



Impact of Oncotype DX breast Recurrence Score testing on adjuvant chemotherapy use in early breast cancer: Real world experience in Greater Manchester, UK

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Abstract

Background: The National Institute for Health and Clinical Excellence (NICE) recommended the Oncotype DX[®] Breast Recurrence Score[®] (RS) assay as an option for informing adjuvant chemotherapy decisions in node-negative, oestrogen receptor (ER)+, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer assessed to be at intermediate risk of recurrence based on clinicopathological factors. We evaluated the impact of RS testing on adjuvant chemotherapy decision-making in routine clinical practice in a UK Cancer Network.

Methods: RS testing was performed in 201 females with newly diagnosed, ER+, HER2-negative, invasive breast cancer who underwent breast surgery with curative intent, were calculated to have a >3% overall survival benefit at 10 years from adjuvant chemotherapy based on PREDICT, and were considered for adjuvant chemotherapy. The impact of RS testing on adjuvant treatment decisions/associated cost was assessed.

Results: In all patients, the multi-disciplinary team recommended chemotherapy but the RS result allowed 127/201 patients (63.2%) to avoid unnecessary adjuvant chemotherapy. Amongst ER+, HER2-negative, node-negative patients (eligible for Oncotype DX testing in UK guidelines), 60.3% were spared chemotherapy. In node-positive patients, the assay reduced the use of chemotherapy by 69.2%. The use of RS testing to guide treatment in these 201 patients was associated with significant cost saving (when considering the cost of RS testing for all patients plus chemotherapy and its associated cost for 74 patients).

Conclusions: Incorporating RS testing into routine clinical practice for selected node-negative and node-positive breast cancer patients significantly reduces the use of chemotherapy ($p < 0.001$) with its associated morbidity and costs.

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Keywords: Breast cancer; Chemotherapy; Molecular diagnostic testing; Evidence-based medicine; Prognosis

Introduction

Breast cancer is the most common cancer in women in the UK and, despite significant advances in screening,

diagnosis and treatment, it resulted in almost 12 000 deaths in 2012.¹ Although adjuvant chemotherapy improves survival in early breast cancer,² for some patients, the associated potential toxicities and the negative impact on quality-of-life may outweigh the benefits. The diverse clinical behaviour of breast cancer relates to its individual molecular pathology. Gene expression profiling can provide better risk discrimination relative to traditional clinicopathological factors and more accurately identify breast cancer patients with a low risk of recurrence who are predicted to

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derive minimal benefit from chemotherapy. The ability to personalise treatment based on tumour biology and thus to reduce unnecessary chemotherapy is key to optimising patient care.^{3,4}

The Oncotype DX[®] Breast Recurrence Score[®] Assay (Genomic Health Inc., Redwood City, CA) is a 21-gene assay from which a Recurrence Score (RS) result between 0 and 100 is calculated. It has been validated as an assay that is prognostic as well as predictive of benefit from adjuvant chemotherapy in patients with oestrogen receptor (ER)+, human epidermal growth factor receptor 2 (HER2)-negative, early stage, invasive breast cancer treated with endocrine therapy.^{5–10} Patients are classified as being at low, intermediate or high risk of distant recurrence based on their RS result. The RS has been validated in node-negative patients (for example, in prospectively-defined analyses using archived samples from the NSABP B-14 and B-20 studies)^{5,10} as well as in node-positive patients (in prospectively-defined analyses using archived samples from the SWOG-8814 and TransATAC studies).^{6,7}

RS testing is included in guidelines from the American Society of Clinical Oncology, National Comprehensive Cancer Network, European Society for Medical Oncology (ESMO) and St. Gallen.^{11–14} In 2013, the National Institute for Health and Care Excellence (NICE) in the UK, recommended RS testing, as an option for informing adjuvant chemotherapy decisions in node-negative, early breast cancer assessed to be at intermediate risk of recurrence based on clinicopathological factors.¹⁵ Consequently, in the UK, RS testing has been available since 2015 to all patients treated in the National Health Service (NHS) and meet the NICE recommendation.

In the NICE DG10 guidance, support for using the assay was based on “the clinical utility of the test, including robust evidence on the impact of Oncotype DX on clinical decision-making”.¹⁵ To inform healthcare decisions further, NICE recommended that collection of data on the clinical utility of the assay in routine UK clinical practice should be undertaken.

Before the NICE recommendation, the clinical utility of RS testing was evaluated in a Greater Manchester-based, prospective pilot study from May to December 2012. The data from the pilot study, together with retrospective audit of a series of patients who underwent RS testing beyond the pilot study, collected between December 2012 and March 2015, are included in the present analysis. Prior to the NICE DG10 guidance, the study included both node-negative and node-positive patients. The aim of the present analysis was to evaluate the impact of RS testing on chemotherapy use in the cohort, as well as in subpopulations relevant to breast cancer clinical practice.

Patients and methods

The primary objective of this analysis was to evaluate the impact of RS testing on adjuvant chemotherapy

decision making in ER+, HER2-negative breast cancer patients in routine clinical practice in the NHS. The study was prospective registration with analysis retrospectively following treatment decisions made based on standard clinicopathological data and the RS result. No ethical approval was required as the analysis included patients from a prospective pilot study and additional patients that were audited after the pilot study.

Patient population

The current analysis includes 201 patients: 82 patients from a Greater Manchester-based, prospective pilot study designed to evaluate the clinical value of RS testing (timeframe of testing: 5/2012–12/2012) plus 119 patients from an audit beyond the pilot study (timeframe of testing: 12/2012–3/2015). The inclusion criteria were: (1) females with newly diagnosed invasive breast cancer who underwent breast and axillary surgery with curative intent; (2) a decision to refer the patient to an oncologist for chemotherapy made at a breast cancer multi-disciplinary team (MDT) meeting; (3) ER+ (Quick score $\geq 5/8$) and HER2 0, 1 + or non-amplified; (4) axillary lymph node-negative or node-positive (post-menopausal females only); and (5) at least intermediate risk disease (PREDICT overall survival benefit from chemotherapy estimated to be $>3\%$ at 10 years). In addition, patients had to be considered fit for chemotherapy.

Data analysis

During the study period, data on clinicopathological factors, RS results and subsequent chemotherapy usage were collected. The data were analysed retrospectively to determine the percentage of patients who received chemotherapy following RS testing. Descriptive statistics were used for all analyses. Chi-squared tests were performed to determine whether there was a significant relationship between the RS category (low, RS < 18 , intermediate RS 18–30, high, RS ≥ 31) and chemotherapy use with *p*-values quoted at a 0.05 significance level. Scatterplots were generated to evaluate correlation between PREDICT or Ki67 and the RS, with correlation coefficients (R^2) generated using Microsoft Excel (Microsoft Corporation, Redmond, WA).

Clinical utility

All patients in this study had a MDT recommendation for adjuvant chemotherapy based on clinicopathological factors and PREDICT (a prognostic tool designed to estimate breast cancer survival and the benefits of hormonal therapy, chemotherapy and trastuzumab)¹⁶ calculation. It was assumed that without a RS result, all patients would have received chemotherapy. Treatment recommendations were informed by the assay as follows: no chemotherapy

for low RS (<18) patients and chemotherapy for high RS (≥ 31) patients. For intermediate RS (18–30) patients, a consultation was held with the patient to discuss the potential chemotherapy benefits, informed by the RS result, and a treatment decision was made with the patient.

Budget impact

A model was constructed to evaluate the budgetary implications of RS testing in this population. The calculation captured the acquisition costs of the RS assay, based on the published commercial list price (GBP 2580), and savings from reductions in chemotherapy. Chemotherapy costs were taken from the NICE health technology assessment published by Ward et al. (2013), reported as GBP 6181.16 per patient and taking into account the total cost of chemotherapy including drug acquisition cost, administration and monitoring, costs of treating short-term adverse events, secondary prevention of febrile neutropenia, and long-term adverse event costs.¹⁷ As actualised costs were used for chemotherapy, and RS testing represented a one-off initial cost, no discounting was applied to future costs or clinical benefits. The base-case budget impact analysis assumed that all patients referred from the MDT to an oncologist for chemotherapy would receive it in the absence of RS testing. To explore the impact of a proportion of patients refusing chemotherapy, sensitivity analysis was performed with the alternative assumption that only 84.6% of these patients would receive chemotherapy (in line with the percentage of patients who received chemotherapy in the high RS group following RS testing in the present study).

Results

Patient and tumour characteristics

The study included 201 patients who were treated for early breast cancer in Greater Manchester between May 2012 and March 2015. Patients and tumour characteristics are detailed in Table 1. The mean age was 55.2 years (range, 24–77). The mean tumour size was 26.1 mm (range, 2–80).

Of the 201 patients, 136 (67.7%) had node-negative disease, and would therefore be eligible for RS testing according to current NICE guidance.

RS results and clinicopathological factors

The mean RS result was 20.5 (range, 4–54). Most patients had a low or intermediate RS result. The distribution of patients by RS categories was: 86 (42.8%) low, 89 (44.3%) intermediate, and 26 (12.9%) high. The mean 10-year survival benefit for chemotherapy according to PREDICT was 5.8% (range, 3.1–15.5%). There was no correlation between the RS and the PREDICT tool estimates of 10-year overall survival percentage benefit from chemotherapy ($R^2 = 0.05$, Fig. 1A). A Ki67 result was available in 188 patients (93.5%) with a mean Ki67 of 28.9 (range, 1–81). There was a weak correlation between the RS result and Ki67 ($R^2 = 0.22$, Fig. 1B).

Impact of the RS results on treatment recommendations

The additional information provided by the RS result had a significant chemotherapy sparing impact overall, with only 74 patients (36.8%) receiving chemotherapy ($p < 0.001$, Table 2). The remaining 127 patients (63.2%) received endocrine therapy as their only systemic treatment.

In the low RS group, only 4 of 86 patients (4.7%) received chemotherapy following RS testing compared with 48 of 89 (53.9%) in the intermediate RS group (Table 2, Fig. 2). Within the intermediate RS group, the magnitude of the RS result influenced the treatment decision, with 23 of 54 patients (42.6%) with RS result of 18–24 receiving chemotherapy, compared with 25 of 35 patients (71.4%) with RS results of 25–30. In the high RS group, 22 of 26 patients (84.6%) received chemotherapy. There was a significant association between the RS group and chemotherapy treatment ($p < 0.001$).

Within the group of patients with node-negative disease eligible for testing based on current NICE guidelines, 1 of 46 (2.2%) with a low RS result subsequently received

Table 1
Study population characteristics at baseline.

	Overall n = 201	Node-negative n = 136	Node-positive n = 65
Age, years [mean (SD), range]	55.2 (10.0), 24–77	53.6 (10.1), 24–76	58.7 (8.8), 41–77
Tumour grade ^a			
Grade 1 [n (%)]	2 (1%)	0 (0%)	3 (5%)
Grade 2 [n (%)]	104 (52%)	54 (40%)	50 (77%)
Grade 3 [n (%)]	93 (46%)	81 (60%)	12 (18%)
Tumour size, mm [mean (SD), range]	26.1 (14.3), 2–80	26.0 (12.7), 2–70	26.3 (17.2), 3–80
Node-positive disease, %	32.3	0.0	100.0
PREDICT [mean (SD), range]	5.8 (2.4), 3.1–15.5	5.7 (2.1), 3.1–12.6	6.0 (2.9), 3.1–15.5
RS result [mean (SD), range]	20.5 (10.2), 4–54	21.8 (10.6), 4–54	17.6 (8.4), 4–44

RS, Recurrence Score; SD, Standard deviation.

^a Tumour grade was missing for one patient with node-negative disease.



Figure 1. Scatterplots of PREDICT versus RS results (A) and Ki67 versus RS results (B) in the overall population.

chemotherapy, compared with 36 of 70 (51.4%) in the intermediate RS group (Fig. 2). In the high RS group of node-negative patients, 17 of 20 (85.0%) received chemotherapy. In the node-positive group, 3 of 40 patients

(7.5%) received chemotherapy in the low RS group, compared with 12 of 19 (73.2%) in the intermediate RS group, and 5 of 6 (83.3%) in the high RS group (Fig. 2). Thus, 69.2% of node-positive patients (i.e., patients who

Table 2

Treatment by patient group in relation and the RS result.

	Overall population n = 201		Node-negative n = 136		Node-positive n = 65	
	Chemotherapy	No chemotherapy	Chemotherapy	No chemotherapy	Chemotherapy	No chemotherapy
Low RS	4 (2.0%)	82 (40.8%)	3 (4.6%)	37 (56.9%)	1 (0.7%)	45 (33.1%)
Intermediate RS	48 (23.9%)	41 (20.4%)	12 (18.5%)	7 (10.8%)	36 (26.5%)	34 (25.0%)
High RS	22 (10.9%)	4 (2.0%)	5 (7.7%)	1 (1.5%)	17 (12.5%)	3 (2.2)
Total	74 (36.8%)	127 (63.2%)	20 (30.8%)	45 (69.2%)	54 (39.7%)	82 (60.3%)

RS, Recurrence Score (low, <18; intermediate, 18–30; high \geq 31).

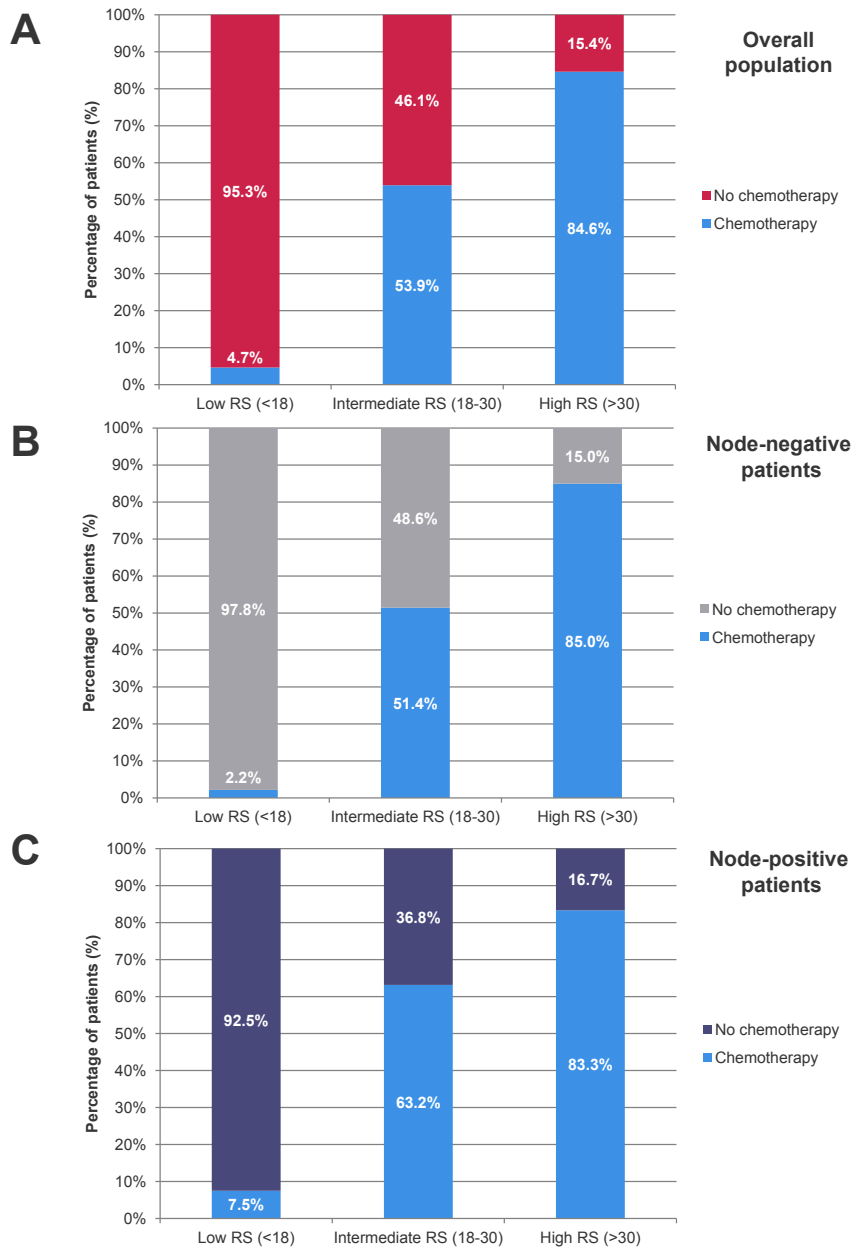


Figure 2. Adjuvant chemotherapy decision making by the RS result. Stacked bar charts are shown for (A) the overall population ($N = 201$), (B) patients with node-negative disease ($n = 136$), and (C) patients with node-positive disease ($n = 65$).

are currently ineligible for RS testing within NHS) avoided chemotherapy.

Budget impact

The estimated cost of chemotherapy for the study population assuming no RS testing, would have been GBP 1,242,413 based on the health technology assessment referenced by the NICE DG10 recommendation.¹⁷ Of the 201 patients who were tested, only 74 received chemotherapy, leading to a total cost (chemotherapy cost plus test cost) of GBP 975,986. This equates to a total cost saving of GBP 266,427 as 127 patients were spared chemotherapy.

In the population eligible for RS testing based on NICE guidance (node-negative patients), the total cost without RS testing was estimated at GBP 840,638 for 136 patients. RS testing spared chemotherapy for 82 patients, at a total cost (chemotherapy cost plus test cost) of GBP 684,663, which is a cost saving of approximately GBP 155,975. In node-positive patients, who are not eligible for RS testing under the current NICE DG10 recommendations, testing reduced overall costs by GBP 110,452 as 45 of 65 patients were spared chemotherapy.

Sensitivity analysis assuming that only 84.6% of patients would have agreed to receive chemotherapy in the scenario without RS testing, indicated that the total cost of

chemotherapy would be approximately GBP 1,051,082. RS testing of all patients in this scenario led to an overall cost saving of GBP 75,096 due to chemotherapy sparing, comprised of a savings of GBP 26,517 in node-negative patients and GBP 48,579 in node-positive patients.

Discussion

Our findings demonstrated that using the RS assay significantly influenced adjuvant chemotherapy decisions in women with intermediate risk ER + HER2-negative early breast cancer ($p < 0.001$). In this analysis of 201 patients from the Greater Manchester area, using the RS assay resulted in avoidance of chemotherapy in 63.2% of patients.

Previous clinical studies have demonstrated the predictive and prognostic information provided by the RS assay with respect to chemotherapy outcomes.^{5–10} The present study was designed to investigate the influence of the assay on adjuvant treatment decisions in routine clinical practice. The distribution of RS categories in our study was comparable with those seen in a meta-analysis of previous studies.¹⁸ The reduction in chemotherapy use observed in the present study is greater than that reported previously.^{19–21} This is because in the current study, a threshold for chemotherapy benefit (PREDICT 10-year overall survival benefit of >3%) was required before RS testing was undertaken, whereas previous studies performed the test on sequential patients with ER + HER2-negative breast cancer discussed at the MDT.

This study demonstrates the impact of testing in routine clinical practice in patients assessed as having at least an intermediate risk breast cancer based on PREDICT, and includes not only patients meeting NICE criteria, but additionally those with node-positive disease. Use of the assay changed chemotherapy prescribing practices in the hospitals included in this study. There was a strong association between the RS result and the decision to prescribe chemotherapy. Still, individual patient wishes and other clinician-patient considerations resulted in some patients with low RS results receiving chemotherapy and some with high RS results not receiving chemotherapy. Overall, 60.3% of node-negative patients and 69.2% of node-positive patients were spared chemotherapy following RS testing.

It is well established that chemotherapy is associated with long-term adverse effects including cardiotoxicity, secondary leukaemia, or effects on cognitive impairment, as well as having a dramatic impact on quality-of-life.²² For example, cognitive impairment alone following chemotherapy can have a huge effect on working life and is often a cause of increased absenteeism and lost workplace productivity.^{23,24} An economic assessment of routine RS testing in the UK by Holt et al. (2013) demonstrated that the use of the assay is associated with improved life expectancy and quality-adjusted life expectancy compared to current clinical practice and is likely to be cost-effective in the UK using current thresholds.¹⁹ The budget impact analysis

from the present study confirms that there is a substantial cost saving in both NICE eligible (node-negative patients) as well as node-positive patients. Additionally, it should be noted that this analysis used the list price for the RS assay as opposed to the confidential price agreed with NICE, and is therefore a conservative estimate of cost savings.

Our findings suggest that using the RS assay to inform treatment decisions in node-positive patients may be just as influential as in node-negative cases, although current NICE recommendations limits its use to node-negative patients.¹⁵ Our findings are consistent with results from 2 prospective trials. The TAILORx trial in node-negative, ER+, HER2-negative breast cancer has recently reported that patients with RS < 11 who were not given chemotherapy had a 93.8% 5-year invasive disease free survival.⁸ Similarly, the German PlanB study in patients with high-risk node-negative or node-positive disease (1–3 positive nodes) reported a 94% disease-free survival at 5 years for patients with RS ≤ 11.⁹ The results from these 2 studies indicate that RS testing can be used to reliably identify both node-negative and node-positive patients who are unlikely to benefit from chemotherapy but who would have suffered the short and long-term sequelae of treatment.

A potential limitation of the study is the assumption that all patients recommended chemotherapy by the MDT would have received it in routine clinical practice without RS testing. To address this, a sensitivity analysis was performed in the budget impact analysis. Another limitation is that RS testing was only performed in a proportion of patients who fulfilled the eligibility criteria. It is possible that the clinicians and patients choosing to use the assay were those who were more likely to be influenced by its results. Also, this is a retrospective analysis of patients who underwent RS testing.

In conclusion, this study demonstrates the clinical utility of RS testing in routine practice showing that it reduces chemotherapy use in ER+, HER2-negative early breast cancer. Current NICE guidance is restricted to patients with node-negative breast cancer, and this study demonstrates similar clinician confidence in the assay for both node-negative patients and post-menopausal node-positive patients. The reduction in chemotherapy use, in appropriately selected patients, for whom chemotherapy would have otherwise been recommended, is greater than reported in other studies. Using the RS assay in routine clinical practice in the UK, even in node-positive patients, could help maintain patients' quality-of-life and reduce the economic burden of breast cancer care.

Conflict of interest

JA Armstrong, S Howell, and NJ Bundred report consulting for Genomic Health. NJ Bundred also reports serving on the speaker's bureau of Genomic Health. The other authors report no conflict of interest.

Role of the funding source

This study was supported by a cost-share agreement between the Greater Manchester Cancer Network, Genomic Health and the Christie Hospital. Genomic Health had a role in pilot study design, and revising the initial draft of the manuscript. Christie Hospital had a role in study design, data collection, analysis and interpretation, and drafting the manuscript. Genomic Health funded 3rd party medical editing support (by Avital Bareket-Samish, PhD).

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