results

In total, 173,022 patients were included, of which 6.7% had a MammaPrint, 0.8% had an Oncotype DX, and 92.5% had no test (Figure 2). After the patients had been categorized by test, they were categorized based on whether they had received chemotherapy or not. Among all patients who undergo MammaPrint testing, 62.3% do not receive chemotherapy, while 37.7% do. For Oncotype DX, 77.8% do not receive chemotherapy, compared to 22.2% who do. Similarly, for those not undergoing any testing, 62.1% do not receive chemotherapy, while 37.9% do.

For further analysis in this study, only the subset of 'eligible for reimbursement GEP' was included (n=17,836). The patient characteristics of the subset were depicted (Table 1). Significant differences were apparent across most variables among the groups. As an example regarding age distribution, the largest age group among those not tested comprises patients aged 70 and older. However, for those undergoing MammaPrint testing, the predominant age range was 50-59 years, while for Oncotype DX, this was 60-69 years. In terms of tumor grade, compared to the no-test group, MammaPrint and Oncotype DX exhibit a higher percentage of grade 3 tumors and a lower percentage of grade 2 tumors. Additionally, the number of incidences per year associated with Oncotype DX was relatively low, but it has been consistently rising over time. Conversely, the occurrence of MammaPrint incidences per year has shown a gradual decrease during the same period. While the no-test group remained constant.

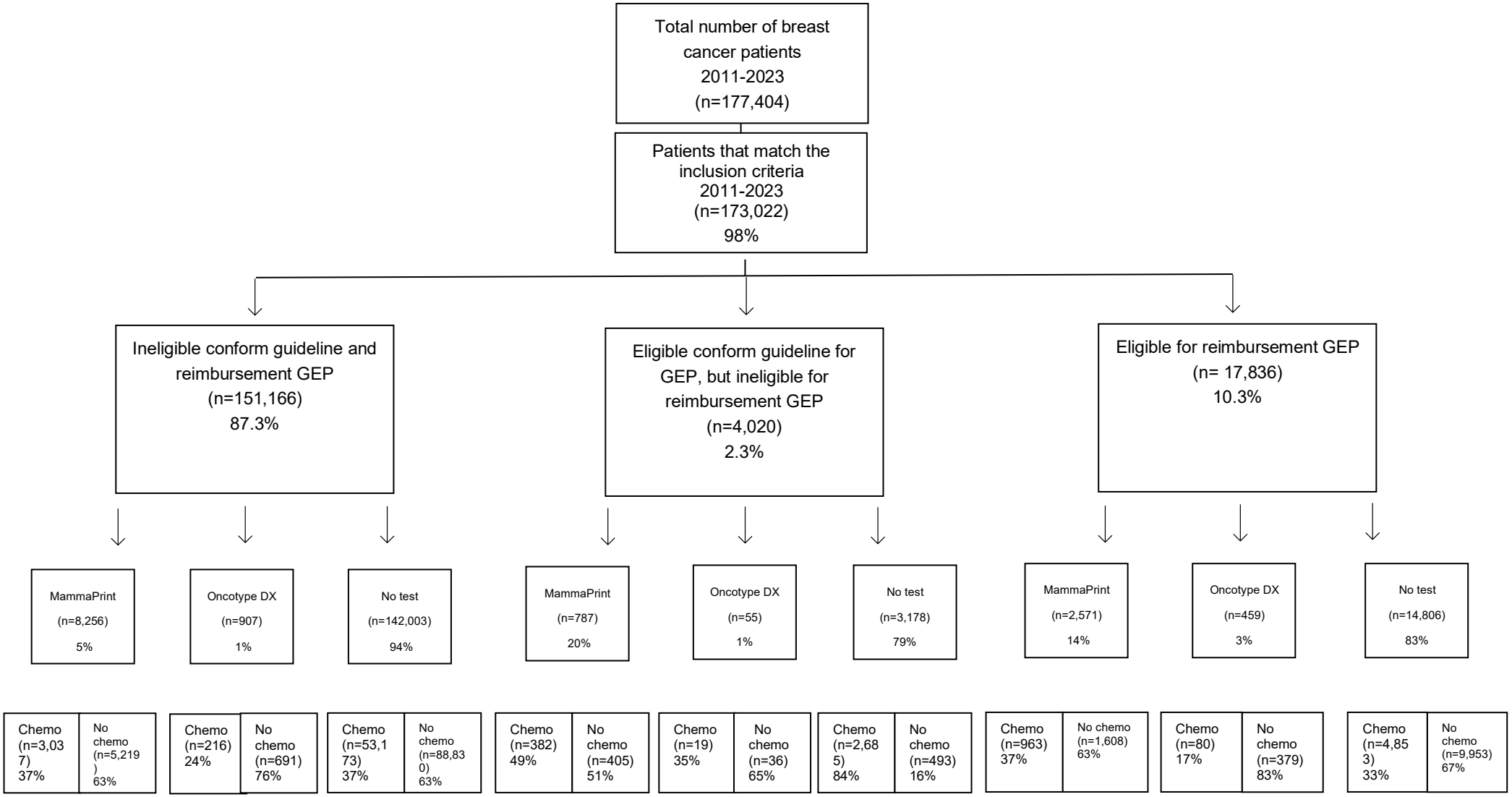


Figure 2. Flowchart for number of included breast cancer patients.

Table 1. Patient characteristics for patients who are eligible for reimbursement GEP* (n=17,836).

		No test	**MammaPrint**		**Oncotype DX**	
		***N* (%)**	***N* (%)**	***p*-value**	***N* (%)**	***p*-value**
Patients	*N* (%)	14,806	2,571		459	
Age group	50-59	4,013 (27.1)	1,270 (49.4)	<0.05	201 (43.8)	<0.05
	60-69	4,589 (31.0)	1,141 (44.4)		227 (49.5)	
	≥ 70	6,204 (41.9)	160 (6.2)		31 (6.7)	
Incidence year	2011	1,120 (7.6)	96 (3.7)	<0.05	0 (0.0)	<0.05
	2012	1,174 (7.9)	52 (2.0)		0 (0.0)	
	2013	1,244 (8.4)	133 (5.2)		2 (0.4)	
	2014	1,237 (8.3)	168 (6.5)		9 (2.0)	
	2015	1,234 (8.3)	141 (5.5)		18 (3.9)	
	2016	1,088 (7.4)	379(14.7)		10 (2.2)	
	2017	1,092 (7.4)	358 (13.9)		13 (2.8)	
	2018	1,052 (7.1)	318 (12.4)		15 (3.3)	
	2019	1,137 (7.7)	303 (11.8)		22 (4.8)	
	2020	1,022 (6.9)	245 (9.5)		21 (4.6)	
	2021	1,207 (8.1)	269 (10.5)		31 (6.7)	
	2022	1,304 (8.8)	61 (2.4)		180 (39.2)	
	2023	895 (6.0)	48 (1.9)		138 (30.1)	
TNM stage	Stage I	3,115 (21.0)	739 (28.8)	<0.05	124 (27.0)	<0.05
	Stage II	11,147 (75.3)	1,826 (71.0)		333 (72.6)	
	Stage III	544 (3.7)	6 (0.2)		2 (0.4)	
Tumor grade	Grade 1	1,154 (7.8)	148 (5.7)	<0.05	17 (3.7)	<0.05
	Grade 2	11,633 (78.6)	1,910 (74.3)		346 (75.4)	
	Grade 3	2,019 (13.6)	513 (20.0)		96 (20.9)	
Lymph nodes	0	6,832 (46.1)	1,306 (50.8)	<0.05	313 (68.2)	<0.05
	1-3	7,974 (53.9)	1,265 (49.2)		146 (31.8)	
Tumor size (cm)	< 1.1	819 (5.5)	105 (4.1)	<0.05	13 (2.8)	<0.05
	11-2.0	5,142(34.7)	1,178(45.8)		168 (36.6)	
	2.1-3.0	5,935(40.1)	1,024(39.8)		210 (45.8)	
	3.1-5.0	2,910(19.7)	264 (10.3)		68 (14.8)	
Chemotherapy	No	9,953 (67.2)	1,608 (62.6)	<0.05	379 (82.6)	<0.05
	Neoadjuvant	1,375 (9.3)	78 (3.0)		3 (0.6)	
	Adjuvant	3,402 (23.0)	882 (34.3)		77 (16.8)	
	Neo- and adjuvant	76 (0.5)	3 (0.1)		0 (0.0)	
Radiotherapy	No	4,747 (32.1)	493 (19.2)	<0.05	83 (18.1)	<0.05
	Neoadjuvant	2 (0.0)	0 (0.0)		0 (0.0)	
	Adjuvant	10,057 (67.9)	2,078 (80.8)		376 (81.9)	
Hormone therapy	No	1,838 (12.4)	153 (5.9)	<0.05	23 (5.0)	<0.05
	Neoadjuvant	35 (0.3)	7 (0.3)		0 (0.0)	
	Adjuvant	12,055 (81.4)	2,275 (88.5)		416 (90.6)	
	Both	878 (5.9)	136 (5.3)		20 (4.4)	
Targeted therapy	No	14,738 (99.5)	2,567 (99.9)	0.169	459 (100.0)	0.548
	Neoadjuvant	11 (0.1)	1 (0.0)		0 (0.0)	
	Adjuvant	32 (0.2)	2 (0.1)		0 (0.0)	
	Both	25 (0.2)	1 (0.0)		0 (0.0)	

Test result	High	na	1,044(40.6)		70 (15.3)	
				<0.05		<0.05
	Intermediate	na	na		103 (22.4)	
	Low	na	1,456 (56.6)		284 (61.9)	
	Unknown	na	71 (2.8)		2 (0.4)	
Region	Mid	1,283 (8.7)	249 (9.7)	<0.05	32 (7.0)	
						<0.05
	Northeast	2,069 (14.0)	382 (14.9)		68 (14.8)	
	Northwest	2,754 (18.6)	695 (27.0)		74 (16.1)	
	East	2,814 (19.0)	479 (18.6)		64 (13.9)	
	West	1,119 (7.6)	137 (5.3)		20 (4.4)	
	Southeast	1,960 (13.2)	266 (10.4)		39 (8.5)	
	Southwest	2,804 (18.9)	363 (14.1)		162 (35.3)	
	Unknown	3 (0.0)	0 (0.0)		0 (0.0)	

***** This table was organized in line with section ‘eligible for reimbursement GEP’ in the flowchart (Figure 2).

The use of chemotherapy with the utilization of a GEP test

When a GEP test was employed, the distribution of the utilization of neoadjuvant chemotherapy among patients was lower (2.7%) and of adjuvant chemotherapy was higher (31.6%), compared to patients who did not receive a GEP test (9.3% and 23.0%, respectively) (Table 2). Furthermore, among patients who received a GEP test, 34.4% received chemotherapy, while 65.6% did not. In contrast, among individuals without a GEP test, 32.8% received chemotherapy, and 67.2% did not.

Table 2. Chemo utilization with or without GEP test by eligible for reimbursement patients (n = 17,836).

Chemo		**No GEP**	**GEP**
		%	**%**
No chemo	**Total**	67.2	65.6
Chemo	**Neoadjuvant**	9.3	2.7
	Adjuvant	23.0	31.6
	Neo- and adjuvant	0.5	0.1
	Total	32.8	34.4
Total		100.0	100.0

Trend in use GEP tests related to reimbursement periods

The trend in the utilization of MammaPrint and Oncotype DX in relation to reimbursement periods was shown (Figure 3). Initially, from 2014 through 2015, there was a slight decrease in MammaPrint usage (from 11.8% to 10.1%, respectively), coinciding with a modest increase in Oncotype DX utilization (from 0.6% to 1.3%, respectively). From 2015 through 2016, there was an increase in the use of MammaPrint (from 10.1% to 25.7%). However, MammaPrint employment steadily declined post-2016. During the introduction of the initial reimbursement period in 2018-2019, there was a continued decrease in MammaPrint usage (from 23.0% to 20.7%, respectively). During the introduction of the reimbursement for Oncotype DX in 2021, the utilization of MammaPrint from 2021 to 2022 decreased (from 17.9% to 4.0%, respectively). However, with the (re)introduction of reimbursement for MammaPrint in November 2023, there was a slight resurgence in MammaPrint usage (4.4%).

Conversely, the utilization of Oncotype DX saw a small peak in 2015 (1.3%), followed by a gradual increase starting in 2016. This upward trend persisted, particularly after the initiation of reimbursement in August 2021 (2.1%). In 2022, it had an uptake (11.7%). Subsequently, with the expansion of reimbursement eligibility for a broader patient group for Oncotype DX from November 2023 onwards, the trend continued to ascend (12.8%).

The total utilization of MammaPrint and Oncotype DX exhibited a declining trend from 2016 (26.3%). In 2022, a notable decrease was observed (15.6%), but in 2023, it began to rise again (17.2%).

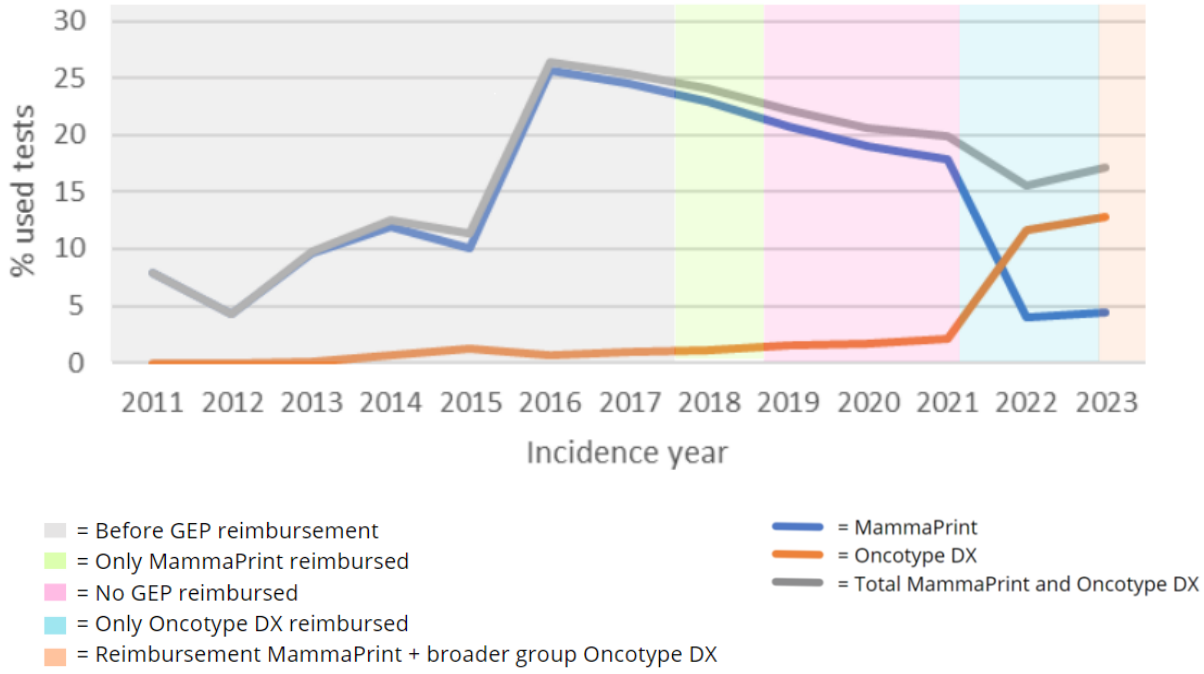


Figure 3. Trend in use GEP tests related to reimbursement periods in the Netherlands (n = 17,836).

The use of GEP tests within regions

The use of MammaPrint and Oncotype DX among hospitals across different regions is illustrated in Figures 4A (MammaPrint) and 4B (Oncotype DX). Three patients were excluded from this analysis due to missing region values, rendering them ineligible for allocation.

In 2013, the Southwest region initiated the use of Oncotype DX (0.8%) alongside MammaPrint (7.4%), followed by the West in 2014 (2.1% and 12.4%, respectively) and the East in 2015 (0.7% and 13.8%, respectively). This gradual integration culminated in a noticeable shift in 2022: a decline from the Southwest, West, and East in the utilization of MammaPrint (1.8%, 3.3%, and 4.1%, respectively) and a corresponding increase in the use of Oncotype DX (13.6%, 8.9%, and 8.6%, respectively) by 2022.

In 2016, the Northwest region incorporated Oncotype DX (0.4%) alongside MammaPrint (35.5%). Additionally, the Northwest had the highest utilization of MammaPrint from 2016 onwards. Furthermore, in 2018, the Southeast region also adopted Oncotype DX (0.5%). The Northwest and the Southeast witnessed a shift in usage patterns from 2022 onwards, with a significant increase in Oncotype DX usage (12.5% and 8.0%, respectively) compared to MammaPrint (6.9% and 3.7%, respectively).

By 2019, the Northeast and by 2020, the Central had integrated the Oncotype DX. Both regions showed a shift in the use of MammaPrint (2.5% and 4.8%, respectively) to Oncotype DX (15.1% and 12.7%, respectively) in 2022. Additionally, all the comparisons between the type of test and the reimbursement periods per region were statistically significant.

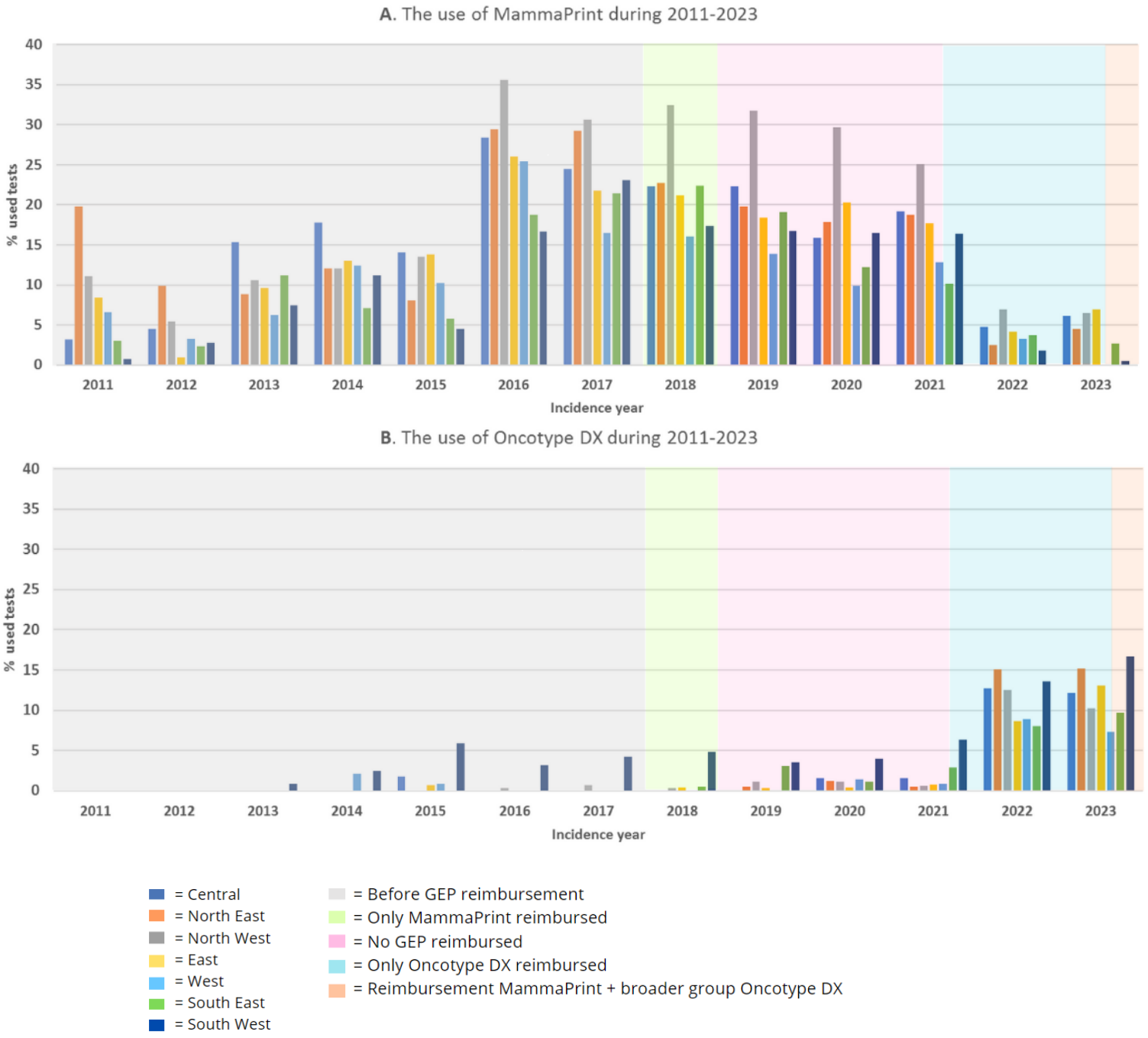


Figure 4. The trend of the use of MammaPrint (A) or Oncotype DX (B) during 2011-2023 within regions in the Netherlands (n = 17,833).

Exploring factors impacting GEP test utilization

Among patients who were eligible for reimbursement for GEP tests, there was a significant correlation between the utilization of GEP tests and reimbursement of these GEP tests (Table 3). The correlation showed that reimbursement periods are associated with a higher odds of receiving a GEP test, both for MammaPrint and Oncotype DX separately. The complete set of possible confounders is presented in Supplementary Table 1. Three patients with missing values for region were excluded.

For receiving a GEP test, reimbursement periods were significant. The highest odds ratio (OR) of receiving a GEP test within these reimbursement periods was observed in the period where both MammaPrint and Oncotype DX were reimbursed (OR: 5.6, 95% CI 3.70 to 8.45). The lowest OR compared to the ‘before reimbursement’ period occurred when Oncotype DX was reimbursed (OR: 1.4, 95% CI 1.21 to 1.53).

For MammaPrint, the period 'reimbursement for MammaPrint and the broader group of Oncotype DX' was not significant. The odds of receiving a MammaPrint was higher for the group with ‘only MammaPrint reimbursed’ (OR: 2.1, 95% CI 1.79 to 2.41) and the group with ‘no GEP reimbursed’ (OR: 1.8, 95% CI 1.64 to 2.04). Conversely, the odds was lower for the group with ‘only Oncotype DX reimbursed’ (OR: 0.5, 95% CI 0.41 to 0.56).

For Oncotype DX, the periods ‘only MammaPrint reimbursed’ (OR: 2.2, 95% CI 1.21 to 3.90), ‘no GEP reimbursed’ (OR: 2.9, 95% CI 1.95 to 4.31), and ‘only Oncotype DX reimbursed’ (OR: 26.2, 95% CI 19.22 to 35.67) exhibited higher odds of receiving Oncotype DX compared to ‘before GEP reimbursement’ (reference category). But the period with ‘reimbursement MammaPrint and broader Oncotype DX’ had the highest odds for receiving an Oncotype DX (OR: 77.2, 95% CI 45.36 to 131.50).

In the three analyses, the factors age at diagnosis, tumor size, lymph node involvement, geographic region, and tumor grade were corrected for receiving a test in relation to the reimbursement periods (Supplementary Table 1). For Oncotype DX, tumor size did not need to be included as a confounder since it was not significant in the univariable analysis.

Table 3. The influence of reimbursement on the utilization of a GEP test, MammaPrint and Oncotype DX*.

		Patients N	Odds ratio (95% Confidence Interval)	*p*-value
GEP				
Reimbursement periods	Before GEP reimbursement	1,346	Reference	Na
	Only MammaPrint reimbursed	329	2.12 (1.83 – 2.46)	0.000
	No GEP reimbursed	773	1.92 (1.73 – 2.14)	0.000
	Only Oncotype DX reimbursed	527	1.36 (1.21 – 1.53)	0.000
	Reimbursement MammaPrint and broader group Oncotype DX	55	5.59 (3.70 – 8.45)	0.000
MammaPrint				
Reimbursement periods	Before GEP reimbursement	1,296	Reference	Na
	Only MammaPrint reimbursed	314	2.07 (1.79 – 2.41)	0.000
	No GEP reimbursed	722	1.83 (1.64 – 2.04)	0.000
	Only Oncotype DX reimbursed	215	0.48 (0.41 – 0.56)	0.000
	Reimbursement MammaPrint and broader group Oncotype DX	24	1.37 (0.85 – 2.21)	0.195
Oncotype DX				
Reimbursement periods	Before GEP reimbursement	50	Reference	Na
	Only MammaPrint reimbursed	15	2.18 (1.21 – 3.90)	0.000
	No GEP reimbursed	51	2.90 (1.95 – 4.31)	0.000
	Only Oncotype DX reimbursed	312	26.18 (19.22 – 35.67)	0.000
	Reimbursement MammaPrint and broader group Oncotype DX	31	77.23 (45.36 – 131.50)	0.000

* Multivariable logistic regression analysis adjusted for the following factors: age, tumor size, lymph node involvement, region, and tumor grade. The Oncotype DX regression was not adjusted for tumor size. Statistically significant when *p*-value < 0.05.

Discussion

The objective of this study was to investigate the utilization of GEP tests, MammaPrint and Oncotype DX, in relation to reimbursement and their influence on chemotherapy decision-making among invasive non-metastatic breast cancer patients who underwent surgery in the Netherlands between 2011 and 2023. Additionally, the influencing factors for receiving a GEP test were examined. Among patients who were eligible for reimbursement, only 17.0% received a GEP test. Among those who did receive a GEP test, it was observed that less neoadjuvant and more adjuvant chemotherapy was administered compared to the patients who did not receive a GEP test. From 2021 to 2022, a shift from MammaPrint to Oncotype DX usage was observed. This shift was evident in all regions. Furthermore, higher odds were observed when reimbursement influenced the utilization of a GEP test, MammaPrint, and Oncotype DX, taking other factors such as age, tumor size, lymph node involvement, region, and tumor grade into account.

First of all, among the 173,022 included patients, there was only a 2.0% difference in receiving chemotherapy with or without a GEP test. As expected, the group that underwent a GEP test potentially received slightly less chemotherapy, as it facilitates a more accurate assessment of chemotherapy's potential benefits. A Canadian(30) and an Italian(31) study demonstrated that using Oncotype DX resulted in a reduction in chemotherapy use, thereby enabling a safer consideration of whether chemotherapy can be safely omitted. When uncertainty arises regarding chemotherapy's benefits and the GEP test indicates a low result, chemotherapy is probably more likely to be omitted, in contrast to situations where no GEP test was performed(32).

Only 17.0% of the eligible patients, regarding the reimbursement policies, received a GEP test. This percentage aligns with expectations because the analysis included all patients from 2011 to 2023 who met the eligibility criteria for reimbursement. However, not all patients fell within the reimbursement period. Some patients were eligible for reimbursement but did not fall within the specified timeframe. Since the reimbursement policies for GEP tests did not cover the entire period from 2011 to 2023, this likely contributed to the lower observed percentage.

When the Chi-squared was conducted, most variables of the tumor and patient characteristics among the MammaPrint with no-test group and Oncotype DX with no-test group exhibited significant differences. This was expected since distinct characteristics were required for undergoing a test compared to not undergoing one.

Furthermore, considering patients who did not undergo GEP testing, there was a higher percentage of neoadjuvant chemotherapy (9.3%) and slightly less adjuvant chemotherapy (23.0%) compared to patients who did undergo GEP testing (2.7% and 31.6%, respectively). A study has demonstrated that adherence to Dutch guidelines regarding GEP test usage was linked to a 10.0% reduction in adjuvant chemotherapy utilization(33). However, the findings of this study did not indicate reduced adjuvant chemotherapy usage, as the adjuvant chemotherapy utilization was proportionally higher with (31.6%) than without (23.0%) a GEP test.

From 2015 through 2016, in the period before GEP reimbursement, there was an increase in the utilization of MammaPrint, from 10.1% to 25.7%, respectively. This might have been attributed to the publication of the MINDACT study in 2016(34), which demonstrated the effectiveness of MammaPrint in clinical practice. As a result, clinicians and patients could have recognized the positive effects of using the test in determining treatment, potentially leading to an increase in the utilization of MammaPrint. This trend was irrespective of whether reimbursement was provided or not.

Despite the temporary reimbursement of MammaPrint during 2018-2019(35), which would typically lead to an anticipated increase in its utilization, there was actually a slight decrease observed instead (from 23.0% to 20.7%). This trend could be due to uncertainty among clinicians and patients about reimbursement changes. If they were unaware of these changes, discussions about GEP testing between patients and clinicians would likely be less frequent, despite efforts to encourage patient engagement(20, 36). Uncertainty about reimbursement likely contributed to this lack of awareness, potentially limiting discussions and reducing the use of MammaPrint.

From 2021 to 2022, there was a subsequent decline in the utilization of MammaPrint and an increase in the utilization of Oncotype DX, as expected due to the reimbursement of Oncotype DX starting in August 2021. This reimbursement change might have influenced clinicians' and patients' preferences, leading them to favor Oncotype DX over MammaPrint, which was not yet reimbursed(15).

In 2020, COVID-19 affected healthcare, influencing treatment strategies, early-stage diagnoses, and the weekly initiation of breast cancer treatments(7, 37). Despite these disruptions, the use of GEP testing remained unaffected during this period. The temporary halt of the screening program in the Netherlands(38, 39) resulted in a decline of mainly the smaller tumors(40, 41), which did not influence the patient group eligible for GEP testing. Moreover, performing surgery was a bigger challenge during the COVID-19 period(40) than administering chemotherapy, according to clinicians. So, GEP tests were used specifically to postpone surgery, if possible, and administer neoadjuvant chemotherapy first. This could explain why GEP testing stayed unaffected during the COVID period.

From 2016 to 2022, there has been an overall decrease in the use of GEP tests. Within this period, there was a notable decline from 2021 to 2022. This decline was remarkable because the incidence rate of breast cancer remained constant(42). Consequently, there was a possibility that patients were not receiving the care they deserved, as they may not have been getting GEP tests that could have benefited their treatment strategy. Discussions with clinicians indicated that during the transition period from MammaPrint to Oncotype DX in hospitals, between 2021 and 2022, there was considerable uncertainty and confusion about the GEP test policy. This could have resulted in patients missing out on GEP testing, because in 2021, 300 people received GEP testing, and in 2022, that number decreased to 241.

A switch from using MammaPrint to using Oncotype DX was seen in various regions between 2021 and 2022. The expectation was that some regions might transition, but all regions transitioned. It seemed like a logical consequence, considering the total increased adoption of Oncotype DX and the decreased usage of MammaPrint from 2021 to 2022. It seemed that reimbursement is deemed a critical factor for the utilization of GEP tests across all regions, indicating a national trend.

The odds of the reimbursement periods of receiving a GEP test was always higher compared to ‘before GEP reimbursement’ (reference category). A reason for this could have been the limited utilization of GEP tests, especially Oncotype DX, during the ‘before GEP reimbursement’ period. This comparison was still selected because Oncotype DX started to gain widespread adoption only after reimbursement was implemented. In the period before reimbursement, the utilization of Oncotype DX was minimal. This was likely also the case for the reimbursement periods for Oncotype DX, which showed a clear trend of increasing odds over time, especially with initial (OR: 26.2, 95% CI 19.22 to 35.67) and broader (OR: 77.2, 95% CI 45.36 to 131.50) reimbursement availability.
Furthermore, about the GEP test, it became apparent that ‘only Oncotype DX reimbursed’ had slightly lower odds (OR: 1.4, 95% CI 1.21 to 1.53) than the other periods as ‘only MammaPrint reimbursed’ (OR: 2.1, 95% CI 1.83 to 2.46), ‘no GEP reimbursed’ (OR: 1.9, 95% CI 1.73 to 2.14) and ‘reimbursement MammaPrint and broader group Oncotype DX’ (OR: 5.6, 95% CI 3.70 to 8.45). The slightly lower odds of the period ‘only Oncotype DX reimbursed’ was expected due to a concurrent decrease in total GEP test usage.

For the reimbursement periods in relation to receiving a MammaPrint, the period 'reimbursement for MammaPrint and the broader group of Oncotype DX' was not significant. The reason for this could have been because this period only consisted of two months, resulting in a relatively lower number of MammaPrints being conducted. In terms of the odds of the reimbursement periods, we observed an expected pattern. When ‘only MammaPrint was reimbursed’, the odds increased (OR: 2.1, 95% CI 1.79 to 2.41), and when Oncotype DX was reimbursed, the odds of receiving a MammaPrint decreased (OR: 0.5, 95% CI 0.41 to 0.56). This was understandable, as when MammaPrint was reimbursed, the odds of receiving a MammaPrint increased. Conversely, when Oncotype DX was reimbursed, the usage of MammaPrint decreased.

The Northwest region showed the highest odds for receiving a GEP test, which included MammaPrint and Oncotype DX together and also for the MammaPrint test separately. The reason why the Northwest region has the highest odds for GEP testing and MammaPrint separately is likely attributed to a few hospitals, like the Antoni van Leeuwenhoek and the Dutch Cancer Institute, that were involved in the development and integration of MammaPrint(11, 12).
For Oncotype DX, only the Southwest region was significant, likely because it was the region where Oncotype DX was most utilized.

Strengths and limitations

This was a population-based, nationwide study, which enhanced its external validity. By utilizing population-based data from the Netherlands, the findings were representative of the general population, allowing for a broader generalization of the results.

The MammaPrint test offered an added benefit by identifying an 'ultralow risk' category, signifying an exceptionally favorable prognosis for breast cancer-free survival at the 15-year mark among patients(43, 44). But this distinction was not captured in the Netherlands Cancer Registry (NCR), thus precluding its incorporation into the analyses.

The reimbursement periods were not evenly distributed over time, but since percentages were used, this may not have played a crucial role. However, the period 'reimbursement for MammaPrint and the broader group of Oncotype DX' only spanned two months.
Furthermore, the reimbursement periods in this study were categorized according to what the Dutch National Health Care Institute (ZIN) specified. In discussions with clinicians, it became apparent that before and between these reimbursement periods, several healthcare insurers and Agendia, the producer of MammaPrint, also reimbursed GEP testing. This may have influenced the use of MammaPrint. Despite the lack of reimbursement, MammaPrint was still utilized. This could have led to an underestimation of the impact of reimbursement.

Moreover, when patients did not have recorded dates for their GEP test results, another date, namely when they were diagnosed, was used instead. This way, all patients could still be included when looking at reimbursement periods.

For the period ‘reimbursement MammaPrint and the broader group Oncotype DX’, the publication date was used instead of the retrospective reimbursement date. This means the dates when these reimbursements were announced were included in the analyses (Figure 1). Physicians and patients were only made aware of the reimbursement status for MammaPrint and the broader group for Oncotype DX at that time.

Conclusion

In the Netherlands, reimbursement played a role in the utilization of GEP tests among eligible patients for reimbursement. The odds of GEP test utilization increased during reimbursement periods. The introduction of reimbursement for Oncotype DX led to a notable shift in preferences, with several regions transitioning from MammaPrint to Oncotype DX between 2021 and 2022. This underscored the influence of reimbursement on testing choices. Additionally, more research is needed to explore why there is a difference in the use of neoadjuvant and adjuvant chemotherapy when combined with GEP testing.

Furthermore, fluctuations in reimbursement policies could lead to confusion, potentially resulting in some patients being unjustly excluded from receiving a GEP test. This raised concerns about equitable access to these supportive diagnostics. Standardizing reimbursement policies nationwide could probably have reduced variations and ensured that all eligible patients had fair access to GEP testing.

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Supplementary

Table 1. The influence of reimbursement on the utilization of a GEP test, MammaPrint and Oncotype DX corrected by factors as age, tumor size, lymph nodes, region and grade.

			Odds ratio (95% Confidence Interval)	***p*-value**
GEP				
	Reimbursement periods	Before GEP reimbursement	Reference	Na
		Only MammaPrint reimbursed	2.12 (1.83 – 2.46)	0.000
		No GEP reimbursed	1.92 (1.73 – 2.14)	0.000
		Only Oncotype DX reimbursed	1.36 (1.21 – 1.53)	0.000
		Reimbursement MammaPrint and broader group Oncotype DX	5.59 (3.70 – 8.45)	0.000
	Age (years)	≥50-59	Reference	Na
		≥60-69	0.71 (0.73 – 0.87)	0.000
		≥ 70	0.08 (0.07 – 0.09)	0.000
	Tumor size (cm)	≤1.0	0.71 (0.57 – 0.89)	0.003
		1.1-2.0	1.33 (1.17 – 1.53)	0.000
		2.1-3.0	Reference	Na
		3.1-5.0	0.56 (0.49 – 0.65)	0.000
	Lymph nodes	0	Reference	Na
		1-3	0.55 (0.49 – 0.62)	0.000
	Region	Central	0.67 (0.57 – 0.79)	0.000
		Northeast	0.76 (0.66 – 0.87)	0.000
		Northwest	Reference	Na
		East	0.65 (0.57 – 0.75)	0.000
		West	0.44 (0.37 – 0.54)	0.000
		Southeast	0.56 (0.48 – 0.65)	0.000
		Southwest	0.68 (0.60 – 0.78)	0.000
	Grade	1	1.06 (0.88 – 1.29)	0.532
		2	Reference	Na
		3	0.77 (0.64 – 0.91)	0.003
MammaPrint				
	Reimbursement periods	Before GEP reimbursement	Reference	Na
		Only MammaPrint reimbursed	2.07 (1.79 – 2.41)	0.000
		No GEP reimbursed	1.83 (1.64 – 2.04)	0.000
		Only Oncotype DX reimbursed	0.48 (0.41 – 0.56)	0.000
		Reimbursement MammaPrint and broader group Oncotype DX	1.37 (0.85 – 2.21)	0.195
	Age (years)	≥50-59	Reference	Na
		≥60-69	0.79 (0.72 – 0.86)	0.000
		≥ 70	0.08 (0.07 – 0.10)	0.000

Tumor size (cm)	≤1.0	0.75 (0.59 – 0.95)	0.017
	1.1-2.0	1.38 (1.20 – 1.59)	0.000
	2.1-3.0	Reference	Na
	3.1-5.0	0.54 (0.47 – 0.63)	0.000
Lymph nodes	0	Reference	Na
	1-3	0.61 (0.53 – 0.70)	0.000
Region	Central	0.66 (0.55 – 0.78)	0.000
	Northeast	0.71 (0.61 – 0.82)	0.000
	Northwest	Reference	Na
	East	0.64 (0.56 – 0.74)	0.000
	West	0.43 (0.35 – 0.52)	0.000
	Southeast	0.53 (0.45 – 0.62)	0.000
	Southwest	0.48 (0.42 – 0.56)	0.000
Grade	1	1.12 (0.91 – 1.37)	0.287
	2	Reference	Na
	3	0.74 (0.61 – 0.89)	0.002
Oncotype DX			
Reimbursement periods	Before GEP reimbursement	Reference	Na
	Only MammaPrint reimbursed	2.18 (1.21 – 3.90)	0.000
	No GEP reimbursed	2.90 (1.95 – 4.31)	0.000
	Only Oncotype DX reimbursed	26.18 (19.22 – 35.67)	0.000
	Reimbursement MammaPrint and broader group Oncotype DX	77.23 (45.36 – 131.50)	0.000
Age (years)	≥50-59	Reference	Na
	≥60-69	0.91 (0.74 – 1.12)	0.385
	≥ 70	0.08 (0.05 – 0.12)	0.000
Lymph nodes	0	Reference	Na
	1-3	0.37 (0.30 – 0.47)	0.000
Region	Central	0.94 (0.60 – 1.47)	0.792
	Northeast	1.24 (0.87 – 1.77)	0.235
	Northwest	Reference	Na
	East	0.88 (0.61 – 1.26)	0.475
	West	0.76 (0.45 – 1.28)	0.305
	Southeast	0.97 (0.64 – 1.47)	0.898
	Southwest	3.36 (2.48 – 4.55)	0.000
Grade	1	0.73 (0.43 – 1.23)	0.240
	2	Reference	Na
	3	1.17 (0.89 – 1.54)	0.251