Is the 21-Gene Recurrence Score Validated for Real-World use in Node Positive Breast Cancer? A Retrospective UK Cohort Study

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Background & Objectives

Clinical Context
- The 21-gene recurrence score (RS) is used widely to guide adjuvant chemotherapy and endocrine therapy decisions in early ER+/HER2- Breast cancer

Trial-based evidence
- RxPONDER[1] established the prognostic value of RS and informed guideline recommendations in selected node-positive (N+) disease.

Evidence Gap/rationale
- In N+ patients, most data come from highly selected trial populations; UK/NHS real-world evidence on RS, especially for overall survival (OS) and breast cancer-specific mortality, making it unclear how RS should guide chemotherapy in routine practice.
- Interpretation of RS alongside grade, T stage, nodal burden, comorbidity and MDT opinion is variable, and RxPONDER[1] leaves uncertainty around chemotherapy benefit in pre- vs postmenopausal N+ women.
- Within the NHS, chemotherapy plus endocrine therapy (CET), ET alone and ET continuation/adherence differ by menopausal status and RS band.

Aim:
- To validate the prognostic performance of the 21-gene RS in node-positive ER+/HER2− breast cancer in routine NHS practice and describe real-world treatment patterns.

Objectives:
- Assess associations between RS and overall survival, recurrence-free survival and breast cancer–specific mortality.
- Describe use of chemotherapy plus endocrine therapy (CET) vs endocrine therapy (ET) alone across RS bands and menopausal status.
- Explore how RS is used alongside clinicopathological factors and MDT decision-making in N+ patients.

Methods

Design and Setting
- Retrospective single-centre NHS cohort (Norfolk & Norwich University Hospital), ER+/HER2− early breast cancer tested with Oncotype DX®, 2015–2024. Node-positive (N+) patients analysed as a predefined subgroup (n = 282; total cohort n = 789).
- Invasive ER+/HER2− tumour, primary surgery, available Recurrence Score, documented systemic therapy and follow-up; excluded if HER2-positive, no systemic treatment, incomplete data, or lost to follow-up.

Risk bands
- RS 0-10 (Low), RS 11-25 (Intermediate), >= 26 (High), aligned with TAILORx/RxPONDER[1] thresholds

Data sources
- Exact Sciences dataset linked with ICE, MDT/clinic letters, Somerset Cancer Register and EDT to capture tumour features, treatment, recurrence and mortality.

Outcomes
- Overall survival (OS), recurrence-free survival (RFS), and breast cancer-specific mortality (BCSM); events defined as recurrence (local/distant) or breast cancer–related death.

Analysis
- Kaplan–Meier curves with log-rank tests and multivariable Cox regression adjusted for clinicopathological covariates (age, grade, T stage, nodal burden, treatment, etc.).

Pre-specified N+ subgroups
- Menopausal status (premenopausal vs postmenopausal; RxPONDER comparison)
- Treatment modality: Chemotherapy + Endocrine therapy vs Endocrine therapy alone
- Endocrine therapy adherence

Clinicopathological factors
- Tumour size, Age, Grade, Hormone-receptor status, Combined T-stage and Grade

Figure 1. Node-Positive Patients by Oncotype DX Risk Group

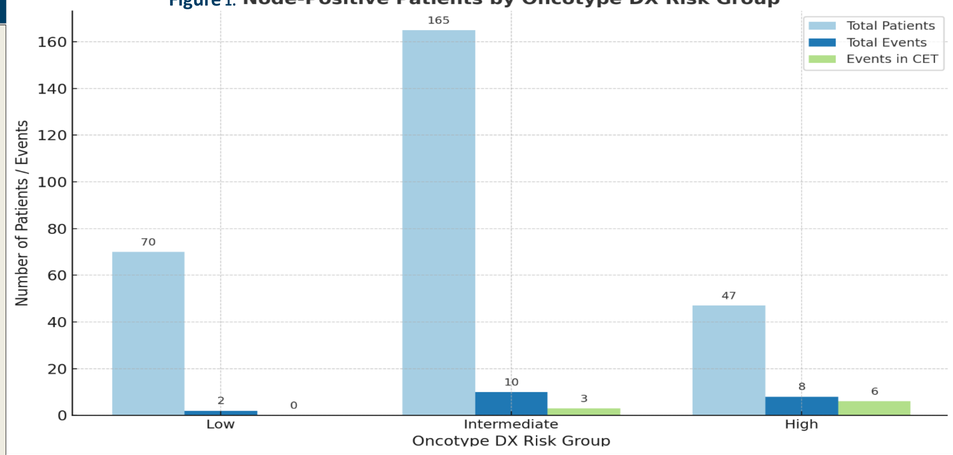
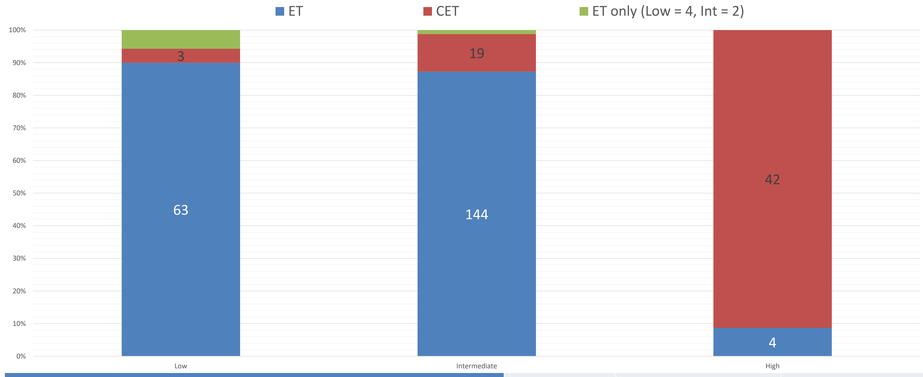


Figure 2: Treatment Usage By Recurrence score groups



High RS vs low (adjusted)	6.59	1.39 - 31.15	0.017
ET continuation vs discontinuation	0.012	0.0006 – 0.225	0.003

Figure 3. Multivariable cox regression for Recurrence score and treatment adherence

Results (n = 282)

Cohort and Events
- 282 N+ patients: Low RS 25% (n = 70), Intermediate 59% (n = 165) and High 17% (n = 47)
- Events (recurrence or breast cancer–related death) occurred in **2/70 low-**, **10/165 intermediate-**, and **8/47 high-risk** patients (Figure 1)

Treatment Patterns by RS
- Most low-risk patients received ET alone (63 ET, 3 CET; 4 declined ET). Only 2 events occurred, both in ET recipients.
- In the intermediate-risk group, ET was predominant (144 ET, 18 CET, 1 CT alone). Ten events were observed (7 ET, 3 CET).
- High-risk patients were almost universally treated with CET (42 CET, 1 CT alone, 4 ET); 8 events occurred (6 CET, 1 CT, 1 ET) (Figure 2).
- Overall, CET use increased with RS (CET in 10.9% intermediate vs 89.4% high-risk N+ patients), reflecting guideline-driven escalation of chemotherapy in high-RS disease.

Survival by recurrence score
- Kaplan–Meier by RS (node-positive) showed clear, graded separation, with worse survival at higher RS (log-rank p = 0.011), confirming the prognostic value of Oncotype DX® in N+ disease.
- CET vs ET curves overlapped with no significant overall survival difference (log-rank p = 0.80): likely reflecting non-random treatment allocation and confounding by indication.

Multivariable cox regression (Figure 3)
- After adjustment for clinicopathological factors, high RS remained strongly associated with worse outcome vs low RS (aHR 6.59, 95% CI 1.39–31.15, p = 0.017).
- Endocrine therapy continuation was associated with a markedly lower hazard compared with discontinuation (aHR 0.012, 95% CI 0.0006–0.225, p = 0.003), highlighting the importance of ET adherence in N+ patients.
- Higher histological grade showed a positive but non-significant association with hazard (Grade 2 aHR 4.34; Grade 3 aHR 3.55), reflecting limited power.

Menopausal Status – Comparison to RxPONDER
- In node-positive patients, CET was associated with better survival in **premenopausal** women, but **no clear benefit** was seen in **postmenopausal** women; perimenopausal results were inconclusive (log-rank p = 0.01).
- This pattern is similar to **RxPONDER**, with limited chemotherapy benefit in postmenopausal N+ patients and greater benefit suggested in premenopausal women.

Conclusions

- The 21-gene Recurrence Score is **prognostic in real-world node-positive ER+/HER2− NHS practice**; high RS is associated with substantially worse outcomes (aHR **6.59** vs low RS).
- Chemotherapy use increases with RS, but in this observational N+ cohort **CET did not show a clear overall survival advantage over ET alone**, likely reflecting confounding by indication.
- **Endocrine therapy continuation is strongly protective**; discontinuation was associated with a markedly higher hazard (aHR **0.012**), underlining the importance of ET adherence.
- In line with **RxPONDER**, chemotherapy benefit appeared **greater in premenopausal** N+ women, with **limited benefit postmenopause**.
- RS should be interpreted alongside clinicopathological factors and menopausal status, with a focus on **optimising ET and individualising chemotherapy decisions** in node-positive disease.

Clinical implications
- Prioritise ET optimisation and adherence in N+ patients across RS bands.
- Use RS with menopausal status and clinicopathological factors to individualise chemotherapy decisions rather than defaulting to CET.

Abbreviations
RS – Recurrence Score
N+ – Node-positive
ET – Endocrine therapy
CET – Chemotherapy plus endocrine therapy
BCSM – Breast cancer-specific mortality
KM – Kaplan–Meier
MDT – Multidisciplinary team

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References: 1. Kalinsky, K. et al. (2021) '21-gene assay to inform chemotherapy benefit in node-positive breast cancer', New England Journal of Medicine, 385(25), pp. 2336–2347. Available at: https://doi.org/10.1056/NEJMoa2108873.