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Enhancing Clinical Decision Support with Genomic Tools in Breast Cancer: A Scottish Perspective

AL Peters^{1,2}, PS Hall³, LB Jordan⁴, FY Soh⁵, L Hannington¹, S Makaranka⁶, G Urquhart⁷, M Vallet³, D Cartwright^{1,2}, H Marashi^{1*}, B Elsberger^{6*}

- 1- Beatson West of Scotland Cancer Centre, Gartnavel Hospital, NHS Greater Glasgow & Clyde, 1053 Great Western Rd, Glasgow G12 0YN
- 2- Cancer Research UK (CRUK) Scotland Institute, Switchback Road, Bearsden, Glasgow G61 1BD
- 3- Edinburgh Cancer Research Centre, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XR
- 4- Ninewells Hospital & Medical School, NHS Tayside, Department of Pathology, Dundee, DD1 9SY
- 5- Raigmore Hospital, NHS Highland, Department of Oncology, Inverness IV2 3UJ
- 6- Aberdeen Royal Infirmary, NHS Grampian, Department of Breast Surgery, Aberdeen AB25 2ZN
- 7- Aberdeen Royal Infirmary, NHS Grampian, Department of Oncology, Aberdeen AB25 2ZN

* Combined last author

Correspondence to: adam.peters@glasgow.ac.uk

Abstract

Key words: breast cancer, genomic test, recurrence score, chemotherapy, progesterone receptor

Introduction:

The *Oncotype DX Breast RS* test has been adopted in Scotland and has been the subject of a large population-based study by a Scottish Consensus Group to assess the uptake of the recurrence score (RS), evaluate co-variables associated with the RS and to analyse the effect it may have had on clinical practice.

Materials & Methods:

Pan-Scotland study between August 2018 – August 2021 evaluating 833 patients who had a RS test performed as part of their diagnostic pathway. Data was extracted retrospectively from electronic records and analysis conducted to describe change in chemotherapy administration (by direct comparison with conventional risk assessment tools), and univariate/multivariate analysis to assess relationship between covariates and the RS.

Results:

Chemotherapy treatment was strongly influenced by the RS ($p < 0.001$). Only 30% of patients received chemotherapy treatment in the intermediate and high risk PREDICT groups, where chemotherapy is considered. Additionally, 55.5% of patients with a high risk PREDICT had a low RS and did not receive chemotherapy. There were 17% of patients with a low risk PREDICT but high RS who received chemotherapy.

Multivariate regression analysis showed the progesterone receptor Allred score (PR score) to be a strong independent predictor of the RS, with a negative PR score being associated with high RS (OR 4.49, $p < 0.001$). Increasing grade was also associated with high RS (OR 3.81, $p < 0.001$). Classic lobular pathology was associated with a low RS in comparison to other tumour pathology ($p < 0.01$). Nodal disease was associated with a lower RS ($p = 0.012$) on univariate analysis, with menopausal status ($p = 0.43$) not influencing the RS on univariate or multivariate analysis.

Conclusions:

Genomic assays offer the potential for risk-stratified decision making regarding the use of chemotherapy. They can help reduce unnecessary chemotherapy treatment and identify a subgroup of patients with more adverse genomic tumour biology. A recent publication by Health Improvement Scotland (HIS) has updated guidance on use of the RS test for NHS Scotland (1). It suggests to limit its use to the intermediate risk PREDICT group. Our study shows the impact of the RS test in the low and high risk PREDICT groups. The implementation across Scotland has resulted in a notable shift in practice, leading to a significant reduction in chemotherapy administration in the setting of high risk PREDICT scores returning low risk RS. There has also been utility for the test in the low risk PREDICT group to detect a small subgroup with a high RS.

We have found the PR score to have a strong independent association with high risk RS. This finding was not evaluated by the key RS test papers, and the potential prognostic information provided by the PR score as a surrogate biomarker is an outstanding question that requires more research to validate.

Introduction

Personalised decision making is essential in the management of early breast cancer (EBC). This will lead to improved outcomes for patients, and facilitate an individualised cancer journey. Improved knowledge of tumour heterogeneity and differentially expressed genes has led to the development of genomic signature assays.

There are various validated genomic tests currently available, with initial evidence from the retrospective analysis of the *TransATAC* database (2). These include the Oncotype DX® Breast Recurrence Score® (RS) assay (Genomic Health Inc., Redwood City, CA), MammaPrint® (Agendia BV, Amsterdam, The Netherlands), Prosigna (PAM50 assay, Veracyte, San Francisco, CA) and EndoPredict (EPclin, Myriad Genetics, Zurich, Switzerland) (2-9). The RS test, according to numerous guidelines has prognostic validity (10-22). It has been approved for use in hormone positive breast cancer in patients with node negative or up to three lymph nodes positive disease across Scotland, and is included in the ESMO Early Breast Cancer Guidelines (10, 23).

The objective of this pan-Scotland study was to assess its use as a decision-making tool, and to investigate patient and tumour factors that may be associated with the RS. An additional objective was to describe the RS test's concordance with conventional decision tools such as PREDICT.

Background

There has always been uncertainty regarding which patients with EBC will benefit from adjuvant chemotherapy. It is clear that patients with HER2 positive or triple negative breast cancer benefit from systemic chemotherapy (24-26). Evidence for substantial benefit from chemotherapy in patients with HR positive, HER2 negative EBC is less robust.

Due to this uncertainty and the need to try to reduce treatment side effects, several risk assessment tools have been developed over the years. The first of these was the *Nottingham Prognostic Index* (NPI) (26). The NPI groups patients into a high risk (>5.4), moderate risk (3.4-5.4) or low risk (<3.4) group considering factors such as tumour size, nodal involvement and tumour grade.

Following on from NPI, Adjuvant Online! and then the PREDICT Breast NHS tool (PREDICT) were developed using national cancer registry data, and utilise clinicopathological factors from the patient and their tumour to estimate individual benefit from chemotherapy (28). PREDICT is the decision tool most commonly in use in Scotland, and is available open access online allowing use in the routine clinical setting. PREDICT has been validated in a Scottish general EBC population (29).

Genomic tests will complement conventional decision tools as they provide independent additional prognostic information. The RS test has been validated for this purpose by *TAILORx* (11), and more recently in the node positive setting by *RxPONDER* (12). It has also been proposed that the RS test may predict which patients benefit more from chemotherapy

The National Institute for Health and Care Excellence Diagnostic Guidance 10/34 (NICE DG10/34) publications assessed current evidence for its use as a prognostic and predictive tool, its clinical utility, decision impact and also its cost effectiveness (10). The prognostic ability of the RS test has been displayed clearly by several studies, with a high score being independently associated with a higher risk of recurrence and hence larger absolute benefit from chemotherapy (11-17).

The prognostic utility of the RS test was also shown across multiple studies (e.g. *WSG-PlanB*), displaying the correlation with increasing score and poorer prognosis (18-21). Whilst a low or high RS is clearly able to differentiate between patients with a high risk of recurrence and a low risk of recurrence, it is less clear for scores between 18-30 where the risk of recurrence is less certain. This led to further assessment in the *TAILORx* study.

TAILORx was a large prospective trial that assessed the clinical validity of the RS test (11). Patients had a RS test performed on their tumour sample post operatively and were split into 3 groups. Group 1 (RS 0-10) received

endocrine therapy alone. Group 2 (RS 11-25) received endocrine therapy or chemoendocrine therapy by randomisation. Group 3 (RS >25) were registered to receive chemoendocrine therapy but were not randomised. The trial assessed both the predictive and prognostic ability of the RS test, concluding that for patients <50 years of age chemotherapy likely would have benefit in the intermediate score (11-25) range. For patients >50 years of age, a score of 25 or less indicated that chemotherapy is not required. TAILORx therefore provided a crucial insight into the cut offs for low or high risk of recurrence with regards to the RS test, and showed that it was likely to be age dependent.

The decision impact of the RS test was also shown across a number of UK and EU based studies which compared post-test chemotherapy decisions with a hypothetical pre-test decision (19-28, 30-35). A change in treatment was found across all of these studies, suggesting an impact of genomic testing as a decision tool in determining chemotherapy administration. Additionally, cost effectiveness was displayed across many studies, subject to a range of test price discounts (36-46).

RxPONDER has recently been published as a follow-on trial after *TAILORx* in the node positive setting. Retrospective analysis from the *SWOG 8814* trial had suggested a predictive utility in the node positive (1-3 nodes) setting for the RS test (15, 16). The *RxPONDER* trial randomised patients with a low RS test (0-25) to endocrine or chemoendocrine therapy. The initial interim analysis found that patients with a low recurrence score in the postmenopausal group could safely avoid chemotherapy, but that an intermediate (11-25) score group exists for premenopausal patients where chemoendocrine therapy is still indicated. The effects of ovarian function suppression (OFS) were not directly assessed and may have been a confounding factor. There were 16% of patients in the endocrine arm that had OFS, but only 3% in the chemoendocrine arm (12).

Based on a review of the evidence behind the RS test, Health Improvement Scotland (HIS) recommended its use throughout NHS Scotland and have included in an update its use in patients with up to 3 positive lymph nodes. The updated recommendation also suggests that the RS test is used for patients who have intermediate risk scores either from NPI or from PREDICT, and that the test is unlikely to derive additional benefit for patients in the low risk or high risk setting (1). Since the initial recommendation, there have been several large real world retrospective studies that have investigated the RS test.

A large study by *L. M. McSorley et al* assessing the experience of the RS test across Ireland was published recently (30). They included 963 patients between October 2011 and February 2019 who were node negative and hormone receptor positive, and had the RS test, were analysed. They found that 62.5% had a change in treatment due to the RS test and were switched to endocrine therapy only. Cost analysis was performed with a predicted estimate of 1.9 million Euros saved and 73% of patients avoiding chemotherapy.

There have been two retrospective studies by *C. Markopoulos et al*, published in 2016 and then in 2019 with updated data (46, 47). They looked at the health economics of using genomic decision tools and showed a possible relationship between the steroid receptor status and the RS test.

Materials/Methods

Patients throughout NHS Scotland who received an RS test as part of their decision-making regarding adjuvant therapy for EBC were included. We retrospectively collected all 833 consecutive patients between August 2018 – August 2021. The patient list was accessed via the company *Exact Science*, which provides the RS test for NHS Scotland. This was the only involvement of industry in the study.

Patient demographics (*Table 1*) were collected along with details of their treatment decisions and their tumour pathology. The data was collated anonymously on *Excel* by a group of collaborating clinicians, located in the different health boards covering all of Scotland, agreeing on variables to be included prior to any data collection to unify the data and avoid missing data points. After successful Caldicott approval and completion of the data collection locally, data was anonymised and collated in an overall national master database for analysis. The database was analysed on *R v4.1.0* with descriptive statistics and logistic regression being performed.

Tables were created using the `gtsummary` package on R, with p values calculated using either Pearson's Chi-squared, Fisher's exact or Wilcoxon rank sum tests depending on distribution and size of the variables. The Charlson Comorbidity Index was calculated, excluding the index breast cancer diagnosis, using an online calculator (<https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci>). Boxplots show univariate assessment of the RS and covariates, with either a T Test, Wilcoxon rank sum or an ANOVA test used to calculate p values depending on distribution of the variable and number of groups involved.

PREDICT scores were calculated using the NHS online tool (<https://breast.predict.nhs.uk/>) based on each patient's clinicopathological parameters. The PREDICT scores were split into risk categories <3% (low risk), 3-5% (intermediate risk) and >5% (high risk) absolute benefit from chemotherapy at 10 years.

To further investigate the relationship between variables and the RS we constructed a multivariate logistic regression model. The outcome variable was RS and was split into either ≤ 25 or > 25 . We constructed this model for the whole cohort, and also for the low risk (<3%) PREDICT group to investigate further the small number of high risk RS patients.

Results

Demographics

Patient demographics split into treatment categories are available on *Table 1*, with statistically significant results indicated in bold. A total of 833 patients were analysed with 70% of patients having endocrine therapy alone, and 30% having chemotherapy in addition to endocrine therapy. There were 76% of patients with a PREDICT Breast score of >3% estimated 10 year mortality benefit from chemotherapy, for whom chemotherapy would be routinely considered. The median age and IQR in the endocrine therapy alone group was higher at 57 (49-64) vs 53 (46-61) in the chemoendocrine group ($p < 0.001$). The Charlson Comorbidity Index Score was higher in the endocrine group also, reflective of an older patient group ($p < 0.05$). Most of the patients were node negative, but we have a small node positive cohort of 86 patients included for analysis.

Steroid endocrine receptor status was classified as per Allred criteria into strong positive (7-8), moderately positive (3-6) and negative (0-2). The RS test provided the results of the ER and PR single gene scores. For clarity, any use of the terms ER score or PR score in this study pertain to the Allred score provided by routine pathology. The single gene scores will be referenced as the ER or PR single gene score. In this population of early breast cancer, 6.5% of patients were ER score moderately positive. In contrast, 29% of patients had PR score moderately positive and 15% were negative.

PREDICT Breast NHS Score

With regards to PREDICT Breast, 23.6% of patients returned a score of <3%. Of this low risk group normally not offered chemotherapy it was found that 17% received, due to a high RS.

Additional to this finding, 27% of patients returned a PREDICT Breast score >5%. It is expected to discuss chemotherapy in this high risk group (unless contraindicated due to patient comorbidities or otherwise), however 55.2% were given endocrine therapy alone ($p < 0.001$).

Across the >3% group where chemotherapy is discussed, only 33.8% of this group had chemotherapy ($p < 0.001$). This contrasts with the intermediate to high risk RS groups where 73% of patients had chemotherapy. Only 5% of patients with a low risk RS had chemotherapy ($p < 0.001$).

The relationship between PREDICT score and the ER/PR score with the RS is shown in *Figure 1*. *Boxplots A and B* show the influence both scores have on treatment, with the RS having a much stronger relationship ($p < 0.001$). Whilst *Boxplot C* does show that higher RS is associated with high risk PREDICT score >5%, there is not a clear separation and the distribution of the low risk <3% group does cross into high RS values.

The relationship with the ER/PR score and the RS is shown on *Boxplots D and E*. Moderately positive ER/PR score and negative PR score is associated with a high RS ($p < 0.001$).

Figure 2 displays the *Scatterplots G and H*, showing the relationship between the single gene scores and the RS. Whilst both are inversely proportional to the RS, the PR single gene score is the strongest predictor (Spearman's correlation coefficient $\rho = -0.66$, $p < 0.001$). *Boxplots I and J* show that the ER/PR scores are directly related to the ER/PR single gene scores.

The relationship between the other covariates and the RS are shown on *Figure 1 & 2 (Boxplots F & K-L)*. Nodal positivity and menopausal status did not seem to influence the RS. Tumour grade 3 and (to a lesser extent) LSVI were associated with high RS, but nevertheless 59% of patients with grade 3 had endocrine therapy alone due to low RS.

Regression Analysis

Table 2 contains the results from the multivariate logistic regression. The influence covariates had on the RS (≤ 25 versus > 25) was analysed.

The factors associated with a low RS were PREDICT $< 3\%$, strong positive ER/PR and classic lobular pathology.

Factors associated with a high risk RS were negative PR score OR 4.49 (2.52 to 8.23, $p < 0.001$) and increasing Grade OR 3.81 (2.10 to 7.09, $p < 0.001$). Nodal stage and menopausal status did not show an association with the RS.

Separate regression analysis on *Table 3* was performed in the $< 3\%$ low risk PREDICT group to assess for factors associated with a high RS (found in 17%).

The factor associated with a high risk RS in the $< 3\%$ group was a negative PR score OR 9.73 (3.14 to 33.4, $p < 0.001$). Again, menopausal status had no association. There were no patients with N1mic with a high RS, in the $< 3\%$ group, so interpretation in this group was difficult and therefore nodal stage was not included in the regression model.

The adoption of the RS test has resulted in a significant change in clinical practice, as evidenced by the difference in chemotherapy administration (30%) compared to the $> 3\%$ PREDICT Breast NHS group (76%), where chemotherapy would be considered. Among the $> 5\%$ high risk PREDICT Breast NHS group (27%), traditionally associated with almost always receiving chemotherapy, endocrine therapy was administered 55.5% of the time. This highlights the substantial clinical impact of the RS test, leading to a reduction in chemotherapy administration by over 50% in the high risk PREDICT group.

Table 1: Patient Demographics by Treatment Received

Variable	N	Treatment Received		p-value
		Chemotherapy, N = 248	Endocrine Alone, N = 585	
Age	833	53 (46 – 61)	57 (49 – 64)	<0.001
Presentation	833			0.30
Screening/Other		128 (28)	325 (72)	
Symptomatic		120 (32)	260 (68)	
Menopausal status	833			0.067
Postmenopausal		152 (28)	397 (72)	
Premenopausal		96 (34)	188 (66)	
Charlson Comorbidity Index Score	833	1.00 (0.00 – 2.00)	2.00 (1.00 – 3.00)	0.014
RS Value	833	31 (27 – 40)	15 (11 – 20)	<0.001
Recurrence Score	833			<0.001
<25		37 (6.3)	546 (94)	
>25		212 (85)	38 (15)	
Predict Score (%)	833	4.72 (3.50 – 6.00)	3.80 (2.90 – 4.71)	<0.001
Predict Score	833			<0.001
<3 (Low risk)		33 (17)	164 (83)	
3-5 (Intermediate risk)		115 (28)	298 (72)	
>5 (High risk)		100 (45)	123 (55)	
NPI score	833	4.44 (4.30 – 4.60)	4.30 (3.70 – 4.48)	<0.001
Tumour Pathology	833			<0.001
Classic Lobular		12 (10)	107 (90)	
Invasive Ductal		223 (36)	397 (64)	
Other		9 (17)	45 (83)	
Pleomorphic Lobular		4 (10)	36 (90)	
Grade (Vertical Proportionality)	833			<0.001
1		0 (0)	4 (0.7)	
2		48 (19.4)	296 (50.6)	
3		200 (80.6)	285 (48.7)	
Tumour size	833	23 (18 – 30)	24 (18 – 34)	0.14
Multi-focal	833	30 (20)	120 (80)	0.004
LVSI	833	95 (37)	163 (63)	0.003
Nodal Stage	833			0.36
N0		216 (30)	497 (70)	
N1		16 (33)	33 (67)	
N1mic		16 (23)	55 (77)	
LN Pathology	132			0.20
ITC		1 (8.3)	11 (92)	
Macrometastasis		16 (33)	33 (67)	
Micrometastasis		16 (23)	55 (77)	
ER score	833			<0.001
Moderately Positive		30 (56)	24 (44)	
Strong Positive		218 (28)	561 (72)	
PR score	833			<0.001
Moderately Positive		98 (41)	140 (59)	
Negative		68 (59)	47 (41)	
Strong Positive		77 (16)	395 (84)	

Unknown		5 (62)	3 (38)	
Type of breast surgery	833			0.28
Breast Conserving Surgery		187 (31)	420 (69)	
Mastectomy		61 (27)	165 (73)	
	833			0.15

Type of axillary surgery

ANC		8 (44)	10 (56)
N/A		0 (0)	2 (100)
SLNB		239 (29)	573 (71)
Unknown		1 (100)	0 (0)

¹Median (IQR); n (%)²Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2: Logistic Regression Analysis of Recurrence Score ≤ 25 vs >25

Characteristic	N	Univariate			Multivariate		
		OR ¹	95% CI ¹	p-value	OR ¹	95% CI ¹	p-value
PREDICT Score	833						
<3		—	—		—	—	
3-5		2.40	1.55 to 3.81	<0.001	2.20	1.23 to 4.01	0.009
>5		4.71	2.96 to 7.67	<0.001	4.22	1.97 to 9.21	<0.001
ER Score	833						
Moderately Positive		—	—		—	—	
Strong Positive		0.29	0.16 to 0.51	<0.001	0.39	0.18 to 0.82	0.014
PR Score	825						
Moderately Positive		—	—		—	—	
Negative		2.78	1.76 to 4.46	<0.001	4.49	2.52 to 8.23	<0.001
Strong Positive		0.26	0.18 to 0.37	<0.001	0.26	0.17 to 0.40	<0.001
Grade	833	7.35	5.01 to 11.1	<0.001	3.81	2.10 to 7.09	<0.001
Tumour Size	833						
<2cm		—	—		—	—	
2-5cm		0.81	0.60 to 1.11	0.20	0.92	0.57 to 1.48	0.73
>5cm		0.29	0.12 to 0.60	0.002	0.43	0.12 to 1.46	0.18
Nodal Stage	833						
N0		—	—		—	—	
N1		0.56	0.26 to 1.11	0.11	0.68	0.25 to 1.73	0.43
N1mic		0.69	0.38 to 1.20	0.20	0.55	0.26 to 1.15	0.12
LVSI	833						
No		—	—		—	—	
Yes		1.66	1.21 to 2.27	0.001	1.35	0.90 to 2.04	0.15
Menopausal status	833						
Postmenopausal		—	—		—	—	
Premenopausal		0.83	0.60 to 1.14	0.25	1.11	0.73 to 1.68	0.63
Tumour Pathology	833						
Classic Lobular		—	—		—	—	
Invasive Ductal		13.6	6.07 to 39.0	<0.001	6.55	2.40 to 21.7	<0.001
Other		3.97	1.26 to 13.7	0.021	2.36	0.61 to 9.78	0.22
Pleomorphic Lobular		3.26	0.86 to 12.3	0.074	1.42	0.33 to 6.09	0.63

¹OR = Odds Ratio, CI = Confidence Interval

Table 3: Logistic Regression Analysis of Recurrence Score ≤ 25 vs >25 in low risk PREDICT $<3\%$

Characteristic	N	Univariate			Multivariate		
		OR ¹	95% CI ¹	p-value	OR ¹	95% CI ¹	p-value
ER Score	197						
Moderately Positive		—	—		—	—	
Strong Positive		0.35	0.11 to 1.38	0.10	0.48	0.10 to 2.57	0.37
PR Score	195						
Moderately Positive		—	—		—	—	
Negative		9.81	3.42 to 30.6	<0.001	9.73	3.14 to 33.4	<0.001
Strong Positive		0.22	0.06 to 0.72	0.017	0.25	0.06 to 0.86	0.034
Grade	197	4.21	1.88 to 9.59	<0.001	1.67	0.45 to 7.34	0.47
Tumour Size	197						
<2cm		—	—		—	—	
2-5cm		0.39	0.16 to 0.86	0.023	0.44	0.11 to 1.79	0.23
LVSI	197						
No		—	—		—	—	
Yes		1.26	0.49 to 2.98	0.61	1.66	0.53 to 5.00	0.37
Menopausal status	197						
Postmenopausal		—	—		—	—	
Premenopausal		0.42	0.15 to 1.04	0.077	0.82	0.23 to 2.74	0.75

¹OR = Odds Ratio, CI = Confidence Interval

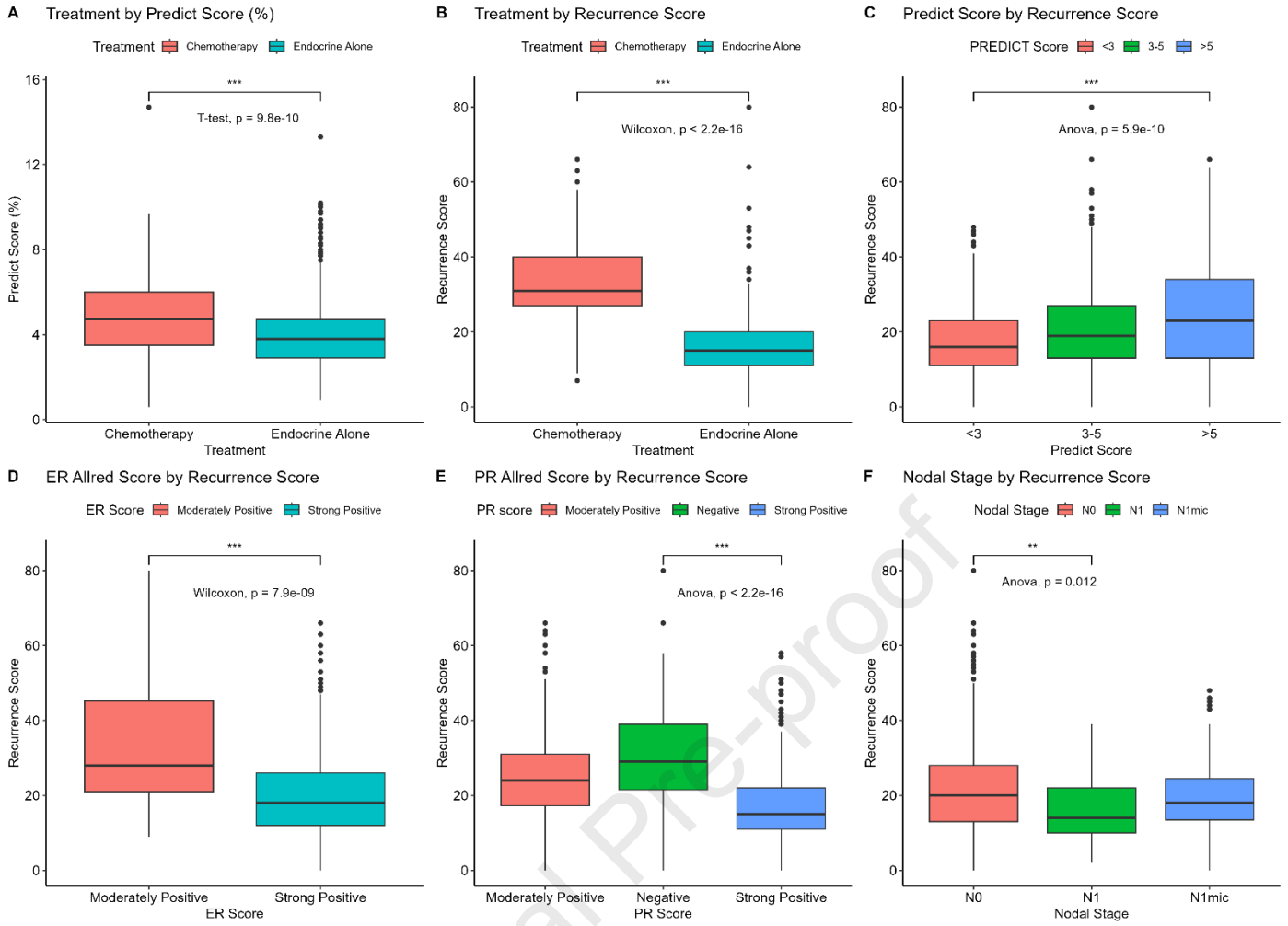


Figure 1: Boxplots A and B show relationship between Predict and Recurrence Score with Treatment. C-E show relationship between Predict score and ER/PR with Recurrence Score. Boxplot F shows relationship between nodal stage and Recurrence Score

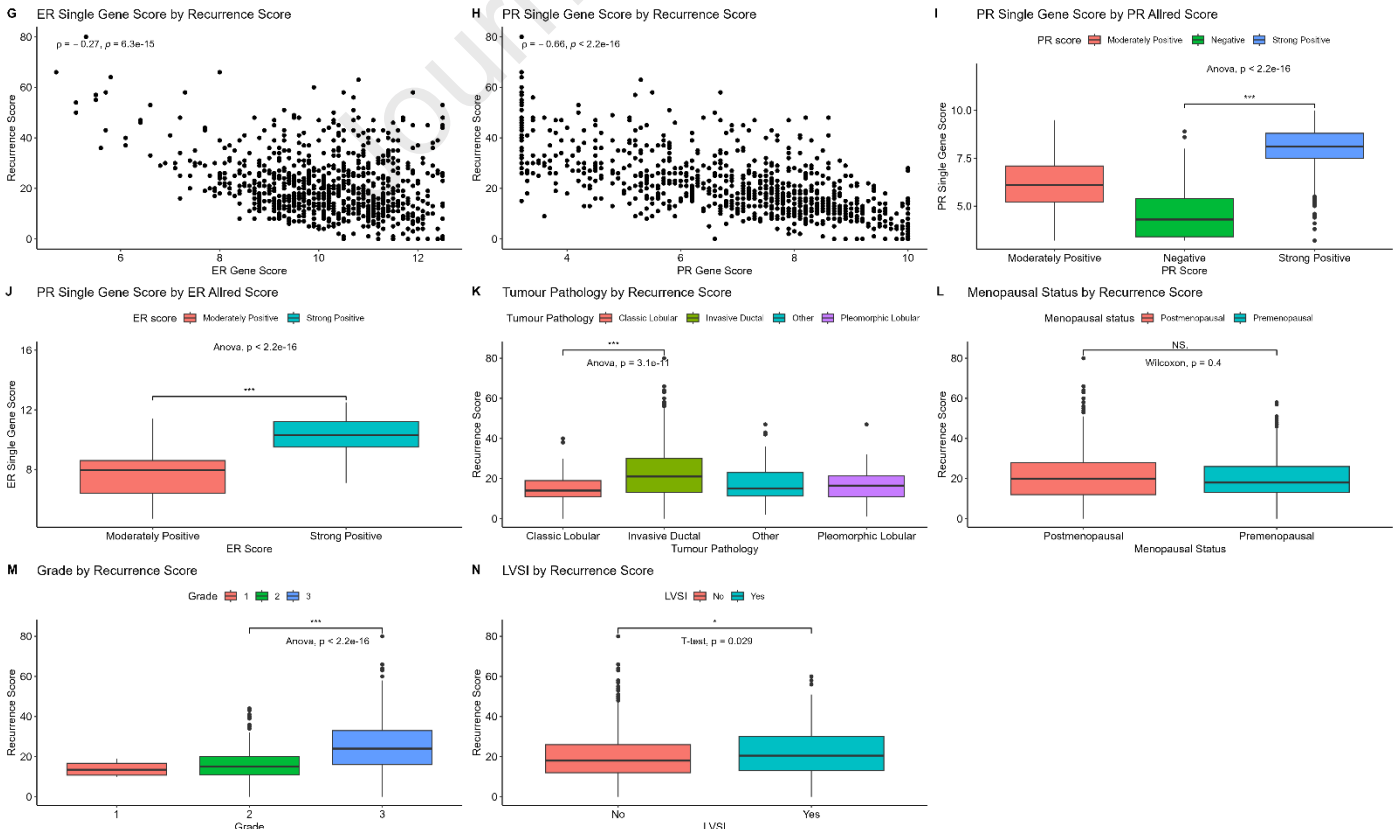


Figure 2: Scatter Plots showing relationship between Single Gene Scores and Recurrence Score with Spearman's correlation coefficient. Boxplots I and J show relationship between the Allred score and the single gene scores. Boxplot K-N shows relationship between other covariates and Recurrence Score

Discussion

This study shows real world population data exhibiting the use of a genomic decision tool in EBC throughout NHS Scotland. The PR score plays a significant role in influencing the risk of recurrence, as demonstrated in this study. It is worth noting that PREDICT does not consider the PR score when calculating risk. In contrast, the RS test provides a more precise assessment through the ER and PR single gene scores. Notably, we found that the PR single gene score exhibits the strongest association in comparison to the ER single gene score.

Through multivariate regression, we have found the PR score to be a strong independent predictor of the RS with an inverse relationship. It has previously been shown to be an independent prognostic variable, with a negative PR score associated with poor prognosis (48). We are not the first to report an association between the PR score and the RS (49-60), however the key Oncotype trials did not look at the PR score and therefore this relationship has only been shown by real world data out with clinical trial settings. We have one of the larger datasets showing this association. Work by Pawloski K *et al* developed a supervised machine learning algorithm with a high degree of accuracy for predicting the RS, with the PR score being the strongest independent predictor (61). The PR score is potentially a cheap and ready for use surrogate marker of the risk of recurrence, and more research to validate this finding is one of the outstanding questions. The recent HIS publication recommending using the RS test only in the intermediate risk PREDICT group makes no mention of incorporating the PR score into this assessment.

Conventional risk assessment tools such as PREDICT and NPI rely on clinicopathological factors. Our study demonstrates a correlation between the PREDICT score and the RS, but this linkage is not strong. It appears that while conventional clinicopathological factors are related to the RS, there is a tendency to overestimate risk, as described earlier. Within the low risk subgroup, we identified a small subset where risk is underestimated, indicated by a high RS, leading to chemotherapy administration. These patients would not have routinely received chemotherapy. This study would support ongoing consideration to use genomic tests in the low and high risk PREDICT groups, especially when the PR score is not strongly positive. A combination approach offered by RSclin, EPclin or Prosignia would appear to be an effective means of assessing risk of recurrence. Whether these tests could be improved by incorporating the PR score is one of the questions this work raises.

The clinical uptake of the test, and its effect on the individualised management of breast cancer patients, has been assessed across all regions of Scotland. Since the publication of *TAILORx*, and NICE DG34/10, the RS test has been adopted throughout NHS Scotland in EBC. The RS test has led to a substantial decrease in chemotherapy administration when compared to PREDICT. This has profound multifactorial implications for service delivery and patient experience.

It is anticipated that genomic tools will increasingly be employed in Oncology across various tumour types. Estimating risk solely based on clinicopathological parameters, such as those used by PREDICT and NPI, is imperfect as they fail to capture the true heterogeneity of genomic and transcriptional expressions that drive tumorigenesis and metastasis. The RS test has demonstrated, particularly through a dedicated retrospective analysis of the TransATAC dataset, the provision of additional prognostic information not offered by current risk assessment tools (2). As previously mentioned we suggest a combined genomic/clinicopathological approach to be the future of breast cancer recurrence risk assessment, and more research is required in this area to develop new tests and validate existing ones.

We assessed the relationship between clinicopathological parameters and the RS. Consistent with findings from the *TAILORx* study (11), we observed that some of these parameters do not correlate with the RS. Specifically, factors such as nodal staging and menopausal status did not demonstrate an association with a high RS in our small node positive group. Our findings align with the initial interim results of the *RxPONDER* study, which suggested that nodal staging may not influence the RS (12). Clinical trials like *POSNO*C are investigating the existence of a low risk node positive group, which could potentially avoid local axillary management if other adjuvant therapies are administered (62).

We found that increasing tumour grade and the presence of lymphovascular space invasion (LVSI) were associated with higher RS, which is in line with expectations as grade reflects cancer cell activity, and the RS test report includes the Ki67 gene. Although PREDICT takes these factors into account, the lack of standardized Ki67 reporting across pathology departments often limits its availability. Perhaps future directions with machine read Ki67, digitalised pathology and potentially AI driven reporting could lead to further improvements. This is clearly another crucial area of future research.

Classic Lobular pathology was shown to be strongly linked to a low RS. It is important to highlight that this study differentiated between classical and pleomorphic lobular subtypes, the latter being known to be more aggressive in nature.

Considering the cost implications of the RS test for the NHS, there may be clinical scenarios where the test could potentially be avoided, and patients could proceed directly to endocrine therapy. For instance, in cases of classic lobular subtype with a strong PR Allred score. However, it is evident that the RS test provides cost-effective benefits by reducing unnecessary chemotherapy administration in many other patient scenarios, particularly the high risk PREDICT group.

Additionally, patients with a low risk PREDICT score should still be considered for the RS test as some patients exhibited a high RS nevertheless. These patients had a RS test mainly due to either an intermediate NPI score or due to the presence of nodal disease. There were 16 patients in our database that did not fit into any of these categories, so the reason for testing is unclear as out with DG34/10 approval and also the updated HIS recommendation; however 4 of these patients did have a high risk RS test. The risk in these seemingly lower-risk patients appeared to be driven by the PR score. This lends further support to the combined approach and the introduction of the forthcoming RSclin test is expected to further enhance treatment decision-making in EBC (63). EPclin and Prosignia clearly also have a role to play in this setting, and more research to delineate the best test moving forward is required.

Further advancements in adjuvant therapy for EBC are anticipated. Targeted therapies like CDK4/6 inhibitors, already extensively used as first-line treatment in advanced hormone-positive breast cancer (64), and antibody-drug conjugates (ADCs) may reshape the adjuvant treatment landscape. Having precise risk assessment tools with robust validation will become increasingly necessary.

Another potential avenue for further research in the RS test landscape is its use in the neoadjuvant setting. Knowing the risk of recurrence preoperatively in the setting of large tumours, or large tumour to breast ratio could be advantageous as we could give downstaging chemotherapy in such cases with confidence that they would have required adjuvant chemotherapy anyway if there was a high risk RS test. Surgical planning for advanced reconstruction can be facilitated by the patient undergoing systemic therapy upfront leading to a more efficient patient cancer treatment journey.

The strengths of this study include the substantial patient population of over 800 patients and its pan-Scotland scope, which helped mitigate regional biases. Limitations of the study include its retrospective nature, absence of recurrence and survival data at present, limiting the analysis to logistic regression. Additionally, accurate recording of ovarian function suppression was not consistent across all regions, but this data will be valuable for future analysis as it matures.

Conclusion

In summary, the implementation of genomic assays in the management of EBC will facilitate personalised decision-making regarding adjuvant therapy by providing accurate information on individual tumour risk for recurrence and metastasis. These assays have the potential to reduce unnecessary chemotherapy administration, especially in the high risk PREDICT group. Additionally, they enable treatment intensification for a subgroup within the low risk PREDICT group who exhibit more adverse genomic tumour biology. The use of genomic decision tools ultimately improves patient outcomes and this study supports their continued use in low and high risk PREDICT settings. Patients with indolent disease can be spared the morbidity of chemotherapy, while those with higher-risk profiles can receive beneficial treatment. This personalised approach enhances overall patient care.

We have found the PR score to be a strong independent predictor of the RS and support other real world studies who have also shown this. This is an area of important future research, and potential incorporation into next generation combined clinical/genomic assays. Work to better stratify which patient groups should receive a RS test could be centred around the PR score on the basis of the strong real world evidence that has emerged.

Moreover, the reduction in chemotherapy observed in this study suggests cost savings for the NHS. This is particularly crucial given the budgetary challenges faced by healthcare systems in addressing the growing complexities of Oncology and other medical fields. A health economic analysis in Scotland is currently on the way.

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Ethical Approval

As this was a retrospective observational study formal ethical approval was not required. However, this work was approved by the local Caldicott Guardian at all regional sites that contributed to the study. The Caldicott Guardian ensures that the information sharing process and handling of any anonymised patient data is upheld to the highest standards.

Declaration of Interests

Dr Adam L Peters has received a travel grant to attend the Royal College of Radiology Clinical Oncology academic training day from the Beatson Cancer Charity

Miss Beatrix Elsberger has had an advisor role with Exact Sciences, and has received a travel grant to attend a meeting in London. The funds received were put back into the departmental pot to help fund a research nurse.

References

1. Kelly, J; Chappell J; Parkinson E; Herbert, P; Stewart, J; Aslam, U. (2023). Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Glasgow/Edinburgh. NHS Healthcare Improvement Scotland. <https://shtg.scot/our-advice/> (accessed on 9/10/2023)
2. Cuzick J, Sestak I, Baum M et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial, *The Lancet Oncology*, Volume 11, Issue 12, 2010, Pages 1135-1141, ISSN 1470-2045, [https://doi.org/10.1016/S1470-2045\(10\)70257-6](https://doi.org/10.1016/S1470-2045(10)70257-6)
3. Cardoso F, Piccart-Gebhart M, Van't Veer L, Rutgers E; TRANSBIG Consortium. The MINDACT trial: the first prospective clinical validation of a genomic tool. *Mol Oncol*. 2007 Dec;1(3):246-51. doi: 10.1016/j.molonc.2007.10.004. Epub 2007 Oct 22. PMID: 19383299; PMCID: PMC5543876.
4. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, Pierga JY, Brain E, Causeret S, DeLorenzi M, Glas AM, Goulinopoulos V, Goulioti T, Knox S, Matos E, Meulemans B, Neijenhuis PA, Nitz U, Passalacqua R, Ravdin P, Rubio IT, Saghatchian M, Smilde TJ, Sotiriou C, Stork L, Straehle C, Thomas G, Thompson AM, van der Hoeven JM, Vuylsteke P, Bernardis R, Tryfonidis K, Rutgers E, Piccart M; MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med*. 2016 Aug 25;375(8):717-29. doi: 10.1056/NEJMoa1602253. PMID: 27557300.
5. Fatima Cardoso, Laura van 't Veer, Coralie Poncet, Josephine Lopes Cardozo, Suzette Delaloge, Jean-Yves Pierga, Peter Vuylsteke, Etienne Brain, Giuseppe Viale, Sherko Kuemmel, Isabel T. Rubio, Gabriele Zoppi, Alastair Mark Thompson, Erika Matos, Khalil Zaman, Florentine Hilbers, Aleksandra Dudek-Perić, Bart Meulemans, Martine J. Piccart-Gebhart, and Emiel J. Rutgers. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. *Journal of Clinical Oncology* 2020 38:15_suppl, 506-506
6. Wallden, B., Storhoff, J., Nielsen, T. et al. Development and verification of the PAM50-based Prosigna breast cancer gene signature assay. *BMC Med Genomics* 8, 54 (2015). <https://doi.org/10.1186/s12920-015-0129-6>
7. Filipits M, Nielsen TO, Rudas M, Greil R, Stöger H, Jakesz R, Bago-Horvath Z, Dietze O, Regitnig P, Gruber-Rossipal C, Müller-Holzner E, Singer CF, Mlineritsch B, Dubsy P, Bauernhofer T, Hubalek M, Knauer M, Trapl H, Fesl C, Schaper C, Ferree S, Liu S, Cowens JW, Gnant M; Austrian Breast and Colorectal Cancer Study Group. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clin Cancer Res*. 2014 Mar 1;20(5):1298-305. doi: 10.1158/1078-0432.CCR-13-1845. Epub 2014 Feb 11. PMID: 24520097.
8. Martin M, Brase JC, Calvo L, Krappmann K, Ruiz-Borrego M, Fisch K, Ruiz A, Weber KE, Munarriz B, Petry C, Rodriguez CA, Kronenwett R, Crespo C, Alba E, Carrasco E, Casas M, Caballero R, Rodriguez-Lescure A. Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM 9906 trial. *Breast Cancer Res*. 2014 Apr 12;16(2):R38. doi: 10.1186/bcr3642. PMID: 24725534; PMCID: PMC4076639.
9. Dubsy P, Brase JC, Jakesz R, Rudas M, Singer CF, Greil R, Dietze O, Luisser I, Klug E, Sedivy R, Bachner M, Mayr D, Schmidt M, Gehrmann MC, Petry C, Weber KE, Fisch K, Kronenwett R, Gnant M, Filipits M; Austrian Breast and Colorectal Cancer Study Group (ABCSG). The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. *Br J Cancer*. 2013 Dec 10;109(12):2959-64. doi: 10.1038/bjc.2013.671. Epub 2013 Oct 24. PMID: 24157828; PMCID: PMC3859949.
10. NICE DG34: Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Diagnostics guidance [DG34]. Published: 19 December 2018 <https://www.nice.org.uk/guidance/DG34> (first accessed 01/05/2022)
11. Sparano J, Gray R, Makower D, Pritchard K, Albain K, Hayes D et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. July 12, 2018. *N Engl J Med* 2018; 379:111-121. DOI: 10.1056/NEJMoa1804710
12. Kalinsky K, Barlow W, Gralow J et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. December 16, 2021. *N Engl J Med* 2021; 385:2336-2347. DOI: 10.1056/NEJMoa2108873
13. Fisher B, Jeong J, Bryant J et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. *The Lancet*, (2004), 858-868, 364(9437). DOI: [https://doi.org/10.1016/S0140-6736\(04\)16981-X](https://doi.org/10.1016/S0140-6736(04)16981-X)
14. Nitz U et al. West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer. *J Clin Oncol* 2019 Apr 1;37(10):799-808. DOI: 10.1200/JCO.18.00028.
15. Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark. Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor-Positive Breast Cancer. *Journal of Clinical Oncology* 2006 24:23, 3726-3734. DOI: 10.1200/JCO.2005.04.7985

16. Albain K, Barlow W, Shak S et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *The Lancet Oncology*, (2010), 55-65, 11(1). [https://doi.org/10.1016/S1470-2045\(09\)70314-6](https://doi.org/10.1016/S1470-2045(09)70314-6).
17. Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004 Dec 30;351(27):2817-26. DOI: 10.1056/NEJMoa041588.
18. Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006 Aug 10;24(23):3726-34. DOI: 10.1200/JCO.2005.04.7985
19. Sparano J, Gray R, Ravdin P et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. *New England Journal of Medicine*, (2019), 2395-2405, 380(25). <https://doi.org/10.1056/NEJMoa1904819>
20. GN Hortobagyi, S Shak, GW Sledge, EP Winer, KS Albain, EP Mamounas, DM Jakubowski, VI Petkov, N Wolmark; Abstract P3-11-02: Breast cancer-specific mortality (BCSM) in patients (pts) with node-negative (N0) and node-positive (N+) breast cancer (BC) guided by the 21-gene assay: A SEER-genomic population-based study. *Cancer Res* 15 February 2019; 79 (4_Supplement): P3-11-02. <https://doi.org/10.1158/1538-7445.SABCS18-P3-11-02>
21. Roberts, M.C., Miller, D.P., Shak, S. et al. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. *Breast Cancer Res Treat* 163, 303–310 (2017). <https://doi.org/10.1007/s10549-017-4162-3>
22. Stemmer, S.M., Steiner, M., Rizel, S. et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. *npj Breast Cancer* 3, 32 (2017). <https://doi.org/10.1038/s41523-017-0033-7>
23. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019 Aug 1;30(8):1194-1220. doi: 10.1093/annonc/mdz173. Erratum in: *Ann Oncol*. 2019 Oct 1;30(10):1674. Erratum in: *Ann Oncol*. 2021 Feb;32(2):284. PMID: 31161190.
24. Coates A, Winer E, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Annals of Oncology*, (2015), 1533-1546, 26(8). DOI: 10.1093/annonc/mdv221.
25. Ines Vaz-Luis, Rebecca A. Ottesen, Melissa E. Hughes, Rizvan Mamet, Harold J. Burstein, Stephen B. Edge, Ana M. Gonzalez-Angulo, Beverly Moy, Hope S. Rugo, Richard L. Theriault, Jane C. Weeks, Eric P. Winer, and Nancy U. Lin. Outcomes by Tumor Subtype and Treatment Pattern in Women With Small, Node-Negative Breast Cancer: A Multi-Institutional Study. *Journal of Clinical Oncology* 2014 32:20, 2142-2150. DOI : 10.1200/JCO.2013.53.1608
26. Tolaney S, Barry W, Dang C et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *New England Journal of Medicine*, (2015), 134-141, 372(2). doi: 10.1056/NEJMoa1406281
27. Galea, M.H., Blamey, R.W., Elston, C.E. et al. The Nottingham prognostic index in primary breast cancer. *Breast Cancer Res Tr* 22, 207–219 (1992). <https://doi.org/10.1007/BF01840834>
28. Wishart, G.C., Azzato, E.M., Greenberg, D.C. et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. *Breast Cancer Res* 12, R1 (2010). <https://doi.org/10.1186/bcr2464>
29. Gray, E., Marti, J., Brewster, D.H Wyatt JC, Hall PS. et al. Independent validation of the PREDICT breast cancer prognosis prediction tool in 45,789 patients using Scottish Cancer Registry data. *Br J Cancer* 119, 808–814 (2018). <https://doi.org/10.1038/s41416-018-0256-x>
30. McSorley, L.M., Tharmabala, M., Al Rahbi, F. et al. Real-world analysis of clinical and economic impact of 21-gene recurrence score (RS) testing in early-stage breast cancer (ESBC) in Ireland. *Breast Cancer Res Treat* 188, 789–798 (2021). <https://doi.org/10.1007/s10549-021-06211-w>
31. Crolley VE, Marashi H, Rawther S, Sirohi B, Parton M, Graham J, Vinayan A, Sutherland S, Rigg A, Wadhawan A, Harper-Wynne C, Spurrell E, Bond H, Raja F, King J. The impact of Oncotype DX breast cancer assay results on clinical practice: a UK experience. *Breast Cancer Res Treat*. 2020 Apr;180(3):809-817. doi: 10.1007/s10549-020-05578-6. Epub 2020 Mar 13. PMID: 32170635; PMCID: PMC7103011.
32. Maria Vittoria Dieci, Valentina Guarneri, Fable Zustovich, Marta Mion, Paolo Morandi, Emilio Bria, Laura Merlini, Pierluigi Bullian, Cristina Olinari, Stefania Gori, Tommaso Giarratano, Enrico Orvieto, Gaia Griguolo, Silvia Michieletto, Tania Saibene, Paola Del Bianco, Gian Luca De Salvo, PierFranco Conte, on behalf of the Veneto Oncology Network, Impact of 21-Gene Breast Cancer Assay on Treatment Decision for Patients with T1–T3, N0–N1, Estrogen Receptor-Positive/Human Epidermal Growth Receptor 2-Negative Breast Cancer: Final Results of the Prospective Multicenter ROXANE Study, *The Oncologist*, Volume 24, Issue 11, November 2019, Pages 1424–1431, <https://doi.org/10.1634/theoncologist.2019-0103>
33. Shelly S. Lo, Patricia B. Mumby, John Norton, Karen Rychlik, Jeffrey Smerage, Joseph Kash, Helen K. Chew, Ellen R. Gaynor, Daniel F. Hayes, Andrew Epstein, and Kathy S. Albain. Prospective multicenter study of the impact of the 21-

- gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *Journal of Clinical Oncology* 2010 28:10, 1671-1676. <https://doi.org/10.1200/JCO.2008.20.2119>
34. Mashuk Alam Khan, Laura Henderson, Dayalan Clarke, Simon Harries, Lucie Jones; The Warwick Experience of the Oncotype DX® Breast Recurrence Score® Assay as a Predictor of Chemotherapy Administration. *Breast Care* 29 October 2018; 13 (5): 369–372. <https://doi.org/10.1159/000489131>
 35. Albanell J, Svedman C, Gligorov J et al. Pooled analysis of prospective European studies assessing the impact of using the 21-gene Recurrence Score assay on clinical decision making in women with oestrogen receptor–positive, human epidermal growth factor receptor 2–negative early-stage breast cancer. *European Journal of Cancer*, (2016), 104-113, 66. <https://doi.org/10.1016/j.ejca.2016.06.027>
 36. Stein RC, Dunn JA, Bartlett JM, Campbell AF, Marshall A, Hall P, Rooshenas L, Morgan A, Poole C, Pinder SE, Cameron DA, Stallard N, Donovan JL, McCabe C, Hughes-Davies L, Makris A; OPTIMA Trial Management Group. OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer. *Health Technol Assess*. 2016 Feb;20(10):xxiii-xxix, 1-201. doi: 10.3310/hta20100. PMID: 26867046; PMCID: PMC4781175.
 37. Hall P, Smith A, Hulme C et al. Analysis of Multiparameter Tests for Chemotherapy in Early Breast Cancer: The OPTIMA Prelim Trial. *Value in Health*, (2017), 1311-1318, 20(10). DOI: 10.1016/j.jval.2017.04.021
 38. Angela Mariotto, Jinani Jayasekera, Valentina Petkov, Clyde B Schechter, Lindsey Enewold, Kathy J Helzlsouer, Eric J Feuer, Jeanne S Mandelblatt, Expected Monetary Impact of Oncotype DX Score-Concordant Systemic Breast Cancer Therapy Based on the TAILORx Trial, *JNCI: Journal of the National Cancer Institute*, Volume 112, Issue 2, February 2020, Pages 154–160, <https://doi.org/10.1093/jnci/djz068>
 39. Harnan S, Tappenden P, Cooper K, Stevens J, Bessey A, Rafia R, Ward S, Wong R, Stein RC, Brown J. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: a systematic review and economic analysis. *Health Technol Assess*. 2019 Jun;23(30):1-328. doi: 10.3310/hta23300. PMID: 31264581; PMCID: PMC6627008.
 40. Smyth, L., Watson, G., Walsh, E.M. et al. Economic impact of 21-gene recurrence score testing on early-stage breast cancer in Ireland. *Breast Cancer Res Treat* 153, 573–582 (2015). <https://doi.org/10.1007/s10549-015-3555-4>
 41. National Centre for Pharmacoeconomics (2011) Cost-effectiveness of Oncotype DX® to target chemotherapy use in lymph node-negative, oestrogen-receptor-positive, early-stage breast cancer in Ireland. <http://www.ncpe.ie/wp-content/uploads/2011/10/Oncotype-DX-summary1.pdf>. Accessed 15th April 2022
 42. Klang SH, Hammerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. *Value Health*. 2010 Jun-Jul;13(4):381-7. doi: 10.1111/j.1524-4733.2010.00724.x. Epub 2010 Apr 15. PMID: 20412544.
 43. Plun-Favreau J, Suarez S, Chivardy H, et al. Cost-Effectiveness Analysis Of The Use Of Oncotype Dx To Guide Adjuvant Chemotherapy Decisions In Breast Cancer Patients In Mexico. *Value in Health*, (2013), A140, 16(3). DOI: 10.1016/j.jval.2013.03.684.
 44. Yamauchi, H., Nakagawa, C., Yamashige, S. et al. Societal cost-effectiveness analysis of the 21-gene assay in estrogen-receptor–positive, lymph-node–negative early-stage breast cancer in Japan. *BMC Health Serv Res* 14, 372 (2014). <https://doi.org/10.1186/1472-6963-14-372>
 45. Daphne T. Tsoi, Miho Inoue, Catherine M. Kelly, Sunil Verma, Kathleen I. Pritchard, Cost-Effectiveness Analysis of Recurrence Score-Guided Treatment Using a 21-Gene Assay in Early Breast Cancer, *The Oncologist*, Volume 15, Issue 5, May 2010, Pages 457–465, <https://doi.org/10.1634/theoncologist.2009-0275>
 46. Markopoulos C, van de Velde C, Zarca D et al. Clinical evidence supporting genomic tests in early breast cancer: Do all genomic tests provide the same information? *EJSO* 2017. *European Journal of Surgical Oncology (EJSO)*, (2017), 909-920, 43(5). <https://doi.org/10.1016/j.ejso.2016.08.012>
 47. Markopoulos C, Hyams D, Gomez H et al. Multigene assays in early breast cancer: Insights from recent phase 3 studies. *European Journal of Surgical Oncology*, (2020), 656-666, 46(4). <https://doi.org/10.1016/j.ejso.2019.10.019>
 48. Purdie CA, Quinlan P, Jordan LB, Ashfield A, Ogston S, Dewar JA, Thompson AM. Progesterone receptor expression is an independent prognostic variable in early breast cancer: a population-based study. *Br J Cancer*. 2014 Feb 4;110(3):565-72. doi: 10.1038/bjc.2013.756. Epub 2013 Dec 3. PMID: 24300977; PMCID: PMC3915123.
 49. Allison, K.H., Kandalaf, P.L., Sitlani, C.M. et al. Routine pathologic parameters can predict Oncotype DXTM recurrence scores in subsets of ER positive patients: who does not always need testing?. *Breast Cancer Res Treat* 131, 413–424 (2012). <https://doi.org/10.1007/s10549-011-1416-3>
 50. Gagnet, S.; Diorio, C.; Provencher, L.; Mbuya-Bienge, C.; Lapointe, J.; Morin, C.; Lemieux, J.; Nabi, H. Identifying Clinicopathological Factors Associated with Oncotype DX® 21-Gene Recurrence Score: A Real-World Retrospective Cohort Study of Breast Cancer Patients in Quebec City, Canada. *J. Pers. Med.* 2021, 11, 858. <https://doi.org/10.3390/jpm11090858>

51. Ma, S.J., Gill, J., Yendamuri, K. et al. Association of progesterone receptor status with 21-gene recurrence score and survival among patients with estrogen receptor-positive breast cancer. *BMC Cancer* 23, 330 (2023). <https://doi.org/10.1186/s12885-023-10796-4>
52. Kim MC, Kwon SY, Choi JE, Kang SH, Bae YK. Prediction of Oncotype DX Recurrence Score Using Clinicopathological Variables in Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer. *J Breast Cancer*. 2023 Apr;26(2):105-116. <https://doi.org/10.4048/jbc.2023.26.e19>
53. Huang, J.L., Kizy, S., Marmor, S. et al. Tumor grade and progesterone receptor status predict 21-gene recurrence score in early stage invasive breast carcinoma. *Breast Cancer Res Treat* 172, 671–677 (2018). <https://doi.org/10.1007/s10549-018-4955-z>
54. San-Gang Wu, Wen-Wen Zhang, Jun Wang, Chen-Lu Lian, Jia-Yuan Sun, Yong-Xiong Chen, and Zhen-Yu He. Progesterone receptor status and tumor grade predict the 21-gene recurrence score of invasive lobular breast cancer. *Biomarkers in Medicine* 2019 13:12, 1005-1012. DOI: 10.2217/bmm-2019-0209
55. Alkushi A, Omair A, Arabi H, Masuadi E, Abualkhair O. Predictability of 21-Gene Recurrence Score Assay by Using Pathological and Immunohistochemical Parameters in Breast Cancer. *Breast Cancer: Basic and Clinical Research*. 2020;14. doi:10.1177/1178223420977848
56. Stephane Thibodeau, Ioannis A. Voutsadakis. Prediction of Oncotype Dx recurrence score using clinical parameters: A comparison of available tools and a simple predictor based on grade and progesterone receptor, *Hematology/Oncology and Stem Cell Therapy*, Volume 12, Issue 2, 2019, Pages 89-96, ISSN 1658-3876, <https://doi.org/10.1016/j.hemonc.2019.02.001>.
57. Özmen V, Atasoy A, Gökmen E, Özdoğan M, Güler N, Uras C, Ok E, Demircan O, Işıkkdoğan A, Cabioglu N, Şen F, Saip P. Correlations Between Oncotype DX Recurrence Score and Classic Risk Factors in Early Breast Cancer: Results of A Prospective Multicenter Study in Turkey. *J Breast Health*. 2016 Jul 1;12(3):107-111. doi: 10.5152/tjbh.2016.2874. PMID: 28331745; PMCID: PMC5351479.
58. Matthew G. Hanna, Ira J. Bleiweiss, Anupma Nayak, Shabnam Jaffer, "Correlation of Oncotype DX Recurrence Score with Histomorphology and Immunohistochemistry in over 500 Patients", *International Journal of Breast Cancer*, vol. 2017, Article ID 1257078, 6 pages, 2017. <https://doi.org/10.1155/2017/1257078>
59. Lashen, A., Toss, M.S., Fadhil, W., Oni, G., Madhusudan, S. and Rakha, E. (2023), Evaluation oncotype DX® 21-gene recurrence score and clinicopathological parameters: a single institutional experience. *Histopathology*, 82: 755-766. <https://doi.org/10.1111/his.14863>
60. Lubna N. Chaudhary, Zeeshan Jawa, Aniko Szabo, Alexis Visotcky, Christopher R. Chitambar. Relevance of progesterone receptor immunohistochemical staining to Oncotype DX recurrence score, *Hematology/Oncology and Stem Cell Therapy*, Volume 9, Issue 2, 2016, Pages 48-54, ISSN 1658-3876. <https://doi.org/10.1016/j.hemonc.2015.12.001>.
61. Pawloski, K.R., Gonen, M., Wen, H.Y. et al. Supervised machine learning model to predict oncotype DX risk category in patients over age 50. *Breast Cancer Res Treat* 191, 423–430 (2022). <https://doi.org/10.1007/s10549-021-06443-w>
62. Goyal A, Dodwell D. POSNOC: A Randomised Trial Looking at Axillary Treatment in Women with One or Two Sentinel Nodes with Macrometastases. *Clinical Oncology*, (2015), 692-695, 27(12). DOI: 10.1016/j.clon.2015.07.005.
63. Sparano JA, Crager MR, Tang G, Gray RJ, Stemmer SM, Shak S. Development and Validation of a Tool Integrating the 21-Gene Recurrence Score and Clinical-Pathological Features to Individualize Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer. *J Clin Oncol*. 2021 Feb 20;39(6):557-564. doi: 10.1200/JCO.20.03007. Epub 2020 Dec 11. PMID: 33306425; PMCID: PMC8078482.
64. Finn R, Martin M, Rugo H, et al. Palbociclib and Letrozole in Advanced Breast Cancer (PALOMA-2). *New England Journal of Medicine*, (2016), 1925-1936, 375(20). <https://doi.org/10.1056/NEJMoa1607303>

1. We present real-world population data from across every region of NHS Scotland, providing valuable insights into the practical implementation of genomic decision tools in the management of early breast cancer
2. Findings from this study show a significant decrease in chemotherapy administration across Scotland as a consequence of the RS test, when compared to conventional risk assessment tools such as PREDICT Breast. There are significant benefits such as reduced cost to the health care system, and a reduction in patient morbidity from chemotherapy associated with this
3. This study highlights the PR score as a strong independent predictor of the RS. Patients with moderately positive or negative PR scores are strongly associated with high RS. An outstanding research question from this study is how the PR score can be used in the future to guide the use of genomic tests, and also direct treatment