

Review began 07/17/2022  
Review ended 07/26/2022  
Published 07/27/2022

© Copyright 2022  
Saad Abdalla Al-Zawi et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

# The Oncotype DX Recurrence Score's Impact on the Management of Oestrogen-Positive/Human Epidermal Growth Factor Receptor 2-Negative, Low-Burden Axillary Status Breast Cancer (REHAB Study): Results of a Single Centre

Abdalla Saad Abdalla Al-Zawi <sup>1, 2, 3</sup>, Su-Lei Yin <sup>4</sup>, Bayan Mahmood <sup>4</sup>, Awais Jalil <sup>4</sup>, Zina Aladili <sup>4</sup>

1. General and Breast Surgery, Mid and South Essex University Hospitals Group, Basildon, GBR 2. General and Breast Surgery, Basildon and Thurrock University Hospital, Basildon, GBR 3. General and Breast Surgery, Anglia Ruskin University, Chelmsford, GBR 4. Oncology, Southend University Hospital, Southend-on-Sea, GBR

Corresponding author: Abdalla Saad Abdalla Al-Zawi, [abdalasaad@gmail.com](mailto:abdalasaad@gmail.com)

---

---

## Abstract

### Background

The Oncotype DX Recurrence Score (ODX-RS) is increasingly utilized in oestrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative, low-burden axillary disease early operable breast cancer. It has been demonstrated to predict the benefits of adjuvant chemotherapy, hence supporting individualized decisions on adjuvant therapy.

### Aim

To investigate the application of ODX-RS as an adjuvant treatment decision tool in breast cancer operated in our unit.

### Methods

A total of 107 eligible patients who were operated on between 2017 and 2021 in Basildon University Hospital, UK were enrolled in this study. In this retrospective study, the clinical data, including patient's age, tumour size, ER status, HER2 status, Ki67 proliferative index (Ki67-PI), nodal status, tumour grade, and ODX-RS, were collected. In the study design, the oncologist had the opportunity to assess the need for adjuvant chemotherapy for patients with ER-positive, HER2-negative, low-burden axillary lymph node disease, early breast cancer by using tumour characteristics and the PREDICT tool without knowing the ODX-RS results. The clinician's decision was matched against the breast multidisciplinary team's recommendations after ODX-RS utilisation, and the results were explored.

### Results

The median ODX-RS of cohort tumours was 18 in the age group > 50 years, with ODX-RS  $\geq$  26 found in 18% of the group (n = 12). In the age group  $\leq$  50 years, 17% (n = 7) had ODX-RS between 21 and 25 and only 7% (n = 3) had ODX-RS  $\geq$  26. Without using ODX-RS, only 16% of the patients had been offered adjuvant chemotherapy in addition to the hormonal manipulation therapy; however, after using ODX-RS, up to 33% of the cohort was suitable for adjuvant chemotherapy in addition to the hormonal manipulation therapy. The changes in the recommendations after ODX-RS utilisation have been noticed in 29% of the cohort.

### Conclusion

This study revealed that ODX-RS supported decision-making regarding postoperative adjuvant chemotherapy, especially when other tumour biomarkers, such as tumour size, grading, or Ki-67, indicated lower risk criteria. Patients with a high ODX-RS were offered chemotherapy where appropriate and its use led to a 15% rate of initial decision change in adjuvant treatment decisions; this involved either recommending chemotherapy or its omission.

---

**Categories:** Genetics, Pathology, Oncology

**Keywords:** axillary lymph node metastasis, human epidermal growth factor receptor-2, oestrogen receptors, chemotherapy, oncotype dx recurrence score, breast cancer

## Introduction

The Oncotype DX Recurrence Score (ODX-RS) has been considered a crucial element in the management pathway of oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative,

### How to cite this article

Saad Abdalla Al-Zawi A, Yin S, Mahmood B, et al. (July 27, 2022) The Oncotype DX Recurrence Score's Impact on the Management of Oestrogen-Positive/Human Epidermal Growth Factor Receptor 2-Negative, Low-Burden Axillary Status Breast Cancer (REHAB Study): Results of a Single Centre. *Cureus* 14(7): e27341. DOI 10.7759/cureus.27341

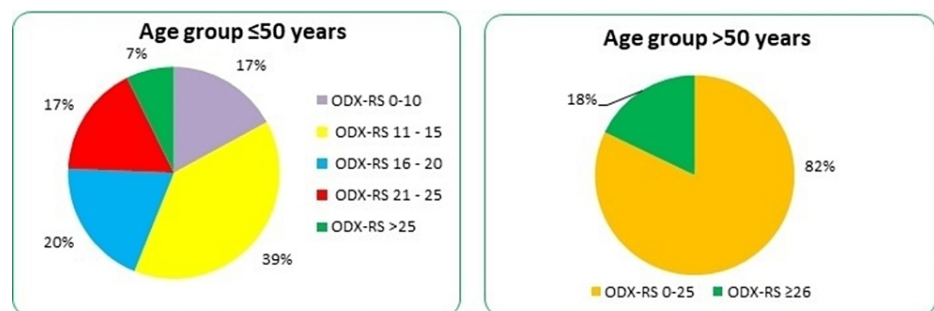
lymph node-negative/micrometastasis/N1 (one to three nodes positive) early invasive breast cancer and aids the physician to predict which patients would attain minimal or no benefit from adjuvant chemotherapy and would be safely spared from its adverse effects, without compromising outcomes [1]. On the other hand, it informs the physician about the patients associated with a higher risk of disease recurrence, and these patients will benefit from adjuvant chemotherapy in addition to hormonal manipulation treatment [2].

## Materials And Methods

In this study, 107 patients who were operated on between 2017 and 2021 in Basildon University Hospital, UK were enrolled. This is a retrospective study where the clinical data, including patient's age, tumour size, ER status, HER2 status, Ki67 proliferative index (Ki67-PI), nodal status, tumour grade, and ODX-RS, were collected. In the study design, the oncology team had the opportunity to assess patients' need for adjuvant chemotherapy in addition to hormonal manipulation treatment by using tumour biological characteristics and the PREDICT tool. For the study cohort, the pre-ODX-RS adjuvant treatment oncologist's recommendation was matched against the breast multidisciplinary team's decision after using the ODX-RS results, and the data were analysed.

## Results

Among the eligible 103 breast cancer patients, five had bilateral disease. The mean age was  $55.8 \pm 10.07$  years. The total excised tumours were 108 lesions. Of them, 87% were T2 tumours, 8% were T1 tumours, and only 4.6% were T3 tumours. About 39% ( $n = 40$ ) of the patients belonged to the age group  $\leq 50$  years, whereas 61% ( $n = 63$ ) aged  $> 50$  years. The median ODX-RS of cohort tumours was 18 (range: 0-73). In the age group  $> 50$  years, ODX-RS results were as follows:  $\leq 25$  ( $n = 55$ , 82%) and  $\geq 26$  ( $n = 12$ , 18%) (Figure 1). In the age group  $\leq 50$  years, 17% of patients ( $n = 7$ ) had ODX-RS of  $< 11$ , 39% ( $n = 16$ ) had ODX-RS between 11 and 15, 20% ( $n = 8$ ) had ODX-RS between 16 and 20, 17% ( $n = 7$ ) had ODX-RS between 21 and 25, and only 7% ( $n = 3$ ) had ODX-RS  $\geq 26$  (Figure 1).

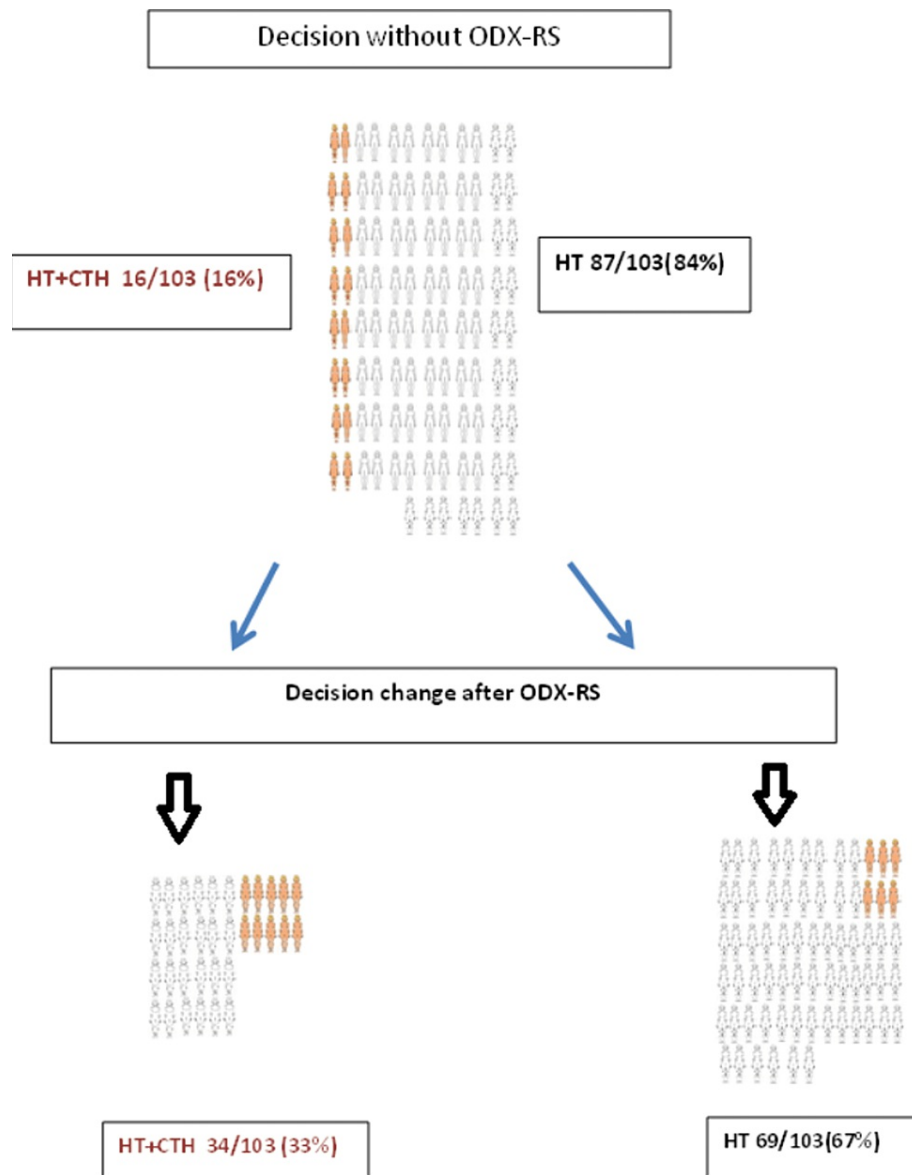


**FIGURE 1: The ODX-RS results in the cohort according to the age groups.**

ODX-RS: Oncotype DX Recurrence Score.

In the cohort, 29 tumours (27.1%) showed borderline HER2 expression, approximately 55% of them were associated with lower Ki-67 ( $p = 0.63$ ), and 93.1% ( $n = 27$ ) of them had T2 tumour grade. Also, in the total cohort, the majority of the tumours (87%) were T2. Without knowing the ODX-RS results, the PREDICT tool was used to aid the physician in adjuvant chemotherapy decision-making. The results at this stage showed that only 16% of the patients could be offered adjuvant chemotherapy in addition to hormonal manipulation therapy. Those recommendations were matched against the multidisciplinary team's decisions after testing the ODX-RS.

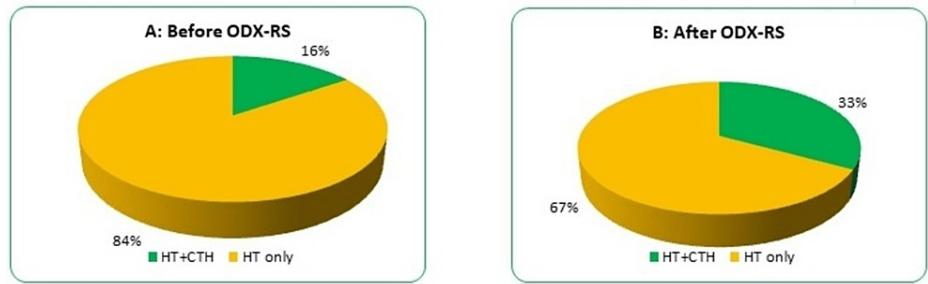
About 16% of the patients were recommended for hormone therapy + chemotherapy before ODX-RS utilisation, and 62% of them had their treatment changed to hormone therapy only after ODX-RS utilisation. On other hand, 84% ( $n = 87$ ) of the cohort had recommendations for hormone therapy only before ODX-RS utilisation, and 28% of them ( $n = 24$ ) had treatment changed to hormone therapy + chemotherapy after ODX-RS utilisation (Figure 2).



**FIGURE 2: Adjuvant treatment recommendation change after ODX-RS utilisation.**

ODX-RS: Oncotype DX Recurrence Score; CTH: chemotherapy; HT: hormone therapy.

The changes in the recommendations after ODX-RS utilisation have been noticed in 29% of the total cohort. Finally, in this study, up to 33% of the cohort was suitable for adjuvant chemotherapy in addition to hormonal manipulation (Figure 3).



**FIGURE 3: Impact of ODX-RS on breast cancer management.**

(A) Recommendation before ODX-RS. (B) Change in treatment recommendation after ODX-RS.

ODX-RS: Oncotype DX Recurrence Score; CTH: chemotherapy; HT: hormone therapy.

The authors analysed the impact of Ki67-PI on such a situation, and the 10% value has been used as a cut-off point. The results of  $\leq 10\%$  were categorised as low expression and values of  $>10\%$  were classified as high Ki67-PI. In the group with low Ki67-PI expression, about 14% had chemotherapy recommended/offered without knowing ODX-RS results; this has been reduced to 10% only after using ODX-RS (Figure 4).



**FIGURE 4: Pre and post-ODX-RS adjuvant treatment recommendations in patients with low Ki-67 proliferation index.**

ODX-RS: Oncotype DX Recurrence Score; CTH: chemotherapy; HT: hormone therapy.

In the category of high Ki67-PI, only 17% had chemotherapy recommended/offered without knowing ODX-RS results; this has changed to 37% after using ODX-RS ( $p = 0.89$ ) (Figure 5).



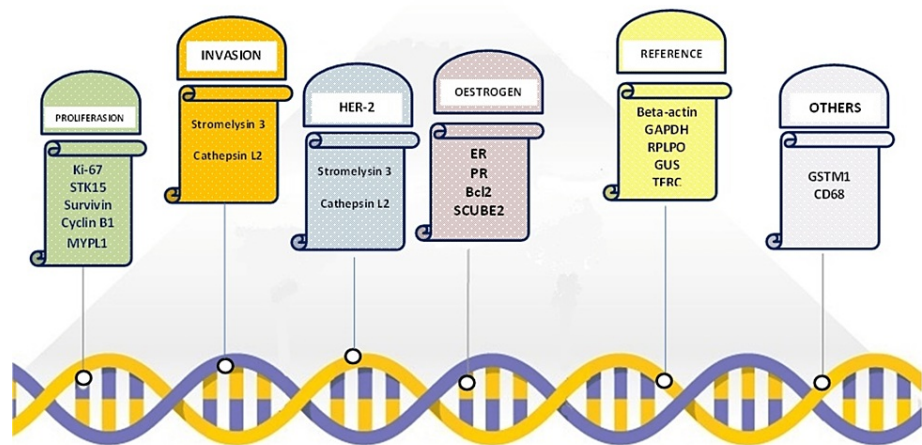
**FIGURE 5: Pre and post-ODX-RS adjuvant treatment recommendations in patients with high Ki-67 proliferation index.**

ODX-RS: Oncotype DX Recurrence Score; CTH: chemotherapy; HT: hormone therapy.

About 10% of patients with low Ki67-PI showed a high ODX-RS; accordingly, chemotherapy had been recommended for them. Also, 8% of the low Ki67-PI group had chemotherapy indicated prior to ODX-RS, and this remained unchanged (ODX-RS ranged between 12 and 24).

## Discussion

Worldwide, breast cancer is the most frequent type of malignancy in females. Its incidence is climbing every year and this trend is expected to continue [3,4]. In the UK, it is recognised as the most common cancer with 55,000 new cases detected every year, and it is responsible for 7% of all cancer deaths [5]. ER-positive, HER2-negative, invasive breast cancer phenotype represents the most common subtype of breast cancer, accounting for 75% of all diagnosed invasive breast cancers [6]. Despite the fact that less than 10% of ER-positive, HER2-negative, low-burden axillary disease, early invasive breast cancers benefit from chemotherapy [7], the utilization of adjuvant chemotherapy in the management of ER-positive early breast cancer has resulted in the reduction of breast cancer-related mortality [8]. These patients may present with locoregional disease (breast with/without early axillary lymph node disease), which would usually suggest a good prognosis. Yet, some of them possess a notable risk of cancer recurrence after treatment [1]. The ODX-RS assay panel is composed of a total of 21 genes. The quantitative analysis of the gene expression involves five reference genes (ACTB, TFRC, GAPDH, GUSB, and RPLP0) and 16 cancer-related genes. The cancer genes are composed of genes that code for HER2 (HER2 and GRB7), oestrogen genes (ER, PGR, BCL2, and SCUBE2), proliferation genes (MKI67, STK15, BIRC5, CCNB1, and MYBL2), and invasion genes (MMP11 and CTSL2) as well as GSTM1, CD68, and BAG1 (Figure 6) [3].

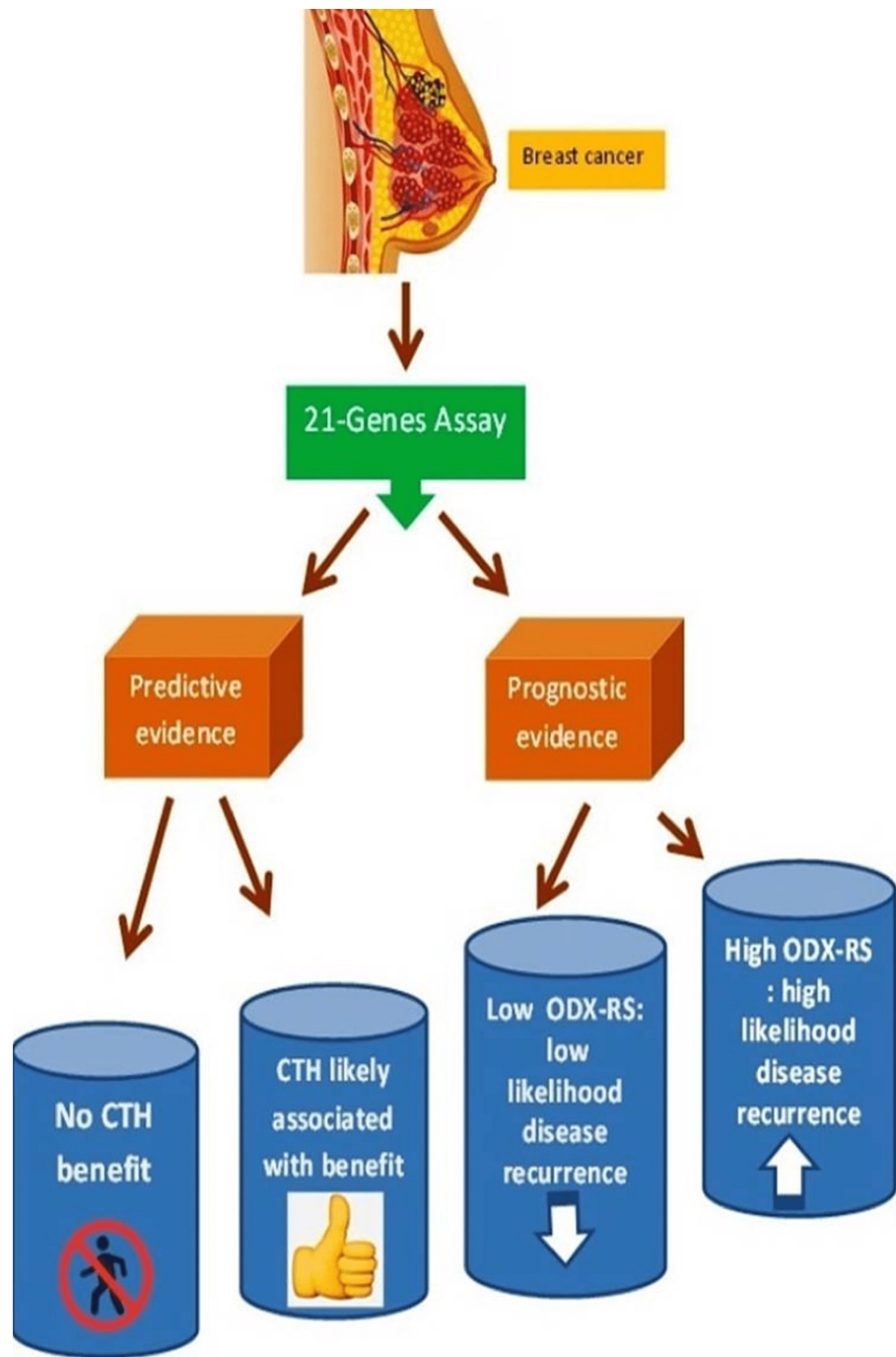


**FIGURE 6: The ODX-RS assay 21-gene panel.**

Adapted from [3].

ODX-RS: Oncotype DX Recurrence Score.

The ODX-RS assay is of both predictive value for potential treatment benefit as well as prognostic merit and provides more information regarding possible management outcomes; broadly speaking, it leads the way towards better treatment individualisation (Figure 7).



**FIGURE 7: The role of ODX-RS in adjuvant chemotherapy decision-making for ER-positive, HER2-negative, low-burden axillary disease, early breast cancer.**

ODX-RS: Oncotype DX Recurrence Score; CTH: chemotherapy; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2.

The HER2-negative subtype of invasive breast cancer includes two genomically distinct categories, labelled as luminal A and luminal B. The latter group has a diminished response to hormonal manipulation therapy and is associated with an inferior prognosis [9]. Therefore, the concealed genetic features of the tumour may be more influential in predicting disease behaviour than the patient’s particular characteristics of the tumour size, grade, and stage at the time of disease presentation. Analysing the results of the Trial Assigning Individualized Options for Treatment-Rx (TAILORx) clinical trial low ODX-RS (<11) arm data from 2015, it was reported that hormonal manipulation treatment alone is associated with good long-term

outcomes; this suggests that patients with low ODX-RS should generally be spared from chemotherapy [10,11].

Nishimura et al. (2010) presented a report related to the clinical significance of Ki67-PI in neoadjuvant chemotherapy for primary breast cancer. The authors reported that the pre-treatment Ki67-PI value prior to the upfront chemotherapy was a critical predictive factor for the effectiveness of neoadjuvant chemotherapy, and the Ki67-PI values after upfront chemotherapy completion were remarkably decreased and correlated with clinical response and disease-free survival (DFS) period; generally speaking, the lower the Ki67-PI value, the longer and favourable the DFS [12,13]. In our study, we have used the 10% value as the Ki67-PI cut-off point. The adjuvant chemotherapy indication has increased by more than 100% after ODX-RS results utilization in the high Ki67-PI group (37% vs. 17%) (Figure 5).

In the TAILORx clinical trial report from 2018, a total of 6711 patients with a midrange ODX-RS between 11 and 25 were enrolled and were randomly assigned to receive either chemo-endocrine therapy or endocrine therapy alone. The authors concluded that adjuvant hormonal manipulation therapy and chemo-endocrine therapy had similar efficacy in patients with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who had a midrange ODX-RS, despite the fact that some benefit of chemotherapy was established in some women of  $\leq 50$  years of age [14]. As we see here, ODX-RS is not solely an indicator of disease prognosis; however, more importantly, it predicts the potential responsiveness for adjuvant chemotherapy.

Ki-67, also known as MKI67 (marker of proliferation Ki-67), is a protein found in actively dividing cells. It is detected in the nuclei of proliferating cells in the G1, S, G2, and M phases of the cell cycle. Its levels are low during the G1 and early S phase, and as the cell division progresses, Ki-67 concentration gradually increases to reach its maximum level during mitosis. For this reason, the Ki67-PI can be a useful marker of cell proliferation [13,15]. The published reports showed that Ki67-PI is related to the disease prognosis and the response to systemic therapy in both the adjuvant and neoadjuvant treatment settings. It is associated with an increased risk of disease recurrence in breast cancer as well as increased breast cancer-related mortality [16].

Walter et al. (2020) presented a retrospective analysis of 4695 patients with hormone receptor-positive and HER2-negative early breast cancer (T1-3: tumour size  $\leq 5$ m; N0-1: node-negative/micrometastasis/one to three nodes positive; M0: no distant metastasis), who had been tested for ODX-RS in Germany in the period between November 2015 and July 2018. The authors were following the TAILORx trial for ODX-RS categorization: low (0-10), midrange (11-25), and high (26-100). The results revealed that 21% of patients were assigned to the low ODX-RS group, 63% to the midrange group, and 15% to the high score group.

The authors also explored the other tumour biomarkers in relation to ODX-RS and found that under the combination of low and midrange ODX-RS groups, there will be 81% of node-negative patients over 50 years of age, 90% of node-positive patients, 79% among tumours with Ki-67-high ( $\geq 20\%$ ), 86% of grade 2 tumours, 70% of grade 3 tumours, 88% of patients with T3 tumours, and 82% among node-negative patients with high-risk tumours. The paper concluded that chemotherapy may not be beneficial in most of the tested groups. Here, we have to highlight the importance of the benefit of the ODX-RS in sparing a good number of patients from the unnecessary adverse effects of chemotherapy [17].

Results of the REHAB study reveal that the utilization of ODX-RS assay has significantly impacted the chemotherapy indication and could lead to a change in adjuvant treatment recommendation in up to 29% of patients for whom the physicians, to begin with, were initially facing uncertainty regarding treatment option based on classical clinical and tumour biological markers. As shown in Table 1, our figures are similar to most of the previously published data [18-30].

Author (year)	Cohort size	Rate
Holt et al. (2013) [18]	142	26.8%
Eiermann et al. (2013) [19]	366	33%
Yamauchi et al. (2014) [20]	124	33%
Jaafar et al. (2014) [21]	47	27.7%
Gligorov et al. (2015) [22]	100	37%
Bargallo et al. (2015) [23]	96	32%
Albanell et al. (2016) [24]	527	32%
Kuchel et al. (2016) [25]	135	22.7%
Levine et al. (2016) [26]	979	38%
Leung et al. (2016) [27]	146	23%
Dieci et al. (2019) [28]	251	30%
Fayaz et al. (2020) [29]	100	37%
Mattar et al. (2021) [30]	179	30%

**TABLE 1: Change in treatment recommendations after ODX-RS utilisation (literature data).**

However, heterogeneity of the results and the differences in rates between the presented cohorts can be accounted for by sample size variation, cohorts' age range, menopausal status, test availability, and patient selection. Also, tumour biomarkers such as grade and size in addition to lymph node status and Ki67-Pi are used as cut-off points. Some authors suggest that some factors such as tumour grade might serve as a guide during decision-making for patients with whom the ODX-RS test can be avoided and just recommend endocrine therapy alone in those low-risk patients; also, they suggest recommending the adjuvant chemotherapy for ER-positive, HER2-negative, N0 high-risk patients without testing the ODX-RS such as those having large, high-grade, or progesterone receptor-negative tumours [26]. Our study was limited, as are others, by the small sample size and lack of long-term patient follow-up in addition to the patient selection issue, especially after the testing for Nmic/N1 patients was introduced into practice.

## Conclusions

This study revealed that ODX-RS supported decision-making regarding postoperative adjuvant chemotherapy, especially when other tumour biomarkers, such as tumour size, grading, and Ki-67, indicated lower risk criteria. Patients with a high ODX-RS were offered chemotherapy where appropriate, and its use led to a 15% rate of change in the adjuvant treatment decision.

## Additional Information

### Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## References

1. Thibodeau S, Voutsadakis IA: The Oncotype DX assay in ER-positive, HER2-negative breast cancer patients: a real life experience from a single cancer center. *Eur J Breast Health.* 2019, 15:163-70. [10.5152/ejbh.2019.4901](https://doi.org/10.5152/ejbh.2019.4901)
2. Durrani S, Al-Mushawa F, Heena H, Wani T, Al-Qahtani A: Relationship of Oncotype DX score with tumor grade, size, nodal status, proliferative marker Ki67 and Nottingham Prognostic Index in early breast cancer tumors in Saudi population. *Ann Diagn Pathol.* 2021, 51:151674. [10.1016/j.anndiagpath.2020.151674](https://doi.org/10.1016/j.anndiagpath.2020.151674)
3. Saad Abdalla Al-Zawi A: The Oncotype DX Recurrence Score impact on the management of ER-positive,



- HER2-negative, node-negative breast cancer. *Med Res J*. 2021, 6:211-6. [10.5603/MRJ.a2021.0041](https://doi.org/10.5603/MRJ.a2021.0041)
4. Schaafsma E, Zhang B, Schaafsma M, Tong CY, Zhang L, Cheng C: Impact of Oncotype DX testing on ER+ breast cancer treatment and survival in the first decade of use. *Breast Cancer Res*. 2021, 23:74. [10.1186/s13058-021-01453-4](https://doi.org/10.1186/s13058-021-01453-4)
  5. Green N, Al-Allak A, Fowler C: Benefits of introduction of Oncotype DX® testing. *Ann R Coll Surg Engl*. 2019, 101:55-9. [10.1308/rcsann.2018.0173](https://doi.org/10.1308/rcsann.2018.0173)
  6. Fallahpour S, Navaneelan T, De P, Borgo A: Breast cancer survival by molecular subtype: a population-based analysis of cancer registry data. *CMAJ Open*. 2017, 5:E734-9. [10.9778/cmajo.20170030](https://doi.org/10.9778/cmajo.20170030)
  7. 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, 24:3726-34. [10.1200/JCO.2005.04.7985](https://doi.org/10.1200/JCO.2005.04.7985)
  8. Siow ZR, De Boer RH, Lindeman GJ, Mann GB: Spotlight on the utility of the Oncotype DX® breast cancer assay. *Int J Womens Health*. 2018, 10:89-100. [10.2147/IJWH.S124520](https://doi.org/10.2147/IJWH.S124520)
  9. Prat A, Pineda E, Adamo B, et al.: Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast*. 2015, 24:S26-35. [10.1016/j.breast.2015.07.008](https://doi.org/10.1016/j.breast.2015.07.008)
  10. Sparano JA, Gray RJ, Makower DF, et al.: Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015, 373:2005-14. [10.1056/NEJMoa1510764](https://doi.org/10.1056/NEJMoa1510764)
  11. Crolley VE, Marashi H, Rawther S, et al.: The impact of Oncotype DX breast cancer assay results on clinical practice: a UK experience. *Breast Cancer Res Treat*. 2020, 180:809-17. [10.1007/s10549-020-05578-6](https://doi.org/10.1007/s10549-020-05578-6)
  12. Nishimura R, Osako T, Okumura Y, Hayashi M, Arima N: Clinical significance of Ki-67 in neoadjuvant chemotherapy for primary breast cancer as a predictor for chemosensitivity and for prognosis. *Breast Cancer*. 2010, 17:269-75. [10.1007/s12282-009-0161-5](https://doi.org/10.1007/s12282-009-0161-5)
  13. Sahebjam S, Aloyz R, Pilavdzic D, et al.: Ki 67 is a major, but not the sole determinant of Oncotype DX Recurrence Score. *Br J Cancer*. 2011, 105:1342-5. [10.1038/bjc.2011.402](https://doi.org/10.1038/bjc.2011.402)
  14. Sparano JA, Gray RJ, Makower DF, et al.: Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018, 379:111-21. [10.1056/NEJMoa1804710](https://doi.org/10.1056/NEJMoa1804710)
  15. Saad Abdalla Al-Zawi A, Yin SL, Aladili Z: Lymphovascular invasion in hormone-positive, human epidermal growth factor-negative, low-burden axillary disease in early breast cancer patients tested for Oncotype DX Recurrence Score. *Contemp Oncol (Pozn)*. 2022, 26:139-43. [10.5114/wo.2022.118220](https://doi.org/10.5114/wo.2022.118220)
  16. Kronqvist P, Kuopio T, Nykänen M, Helenius H, Anttinen J, Klemi P: Predicting aggressive outcome in T1N0M0 breast cancer. *Br J Cancer*. 2004, 91:277-81. [10.1038/sj.bjc.6601948](https://doi.org/10.1038/sj.bjc.6601948)
  17. Walter VP, Taran FA, Wallwiener M, et al.: Distribution of the 21-gene breast recurrence score in patients with primary breast cancer in Germany. *Geburtshilfe Frauenheilkd*. 2020, 80:619-27. [10.1055/a-1111-8734](https://doi.org/10.1055/a-1111-8734)
  18. Holt S, Bertelli G, Humphreys I, et al.: A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pN1mi, ER-positive breast cancer in the UK. *Br J Cancer*. 2013, 108:2250-8. [10.1038/bjc.2013.207](https://doi.org/10.1038/bjc.2013.207)
  19. Eiermann W, Rezaei M, Kümmel S, et al.: The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. *Ann Oncol*. 2013, 24:618-24. [10.1093/annonc/mds512](https://doi.org/10.1093/annonc/mds512)
  20. Yamauchi H, Nakagawa C, Takei H, et al.: Prospective study of the effect of the 21-gene assay on adjuvant clinical decision-making in Japanese women with estrogen receptor-positive, node-negative, and node-positive breast cancer. *Clin Breast Cancer*. 2014, 14:191-7. [10.1016/j.clbc.2013.10.017](https://doi.org/10.1016/j.clbc.2013.10.017)
  21. Jaafar H, Bashir MA, Taher A, Qawasmeh K, Jaloudi M: Impact of Oncotype DX testing on adjuvant treatment decisions in patients with early breast cancer: a single-center study in the United Arab Emirates. *Asia Pac J Clin Oncol*. 2014, 10:354-60. [10.1111/ajco.12259](https://doi.org/10.1111/ajco.12259)
  22. Gligorov J, Pivot XB, Jacot W, et al.: Prospective clinical utility study of the use of the 21-gene assay in adjuvant clinical decision making in women with estrogen receptor-positive early invasive breast cancer: results from the SWITCH study. *Oncologist*. 2015, 20:873-9. [10.1634/theoncologist.2014-0467](https://doi.org/10.1634/theoncologist.2014-0467)
  23. Bargallo JE, Lara F, Shaw-Dulin R, et al.: A study of the impact of the 21-gene breast cancer assay on the use of adjuvant chemotherapy in women with breast cancer in a Mexican public hospital. *J Surg Oncol*. 2015, 111:203-7. [10.1002/jso.23794](https://doi.org/10.1002/jso.23794)
  24. 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. *Eur J Cancer*. 2016, 66:104-13. [10.1016/j.ejca.2016.06.027](https://doi.org/10.1016/j.ejca.2016.06.027)
  25. Kuchel A, Robinson T, Comins C, et al.: The impact of the 21-gene assay on adjuvant treatment decisions in oestrogen receptor-positive early breast cancer: a prospective study. *Br J Cancer*. 2016, 114:731-6. [10.1038/bjc.2016.48](https://doi.org/10.1038/bjc.2016.48)
  26. Levine MN, Julian JA, Bedard PL, et al.: Prospective evaluation of the 21-gene recurrence score assay for breast cancer decision-making in Ontario. *J Clin Oncol*. 2016, 34:1065-71. [10.1200/JCO.2015.62.8503](https://doi.org/10.1200/JCO.2015.62.8503)
  27. Leung RC, Yau TC, Chan MC, et al.: The impact of the Oncotype DX breast cancer assay on treatment decisions for women with estrogen receptor-positive, node-negative breast carcinoma in Hong Kong. *Clin Breast Cancer*. 2016, 16:372-8. [10.1016/j.clbc.2016.03.002](https://doi.org/10.1016/j.clbc.2016.03.002)
  28. Dieci MV, Guarneri V, Zustovich F, et al.: 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. *Oncologist*. 2019, 24:1424-31. [10.1634/theoncologist.2019-0103](https://doi.org/10.1634/theoncologist.2019-0103)
  29. Fayaz S, Eissa HE, Demian GA: Implications of the 21-gene recurrence score assay (Oncotype DX) on adjuvant treatment decisions in ER-positive early-stage breast cancer patients: experience of Kuwait Cancer Control Center. *J Egypt Natl Canc Inst*. 2020, 32:13. [10.1186/s43046-020-00025-5](https://doi.org/10.1186/s43046-020-00025-5)
  30. Mattar A, Fonseca GR, Romão MB, et al.: Substantial reduction in adjuvant chemotherapy with the use of the 21-gene test to manage early breast cancer in a public hospital in Brazil. *JCO Glob Oncol*. 2021, 7:1003-11. [10.1200/GO.20.00609](https://doi.org/10.1200/GO.20.00609)