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The impact and indications for Oncotype DX on adjuvant treatment recommendations when third party funding is unavailable

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Running title: (45 characters, no spaces)

Patient-funded Oncotype DX use for adjuvant therapy

Abstract: 250 words

Objectives

Industry-supported decision impact studies demonstrate that Oncotype Dx (ODX) changes treatment recommendations (TR) in 24-40% of hormone receptor+/HER2- patients. ODX is not reimbursed by third party payers in Australia, potentially resulting in more selective use. We sought to evaluate the impact of self-funded ODX on TRs.

Materials and Methods

Data collected included demographics, tumour characteristics, indication for ODX and pre- and post Recurrence Score (RS) TR. Primary endpoint was frequency of TR change and associations with TR change were sought.

Results

Eighteen physicians contributed 382 patients (median age 54). 232 (61%) of tumours were T1 and were grade 1,2 and 3 in 49 (13%), 252 (66%) and 79 (21%). 257 (67%) were node negative. Assay indications were: confirm need for chemotherapy (CT) (36%), confirm omission of CT (40%), and genuine equipoise (24%). RS was low (≤17) in 55%, intermediate (18-31) in 36% and high (≥32) in 9%.

38% had TR change post-ODX. 65% of patients recommended CT pre-ODX changed to hormone therapy alone (HT) - more likely if lower grade and if ER and/or PR>10%. 14% of patients with pre-ODX TR for HT added CT - more likely if ER and/or PR≤10% and if Ki67 >15% Overall, TR for CT decreased from 47% to 24%.

Conclusion

Patient-funded ODX changed TRs in 38% of patients, de-escalating 65% from CT to HT, and adding CT to 14% of those recommended HT. These changes were greater than an industry-funded study suggesting that physicians can identify situations where the assay may influence decisions.

Keywords:

Hormone receptor-positive, HER2-negative early breast cancer, adjuvant chemotherapy, multigene assay, treatment decision

Introduction:

Breast cancer is the most common cancer in women in Australia and worldwide.(1) The use of adjuvant therapy confers an overall survival benefit for women with breast cancer.(2) For early-stage, hormone-receptor positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer, women are usually recommended hormonal therapy (HT) but may also be recommended chemotherapy (CT). The recommendation of CT has traditionally been based on a combination of pathological factors associated with an increased risk of recurrence and include; tumour size and grade, lymph node involvement and more recently, Ki67 labelling index.

The 21-gene Oncotype DX (ODX) breast cancer assay (Genomic Health, Redwood City, CA) derives a recurrence score (RS) that predicts the risk of distant recurrence and the expected benefit of adjuvant CT in addition to HT with Tamoxifen.(3) This has been validated, and is widely used in clinical care in North America and Europe.(3-5) Treatment guidelines including NCCN, ESMO, St Gallen and ASCO incorporate the use of genomic testing in selected HR-positive, HER2-negative node negative patients where the benefit of CT is unclear.(6-8) Its use in node positive patients is contentious.(8)

ODX was the first genomic assay available in Australia, and an industry-supported study examining the impact of ODX in an Australian setting found treatment recommendations (TRs) changed in 24% of patients.(9) This is at the lower end of the 24-38% range of impact seen in decision impact studies conducted in various countries and settings.(10) There is no public subsidy available in Australia for either ODX or any other genomic assay, due to concerns about the cost effectiveness of the assays. Therefore, all Australian ODX tests are funded directly by the patient at an approximate cost of AUD 4500, with no specific reimbursement available from the government or health insurance funds. This means that a decision to order an ODX in Australia has a direct financial impact on patients, which must be incorporated in the discussion around the potential usefulness of the assay.

The aim of this retrospective study of was to examine the clinical situations where patients were willing to pay for ODX themselves, and the impact of the RS on treatment recommendations. We also evaluated the use of ODX and treatment recommendations according to the 2015 St Gallen consensus guidelines.(7)

Materials and Methods

The distributors of Oncotype DX (Specialised Therapeutics Australia) identified Australian physicians who had ordered more than five tests (including one test ordered in the previous year) that were patient funded. Those physicians were invited to contact the principal authors (GBM, RDB, LCL) if interested in participating in the study. Further information regarding the study and a data collection sheet were then provided to the physicians.

Eligible patients were women with early stage HR-positive, HER2-negative invasive breast cancers. Data collected included de-identified patient age. Histopathology reports details of tumour subtype, size (cm), grade, the presence of any lymphovascular invasion, ki67 labelling index, nodal positive (included nodal metastases >0.2 mm (micro- and macrometastases) but isolated tumour cells were classified as node negative) and hormone receptors; and RS. RS groups were classified by Genomic Health International as low (0-17), intermediate (18-31) and high (32 and above) risk of recurrence at the time these tests were carried out. The physicians' TRs prior to, and following the RS, were recorded.

The physicians were also asked to use medical records to retrospectively determine the indication for recommending and ordering the assay using the following standardised definitions:

- Confirm need for chemotherapy in addition to HT (CHT)
    - Where the ordering practitioner would recommend CHT in the absence of RS

  - Where the multidisciplinary team meeting (MDT) recommends CHT (but the practitioner is unsure of the need for CT)
  - To convince the patient who doesn't want CT that it is required, where the practitioner strongly recommends CT

- Confirm omission of CT
  - Where the ordering practitioner would recommend HT alone in absence of RS
  - To validate the MDT recommendation of HT alone (where the practitioner is unsure of the need for CT)
  - To convince a patient who thinks they need CT that it is not required, if the practitioner strongly feels that CT is not required

- Genuine equipoise
  - This needs to be used sparingly
  - If the MDT does not reach consensus and recommends RS assay (with no recommendation for CT) and the practitioner doesn't have a strong recommendation either way
  - If the practitioner feels they cannot make a recommendation on the current information

As a comparator, the 2015 St Gallen guidelines were used to identify patients who should be considered for CHT. These guidelines include patients with tumours classified as luminal B (low ER and/or PR < 10% or 1+, high Ki67 >15%, that are T3 (>5cm), that have lymphovascular invasion (LVI)) or luminal A tumours with poor prognostic features (more than 3 involved lymph nodes, grade 3 or T3 in size).(7) The St Gallen guidelines were used to form TRs and compared with physicians' TRs following results of the ODX.

Statistical analysis was performed using Stata12 (StataCorp, College station, TX, USA). Relationships between categorical variables were assessed using Chi2 test and logistic regression analysis determined factors associated with TR change post-ODX. The McNemar test was used to assess the change in TRs following ODX.

Ethics approval was obtained from the Melbourne Health ethics committee prior to the commencement of the study, which incorporated the use of external contributors' data following a signed Memorandum of Understanding.

Results

Twenty seven physicians were identified and contacted. Eighteen physicians (16 medical oncologists, 2 surgical oncologists) contributed data from a median of 17 patients (range 5-87) who had self-funded ODX between 2006-2014.

There were 382 eligible patients who were ER-positive, HER2-negative. Nodal status was negative in 257, positive in 122 and unknown in three patients. Patient demographics, tumour characteristics, pre-Oncotype DX TRs and RS are shown in Table 1. As this was a real-world study, data was taken from pathology reports and some data was missing for tumour grade, lymphovascular invasion, hormone receptors and Ki67 labelling index. The indications for ordering ODX were predominantly to confirm omission of CHT in the node-negative group, and confirm the need for CHT in the node positive group. This was also reflected in TRs. Genuine equipoise comprised about a quarter of each group, and in these cases, some practitioners provided a TR that they would have given in the absence of ODX.

Impact of RS on physicians' treatment recommendations

Physicians' TRs changed in 136 out of 355 patients (38%) as shown in Table 2. Of the 168 patients who were recommended CHT prior to receiving the RS, 109 (65%) changed to HT alone following testing. For node negative patients, the proportion of patients recommended CHT decreased from 38% before, to 25% after, testing ($P < 0.01$). For node positive patients, the proportion of patients recommended CHT decreased from 65% before testing, to 23% after testing ($P < 0.01$)

The pathological factors predicting with a change between pre- and post-RS TRs are summarised in Table 3. Overall, on univariate analysis, the recommendation change from CHT to HT was more likely to occur for lower grade tumours ($p<0.001$) and if ER and/or PR >10% ($p=0.025$). There were non-significant trends for changes in node positive patients, where the Ki67 was <15% and for tumours >2cm. Tumour grade 1 or 2 remained significant on multivariate analysis ($p<0.05$).

Of 187 patients with pre-RS recommendation for HT, 27 (14%) changed to CHT, which was more likely to occur if ER and/or PR ≤10% and Ki67 > 15%, with non-significant trends to more changes for tumours that were <2cm and grade 3. There were no significant associations on multivariate analysis.

Using guidelines to select patients in whom CHT should be considered

As an objective comparator, we used the 2015 St Gallen Guidelines to evaluate patients who would be recommended chemotherapy. 202/355 (57%) patients would have been recommended chemotherapy based on clinico-pathological features (Table 4). The post-RS recommendations changed in 44% compared with TRs based upon St Gallen guidelines.

Individual pre-RS recommendations using guidelines were concordant for HT alone in 67% (92/137) and CHT in 56% (123/218) when compared to physicians' recommendations pre-RS. Despite that lack of concordance between physician recommendations and St Gallen guidelines in this group, the overall extent of change in TRs following RS was similar with both physician and guidelines TRs (38% vs 44% overall, with most change being from CHT to HT).

In the node-negative group, the recommendation change for the guidelines TRs was higher than the physicians TRs (42 vs 29%). Conversely in the node-positive group there was more change in the physicians TRs compared with guideline TRs (53 vs 43%).

Final treatment recommendations based on RS

The final TRs based on RS risk categories are summarised in Table 5. Patients with a low risk RS were treated with HT in 98% of cases and those with a high risk RS had CHT in 97%.

The RS was in the intermediate range in 139 patients. The final TR was CHT in 58 (42%) of these patients. The predictors for CHT for these patients were 1) if the TR prior to RS was CHT, and 2) having a higher RS within the intermediate range (data not shown). Those patients who had a final TR of CHT had median RS of 26 (IQR 23-28) versus those recommended HT alone having a median RS of 21 (IQR 20-23)). For patients in the "lower-intermediate" (RS=18-25) RS group, 26/77 (34%) received CHT, and in the "higher-intermediate" (RS=26-30) group, 32/36 (89%) received CHT.

Discussion:

Patient selection for genomic testing

Patient selection for ODX testing is multifactorial. Some clinicians and jurisdictions restrict its use to node negative patients where the supporting data are stronger. It has been found that patients who are younger, have better ECOG performance status and higher grade tumours and/or positive lymph nodes are more likely to undergo RS testing.(11) In Australia, the additional burden of the cost (AUD 4500) has impacted the uptake of Oncotype DX as compared to settings where third party payment is available. Other factors such as the absence of truly prospective trials and the issue of uncertainty regarding management of patients with an intermediate RS are important, but the financial barrier is likely most important.(12-15) Our hypothesis was that clinicians can usually determine when an assay is likely to be useful, and therefore the Australian setting, with this financial aspect needing to be factored in, physicians will identify clinical situations where ODX is more likely to be influential on TR..

Pre-RS TRs and guidelines

Physicians' pre-RS TRs were only concordant with TRs using the St Gallen guidelines in around 60% of cases. Despite this low concordance, post-ODX TRs were changed in a similar percentage (38% based on physicians' recommendations and 44% if St Gallen guidelines). Our interpretation of this is that these are situations where ODX is most likely to be helpful, and that physicians are recommending ODX when they believe that guidelines may be inadequate and that the decision for adjuvant treatment is unclear.

Pathological features vs RS

There have been numerous attempts to correlate the RS with conventional histopathological criteria such as grade, ER/PR status, and Ki67 score. While there are correlations between all these factors and the RS, no robust predictors on which treatment recommendations can reliably be based have been found.(16-20) We found that on univariate analysis, a pre-RS recommendation of HT alone was more likely to change to CHT on receipt of the ODX result if Ki67 was >15% or if there was low ER and/or PR, suggesting these factors may be useful in identifying cases where ODX may be useful.

Which patients had a change of TR?

In this study of patient-funded ODX, TRs changed in 38% of cases, which compares to our previous industry-funded decision impact study that included 151 consecutive HR-positive/HER2-negative patients and which found a TR change of only 24%.(9) This difference between the two studies is likely due to clinicians suggesting self-funded ODX primarily to patients in whom they believe their TRs are equivocal, or where they believe that the addition of CT is unlikely to be of benefit but they seek greater certainty. . In these circumstances clinicians may suggest to the patient that the test is worth the significant financial commitment.

In this study, there was a 14% change toward CHT for patients with a pre-RS recommendation for HT, which was similar to our previous industry-funded study of consecutive patients where there was a 15% change. On the other hand, we found a 65% change in those with pre-RS recommendation for

CHT, changing to HT, compared with a 36% change in the previous study. This suggests that clinicians are able to prospectively identify a subset of patients with HR-positive HER2-negative cancer in whom ODX is more likely to result in a change in TRs away from chemotherapy. Our interpretation of this is that there may be patients who chose to invest in ODX to confirm the omission of CT as a form of reassurance, rather then because there was a great expectation that the TR would change.

Our findings that on univariate analysis, a pre-RS recommendation of HT alone was more likely to change to CHT on receipt of the ODX result if Ki67 was >15% or if there was low ER and/or PR, while for those recommended CHT pre-RS, tumour grade 1 and 2, and high ER and PR were associated with an increased likelihood of a TR change post RS suggest that these are the groups in whom ODX is most likely to be cost-effective.

Impact of RS on final treatment recommendations

ODX is designed to estimate the risk of recurrence and the benefit of adjuvant chemotherapy in order to tailor patients' treatments. Patients with a low RS score are usually treated with HT alone and those with a high RS treated with CHT.(11) This occurred our study in the majority of cases, with patients and physicians relying on the result of the ODX to either confirm or change the TR. Four patients in the low RS group eventually received CHT, and one patient in the high risk RS group was treated with HT alone. In four of these five patients, the final TR was the same as the pre-RS TR, suggesting that they or the patient based their final decision on traditional clinico-pathological factors, or personal preferences, rather than rely on the RS result. A post-RS treatment recommendation that seems inconsistent with the RS result has also been found in other studies.(21-23) This emphasises the importance of clear discussions between the physician and the patient prior to ordering the test as to whether they would act on a low or high RS. The fact that there is some discrepancy in treatment decisions and RS results highlights that physicians and patients take other factors into account when deciding upon adjuvant therapy.(23,24)

Appropriate management of patients in the intermediate risk RS group is unclear with the results of the randomised arm of the TailorX study eagerly awaited. In our study, the proportion of patients with an intermediate risk RS who were recommended CHT pre- and post-RS changed very little (45% vs 42%), similar to other studies.(21,23,25) However, there was still an overall change of 34% (47/139) in TRs following an intermediate RS with TRs changing in both directions. Similar to Fried et al, we found that the "lower-intermediate" group (18-25) had more patients have a final recommendation for HT, while patients in the "higher-intermediate" group (26-30) were more likely to have final recommendations for CHT. A "higher-intermediate" RS and a pre-RS recommendation for CHT were predictors of a final recommendation of CHT. Our findings suggest that for patients in the intermediate RS group clinicians' TRs were somewhat binary with a cut-off around RS 25, but subject to influence from their initial clinical judgement.

The use of ODX in node positive patients is interesting.(26) The data supporting this use is less robust than that supporting ODX in node negative patients.(8) Results from the RxSPONDER trial are expected to address this lack of prospective trial evidence, however physicians and patients are choosing to invest in ODX and act on the information. The node positive patients who had ODX in this series tended to have lower grade cancer with lower Ki67 when compared to the node negative patients, suggesting that ODX was suggested when the case was one where the main indication for CHT was the node positivity, and the physician was looking for reassurance than CHT could be omitted in a node positive patient.

Advantages / Limitations

This study is unique in that it is the only study where the decision to use an assay had a direct financial impact on the patient. This means that this cohort represents patients in whom clinicians and patients expected the assay would be most likely to yield useful information.

Our study is limited by its retrospective nature, particularly regarding the indication for ordering the ODX and the pre-RS TRs. Not all physicians explicitly documented their rationale for ordering ODX or their pre-RS TRs.

Conclusion:

The results of this study show that it is possible to prospectively identify a group in whom ODX is more likely to have a significant impact. Overall TRs changed in 38% of cases compared to 24% in a previous Australia DIS. Importantly, 65% of the patients who were initially recommended CHT were spared chemotherapy following the result of the RS, which has important medical, social and financial implications.

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Conflict of Interest

R De Boer has received fees for speakers bureaus from Genomic Health. N McCarthy and B Kiely have been on an advisory board for Specialised Therapeutics.

Funding

No funding was obtained for this project

Ethical Approval

This project received appropriate ethical approval.

Legend for Tables

Table 1. Patient demographics and tumour characteristics.

Table 2. Physician treatment recommendations before and after RS

Table 3. Pathological factors leading to change in treatment recommendations following RS

Table 4. Treatment recommendations by 2015 St Gallen criteria before and after RS

Table 5. Final treatment recommendations based on RS

Tables

Table 1. Patient demographics and tumour characteristics.

	All patients* N=382	Node negative N=257	Node positive N=122	p
Median age (IQR)	54 (47-61)	54 (47-61)	54 (49-62)	0.373
Tumour size (cm) - median (IQR) <2cm (n,%) >2cm (n,%)	1.7 (1.2-2.5) 232 (61) 150 (39)	1.6 (1.2-2.3) 165 (64) 92 (36)	1.9 (1.3-2.6) 65 (53) 57 (47)	0.042
Histology (n,%) Ductal Lobular Other	 317 (83) 42 (11) 23 (6)	 222 (86) 20 (8) 15 (6)	 92 (75) 22 (18) 8 (7)	0.010
Tumour grade (n,%) 1 2 3 missing	 49 (13) 252 (66) 79 (21) 2	 22 (9) 172 (67) 62 (24) 1	 27 (22) 78 (65) 16 (13) 1	<0.001
Lymphovascular invasion (LVI) (n,%)	85 (23)	44 (18)	40 (35)	<0.001

ER and/or PR <10% (n,%)	63/380 (16)	45/256 (18)	17/121 (14)	0.19
Ki67 labelling index >15% (n,%)	113/231 (49)	88/158 (56)	25/72 (35)	0.002
Indication for ODX (n,%)				
Confirm need for CHT	136 (36)	68 (26)	67 (55)	
Confirm omission of CHT	154 (40)	122 (48)	32 (26)	
Genuine equipoise	92 (24)	67 (26)	23 (19)	
Pre-ODX recommendation (n,%)				
CHT	168 (44)	89 (35)	77 (63)	<0.001
HT	187 (49)	146 (57)	41 (34)	
No recommendation	27 (7)	22 (8)	4 (3)	
Recurrence score (n,%)				
Low (<18)	208 (55)	130 (50)	77 (63)	0.073
Intermediate (18-31)	139 (36)	102 (40)	36 (30)	
High (>31)	35 (9)	25 (10)	9 (7)	

* In 3 cases, nodal status was unknown

Table 2. Physician treatment recommendations before and after RS

	Before RS		After RS		
	Pre-RS TR	Patients	Treated with HT	Treated with CHT	Proportion (%) changed
All patients	HT	187	160	27	27/187 (14)
	CHT	168	109	59	109/168 (65)
	Total	355	269	86	136/355 (38)
Node negative	HT	146	125	21	21/146 (14)
	CHT	89	52	37	52/89 (58)
	Total	235	177	58	73/235 (29)
	No recommendation	22	13	9	
Node positive	HT	41	35	6	6/41 (15)
	CHT	77	56	21	56/77 (73)
	Total	118	91	27	62/118 (53)
	No recommendation	4	3	1	

Table 3. Pathological factors leading to change in TR following RS

	Pre-RS TR of HT				Pre-RS TR of CHT			
	Post-RS HT	Post-RS change to CHT	Univariate analysis	Multivariate analysis	Post-RS CHT	Post-RS change to HT	Univariate analysis	Multivariate analysis
Tumour size <2 cm	109	22	0.181	0.833	35	53	0.185	0.410
Tumour size ≥ 2cm	51	5			24	56		
Tumour grade 1 and 2	142	21	0.125	0.970	30	88	<0.001	0.046
Tumour grade 3	18	6			29	19		
LVI present	24	3	1.000	0.954	17	36	0.353	0.442
Ki67 <15%	55	6	0.024	0.092	14	32	0.196	0.942
Ki67 ≥15%	37	14			22	29		
ER and/or PR ≥10%	139	18	0.037	0.165	44	96	0.025	0.596
ER and/or PR <10%	21	8			15	13		
Node positive	35	6	1.000	0.922	21	56	0.054	0.825

Node negative	125	20			52	37		

Table 4. Treatment recommendations by 2015 St Gallen criteria before and after RS

	TR using 2015 St Gallen criteria for consideration of chemotherapy		TR given after RS		
	TR	Patients	HT	CHT	Proportion (%) changed
All patients	HT	153	133	20	20/153 (13)
	CHT	**202**	136	66	136/202 (67)
	Total	355	269	**86**	156/355 (44)
Node negative	HT	99	90	9	9/99 (9)
	CHT	**158**	100	58	100/158 (63)
	Total	257	190	**67**	109/257 (42)
Node positive	HT	63	52	11	11/63 (17)
	CHT	**59**	42	17	42/59 (71)
	Total	122	94	**28**	53/122 (43)

Table 5. Final treatment recommendations based on RS

	n	Final recommendation HT	Final recommendation CHT
Low RS (<18)	208	204	4
Intermediate (18-31)	139	109	30
Lower intermediate (18-25)	103	77	26
Higher intermediate (26-30)	36	4	32
High (>31)	35	1	34